Food additives in Europe 2000
- Status of safety assessments of food additives presently permitted in the EU

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Preface

This report has been prepared for the Nordic Council of Ministers. The work has been done under the auspices of the Nordic Working Group on Food Toxicology and Risk Assessment (NNT) and was started in 1999.

The monographs have been prepared by Vibeke Breinholt (colours of natural origin), Lars Dragsted (antioxidants), Max Hansen (preservatives, additives of various action), Alireza Hossaini (preservatives), Henrik Rye Lam (synthetic colours and emulsifiers), Alicja Mortensen (Sweeteners), Eva Selzer Rasmussen (glazing agents), all from Institute of Food Safety and Nutrition, Denmark, Trine Husøy (sulphites and biphenyl) from National Institute of Public Health, Norway, Nils-Gunnar Ilbäck (nitrate and nitrite) from National Food Administration, Sweden.

Inge Meyland from the Institute of Food Safety and Nutrition, Denmark, has prepared the text on the specifications for all food additives in the monographs. Pirjo-Liisa Penttilä from the Finnish National Food Administration and Inge Meyland from the Institute of Food Safety and Nutrition, Denmark have delivered the extracts from the EU Monitoring System on Exposure to Food Additives. Torben Hallas-Møller from the Institute of Food Safety and Nutrition, Denmark has developed the summary table in the report.

Torben Hallas-Møller, Max Hansen and Ib Knudsen have edited the report, worked out the prioritisation of the food additives and written introductory chapters, explanatory notes, and concluding remarks.

The report has been supervised and peer-reviewed by a Nordic Steering Group:

- **Denmark** Torben Hallas-Møller, Max Hansen and Ib Knudsen (Chairman), Institute of Food Safety and Nutrition,
- **Finland** Pirjo-Liisa Penttilä, National Food Administration,
- **Iceland** Æsmundur Torkelsson, Environmental and Food Agency of Iceland,
- **Norway** Trine Husøy, National Institute of Public Health,
- **Sweden** Nils-Gunnar Ilbäck, National Food Administration.

Further peer-reviews have been performed by Jørn Gry, Institute of Food Safety and Nutrition, Denmark, Anja Hallikainen, National Food Administration, Finland, Ingvild Tømmerberg, Norwegian Food Control Authority, Norway, Tore Aune, Norwegian Veterinary University, Norway, and Anders Glynn, National Food Administration, Sweden.

Finally the report has been accepted by NNT.
Summary

The use of food additives in the European Union (EU) is regulated by a framework directive of December 1988 concerning food additives for use in foodstuffs intended for human consumption and three specific directives on colouring matters on sweeteners and on additives not covered by the other two directives.

There is no provision for periodic reviews of the safety of the permitted substances, and some of the safety evaluations have not been updated by the Scientific Committee on Food for a long time. Thus of the 163 monographs covering more than 300 food additives with individual E-numbers covers additives with safety evaluations older than 10 years and of these 30 older than 20 years.

The purpose of the present report is to examine whether the evaluations are still valid and adequate in the light of present days standards for safety assessments, to examine whether significant new toxicological studies have been published since the latest evaluation and to facilitate a prioritisation, if a systematic review is to be initiated.

The report contains 163 monographs, some of them containing also related substances, so the review covers all the substances presently allowed for use in EU. All food additives have been registered with the year for last evaluation by the Scientific Committee for Food (SCF) in EU and the Joint Expert Committee on Food Additives (JECFA) under FAO/WHO. A literature search with relevant search profile in Toxline and Medline for compound specific toxicological data published since that last evaluation has been made. Finally the Nordic Working Group on Food Toxicology and Risk Assessment has assessed the scientific relevance of the new data collected and prepared a recommendation for each food additive regarding the need and the priority for a re-assessment of its safety or for other measures.

The prioritisation for new safety evaluations or other actions is given in a ranking order from 0 to 5, where “0” indicates no need for any action and “5” indicates high priority for a re-evaluation or other action. The 10 substances or group of substances presently on the agenda of the SCF have got no ranking. Of the 163 monographs 65 got “0” indicating no need for any action. For 38 monographs some, usually minor, matters ought to be clarified. Other 20 got the designation “2” meaning “Update of evaluation recommended”. This priority is mostly used, if it is assumed that there is no reason to change the present ADI, but new data has been published which preferably should be included in the evaluation. Next 18 monographs got the designation “3”, which means “Some priority for a re-evaluation or other action”. The last 15 monographs got “4”, which means “Priority for a re-evaluation or other action”. No monograph got “5” and thereby high priority for a re-evaluation or other action.

The report demonstrates that there is no need for any urgent action regarding re-assessing the use of the presently approved food additives.

However, the review points out a series of aspects which warrant attention e.g. that many substances have not been re-assessed for many years, although new data are accumulating in the scientific literature and in certain cases calls for a new assessment and that for some additives their uses should be assessed to reassure that the exposure complies with the recommendations of SCF.

It is recommended that a mechanism is put in place in EU, which ensures a systematic, periodic review of all permitted food additives. In the meantime it is suggested to use the data in the present report as help for prioritisation of action.
Sammendrag

Brugen af tilsætningsstoffer inden for De Europæiske Fællesskaber (EU) reguleres via et overordnet rammedirektiv fra december 1988 vedrørende tilsætningsstoffer til brug i levnedsmidler bestemt for humant konsum og tre andre specifikke direktiver om farvestoffer, om sødestoffer og om tilsætningsstoffer, der ikke er omhandlet af de to andre direktiver.

Direktiverne rummer ikke krav om periodisk revurdering af sikkerheden ved de tilladte stoffer, og nogle af sikkerhedsvurderingerne har ikke været opdateret af Den Videnskabelige Komité for Fødevarer i lang tid. Af denne rapports 163 monografier, der dækker de mere end 300 tilladte fødevaretilsætningsstoffer med individuelle E-numre omfattet af de 3 direktiver, er de sikkerhedsmæssige vurderinger i 30 monografier ældre end 20 år og i 124 monografier ældre end 10 år.

Formålet med nærværende rapport er 1) at undersøge, om de sikkerhedsmæssige vurderinger, der danner basis for de nuværende anvendelsesbetingelser for sikker brug, stadig er i orden og tilstrækkelige i lyset af nutidens krav til standarden for sikkerhedsvurderinger, 2) at undersøge, om der er publiceret væsentlige, nye data siden den sidste vurdering og 3) at lette en prioritering, hvis der skal foretages et systematisk revurdering af de tilladte tilsætningsstoffer.

Rapporten har samlet de tilladte fødevaretilsætningsstoffer i 163 monografier, idet kemisk nært beslægtede stoffer indgår i samme monografi. I monografierne er årstallet for sidste evaluering af hvert enkelt tilsætningsstof gennemført af henholdsvis Den Videnskabelige Komité for Fødevarer (SCF) under EU og Joint Expert Committee on Food Additives (JECFA) under FAO/WHO blevet registreret. Med udgangspunkt i disse oplysninger er der gennemført en litteratursøgning i Toxline og Medline efter stofspecifikke toksikologiske data, der måtte være blevet publiceret efter sidste evaluering i komitéerne. Resultaterne af disse søgninger indgår i monografierne. Endelig har Den Nordiske Arbejdsgruppe for Næringsmiddeltoksikologi og Risikovurdering (NNT) vurderet den videnskabelige relevans af de nyinsamlede data og foreslået en prioritering for sikkerhedsmæssig revurdering af det enkelte tilsætningsstof, monografi for monografi, hvis en samlet revurderingsprocedure sættes i gang i EU. NNT har ikke selv lavet en egentlig sikkerhedsmæssig vurdering af det enkelte tilsætningsstof på basis af de nye data.

Prioriteringen af de 163 monografier for et nyt sikkerheds-check er baseret på en rangordning med point fra 0 til 5, hvor "0" betyder, at det ikke er nødvendigt at gøre noget pt, og hvor "5" betyder, at reevaluering eller andre tiltag bør have høj prioritet. For 10 af stofferne eller stofgrupperne gælder, at de i øjeblikket er ved at blive vurderet af SCF. Derfor er de ikke blevet prioriteret. De 65 af monografierne har fået prioriteringen "0", hvorfor der ikke behøver å ske yderligere med dem. I alt 38 monografier fik "1", som betyder at nogle, sædvanligvis mindre, spørgsmål bør afklares. Svarene på disse spørgsmål bestemmer den videre prioritering. Andre 20 monografier fik prioriteringen ”2”, som betyder, at opdatering af den sikkerhedsmæssige vurdering anbefales. Denne prioritering anvender NNT, når der ikke vurderes at være grund til at ændre den nuværende Acceptable Daglige Indtagelse, ADI, men at de nye publicerede data bør inddrages i vurderingen. De næste 18 monografier fik prioriteringen ”3”, hvilket betyder moderat behov for reevaluering eller andre tiltag, og de sidste 15 monografier fik ”4”, hvilket kort og godt betyder behov for reevaluering eller andre tiltag. Ingen af monografierne fik ”5” og dermed høj prioritering for reevaluering eller andre tiltag.

Rapporten viser således, at der ikke er behov for hastende initiative angående revurdering af brugen af de godkendte tilsætningsstoffer.
Imidlertid påpeger rapporten også, at mange af tilsætningsstofferne ikke har været gennem et sikkerhedsmæssigt check i mange år, selv om nye data hober sig op i den videnskabelige litteratur og i visse tilfælde signalerer behov for en ny vurdering og derudover at det for nogle tilsætningsstoffer vedkommende bør sikres, at den nuværende brug er i overensstemmelse med anbefalingerne fra den Videnskabelig Komité for Levnedsmidler.

Rapporten anbefaler, at der etableres en mekanisme i EU, som sikrer et systematisk, periodisk sikkerhedsmæssigt check af alle de tilladte fødevaretilsætningsstoffer. Indtil da anbefales det at bruge data i nærværende rapport til prioritering af de mest påtrængende tiltag.
1. Introduction


While the specific directives have provisions for periodic monitoring of the use of food additives, there is no provision for periodic reviews of the safety of the permitted substances.

The purpose of the present report is

• to examine whether the safety evaluations, which form the basis for present conditions of use, are still valid and adequate in the light of present days standards for safety assessments,
• to examine whether significant new toxicological studies have been published since last evaluation and
• to facilitate a prioritisation, if a systematic review is to be initiated.

The report has been developed in a sequence of steps:

• all food additives have been registered with the year for last evaluation by the Scientific Committee for Food (SCF) in EU and/or the Joint Expert Committee on Food Additives (JECFA) under FAO/WHO
• a literature search with relevant search profile in Tox-line and Med-line for compound specific toxicological data published since last evaluation has been performed
• the scientific relevance of the collected material has been assessed substance by substance and a recommendation for each food additive regarding the need and the priority for a re-assessment of its safety has been prepared
• The aim of this Nordic report is to make it available to the European Commission for consideration.

For each substance a monograph has been made. It has been chosen to include substances with similar toxicological profiles in the same monograph. This compilation has led to the development of 163 individual monographs covering more than 300 substances with individual E-numbers.

Each of the monographs in the report describes the basis for the safety evaluation performed by SCF and JECFA and examines whether new data has been published since the evaluations of SCF and JECFA and whether the quality and importance of the new data justify a re-evaluation. The purpose of the report is not to undertake a full new evaluation of any of the food additives, as this would require access not only to the published data, but also to all the original reports, many of which are submitted by the applicants to SCF and/or JECFA for the assessment and not available in the public domain.

Each monograph also includes the most important features from the EU- and JECFA specifications for the food additive(s) covered by the monograph as well as the assessment of the European exposure taken from the European SCOOP project on intake of food additives.
The review in this report covers all food additives, which were permitted in EU by April 2000, and this date has also been the general deadline for inclusion of new data in the monographs. However, it has been attempted to include also the results of later SCF and JECFA evaluations.
2. Principles for safety assessment of food additives by SCF

In 1980 the Scientific Committee for Food (SCF) issued its first guidelines for the safety assessment of food additives (Tenth Report Series, 1980). When the work on the present report started, these guidelines were still the official guidelines for the toxicological assessment of food additives, but simultaneously with the work on the present report the SCF started the updating of its 1980 report. In 2001, more than 1 year after the formal stop for collection of new data for the present Nordic report, the SCF adopted its new guidelines: “Guidance on Submissions for Food Additive Evaluations by the Scientific Committee on Food” (Opinion expressed on 11 July 2001).

This opinion explains in details the important elements of a dossier: Administrative data, Technical data, Toxicological data, and References and reports. In an annex the SCF describes in details, which studies it considers to be the core toxicological studies for the establishment of the Acceptable Daily Intake (ADI) and which studies are supportive for reaching the most correct ADI seen from a human health point of view. The section on toxicological data in the Guidance document describes very well, how SCF performs the safety evaluation of the individual food additives and thus how the SCF might handle the type of information delivered by the monographs in this report.

Therefore this section from the Guidance Document (Part III) is quoted in total below:

“PART III TOXICOLOGICAL DATA

1. General framework for the toxicological evaluation of food additives

If the technological need and value to consumers of a proposed food additive have been established, it is necessary to evaluate the implications for the health of the consumer due to the presence of that additive in food. The SCF first issued Guidelines for the Safety Assessment of Food Additives in 1980. Many of the principles articulated in that document are still applicable today. However, since that time, a number of other guidance documents have been published on the principles for assessment of food additive safety, including by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and there is now considerable international consensus on these general principles. It is therefore not the intention to reiterate these here, but to outline a framework of core tests required by the SCF for safety evaluation of a food additive. Accordingly, the guidance given here and in the accompanying Annex replaces that given by the SCF in 1980 on the toxicological tests generally required for additives.

The aim of toxicological testing is to determine whether the substance, when used in the manner and in the quantities proposed, would pose any appreciable risk to the health of consumers. Such testing should provide not only information relevant to the average consumer, but also relevant to those population groups whose pattern of food consumption, physiological or health status may make them vulnerable, e.g. young age, pregnancy, diabetes, etc. No fixed programme of testing is laid down, but a general framework covering core tests and other tests is given, which should enable petitioners to determine what information is required to establish the safety-in-use of the food additive. The studies required will depend on the chemical nature of the additive, its (proposed) uses and levels of use in food, whether it is a new additive or a re-examination of an existing additive. In addition to laboratory tests, it may be possible to use human data derived from medical use, occupational epidemiology, or specific studies on volunteers (e.g. on absorption and metabolism) or on critically exposed groups. However, it is
recognised that for new food additives, a safety evaluation generally relies on experimental data largely derived from investigations in laboratory animals. If the biological action of a substance has been ascertained qualitatively and quantitatively in a range of tests on laboratory animals, the likely effects on man can then be estimated by careful extrapolation.

In general, this guidance is intended to apply to the evaluation of a proposed new food additive, or to the re-evaluation of an already approved food additive, directly incorporated into food and fulfilling a defined technical purpose. It does not apply to flavouring substances, substances migrating into food from food packaging materials, or novel foods, on which the SCF has issued separate guidance, nor does it apply to other food contaminants, either naturally occurring or man-made. It is however recognised that many of the tests used for the safety evaluation of food additives are also useful for the toxicological evaluation of other types of food chemicals.

2. Study protocols

Studies on toxicity, kinetics and metabolism of food additives should be conducted using internationally agreed protocols. Test methods described by OECD\textsuperscript{7} or in European Commission Directives \textsuperscript{8,9} are recommended. It is advisable to ensure the most up-to-date edition of any test guideline is followed. Use of any methods differing from internationally agreed protocols should be justified. Protocols for special studies differing from standard tests should be developed on a case-by-case basis.

To ensure mutual recognition by Member States of the data submitted, studies should be carried out according to the principles of Good Laboratory Practice (GLP) described in Council Directive 87/18/EEC\textsuperscript{10} and accompanied by a statement of GLP compliance. The scope of GLP requirements was extended to include food additives in 1988 under Council Directive 88/320/EEC\textsuperscript{11}. Adequate explanation should be provided for divergence from these principles. Studies conducted prior to the introduction of GLP for food additives may be considered, particularly if they relate to older substances or additives already permitted for use in the EU.

Petitioners are reminded that Council Directive 86/609/EEC\textsuperscript{12}, on the protection of animals used for experimental and other scientific purposes, requires that care is taken to avoid unnecessary use of animals. Studies carried out should be those necessary to demonstrate the safety of an additive and planned in accordance with the principles of reduction, refinement and replacement. However, at this point in time, assuming adequate human data are not available, in vivo studies using experimental animals from species relevant to humans are still needed in order to assess possible risks to humans from the ingestion of food additives. There are some exceptions to this (e.g. assessment of genotoxic potential by in vitro studies) and alternative validated methods for other endpoints in toxicity, involving fewer or no animals, are being developed. Studies submitted using alternative methods would be considered on a case-by-case basis.

3. Toxicological section of the dossier

Any proposed food additive should normally undergo a comprehensive examination for potential toxicological effects before its safety-in-use can be accepted. Petitioners should therefore submit the range of studies recommended below as a core set and should consider whether any other types of study might also be appropriate.
There may be circumstances, depending on the substance and its uses, under which it is considered that a full core set is not necessary (e.g. substances which are normal constituents of the diet or of the body, or may be metabolised to such; toxicological data on close homologues or other structure activity considerations; intake considerations). Or, as specified tests are completed, it may be possible that a decision on safety can be taken in the light of the results obtained without further tests. Or it may be decided that tests other than the usual tests are more appropriate.

The reasons for carrying out any unusual studies should be stated, as should the reasons for not submitting a study of a type that might be expected. All the important results obtained, favourable or unfavourable, should be presented and discussed and the original study reports submitted in order to allow independent, critical appraisal. Petitioners should also submit any other existing, relevant data on the substance, including copies of published papers.

### 3.1. Core studies

The core studies normally required for evaluation of the safety of a food additive are set out below. The detailed considerations underlying these core toxicological requirements have been elaborated in the Annex to these guidelines.

#### a) Metabolism/Toxicokinetics

Information on metabolism and toxicokinetics should normally be provided on a new additive. The design of metabolism and toxicokinetic studies should be flexibly adapted to the particular substance being tested. Not all aspects may need to be investigated in every case. In principle, whole animal studies using single and repeat dosing are needed. In vitro studies can also contribute useful information.

#### b) Subchronic toxicity

Any new additive should normally be tested in subchronic toxicity studies, preferably in which the additive is given via the diet, in two laboratory species, usually a rodent and a non-rodent, for a period of at least 90 days. Preceding feeding studies conducted for 14 or 28 days can provide an indication of target organs and help in selection of appropriate doses for 90-day studies, but studies of shorter duration than 90-days are generally not sufficient, by themselves, for evaluation of potential subchronic toxicity.

#### c) Genotoxicity

Any new additive should normally be tested for genotoxicity in order to assess its mutagenic and carcinogenic potential. In general a battery of three genotoxicity tests is required, comprising:

i. A test for induction of gene mutations in bacteria.
ii. A test for induction of gene mutations in mammalian cells in vitro (preferably the mouse lymphoma tk assay).
Positive results in any of the above in vitro tests will normally require further assessment of genotoxicity in vivo.

d) Chronic toxicity and carcinogenicity

Any new additive should normally be tested for chronic toxicity and carcinogenicity in studies, preferably in which the additive is given via the diet, in two laboratory species, usually rat and mouse, covering the majority of the lifespan of the animals, generally 24 months in the rat and 18 or 24 months in the mouse. Combined chronic toxicity/carcinogenicity studies are acceptable.

e) Reproduction and developmental toxicity

A new additive should normally be tested in reproduction and developmental toxicity studies. A multigeneration reproduction study, including assessment of endpoints relevant to endocrine disrupter potential, should be conducted in one laboratory species, usually rat, and comprise at least two generations and one litter per generation. Administration of the test substance should normally be in the diet.

Developmental toxicity studies should be conducted in two laboratory species, usually a rodent and a non-rodent, such as rat or mouse and rabbit. Administration of the test substance should normally be via the diet or by oral gavage and cover not only the period of embryogenesis but continue to the end of gestation in order to ensure detection of, for example, endocrine disrupter potential.

In order to ensure that a new additive does not affect postnatal development and function, including neurological function and behaviour, physical, functional and behavioural development of animals exposed from at least the beginning of embryogenesis through to weaning should be studied. This can be done as a separate study or as part of a multigeneration and/or developmental toxicity study.

3.2 Other studies

In addition to the core studies, other studies may also be helpful or necessary for certain substances, depending on aspects such as chemical structure or class, uses, and known or predicted toxicological properties. Decisions on whether other studies are needed should be taken on a case-by-case basis. Examples of other areas of investigation which might be appropriate include, but are not limited to: immunotoxicity, allergenicity, intolerance reactions, neurotoxicity, human volunteer studies, predictive mechanistic studies and special studies to explore in more depth toxicological effects observed in core studies.

Further discussion on the relevance, scope and use of other studies, including those mentioned above, is provided in the Annex to these guidelines.

There are also other toxicity studies that are not required for evaluation of the safety of food additives, but which may have been conducted for other purposes, such as worker safety (e.g. acute toxicity, irritation and sensitisation studies). If such studies are available, they should be submitted as they may provide useful background information.
4. Data reporting

The data reported for standard toxicological tests should, as far as possible, follow the recommendations for data reporting given in the relevant OECD guidelines. Petitioners are reminded that for each study performed it should be stated whether the test material conforms to the proposed or existing specification. If it does not conform then the specifications of the test material should be given and it should be indicated whether this is representative of the substance intended for the market.

5. Review of results and conclusions

For each study, the significant findings should be highlighted, together with the no adverse-effect level, if one has been determined, and any other relevant information.

Where effects are seen only at high doses/concentrations, the relationship between the exposures giving rise to effects and likely human exposure from use of the substance as an additive should be discussed.

This section should also seek to interpret the data and draw conclusions. The reasons for disregarding any findings should be carefully explained. Where necessary, the conclusions should include an interpretation of the significance of the findings in terms of possible mechanisms of any effects observed, a discussion of whether these are relevant to humans and, if so, the possible significance of the extrapolation of such findings to humans. References to effects (or lack of effects) from known human exposure should be given; evidence from recorded experience for occupational or therapeutic exposure, for example, may be informative. The overall evaluation of potential human risk should be made in the context of known or likely human exposure, including that from other sources."

References to the SCF guidelines as quoted above:


The whole opinion can be found on the homepage of DG SANCO:
http://europa.eu.int/comm/food/fs/sc/scf/out98_en.pdf
3. Structure of the individual monographs in the review.

For each substance (or group of substances with similar toxicological profile) a monograph is prepared. The structure of the individual monograph is given in table 3.1.

It starts with the name(s), E-number(s) and synonyms for the food additive(s), followed by the recommendations for further action (if any). After the specifications and exposure estimates follow the summaries of the SCF and JECFA evaluations. The second part of the monograph is an extract of the background data as reported by SCF and JECFA supplemented with a short description of the core studies for their assessment of the food additive as well as relevant studies on that compound published after the evaluations made by SCF and JECFA. In the end of the monograph comes the overall conclusion from the Nordic Working Group on Food Safety and Risk Assessment (NNT) concerning the safety of the substance(s) together with the references. The individual monographs are brought in Annex I.

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<th>Table 3.1. Monographs on the individual substances, headings and explanations</th>
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<td>Conclusion:</td>
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The principles behind the development of the text under the various headings in the monographs applied by the NNT are given below:
3.1 Recommendation for further action: The primary criteria for the formulation of the recommendations are

1. the age/quality of the toxicological data base and the age of latest evaluation(s)
2. whether the toxicological data cover all the aspects which are required according to present standards
3. the appearance of relevant new toxicological data since latest SCF evaluation
4. a potential high exposure compared to the ADI
5. the compliance between the present conditions and the advice of SCF
6. major changes in specifications, including methods of production

Ad 1: It should be born in mind that just because a test has been performed many years ago and without adhering to formal GLP, the study can still be of a quality, which does not warrant a repetition. When making requests for further studies, the present EU regulations against unnecessary testing on animals should be kept in mind. Thus many of the food additives tested and evaluated long time ago have not been recommended for new evaluation if the existing data have been found to be reassuring for the safety in use at the present conditions.

Food additives, which are on the present agenda of the SCF, have not been subject for special scrutiny or subjected to further recommendations, but rather put on hold, since SCF already has decided to take a look at them.

Ad 2: The mere lack of one or two studies, normally required according to present days guidance for submissions for food additive evaluations, has not automatically led to recommending the performance of additional studies if the existing data package, the nature of the substance or experiences from its present use in food do not indicate any reason for special concern.

Ad 3: New data now in the scientific literature may support, but not necessarily change the old safety assessments made by SCF and should for the sake of clarity be included in the assessment. Therefore an update has been recommended in those cases, but with lower priority.

In other cases the new data may suggest a new outcome of the assessment, which could lead to either a more restrictive or a less restrictive opinion than the previous one. This is expressed by giving the food additive a higher priority for a re-assessment.

Ad 4: In cases where present permitted uses suggest that an ADI may be exceeded, considerations regarding either more accurate exposure estimates or reductions in permitted uses have been recommended. The same recommendation is given when present conditions of use seem to have changed from the past, thereby changing the validity of the past exposure assumptions which play an important part of the risk assessment. For a series of substances the EU food additive monitoring system (see later) already has recommended further investigation of exposure (tier 3).

Ad 5: In some cases the specifications or the conditions in use do not reflect the recommendations of the SCF.

Ad 6: Major changes in the specifications for the individual food additive, maybe due to changed methods of production, may lead to a discrepancy in composition, including inherent impurities, between the substance originally tested and evaluated and the substance now marketed under the same E-number, and thereby also to a recommendation in this report to re-visit the toxicological assessment of the past.
3.2 Specifications: Specifications for food additives are drawn up in order to confirm that the substances are of a quality required for their safe use in food. All authorised food additives in EU have to fulfil purity criteria which are set out in details in three Commission Directives: Commission Directive 95/31/EC laying down specific criteria of purity concerning sweeteners for use in foodstuffs, as amended by Directives 98/66/EC, 2000/51/EC and 2001/52/EC, Commission Directive 95/45/EC laying down specific purity criteria concerning colours for use in foodstuffs, as amended by Directives 99/75/EC and 2001/50/EC, and Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, as amended by Directives 96/86/EC, 2000/63/EC and 2001/30/EC.

For this purpose primarily the identity and composition of the substance that has been toxicologically tested have to be known, and then it has to be assured that articles of commerce are consistent with the toxicologically tested material.

The specifications are thus prepared in order to define the product that is accepted for food use, including as far as possible the principle of manufacture of the product. The method of manufacture is taken into account when relevant, and purity criteria need to be identified accordingly. It is important to bear in mind that different source materials or different methods of manufacture often will result in different purity criteria. In certain cases it may not be possible or feasible to identify and specify all relevant impurities, and in such cases other criteria such as method(s) of production may be included in the specification in order to cover the basic purity aspects.

Until recently most specifications included a criterion for “Heavy metals (as Pb)”. This criterion is a so called “catch-all test” for inorganic impurities like lead, mercury, antimony, copper and cadmium and it was valid for the purpose of avoiding huge contamination with heavy metals at a time when analysis for the impurities in question were expensive, difficult and time consuming. Recently it has been decided by the EU Commissions Specifications Group and by JECFA to delete the “Heavy metals (as Pb)” criterion in future revisions of individual specifications. The criterion will, where relevant, be replaced by limits for individual inorganic impurities for the additive in question.

In the present publication the individual specifications are not printed in full, but assay values and criteria of importance for the toxicological evaluation are shown.

3.3 Exposure: For each substance/group of substances the conditions of use according to the food additive directives (see chapter 1) are specified.

Furthermore are given the results of the summaries of the conclusions made during the first project on monitoring uses and intake of additives in the member states of the European Union. The EU monitoring system is based on the recommendations given in the report of the working group on “Development of methods for monitoring intake of food additives in the European Union”, task 4.2 of the Scientific Co-operation on questions relating to food (published on the Commission website: http://europa.eu.int/comm/food/fs/sfp/addit_flavor/flav15_en.pdf). The report points out the fact that due to the large number of substances covered by the Directives in all potential foodstuffs, the implementation of a detailed monitoring of all these substances would not be feasible in terms of resources. Consequently, based on the intention that it must primarily be ensured that the use of additives will not constitute any health hazard, a programme for prioritised intake assessment has been worked out.
The programme is designed as stepwise calculations, assessments, and exclusions of substances that are primarily assumed to be of no health significance. The principle of the programme is described in Figure 3.1. The width of the pyramid steps illustrates how the number of substances is reduced, when the process moves from a lower tier to a higher tier. For each tier the possible intake of the individual substance is calculated on the basis of the data set indicated. If the calculated intake indicates that the ADI assigned to a substance may be exceeded, the substance is transferred to the next tier. If that is not the case, the substance is excluded from further monitoring since its calculated intake is assumed to be of minor relevance in terms of safety (For further details of the process the reader is referred to the report mentioned above).

Figure 3.1. The tiers of the EU monitoring system for food additives

![Diagram of tiers of the EU monitoring system for food additives]

If a substance does not have a numerical ADI and/or if the substance is permitted quantum satis, then proper calculations at tier 1 is not possible. Considerations made in this respect prior to Tier 1 are mentioned as Tier 0 in the monographs. The calculations carried out at tier 1 and the related conclusions are included in the report of task 4.2. These calculations were made by the co-ordinators of the task.

For the purpose addressing the data demands of tier 2 the EU Commission in August 1999 requested the Member States to submit their data for intake of additives. In order to get the data in comparable formats, guidelines on how to report the data were given at the same time. Only 6 member states were at this stage able to submit data in the requested format for adults. However, the Commission did also from five other countries receive certain information relevant for intake considerations.

3.4 SCF/JECFA status: Here the latest evaluations of the two committees are quoted as the numerical or “not specified” ADI or as “acceptable”, sometimes together with special comments important for the understanding of the evaluation. The term “ADI “not specified” is for both committees not indicating that all kind of uses would necessarily be acceptable, but merely saying that the amounts envisaged to be enough to achieve the required technological effect in the food item(s) considered at the time of the evaluation will not constitute a risk to the consumers. However in most cases the Committees have given no indication of what it considered normal use at that time. In those cases where an “ADI not specified” or “acceptable” has been linked to a special use and/or use level, it is confirmed whether the present uses comply with these assumptions.

In its earliest evaluations JECFA used the phrase “ADI not limited”. As JECFA has abandoned this practise and clearly stressed that also for these earlier evaluations this phrase will fall within the definition of “not specified”, the latter term has generally been used in this review also when the older term has not been specifically changed.
3.5 Background studies: The monographs are listing those studies, which have been part of the SCF and JECFA evaluations as well as relevant studies published after the latest Committee evaluation. In the different entries a review of the existing toxicological studies is given according to the type of study. However, it has not been attempted to give a full record of all existing studies, but rather to concentrate on those studies, which are considered pivotal for the evaluation. The lack of studies, which would normally be required for a new additive, has been commented.

For studies considered by SCF/JECFA in their evaluations the monographs in this report normally quote directly from the reports/toxicological monographs from these committees, partly because the reviewers developing the monographs in this report as a matter of principle not are questioning the scientific quality or validity of past evaluations by SCF or JECFA, and partly because many of the studies quoted have not been published in the open scientific literature and thus are not available to the reviewers.

A common feature for the earliest evaluations of the Committees, especially those of the SCF, is that the reports contain very little details on those studies which were considered as pivotal to the overall evaluations. Also details on toxic effects, no effect levels and chosen safety factors are missing in many of the reports making it difficult to re-construct the thinking of the Committees.

The main objective for the present report is to make a literature search on all additives to identify toxicological data published after latest Committee evaluation(s) and to access the validity of those data for triggering a new evaluation by the SCF. Search has in general been made in Toxline, Medline and RTCS. For practical reasons data published after autumn 2000 have not been included in this review. Not all the literature found has necessarily been quoted in the review, but merely those, where the data is considered most important for the overall evaluation. For substances presently on the SCF agenda no thorough review has been attempted.

3.6 Conclusion: The review is finalised with an overall conclusion on the safety in use of the additive taking into account the latest SCF/JECFA evaluations and new important data through summarising special features leading to the overall recommendation.

3.7 References: The review contains references to the latest SCF and JECFA evaluations and specifications as well as references to scientific literature published after the latest SCF/JECFA evaluations containing new data, which may support the present evaluation or actually may change the view of the Committees if a re-evaluation is made.
4. Overview of recommendations and priorities

The general principles for developing the monographs and recommending re-evaluations or other actions have been described in Chapter 3. These principles have been followed in the writing of the 163 monographs covering the State-Of-The-Art for the safety assessments of the more than 300 food additives presently allowed for use in the food supply in Europe given in Annex I.

To ease the overview the conclusions and subsequent priorities from the 163 monographs have been summarised in Annex II. The priorities for the safety assessments or other actions regarding the different food additives in Annex II are ranked from 0 to 5 according to the criteria listed below, where priority “0” means no further action is needed at present. Priority “1” indicates that some matters should be clarified but considered of low priority, while priority “2” has been used, when new data has been published, which preferably should be included in the evaluation, but which are not expected to change the overall evaluation (e.g. tartrazine). Priority “3” has been used when various matters should be clarified (e.g. if background for ADI is not clear) to ensure that present evaluation is still valid. If the present evaluation of a substance does not include important new data, which indicate unforeseen potential for undesirable effects, or if it is expected that present conditions of use may lead to intakes which are in conflict with the assumptions made in the evaluation of SCF the substance has been classified with priority “4”. Priority “5” has been reserved for substances, which can reasonably be expected to constitute a risk for consumer health at present use levels. In cases where a substance is already is on the agenda of the SCF this substance has not been subject to any further prioritisation (indicated with “-“ in the summary table in Annex II). In this overview it is chosen to divide the comments to various substances to groups according to their (main) technological function. The tables are based upon the information in the 2 first and the 2 last columns of the summary table in Annex II.

**Colouring matters** (Substances from E 100 to E 180)

1. Synthetic colours.

<table>
<thead>
<tr>
<th>E No</th>
<th>Name</th>
<th>Comments/recommendations</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>Sunset Yellow FCF</td>
<td>Re-evaluation because of inadequate reporting and new data</td>
<td>3</td>
</tr>
<tr>
<td>128</td>
<td>Red 2G</td>
<td>Albeit low theoretical exposure re-evaluation recommended if colour is still used</td>
<td>3</td>
</tr>
<tr>
<td>131</td>
<td>Patent Blue V</td>
<td>Clarify basis for ADI and discrepancy between SCF and JECFA</td>
<td>3</td>
</tr>
<tr>
<td>154</td>
<td>Brown FK</td>
<td>Albeit low exposure re-evaluation recommended if colour still used</td>
<td>3</td>
</tr>
<tr>
<td>155</td>
<td>Brown HT</td>
<td>Clarify discrepancy between SCF and JECFA ADI’s. Question on organ disposition should be elucidated</td>
<td>3</td>
</tr>
<tr>
<td>102</td>
<td>Tartrazine</td>
<td>Update evaluation to include new data</td>
<td>2</td>
</tr>
<tr>
<td>124</td>
<td>Ponceau 4R</td>
<td>Clarify basis for ADI and safety factors used</td>
<td>2</td>
</tr>
<tr>
<td>129</td>
<td>Allura Red AC</td>
<td>Update to include new data</td>
<td>2</td>
</tr>
<tr>
<td>132</td>
<td>Indigotine, Indigo Carmine</td>
<td>Update to include new data</td>
<td>2</td>
</tr>
<tr>
<td>133</td>
<td>Brilliant Blue FCF</td>
<td>Update to include new data</td>
<td>2</td>
</tr>
<tr>
<td>142</td>
<td>Green S</td>
<td>Update to include new data</td>
<td>2</td>
</tr>
<tr>
<td>151</td>
<td>Brilliant Black BN, Black PN</td>
<td>Clarify discrepancy between SCF and JECFA ADI’s. JECFA ADI may be exceeded so exposure should be investigated further</td>
<td>2</td>
</tr>
<tr>
<td>180</td>
<td>Litholrubine BK</td>
<td>Albeit low exposure re-evaluation recommended if still used</td>
<td>2</td>
</tr>
<tr>
<td>104</td>
<td>Quinoline Yellow</td>
<td>Clarify apparent discrepancy on safety factors</td>
<td>1</td>
</tr>
<tr>
<td>123</td>
<td>Amaranth</td>
<td>Low exposure. Update to clear discrepancy between ADI’s and to include new data</td>
<td>1</td>
</tr>
</tbody>
</table>

*Priorities: 1 = matters to be clarified; 2 = update of evaluation; 3 = some priority for re-evaluation; 4 = priority for re-evaluation; 5 = high priority for re-evaluation
A common feature for the synthetic colours is that these were among the first additives to be consistently tested and evaluated. This means that in most cases the evaluations are rather old. This is not by itself a reason for requiring further testing or a re-evaluation. However, for some of the colours many new studies have become available since the latest evaluations, and in these cases it could be desirable to include also these studies in the evaluation. This is for example the case for tartrazine. Five substances have been classified as group 3 priority. Of these only Sunset Yellow, Patent Blue V and Brown HT are permitted to any extent, while Red 2G and Brown FK have only been prioritised in this category for the sake of consistency, because the actual exposure is very low. Nine other synthetic colours have been classified in priority groups 2 and 1, mainly to update evaluations and in some cases to clarify discrepancies between JECFA and SCF evaluations.

2. Colours of natural origin.

<table>
<thead>
<tr>
<th>E No</th>
<th>Name</th>
<th>Comments/recommendations</th>
<th>*</th>
</tr>
</thead>
<tbody>
<tr>
<td>160e</td>
<td>Beta-apo-8'-carotenal(C30)</td>
<td>Should be re-evaluated together with beta-carotene.</td>
<td>4</td>
</tr>
<tr>
<td>160f</td>
<td>Ethyl ester of beta-apo-8'-carotenic acid (C30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>Curcumin</td>
<td>Needed: Studies on carcinogenicity and reproductive toxicity; Specification; Exposure data</td>
<td>4</td>
</tr>
<tr>
<td>120</td>
<td>Cochinine, Carminic acid, Carmines</td>
<td>Re-evaluation because of reports on allergy and new reproduction data</td>
<td>4</td>
</tr>
<tr>
<td>141</td>
<td>Copper complexes of chlorophylls and of chlorophyllins</td>
<td>Re-evaluation to clarify significance of Cu-content and cancer promoting effect</td>
<td>4</td>
</tr>
<tr>
<td>160b</td>
<td>Annatto, Bixin, Norbixin</td>
<td>Re-evaluation as previous evaluation old and based on products differing significantly from products used today and as present ADI may be exceeded</td>
<td>4</td>
</tr>
<tr>
<td>160d</td>
<td>Lycopene</td>
<td>Exposure should be monitored. and if exceeding normal exposure new evaluation</td>
<td>4</td>
</tr>
<tr>
<td>173</td>
<td>Aluminium</td>
<td>Aluminium from all sources should be re-evaluated.</td>
<td>4</td>
</tr>
<tr>
<td>160c</td>
<td>Paprika extract (capsanthin, capsorubin)</td>
<td>Should be evaluated. Significant differences between EU and JECFA specifications.</td>
<td>3</td>
</tr>
<tr>
<td>161b</td>
<td>Lutein</td>
<td>Exposure should be monitored. Specification examined.</td>
<td>3</td>
</tr>
<tr>
<td>140</td>
<td>Chlorophylls and Chlorophyllins</td>
<td>Clarify present uses</td>
<td>1</td>
</tr>
<tr>
<td>150c</td>
<td>Ammonia caramel</td>
<td>Further discussion on lymphocyte-suppressing activity.</td>
<td>1</td>
</tr>
<tr>
<td>162</td>
<td>Beetroot Red, Betain</td>
<td>Exposure should be monitored and if significant, toxicology should be examined</td>
<td>1</td>
</tr>
<tr>
<td>163</td>
<td>Anthocyanins</td>
<td>Exposure should be monitored.</td>
<td>1</td>
</tr>
<tr>
<td>172</td>
<td>Iron oxides and hydroxides</td>
<td>Basis for evaluations unclear</td>
<td>1</td>
</tr>
<tr>
<td>160a</td>
<td>i) Mixed carotenes</td>
<td>On SCF agenda</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ii) beta-carotene</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Priorities: 1 = matters to be clarified; 2 = update of evaluation; 3 = some priority for re-evaluation; 4 = priority for re-evaluation; 5 = high priority for re-evaluation; - = on the agenda of SCF, no need for further action;

A general feature for the colours derived from natural sources is that they have been tested to a very limited extend and the evaluations are based more on assumptions than facts. In some of these cases SCF has not performed an evaluation on the substances as such, but each time they were considered (1st, 4th, 8th and 21st report series) the Committee stressed that they are considered acceptable only as long as they are derived from food and not consumed in amounts which significantly differ from what could be expected from consuming the foods in question. However in some cases the existing specifications allow for sources, which cannot be considered part of a normal diet.

Furthermore there is a tendency for many food producers to replace the synthetic colours with those of natural origin. It is thus not certain any longer that the exposures are still within ranges, which can be considered “normal” or “natural”. For those additives special action has been recommended
i.e. chlorophyll, lycopene, lutein, betanin and anthocyanins. Paprika extract has not been evaluated by SCF.

Besides the need to monitor exposure of curcumin, it has also been recommended that this colour is subjected to a more thorough evaluation as crucial data are missing and most of the existing studies are performed on products not representative for those used today. Also cochineal (carmines) has been recommended for a re-evaluation to address the question on allergy, as well as copper complexes of chlorophylls and of chlorophyllins to clarify the significance of the copper content and of noticed cancer promoting effect.

As the composition of annatto (bixin and norbixin) has changed considerably compared with the products originally tested this colour has been recommended for renewed testing.

The ADI of beta-apo-8'-carotenal (C30) and ethyl ester of beta-apo-8'-carotenic acid (C30) is linked to that of beta carotene. Therefore these two colours should be included in the ongoing re-evaluation of beta-carotene.

Preservatives and antioxidants (E 200 – E 252; E 284-5; E 300 – E 321, and E 385).

Table 4.3 Recommendations on preservatives and antioxidants

<table>
<thead>
<tr>
<th>E No</th>
<th>Name</th>
<th>Comments/recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>230</td>
<td>Biphenyl, Diphenyl</td>
<td>Should be evaluated by SCF</td>
</tr>
<tr>
<td>231-2</td>
<td>Orthophenyl phenol and sodium salt</td>
<td>Should be evaluated by SCF</td>
</tr>
<tr>
<td>310</td>
<td>Propyl gallate</td>
<td>Clarify discrepancy between SCF and JECFA ADI’s</td>
</tr>
<tr>
<td>311</td>
<td>Octyl gallate</td>
<td></td>
</tr>
<tr>
<td>312</td>
<td>Dodecyl gallate</td>
<td></td>
</tr>
<tr>
<td>220-8</td>
<td>Sulphites</td>
<td>ADI likely to be exceeded, and keeping the allergy aspect in mind limitations in permitted uses should be considered.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EU specification for E 221 should be re-considered</td>
</tr>
<tr>
<td>239</td>
<td>Hexamethylene tetramine</td>
<td>Albeit low exposure a re-evaluation is recommended if still used</td>
</tr>
<tr>
<td>304</td>
<td>Ascorbyl palmitate and stearate</td>
<td>Needed: metabolism, bioavailability and possibly reproduction studies. Exposure data</td>
</tr>
<tr>
<td>320</td>
<td>Butylated hydroxyanisole</td>
<td>Re-evaluation to remove temporary status. Need for studies on multigeneration and possible accumulation should be discussed</td>
</tr>
<tr>
<td>321</td>
<td>Butylated hydroxytoluene</td>
<td>Clarify discrepancy between SCF and JECFA ADI’s</td>
</tr>
<tr>
<td>249-50</td>
<td>Nitrite</td>
<td>Data needed on actual use levels and exposure.</td>
</tr>
<tr>
<td>300-2</td>
<td>Ascorbates</td>
<td>Clarification of minor points</td>
</tr>
<tr>
<td>308</td>
<td>Tocopherol-rich extract</td>
<td>If gamma- and delta-tocopherol are used at all they should be subject to an evaluation, otherwise deleted Exposure data</td>
</tr>
<tr>
<td>309</td>
<td>Alpha-tocopherol</td>
<td></td>
</tr>
<tr>
<td>315-6</td>
<td>Erythorbic acid and sodium salt</td>
<td>Need for reproductive study should be discussed</td>
</tr>
<tr>
<td>210-3</td>
<td>Benzoates</td>
<td>On SCF agenda. Exposure data needed</td>
</tr>
<tr>
<td>214-9</td>
<td>p-hydroxybenzoates</td>
<td>On SCF agenda.</td>
</tr>
<tr>
<td>234</td>
<td>Nisin</td>
<td>Printing error for ADI in SCF report should be corrected.</td>
</tr>
<tr>
<td>235</td>
<td>Natamycin</td>
<td>On the agenda of SCF for possibility for induction of microbial resistance</td>
</tr>
</tbody>
</table>

*Priorities: 1 = matters to be clarified; 2 = update of evaluation; 3 = some priority for re-evaluation; 4 = priority for re-evaluation; 5 = high priority for re-evaluation; - = on the agenda of SCF, no need for further action;

Biphenyl (E230) and orthophenyl phenol and its sodium salt (E231-2) have never, in contrast to the provisions in the directives, been evaluated by SCF. With respect to the gallates the existing data on octyl gallate and dodecyl gallate are very sparse and JECFA has for that reason removed these substances from the group ADI for gallates. Although the SCF group ADI for gallates is lower than the JECFA ADI for propyl gallate, it is recommended for SCF to look at these additives again.
There seems no reason to re-evaluate the sulphites or nitrite/nitrate. However it may be desirable to investigate how the use of these additives could be minimised.

BHA has only a temporary ADI by SCF, and the SCF ADI for BHT is considerably lower than the ADI allocated by JECFA at a later occasion than SCF. Therefore these two antioxidants are also recommended for re-evaluation. Hexamethylene tetramine has not been directly evaluated by SCF, and although the permitted use is extremely limited, a re-evaluation has been recommended as a matter of consistency. The ascorbyl esters have been accepted on the assumption that full hydrolysis occurs, but apparently no documentation for this assumption has been provided.

A few points have been identified for clarification regarding ascorbic acid and isoascorbic acid and their salts. The monographs also make it clear that no data exists on gamma- and delta-tocopherol. As it appears that the last two substances do not exist commercially, it should be considered to remove them from the directive. Otherwise they should be subject to individual evaluation. As the SCF evaluation of the tocopherols has been made on assumptions of limited exposure, it is recommended that it is investigated whether this assumption still holds.

The benzoates and the para-hydroxy benzoates are on the agenda of SCF and no further action has therefore been recommended. The question regarding the possible induction of microbial resistance to nisin and natamycin is likewise on the agenda of SCF.

Boric acid and borax (E284-5) have been found unfit for use as food additives in general. But as the use is restricted to (real) caviar, the reviewers found no reason to recommend further action.

**Emulsifiers, stabilisers and gelling agents** (E 322; E 400 - E 495; E 1404 - E 1451).

The major part of the substances in this group has not given cause for any comments or only minor ones. The sorbitan esters, however, have been recommended for re-evaluation, as the potential exposure is high compared with the ADI, which is based on older data. Also the polysorbates may need a closer review. Acacia gum (gum arabic) has not been subject to a formal SCF evaluation. While no undesirable side effects are expected with acacia gum from the traditional sources, it has been evident that other sources, not evaluated from a health point of view, may presently be in use as source material, and therefore it has been recommended to consider this aspect, together with the occasional reports on allergy to this product. Also other natural gums as guar gum and tragacanth have been reported to cause allergy problems, apparently after previous exposure through inhalation. It is therefore recommended to investigate further the cause and possible solution to these cases.
### Table 4.4 Recommendations on emulsifiers etc.

<table>
<thead>
<tr>
<th>E No</th>
<th>Name</th>
<th>Comments/recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>491-5</td>
<td>Sorbitan esters</td>
<td>Exposure estimates and re-evaluation</td>
</tr>
<tr>
<td>414</td>
<td>Acacia gum (gum arabic)</td>
<td>Formal SCF evaluation desirable. Questions on allergy and specifications should be clarified</td>
</tr>
<tr>
<td>483</td>
<td>Stearyl tartrate</td>
<td>Data on hydrolysis needed</td>
</tr>
<tr>
<td>410</td>
<td>Locust bean gum (carob bean gum)</td>
<td>Update to include new data</td>
</tr>
<tr>
<td>412</td>
<td>Guar gum</td>
<td>Clarify allergy aspect</td>
</tr>
<tr>
<td>413</td>
<td>Tragacanth</td>
<td>Clarify allergy aspect</td>
</tr>
<tr>
<td>432</td>
<td>Polysorbates</td>
<td>Update of evaluation recommended if exposure significant. SCF is currently evaluating the question of residual ethylene oxide</td>
</tr>
<tr>
<td>481</td>
<td>Sodium stearoyl-2-lactylate</td>
<td>Exposure data desirable</td>
</tr>
<tr>
<td>405</td>
<td>Propane-1,2-diol alginate</td>
<td>Clarification of specification</td>
</tr>
<tr>
<td>415</td>
<td>Xanthan gum</td>
<td>Exposure needed as evaluation linked to exposure estimates</td>
</tr>
<tr>
<td>417</td>
<td>Tara gum</td>
<td>Exposure needed as evaluation linked to exposure estimates</td>
</tr>
<tr>
<td>431</td>
<td>Polyoxyethylene(40)stearate</td>
<td>Re-evaluation if use is continued</td>
</tr>
<tr>
<td>570+</td>
<td>Fatty acids and their sodium, potassium, calcium and magnesium salts</td>
<td>Questions on specification concerning included acids should be clarified</td>
</tr>
<tr>
<td>472f</td>
<td>Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids</td>
<td>Clarify possible identity with E 472e and monitor exposure</td>
</tr>
<tr>
<td>475</td>
<td>Polycylerol esters of fatty acids</td>
<td>Exposure data desirable</td>
</tr>
<tr>
<td>477</td>
<td>Propane-1,2-diol esters of fatty acids</td>
<td>Status for data requested by SCF</td>
</tr>
<tr>
<td>1440</td>
<td>Hydroxy propyl starch</td>
<td>The specification concerning residual propylene chlorohydrin should be compared with the SCF recommendation and exposure estimates considered</td>
</tr>
<tr>
<td>1442</td>
<td>Hydroxy propyl distarch phosphate</td>
<td></td>
</tr>
<tr>
<td>472e</td>
<td>Mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (DATEM)</td>
<td>On SCF agenda</td>
</tr>
</tbody>
</table>

*Priorities: 1 = matters to be clarified; 2 = update of evaluation; 3 = some priority for re-evaluation; 4 = priority for re-evaluation; 5 = high priority for re-evaluation; - = on the agenda of SCF, no need for further action.*

### Sweeteners (E 420 - E 421; E 950 – E 967).

### Table 4.5 Recommendations on sweeteners

<table>
<thead>
<tr>
<th>E No</th>
<th>Name</th>
<th>Comments/recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>959</td>
<td>Neohesperidine dihydrochalcone (NHDC)</td>
<td>An update of evaluation</td>
</tr>
<tr>
<td>420</td>
<td>Sorbitol; Sorbitol syrup</td>
<td>Exposure data of this and the other polyols needed</td>
</tr>
<tr>
<td>421</td>
<td>Mannitol</td>
<td>Exposure data of this and the other polyols needed</td>
</tr>
<tr>
<td>952</td>
<td>Cyclamic acid and its sodium and calcium salts</td>
<td>Exposure data and possibly reduction in use levels</td>
</tr>
<tr>
<td>953</td>
<td>Isomalt</td>
<td>Exposure data of this and the other polyols needed</td>
</tr>
<tr>
<td>965</td>
<td>Maltitol; Maltitol syrup</td>
<td>Exposure data of this and the other polyols needed</td>
</tr>
<tr>
<td>966</td>
<td>Lactitol</td>
<td>Exposure data of this and the other polyols needed</td>
</tr>
<tr>
<td>967</td>
<td>Xylitol</td>
<td>Exposure data of this and the other polyols needed</td>
</tr>
<tr>
<td>950</td>
<td>Acesulfame K</td>
<td>-</td>
</tr>
<tr>
<td>951</td>
<td>Aspartame</td>
<td>On the agenda of SCF</td>
</tr>
</tbody>
</table>

*Priorities: 1 = matters to be clarified; 2 = update of evaluation; 3 = some priority for re-evaluation; 4 = priority for re-evaluation; 5 = high priority for re-evaluation; - = on the agenda of SCF, no need for further action;*
Most of the sweeteners have recently been reviewed by SCF, aspartame is actually on the agenda of this Committee now and therefore no further evaluation is recommended on these substances. However, the report on neohesperidine dihydrochalcone is incomplete and a re-evaluation may be needed. As the ADI for cyclamate has been lowered, it should be considered whether the conditions of use need revision. It has also been recommended that the present usages of the polyols are monitored to facilitate exposure estimates.

**Additives of various technological function** (E 170, E 260-270; E 280 – E 283, E 290 – E 297; E 325-380; E 500-948; E 999-1202; E 1505-1521).

In this group of substances with a variety of different functions and structures talc has been classified with priority 4 as its acceptability is linked to the absence of asbestos, while the specification does not describe any limits. As it is known that some qualities of talc contain considerable amounts of asbestos, this question should be solved.

<table>
<thead>
<tr>
<th>E No</th>
<th>Name</th>
<th>Comments/recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>553b</td>
<td>Talc</td>
<td>The question on asbestos content should be addressed.</td>
</tr>
<tr>
<td>520</td>
<td>Aluminium sulphate</td>
<td></td>
</tr>
<tr>
<td>521</td>
<td>Aluminium sodium sulphate</td>
<td></td>
</tr>
<tr>
<td>522</td>
<td>Aluminium potassium sulphate</td>
<td>Aluminium from all sources should be re-evaluated.</td>
</tr>
<tr>
<td>523</td>
<td>Aluminium ammonium sulphate</td>
<td></td>
</tr>
<tr>
<td>541</td>
<td>Sodium aluminium phosphate,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>acid</td>
<td></td>
</tr>
<tr>
<td>554-9</td>
<td>Aluminium silicates</td>
<td>Needed: data on bioavailability</td>
</tr>
<tr>
<td>558</td>
<td>Bentonite</td>
<td></td>
</tr>
<tr>
<td>338-43</td>
<td>Phosphates</td>
<td>As MTDI is expressed as intake from all sources a more</td>
</tr>
<tr>
<td>450-2</td>
<td>Di-, tri- and polyphosphates</td>
<td>detailed exposure assessment is desirable (preferably</td>
</tr>
<tr>
<td>901</td>
<td>Bees wax, white and yellow</td>
<td>Temporary SCF status</td>
</tr>
<tr>
<td>902</td>
<td>Candelilla wax</td>
<td>Temporary SCF status</td>
</tr>
<tr>
<td>904</td>
<td>Shellac</td>
<td>Temporary SCF status</td>
</tr>
<tr>
<td>914</td>
<td>Oxidized polyethylene wax</td>
<td>Temporary SCF status</td>
</tr>
<tr>
<td>999</td>
<td>Quillia extract</td>
<td>Exposure data and possibly re-evaluation</td>
</tr>
<tr>
<td>280-3</td>
<td>Propionates</td>
<td>Consider the request from SCF</td>
</tr>
<tr>
<td>334-7</td>
<td>Tartrates</td>
<td>Exposure</td>
</tr>
<tr>
<td>353</td>
<td>Metatartaric acid</td>
<td>How much is it actually used?</td>
</tr>
<tr>
<td>355-7</td>
<td>Adipates</td>
<td>Exposure estimate should be performed</td>
</tr>
<tr>
<td>422</td>
<td>Glycerol</td>
<td>Exposure should be monitored to ensure that glycerol is</td>
</tr>
<tr>
<td></td>
<td></td>
<td>not used as sweetener</td>
</tr>
<tr>
<td>620-5</td>
<td>Glutamates (incl. MSG)</td>
<td>Update of evaluation to include new data</td>
</tr>
<tr>
<td>626-9</td>
<td>Guanylates</td>
<td>Exposure needed as evaluation linked to exposure estimates</td>
</tr>
<tr>
<td>630-3</td>
<td>Inosinates</td>
<td></td>
</tr>
<tr>
<td>634-5</td>
<td>5’-ribonucleotides</td>
<td></td>
</tr>
<tr>
<td>900</td>
<td>Dimethyl polysiloxane</td>
<td>Clarification of specification</td>
</tr>
<tr>
<td>1201+2</td>
<td>Polyvinyl pyrrolidone and vinyl</td>
<td>Specification should ensure low residual levels of N-vinyl</td>
</tr>
<tr>
<td></td>
<td>polyvinyl</td>
<td>pyrrolidone</td>
</tr>
<tr>
<td>1520</td>
<td>Propane-1,2-diol (Propylene glycol)</td>
<td>Exposure estimates desirable</td>
</tr>
</tbody>
</table>

*Priorities: 1 = matters to be clarified; 2 = update of evaluation
3 = some priority for re-evaluation; 4 = priority for re-evaluation; 5 = high priority for re-evaluation

The acceptability of the aluminium salts is linked to the provisional tolerable weekly intake, PTWI, of 7 mg/kg bw. It has been found that especially sodium aluminium phosphate can easily be used in amounts exceeding this PTWI, which also shall cover exposure from other sources than aluminium.
from food additives. In the SCF evaluation the aluminium silicates are partly included in evaluation of all the aluminium salts. Although it is unlikely that aluminium is bio-available to any significant extend from the silicates, it is recommended to evaluate the safety in use in food of all the aluminium salts as well as the metallic aluminium and the aluminium lakes in the future.

Regarding acids, bases and salts many of the substances of this group have been tested to a small extend only. However, as many of them are normal constituents of food and/or normal electrolytes in the human intermediary metabolism, there would be little meaning from a safety point of view in performing a lot of animal tests, which may be formally needed, but which are unlikely to add useful knowledge in the safety evaluation. Therefore most of these substances have got no priority for re-evaluation and a few have got lowest priority. The propionates have been given priority because SCF in the past has expressed the wish to see the results of comparative studies on the effect of short chain fatty acids while tartrates, phosphates and polyphosphates, metatartaric acid and adipates have been included to get a reliable estimate of exposure. Fatty acids and their salts have been included merely because the specifications include other acids than foreseen by SCF.

Many of the glazing agents have been only scarcely tested. Therefore they have been only temporarily accepted by SCF. Although there is no reason to expect any safety problems with the present uses, it would be appropriate to see whether they could be fully accepted. There is a continuous discussion regarding the safety of the flavour enhancers, especially MSG, while the SCF report does not describe in any detail the background for the acceptance. It is therefore recommended that the MSG evaluation is updated and a more detailed report is issued.
5. Discussion

The concern which lays behind the concept of this report is that there is no mechanism in place for a periodical safety evaluation of the food additives presently in use in EU, although the scientific literature each month present new toxicological data relating to one or more of the permitted food additives. These new data not only reflect new knowledge, but also depict the developments in toxicological techniques, which allow better and more precise measurements of already studied effects giving higher sensitivity and specificity of the tests performed but also allow toxicologists to look into hitherto not studied effects such as effects on the immune system and the hormone system as well as potential hormonal effects.

The suspicion before the work started was that some of the safety evaluations were rather old and have had no formal “service-check” in any of the recognised international scientific fora for safety assessment of food additives such as EU’s Scientific Committee on Food (SCF) and Joint Expert Committee on Food Additives (JECFA) of WHO/FAO for some time. In the context of EU the Scientific Committee on Food is the scientific guarantor for the safety of food additives in use within EU, and therefore the timing of the evaluation of this Committee is more crucial for EU, than the timing of the work of JECFA, which in an informal manner offers the results of its evaluations to the national governments of the United Nations member states. Nevertheless since the two Committees to a large extend draw on the same data sources in their work it is meaningful to consider the results of their work side by side.

Therefore all the monographs in this compilation look at the data background and consider the conclusions of the safety evaluations coming from both scientific Committees in order to create the best overview of the situation. Also it is reassuring to compare the results of the evaluations from two separate Committees with two independent groups of experts (although there from time to time may be individual overlap).

JECFA is the oldest Committee since it started its work in 1956, while SCF started in 1974. Both Committees have in many cases been evaluating each food additive several times when new data, new requests and new applications for the use of the food additive had come. In most cases the trigger for the safety assessment has not been a new concern, but a formal request for the assessment, either from the EU or from FAO/WHO. Both Committees have been limited by their lack of working capacity due to sparseness of resources put aside for their work.

Each time the Committees have finalised a number of new monographs, they have issued updated reports. Therefore it is also possible to list in which year each Committee has had its latest look at the individual food additives. The result of this exercise is illustrated in the figure 5.1 below.

The figure shows that SCF developed an increasing number of new opinions throughout the 80’ies up to the time when the framework directive of December 1988 on the approximation of the laws of the Member States concerning food additives authorised for use in foodstuffs intended for human consumption as well as the three specific directives on colours, sweeteners and other additives were under preparation to ensure the safety of the food additives to be allowed for use according to these directives. Later in the 90’ies the work intensity directed towards food additives was diminished as other food safety priorities such as novel foods including GM foods, chemical and microbial food contaminants, food flavourings etc. took over the working capacity of SCF. At the same time JECFA works at a more steady state on the food additive issues, but also decreasingly due to the same change of priorities as SCF.
As we expected the figure also illustrates that some of the food additives have not been re-evaluated by SCF for several years. Eleven out of the total of 163 monographs in this report (each monograph covering both individual substances and related groups of substances) were assessed in the 3 first years of existence of SCF in the period 1973-1975 and have never been looked upon again by SCF since then. All in all 30 monographs have not been revisited since 1980, and a total of 124 have not been studied since 1990. Thirty-five food additives have been evaluated or re-evaluated during the 90’ies. More surprisingly 5 food additives allowed according to the directives have never been evaluated by SCF (E No. 160c, 230, 231, 232, 414).

Thus the aim of this project, to take a look at scientific information appearing in the scientific literature after the latest evaluation by SCF addressing the safety of the food additives presently allowed for use in EU according to present directives, is justified.

The literature search is completed, the relevance and importance of the new data assessed and a prioritisation system for re-evaluation or other actions has been developed to facilitate a quick overview of the results and included in the summary table in Annex II.
Following priorities have been used:

- = The substance is presently on the agenda of the SCF and no further action warranted.
0 = No need for any action
1 = Some (usual minor) matters to be clarified
2 = Update of the evaluation recommended. Often this priority has been used if there seems no reason to change present ADI, but new data has been published which preferably should be included in the evaluation.
3 = Some priority for a re-evaluation or other action.
4 = Priority for a re-evaluation or other action.
5 = High priority for a re-evaluation or other action (e.g. modification of present legislation).

The outcome of this prioritisation gave no monograph with “5”. Ten substances or groups of substances presently on the agenda of the SCF have got no ranking. The 65 of the monographs got “0” indicating no need for any action. For 38 monographs some, usually minor, matters ought to be clarified. Other 20 got the designation “2” which means that an update of the evaluation is recommended. This priority is mostly used, if there is no reason to change the present ADI, but new data has been published which preferably should be included in the evaluation. The next 18 monographs have got the designation “3”, which means “Some priority for a re-evaluation or other action”. The last 15 monographs got “4”, which gives priority for a re-evaluation or other action.

In Chapter 4 it is discussed in details why the different substances got their priority the way they did. The overall conclusion is that no major potential safety issues in the present use of food additives are caused by the time delays in updating the monographs. This conclusion probably reflects that the scientists involved with the scientific committees are well informed about major findings appearing in the open literature and have alerted the Committees where new literature indicate problems regarding the safety of the food additives The Committees then have taken such substances on their agenda and renewed the monographs. The problem remains of course if major findings are not published in the open literature and thereby not brought to the attention of the Committees. Whether that is a real or just a theoretical problem cannot be resolved by this study of the open literature, but would need a request from the Commission to the industry about supplying not published reports on the safety of different food additives at the point in time when they appear, in the same way as the industry is supplying data according to the Directive on existing chemicals.

It is important to point out that it will be resource demanding if periodic peer review of the safety of food additives is to be introduced, and manpower in toxicological risk assessment as well as economic resources will be needed.
6. Conclusions and recommendations

The report demonstrates that there is no need for any urgent action regarding re-assessing the use of the presently approved food additives.

However, the review points out a series of aspects which warrant attention e.g. that many substances have not been re-assessed for many years, although new data are accumulating in the scientific literature and in certain cases calls for a new assessment and that for some additives their uses should be assessed to reassure that the exposure complies with the recommendations of SCF.

It is recommended that a mechanism be put in place in EU, which ensures a systematic, periodic review of all permitted food additives. In the meantime it is suggested to use the data in the present report as help for prioritisation of action.
Annex I

Individual substances
E100-1521
### How to read the monographs

#### Format

<table>
<thead>
<tr>
<th>Name:</th>
<th>Official name according to the directive</th>
</tr>
</thead>
<tbody>
<tr>
<td>E Number:</td>
<td>Official number according to the directive</td>
</tr>
<tr>
<td>Recommendation:</td>
<td>The recommendation for further action (or not)</td>
</tr>
<tr>
<td>Chemical name/synonyms:</td>
<td>The common chemical name is given if different from official name. Other main synonyms are also given.</td>
</tr>
<tr>
<td>CAS-Number:</td>
<td>The number allocated by the Chemical Abstract System</td>
</tr>
<tr>
<td>Functional Class:</td>
<td>Function in food e.g. sweetener, colour, .....</td>
</tr>
<tr>
<td>Specification:</td>
<td>A summary of JECFA and EU specifications with most relevant restrictions.</td>
</tr>
<tr>
<td>Exposure:</td>
<td>An estimate of potential maximum daily intake as well as the status in the EU monitoring system. See also the text in section 3.3.</td>
</tr>
<tr>
<td>SCF/JECFA evaluation:</td>
<td>Summary of last evaluations by the two committees and, if relevant, other bodies.</td>
</tr>
</tbody>
</table>

#### Background studies:
Listing of those studies which have been part of the SCF and JECFA evaluations as well as relevant studies published after the last Committee evaluation. Mainly only those studies considered crucial for the overall evaluation have been included.

#### Acute toxicity:
Not requested for the evaluation of food additives and not included in the monographs.

#### Subacute/subchronic toxicity:
Up to 90 days studies.

#### Genotoxicity:
In vitro and in vivo

#### Chronic toxicity/-
carcinogenicity:
-  

#### Reproduction toxicity:
-  

#### Allergy/intolerance:
-  

#### Effects in human:
Other than allergy

#### Other:
Information on effects presently not part of the basic requirements, but which may be relevant for the overall evaluation concerning safety in use, e.g. endocrine effect. Also metabolism and toxicokinetic aspects will be mentioned here

#### Conclusion:
The overall conclusions of the reviewers

#### References:
Studies quoted from SCF/JECFA are normally referenced as such.
<table>
<thead>
<tr>
<th>E No</th>
<th>Name</th>
<th>See E no</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Curcumin</td>
<td></td>
</tr>
<tr>
<td>101</td>
<td>Riboflavin</td>
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</tr>
<tr>
<td></td>
<td>Riboflavin-5'-phosphate</td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>Tartrazine</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>Quinoline Yellow</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>Sunset Yellow FCF</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>Cochineal, Carminic acid, Carmines</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>Azorubine, Carmoisine</td>
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<tr>
<td>123</td>
<td>Amaranth</td>
<td></td>
</tr>
<tr>
<td>124</td>
<td>Ponceau 4R</td>
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<td>127</td>
<td>Erythrosine</td>
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<td>128</td>
<td>Red 2G</td>
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<td>129</td>
<td>Allura Red AC</td>
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<td>131</td>
<td>Patent Blue V</td>
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<tr>
<td>132</td>
<td>Indigotine, Indigo Carmine</td>
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<td>133</td>
<td>Brilliant Blue FCF</td>
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<tr>
<td>140</td>
<td>Chlorophylls and Chlorophyllins</td>
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<tr>
<td>141</td>
<td>Copper complexes of chlorophylls and of chlorophyllins</td>
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</tr>
<tr>
<td>142</td>
<td>Green S</td>
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</tr>
<tr>
<td>150a</td>
<td>Plain caramel</td>
<td></td>
</tr>
<tr>
<td>150b</td>
<td>Caustic sulphite caramel</td>
<td></td>
</tr>
<tr>
<td>150c</td>
<td>Ammonia caramel</td>
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</tr>
<tr>
<td>150d</td>
<td>Sulphite ammonia caramel</td>
<td></td>
</tr>
<tr>
<td>151</td>
<td>Brilliant Black BN, Black PN</td>
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<tr>
<td>152</td>
<td>Vegetable carbon</td>
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</tr>
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<td>154</td>
<td>Brown FK</td>
<td></td>
</tr>
<tr>
<td>155</td>
<td>Brown HT</td>
<td></td>
</tr>
<tr>
<td>160a</td>
<td>i) Mixed carotenes; ii) beta-carotene</td>
<td></td>
</tr>
<tr>
<td>160b</td>
<td>Annatto, Bixin, Norbixin</td>
<td></td>
</tr>
<tr>
<td>160c</td>
<td>Paprika extract (capsanthin, capsorubin)</td>
<td></td>
</tr>
<tr>
<td>160d</td>
<td>Lycopene</td>
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</tr>
<tr>
<td>160e</td>
<td>Beta-apo-8'-carotenal (C30)</td>
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</tr>
<tr>
<td>160f</td>
<td>Ethyl ester of beta-apo-8'-carotenic acid (C30)</td>
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</tr>
<tr>
<td>161b</td>
<td>Lutein</td>
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<tr>
<td>161g</td>
<td>Canthaxanthin</td>
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<tr>
<td>162</td>
<td>Beetroot Red, Betanin</td>
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<tr>
<td>163</td>
<td>Anthocyanins</td>
<td></td>
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<tr>
<td>170</td>
<td>Calcium carbonates</td>
<td>See E 500</td>
</tr>
<tr>
<td>171</td>
<td>Titanium dioxide</td>
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<td>172</td>
<td>Iron oxides and hydroxides</td>
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<td>173</td>
<td>Aluminium</td>
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</tr>
<tr>
<td>174</td>
<td>Silver</td>
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</tr>
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<td>175</td>
<td>Gold</td>
<td></td>
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<tr>
<td>180</td>
<td>Litholrubine BK</td>
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</tr>
<tr>
<td>200</td>
<td>Sorbic acid</td>
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</tr>
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<td>202</td>
<td>Potassium sorbate</td>
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</tr>
<tr>
<td>203</td>
<td>Calcium sorbate</td>
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</tr>
<tr>
<td>210</td>
<td>Benzoic acid</td>
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<td>211</td>
<td>Sodium benzoate</td>
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<tr>
<td>212</td>
<td>Potassium benzoate</td>
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</tr>
<tr>
<td>213</td>
<td>Calcium benzoate</td>
<td></td>
</tr>
<tr>
<td>214</td>
<td>Ethyl-p-hydroxybenzoate</td>
<td></td>
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<tr>
<td>215</td>
<td>Sodium ethyl p-hydroxybenzoate</td>
<td></td>
</tr>
<tr>
<td>216</td>
<td>Propyl-p-hydroxybenzoate</td>
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</tr>
<tr>
<td>217</td>
<td>Sodium propyl p-hydroxybenzoate</td>
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</tr>
<tr>
<td>218</td>
<td>Methyl-p-hydroxybenzoate</td>
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<tr>
<td>219</td>
<td>Sodium methyl p-hydroxybenzoate</td>
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<tr>
<td>220</td>
<td>Sulphur dioxide</td>
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</tr>
<tr>
<td>221</td>
<td>Sodium sulphite</td>
<td></td>
</tr>
<tr>
<td>222</td>
<td>Sodium hydrogen sulphite</td>
<td></td>
</tr>
<tr>
<td>223</td>
<td>Sodium metabisulphite</td>
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<td>953</td>
<td>Isomalt</td>
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<td>Saccharin and its sodium, potassium and calcium salts</td>
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<td>Thaumatin</td>
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<td>959</td>
<td>Neohesperidine dihydrochalcone (NHDC)</td>
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<td>Acetylated oxidized starch</td>
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<td>1505</td>
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<td>1518</td>
<td>Glyceryl tricetate (triacetin)</td>
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<td>1520</td>
<td>Propane-1,2-diol (Propylene glycol)</td>
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<tr>
<td>1521</td>
<td>Polyethylene glycol 6000</td>
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</table>
CURCUMIN

E number: E 100

Recommendation: Further studies with regard to the carcinogenicity of curcumin are warranted. Data on the reproductive toxicity of curcumin as stated previously by JECFA is also needed. The purity of this colour has changed considerably from those previously tested. The required tests should, therefore, be performed on products as used to day. Monitoring of real life exposure is desirable as the theoretical intake estimate exceeds the JECFA ADI and may not be in compliance with the SCF assumption that the intake does not exceed intake from normal sources.

Chemical name/synonyms:
I: 1,7-Bis(4-hydroxy- 3-methoxyphenyl)hepta-1,6-diene-3,5-dione.
II: 1-(4-Hydroxyphenyl)-7-(4-hydroxy- 3-methoxyphenyl-)hepta-1,6-diene-3,5-dione.
III: 1,7 - Bis(4-hydroxyphenyl) hepta-1,6-diene-3,5-dione
/CI Natural Yellow 3, Turmeric Yellow, Diferoyl methane.

Class: Dicinnamoylmethane.

Chemical formula:
I: C_{21}H_{20}O_{6}
II: C_{20}H_{18}O_{5}
III: C_{19}H_{16}O_{4}

EINECS number: 207-280-5

CAS number: 458-37-7

Functional Class: Colour.

Specification:
Manufacture: Curcumin is obtained by solvent extraction of turmeric i.e. the ground rhizomes of Curcuma longa L. followed by crystallisation. Only ethylacetate, acetone, carbondioxide, methanol, ethanol, dichloromethane, hexane and n-butanol may be used in the production.

Definition: Curcumin consists essentially of the three different pigments, curcumin and its desmethoxy- and bisdesmethoxy derivatives.

EC specifications: E 100 Curcumin [1]. Assay: Not less than 90% total colouring matters. The specification includes purity criteria on Solvent residues, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Curcumin [2]. Assay: Not less than 90% total colouring matters. The specification includes purity criteria on Solvent residues and Lead.
**Exposure:** Permitted in all “colourable” foods and in some of those with only limited number of permitted colours. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods

As curcumin has not been allocated a numerical ADI from SCF the colour was not included in the EU monitoring system (tier 0). However, as the acceptance by SCF is linked to exposure and the JECFA ADI is easily exceeded if the colour is used to the permitted maximum levels, information on the present uses is desirable.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation June 1975. Acceptable from natural foods provided intake from use as food colour will not substantially differ from what may be ingested from the normal consumption of food in which it occurs naturally [3].

**JECFA status:** Latest evaluation in 1998. ADI 0-1 mg/kg bw. Temporary until 2001, pending the submission of data concerning reproductive toxicity [4]. In 2001 the temporary status was prolonged until 2003.

**Background data:**

**Subacute/subchronic toxicity:** Administration of curcumin at dietary levels of 0, 0.1, 0.5, 1.0, 2.5 and 5.0% for 13 weeks to 10 male and 10 female mice did not significantly affect body weight, mortality or histopathology, whereas the liver weight increased in a dose-dependent fashion in both sexes [5]. In a similar study conducted in rats, and employing the same dose levels as above induced a dose-related increase in polymorphonuclear lymphocytes at the two highest dose levels and a dose-related increase in liver weight in both sexes. In females a treatment-related decrease in heart and liver weights were observed and there was a tendency of a decreased erythrocyte count. Urinanalysis in male rats indicated a treatment related increase in casts and an increase in red blood cells. In females increased urinary crystals were observed at all dose level [5]. The preparation in these studies was 79% curcumin.

**Genotoxicity:** No *in vitro* genotoxicity studies are available with high-purity curcumin. Employing curcumin preparations of a purity of up to 85%, no mutagenicity has been observed in Ames assay or in assays studying chromosomal aberrations. A recent publication provided evidence that curcumin induced DNA damage (measured as DNA-strand breaks in the Comet assay) in human lymphocytes and gastric mucosa cells *in vitro* when present in the low micromolar range (10-50 uM) and furthermore that curcumin works in an additive fashion with hexavalent chromium, a well known mutagen and carcinogen [6]. Another publication by Antunes et al. (1999) [7] substantiates this finding in that curcumin was found to induce DNA-damage in CHO cells at a concentration of 10 micromolar. Curcumin furthermore potentiated the effect of doxorubicin, a known free radical generator, which is in agreement with the finding by Blasiak et al. (1999)[6].

**Chronic toxicity/Carcinogenicity:** A long-term carcinogenicity study in mice and rats employing a turmeric oleoresin of approximately 79-85% curcumin at concentrations in feed up to 50,000 mg/kg, equivalent to 6000 mg/kg bw/day in mice and 2000 mg/kg bw/day in rats [8]. Despite significant increases in the incidence of hepatocellular adenomas (males and females), small intestinal carcinomas (males) and pituitary gland adenomas (females) in mice and clitoral gland adenomas (females) in rats, curcumin was not concluded to be carcinogenic, due to the lack of dose-responsive effects. Additionally ulcers, hyperplasia and inflammation of the gastrointestinal tract were common in male and female rats at the highest doses, but were not observed in mice. Enlargement of the liver was observed at the two highest doses and a NOEL was established at
220 mg/kg bw/day. This value was used by JECFA to establish the ADI using a safety factor of 200.

**Reproduction toxicity:** Not available, requested by JECFA.

**Allergy/Intolerance:** No relevant data on curcumin-induced food allergy or intolerance is present in the literature.

**Effects in humans:** Although commonly used as spice no data are available regarding toxicity in man.

**Other:** Metabolism: Of a single dose of 400 mg \(^{3}\)H]curcumin (equivalent to 2000 mg/kg bw) administered to rats, only 60% of the radioactivity was excreted during the first 12 days, whereas at lower doses (<400 mg/kg bw) most of the dose was excreted within 72 hours.

**Conclusion:** Further studies with regard to the carcinogenicity and the reproductive toxicity of curcumin are warranted. The common use of curcumin as a spice and a colouring agent, and the absence of adverse effects of curcumin in epidemiological studies, do not suggest major toxic effects of curcumin at levels normally encountered in a human diet.

Curcumin, as defined by the specifications, was not on the market as a food additive when SCF in 1975 evaluated the substances. Significant development has occurred both with regard to manufacture and the use in food of curcumin since then.

Theoretical exposure estimates based on permitted levels suggest a high potential intake compared with the JECFA ADI and the SCF exposure assumptions.

**References:**


4. \[1998, TRS 891-JECFA 51\]


RIBOFLAVIN AND RIBOFLAVIN-5’-PHOSPHATE

E number:
Riboflavin: E 101 (i)
Riboflavin-5’-phosphate: E 101 (ii)

Recommendation: No need for a re-evaluation as no overt toxicity is evident and a sufficient amount of data is available on the various toxicity issues.

Chemical name/synonyms:
Riboflavin: 7,8-Dimethyl-10-(D-ribo-2,3,4,5-tetrahydroxy-pentyl)benzo[γ]pteridine-2,4(3H,10H)-dione, 7,8-dimethyl-10-(1’-D-ribityl)isoalloxazine/ Lactoflavin.

Chemical formula:
Riboflavin: C₁₇H₂₀N₄O₆
Riboflavin-5’-phosphate: C₁₇H₂₀N₄NaO₉P⋅2H₂O (dihydrate).
C₁₇H₂₀N₄NaO₉P (anhydrous).

Class: Isoalloxazine.

EINECS number:
Riboflavin: 201-507-1
Riboflavin-5’-phosphate: 204-988-6

CAS number:
Riboflavin: 83-88-5
Riboflavin-5’-phosphate: 130-40-5

Functional Class: Colour.

Specification:
Manufacture: Riboflavin and riboflavin-5’-phosphate is obtained by chemical synthesis or from microbiological sources.

Riboflavin
Definition: Riboflavin is naturally occurring. It is very slightly soluble in water and very soluble in dilute alkali solutions. Insoluble in ethanol.

EC specifications: E 101 (i) Riboflavin [5].
Assay: Not less than 98% on the anhydrous basis.
Primary aromatic amines: Not more than 100 mg/kg (calculated as aniline).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Riboflavin [4].
Assay: Not less than 98%.
Primary aromatic amines: Not more than 100 mg/kg (calculated as aniline).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Subsidiary colouring matters (Lumiflavin), Arsenic and Lead.

*Riboflavin-5′-phosphate*

**Definition:** Riboflavin-5′-phosphate is the monosodium salt of the phosphate ester of riboflavin. It is soluble in water and insoluble in ethanol.

**EC specifications:** E 101 (ii) Riboflavin-5′-phosphate [5].
Assay: Not less than 95% total colouring matters calculated as C_{17}H_{20}N_{4}NaO_{9}P⋅2H_{2}O.
Primary aromatic amines: Not more than 70 mg/kg (calculated as aniline).
In addition the specification includes purity criteria on Loss on drying, Inorganic phosphate, Subsidiary colouring matters (Riboflavin and Riboflavin diphosphate), Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Riboflavin-5′-phosphate [4].
Assay: Not less than 95% total colouring matters calculated as C_{17}H_{20}N_{4}NaO_{9}P⋅2H_{2}O.
Primary aromatic amines: Not more than 70 mg/kg (calculated as aniline).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Subsidiary colouring matters (Lumiflavin, Riboflavin and Riboflavin diphosphate), Arsenic and Lead.

**Exposure:** Permitted generally in foodstuffs except those where colours are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible, but is also not necessary.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation: Sept 1977. Acceptable as long as the use of the substance does not significantly alter the daily average intake of riboflavin [3]. On 10 December 1998 The Committee accepted the use of riboflavin produced by fermentation using genetically modified *Bacillus subtilis* (http://europa.eu.int/comm/food/fs/sc/scf/out18_en.html). On 7 December 2000 the Committee issued a report on the tolerable intake level of vitamin B2. It was not able to define an upper level, but found overdosing unlikely (http://europa.eu.int/comm/food/fs/sc/scf/out80i_en.pdf).

**JECFA status:** Latest evaluation: 1981: 0.5 mg/kg bw [1]. In 1998 JECFA extended the ADI of 0-0.5 mg/kg bw for synthetic riboflavin and riboflavin-5′-phosphate to cover also the substances derived from a genetically modified strain of *Bacillus subtilis* [2].

**Background data:**

**Subacute toxicity:** In a 90-day study of toxicity, conducted according to OECD guidelines, with riboflavin produced either synthetically or derived from fermentation by a genetically modified strain of *Bacillus subtilis* (both preparations were 98% pure) at doses of 0, 20, 50 or
200 mg/kg bw/day, a reduced weight gain (less than 10%) were observed in the rats at the highest doses [7]. Food conversion was not affected.

Genotoxicity in vitro: Both substances were found negative in several strains of S. typhimurium [6].

Chronic toxicity/Carcinogenicity: Riboflavin and Riboflavin-5’-phosphate are of very low toxicity and thus chronic toxicity/carcinogenicity data is not required to assess the safety of these compounds.

Reproduction toxicity: Weanling male and female rats fed daily doses of 10 mg riboflavin for 140 days did not reveal differences in the development, growth, maturation or reproduction of treated and control animals [11]. At a dose of 100 ppm riboflavin administered prior to and during pregnancy resulted in a decrease in viability of the offspring [8].

Effects in humans: Administration of 5-500 mg riboflavin-5’-phosphate to human volunteers an increase in free riboflavin was observed in plasma and urine [10]. Administration of 4 g riboflavin/day for 9 days did not result in any toxic side effects [9].

Conclusion: No need for a re-evaluation, despite the lack of chronic toxicity/carcinogenicity data, as no overt toxicity is associated with the given compounds and a sufficient amount of data is available on the remaining toxicity issues.

Riboflavin and riboflavin-5’-phosphate as defined by the specifications seem to be covered by the toxicological evaluation.

References:


Tartrazine

E number: E 102

Recommendation: The existing data do not suggest a need for changing the present ADI. However, considering the long time since the previous evaluation(s) and the number of new studies published since then, it is recommended to update the evaluation to include the new data.

Chemical name/synonyms: Trisodium-5-hydroxy-1-(4-sulfonatophenyl)-4-(4-sulfonatophenylazo)-H-pyrazole-3-carboxylate/ CI Food Yellow 4 / FD&C Yellow no. 5.

Chemical formula: $C_{16}H_9N_4Na_3O_9S_2$

Class: Monoazo.

EINECS number: 217-699-5

CAS number: 1934-21-0

Functional Class: Colour.

Specification:

Manufacture: Tartrazine is manufactured by chemical synthesis.

Definition: Tartrazine consists essentially of trisodium-5-hydroxy-1-(4-sulfonato-phenyl)-4-(4-sulfonatophenylazo)-H-pyrazole-3-carboxylate and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Tartrazine is described as the sodium salt. The calcium and the potassium salts are also permitted.

EC specifications: E 102 Tartrazine [5].
Assay: Not less than 85% total colouring matters calculated as the sodium salt.
Subsidiary colouring matters: Not more than 1.0%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Tartrazine [4].
Assay: Not less than 85% total colouring matters calculated as the sodium salt.
Subsidiary colouring matters: Not more than 1.0%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.
Exposure: Permitted in all “colourable” foods and in a few of those with only limited number of permitted colours. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system tartrazine was examined at tier 1 level. As the calculation for children suggested the possibility for exceeding the ADI the EU monitoring system examined the intake at tier 2 level. The calculated intake by young children was thus reported by one member state as 52% of the ADI and it was concluded that no further examination is needed at this stage.

SCF/JECFA evaluation:
SCF status: An ADI of 7.5 mg/kg bw was established by SCF in 1983 [3]. The ADI was based on a no-adverse effect level of 750 mg/kg bw in a long-term study in rats [3], and a safety factor of 100. The study was not specified but seems to be the same study used for the JECFA evaluation in 1964 [1].

JECFA status: An ADI of 7.5 mg/kg bw was established by JECFA in 1964 [1]. The ADI was based on a level causing no significant toxicological effect of 1.5% (equivalent to 750 mg/kg bw/day) (highest dose) in a long-term study in rats (Mannell et al., 1958 in [2]) and a safety factor of 100.

Background data:
Subacute/subchronic toxicity: No obvious toxic effects.

SCF notes that data are available and that there are no obvious toxic effects. No details are reported [3].

Tartrazine (and other synthetic colours) showed different effects in rats on body weight, clinical biochemical parameters, liver and kidney functions after 30-60 days of administration. These effects were not regarded as serious effects according to the authors [6].

Genotoxicity:
No evidence of mutagenic activity in vitro or in vivo.

In vitro: No evidence of mutagenic character in S. typhimurium [23] or in E. coli [21;25;38].

In vivo: The cytogenetic activity of tartrazine given orally during 5 days to mice was studied. The dose interval was 0.5-5.0 mg/kg. No increase in the level of cells with chromosomal damage [19].

Some studies did not specify results in the abstract: Assay in Drosophelia, [56]. Other studies were [11;12;15;27;34;41;42;45].

Chronic toxicity/Carcinogenicity: No indication of carcinogenic potential.

SCF notes that long-term studies are available in mouse and rat. No details reported [3].

To JECFA long-term studies were available in mouse, rat and dog [2].
Mice (60/group/sex) were fed tartrazine in the diet at levels of 0, 0.5, 1.5, or 5% for a maximum of 104 weeks. No consistent adverse effects. NOAEL 5% corresponding to 8103 and 9735 mg/kg bw/day for male and females, respectively [9].

Rats (60/group/sex) were fed tartrazine in the diet at levels of 0, 0.1, 1.0, or 2.0% (original study) or 0 or 5.0% (high-dose study). No compound-related effects were noted. NOAEL 5% corresponding to 2641 and 3348 mg/kg bw/day for male and females, respectively [10].

Tartrazine was administered to rats (50/group/sex) in drinking fluid at levels of 0, 1, or 2% for up to 2 years. No carcinogenic effect [29]

**Reproduction toxicity:** Reproductive function was not affected and no teratogenic potential was noticed.

SCF notes that multigeneration reproduction and teratology studies are available. Reproductive functions are not affected and no teratogenic potential was revealed in rats and rabbits. No details reported [3].

No studies were available to JECFA.

Throughout gestation pregnant rats were dosed with 0, 0.05, 0.1, 0.2, 0.4, or 0.7% in drinking fluid, corresponding to 0, 67.4, 131.8, 292.4, 567.9, or 1064.3 mg/kg bw/day. No dose-related effect on reproduction, teratogenic or other parameters [14].

From gestation day 0-19 rats were administered 0, 60, 100, 200, 400, 600, or 1000 mg/kg bw/day by gavage. Tartrazine was neither toxic nor teratogenic [14].

**Allergy/Intolerance:** Many new studies were found in the database search. They seem not to give rise to additional concern. However, they should be considered for a re-evaluation.

**In general:** A critical review of the medical literature indicates that tartrazine has been confirmed to be only occasionally associated with urticaria or asthma. [49]. Formation of antibodies seems not to be involved in the reaction [46]. A review of the clinical spectrum of adverse reactions is given [13].

Adverse reactions to tartrazine have been known since 1958. The mechanism seems to be a not IgE-mediated anaphylactoid reaction [47].

Food additives can induce a wide range of adverse reactions in sensitive individuals. A prevalence of 0.03% to 0.23% is estimated. The mechanisms of adverse reactions to tartrazine are reviewed [55].

**Cases:** Cases are reported by several authors [7;8;31;36;37;40;50].

**Challenge studies:** [16-18;20;22;24;26;30;32;33;43;44;48;51-54].

**Model studies:** In a human lymphocyte model, tartrazine showed immunosuppressive effects [28].

**Effect in humans:** Childhood behaviour: 19 of 39 children whose behaviour by their parents was found to be reversibly improved on artificial food additive free diet completed a double-blind study. In these 19 children food colour challenge was found to have an adverse effect on a daily Conners’ rating of behaviour, but most parents could not detect these changes. Azorubine (25 mg), tartrazine (50 mg), sunset yellow
(25 mg), and amaranth (25 mg) were studied in combination [39].

Other effects in humans: One challenge study reports unusual reactions to tartrazine involving mainly the CNS (headache, migraine, overactivity, concentration and learning difficulties) [35].

Other: Tartrazine is metabolised by azoreduction in the gut. Un-metabolised tartrazine and metabolites are excreted by urine. There is also faecal excretion [3].

Conjugated metabolites are found in urine of rabbit and man [2].

Conclusion: The evaluations by SCF and JECFA are old. Newer studies including genotoxicity, chronic toxicity/carcinogenicity, and reproduction do not show effects of concern and support the present ADI.

Also many new studies on allergy/intolerance have been reported. They add further data but no new elements and seem not to give rise to additional concern.

Tartrazine as defined by the specifications seem to be covered by the toxicological evaluation.

References:


QUINOLINE YELLOW

E number: E 104

Recommendation: A re-evaluation is not warranted, however, the apparent discrepancy between the NOAEL’s and the safety factors used by SCF and JECFA should be clarified.

Chemical name/synonyms: The disodium salts of the disulfonates of 2-(2-quinolyl) indan-1,3-dione (principal component/ CI Food Yellow 13 / FD&C No. 10.

Chemical formula: C_{18}H_9NNa_2O_8S_2 (principal component).

Class: Quinophthalone.

EINECS number: 305-897-5

CAS number: 8004-92-0 (In JECFA specification incorrectly given as 8004-72-0).

Functional Class: Colour.

Specification:
Manufacture: Quinoline yellow is manufactured by sulfonating 2-(2-quinolyl) indane-1,3-dione or a mixture containing about two-thirds 2-(2-quinolyl) indane-1,3-dione and one third 2-(2-(6-methyl-quinolyl)) indane-1,3-dione.

Definition: Quinoline yellow consists essentially of a mixture of sodium salts of disulfonates (principally), monosulfonates and trisulfonates of 2-(2-quinolyl) indane-1,3-dione and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Quinoline yellow is described as the sodium salt. The calcium and the potassium salt are also permitted.

EC specifications: E 104 Quinoline yellow [1].
Assay: Not less than 70% total colouring matters.
Quinoline yellow shall have the following composition:
Of the total colouring matters present:
- Not less than 80% shall be disodium 2-(2-quinolyl)indane-1,3-dione-disulfonates
- Not more than 15% shall be sodium 2-(2-quinolyl)indane-1,3-dione-monosulfonates
- Not more than 7.0% shall be trisodium-2-(2-quinolyl)indane-1,3-dione-trisulfonates
Subsidiary colouring matters: Not more than 4.0%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulphonated primary aromatic amines), Water insoluble matter, Ether, extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.
**JECFA specifications:** Quinoline yellow [2].

Assay: Not less than 70% total colouring matters.

Quinoline yellow shall have the following composition:

Of the total colouring matters present:
- Not less than 80% shall be disodium 2-(2-quinolyl) indane-1,3-dione-disulfonates
- Not more than 15% shall be sodium 2-(2-quinolyl) indane-1,3-dione-monosulfonates
- Not more than 7.0% shall be trisodium 2-(2-quinolyl) indane-1,3-dione-trisulfonates

Subsidiary colouring matters: Not more than 4 mg/kg of 2-(2-quinolyl)-1,3-indanedione and 2-[2-(6-methylquinolyls)-1,3-indanedione.

In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Zinc and Heavy metals.

**Exposure:** Permitted in all “colourable” foods and in a few of those with only limited number of permitted colours. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system quinoline yellow was examined at tier 1 level. As the calculation suggested the possibility for children exceeding the ADI, the intake was examined at tier 2 level. The calculated intake by young children was reported by one member state as 20% of the ADI and it was concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** An ADI of 10 mg/kg bw was established by SCF in 1983 [3]. This ADI was based on the 1000 mg/kg bw no-adverse level (highest dose) referred to by SCF from a long-term study in mouse [3] and a safety factor of 100. The study was not specified but cited from an unpublished report from the EEC Colours Group [4]. It is unclear whether the study is the same as that evaluated by JECFA, in which case the calculated dose may be 1500 mg/kg bw instead of the quoted 1000.

**JECFA status:** An ADI of 10 mg/kg bw was established by JECFA in 1984 [5]. This ADI was based on the 1% level (corresponding to 1500 mg/kg bw, see above) (highest dose) causing no toxicological effects in mice [4] and a safety factor of 150. The reason for applying this factor was not explained.

**BIBRA:** The toxicological data for quinoline yellow within classical endpoints (local effects, Skin irritation, sensitisation, intolerance, oral provocation, acute toxicity, and target organ toxicity) have been reviewed by BIBRA. No adverse effects. Specifically, no convincing evidence for carcinogenicity or a genotoxic potential [6].

**Background data:**

**Subacute/subchronic toxicity:** A 90 days and a 7 months study in rats dosed with the methylated component are available. No significant toxic effects [7].

**Genotoxicity:**

_In vitro:_ The methylated colour component was studied [7]: No mutagenic effect
**Chronic toxicity/Carcinogenicity:** Rats (the methylated component) (2 studies)[7]: No significant toxic effects. No increased tumour incidence. Rats (the non-methylated component) [7]: No significant toxic effects.

A well conducted two-generation study was performed in the 0FI mouse following exposure in utero, during gestation and lactation, and the following 21-23 months [7]. The highest level in diet was 1% corresponding to a dose of 1500 mg/kg bw/day. No significant dose-related effects. No tumour induction. This was the study also used for the SCF and JECFA ADI settings.

Dogs (2 years) (the methylated component) [7]: No significant toxic effects.

**Reproduction toxicity:** A multi-generation study has been conducted in rats. No compound-related effects on biological, reproductive, or histological parameters. Special studies on embryotoxicity and teratology have been performed in rats and rabbits. No dose related effects[7].

**Allergy/Intolerance:** Several studies were found in the database search. The results indicate that a small subgroup respond to oral provocation with a mixture of food additives including quinoline yellow [8].

**Other:** Biochemical aspects:
The colour is poorly absorbed and hardly metabolised. The nature of the metabolites has not been established [3].

Whole body autoradiography and distribution studies after p.o. administration have been performed in male rats: 3-4% of a p.o. dose was absorbed from g-i tract [7]. Distribution has been studied in dogs and rats after p.o. administration: 2% of a single 4 mg p.o. dose was excreted via urine in rats, 94% via faeces within 120 hr. A distribution and biotransformation study in dogs after i.v. and p.o. is available. Only minor biotransformation [7].

**Conclusion:** The toxicological data include what would normally be required for an ADI to be set for a food additive and are sufficient for the setting of ADI. However, it would be desirable to clarify the discrepancies between the reporting of SCF and JECFA.

Quinoline yellow as defined by the specifications seems to be covered by the toxicological evaluation.

**References:**


5. \[1984, TRS 710-JECFA 28\]


7. \[1984, FAS 19-JECFA 28\]

**SUNSET YELLOW FCF**

**E number:** E 110

**Recommendation:** The basis for the present ADI is poorly reported and new data on reproductive functions and neurobehaviour have been published. It is therefore recommended that the basis for the ADI is clarified and the new data are included in the evaluation.

**Chemical name/synonyms:** Disodium 2-hydroxy-1-(4-sulfonatophenylazo) naphthalene-6-sulfonate/CI Food Yellow 3, Orange yellow S.

**Chemical formula:** $C_{16}H_{10}N_{2}Na_{2}O_{7}S_{2}$

**Class:** Monoazo.

**EINECS number:** 220-491-7

**CAS number:** 2783-94-0

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Sunset yellow FCF is manufactured by chemical synthesis.

**Definition:** Sunset yellow FCF consists essentially of disodium 2-hydroxy-1-(4-sulfonatophenylazo) naphthalene-6-sulfonate and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Disodium 2-hydroxy-1-(4-sulfonatophenylazo) naphthalen-6-sulfonate is described as the sodium salt. The calcium and the potassium salts are also permitted.

**EC specifications:** E 110 Sunset yellow FCF [1].
Assay: Not less than 85% total colouring matters calculated as the sodium salt.
Subsidiary colouring matters: Not more than 5%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Sunset yellow FCF [2].
Assay: Not less than 85% total colouring matters.
Subsidiary colouring matters: Not more than 5%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.
**Exposure:** Permitted in all “colourable” foods and in a few of those with only limited number of permitted colours. Maximum level in soft drinks 50 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system the substance was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 2 – 26% of ADI, while the calculated intake by young children is reported by one member state as 80%. It was concluded that no further examination was needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** An ADI of 2,5 mg/kg bw was established by SCF in 1983 [3] on the basis of a no-adverse-effect level corresponding to 250 mg/kg bw/day in a long-term study in dogs. No details were reported. The study was not specified. The applied safety-factor was 100.

**JECFA status:** An ADI of 2,5 mg/kg bw was established by JECFA in 1982 [4]. The basis was the levels causing no toxicological effects in rats (1% in diet equivalent to 500 mg/kg bw/day) (the reference was not specified) and dogs (2% in diet equivalent to 500 mg/kg bw/day) [5] and a 200 safety-factor.

In brief, the basal studies were not identified, data not specified, and the reason for the 200 safety-factor not given.

**BIBRA:** The toxicological data for sunset yellow within classical endpoints (local effects, skin irritation, sensitisation, intolerance, oral provocation, acute toxicity, target organ toxicity, foetal malformations) have been reviewed by BIBRA. No adverse effects. Specifically, no convincing evidence for carcinogenicity or genotoxic potential was noticed [6].

**Background data:**

**Subacute/subchronic toxicity:** No obvious toxic effects.

Studies are available in rats (4 studies) and mini-pigs (1 study). No significant toxic effect [7].

Sunset yellow (and other synthetic colours) showed different effects in rats on body weight, clinical biochemical parameters, liver and kidney functions after 30-60 days of administration. These effects were not regarded as serious effects by the authors [8].

**Genotoxicity:**

*In vitro:* Data were available to SCF, which notes that there is no genotoxic activity, but no details reported [3].

Several studies on the genotoxicity *in vitro* have been published since the SCF and JECFA evaluations were done including salmonella/microsome test, mouse lymphoma test and SCE. Overall these studies provide no evidence for genotoxicity [9-17]. One paper reports indication of direct-acting oxidative genotoxicity by reaction products of azo dyes (including sunset yellow) but the relevance is questionable and it does not change the overall conclusion that sunset yellow is not genotoxic [14].
**In vivo:** Negative results in both rat and mouse bone marrow micronucleus test after single oral exposure to 2000 mg/kg bw [18]. Sunset yellow has also been tested for genotoxicity in different laboratory animal species. It was concluded that no genotoxic harm was to be expected from ingestion of sunset yellow [19]. The cytogenetic activity of colours given orally during 5 days to mice was studied. The doses of sunset yellow were 0.17-1.7 mg/kg. No increased level of cells with chromosomal damage [20].

**Chronic toxicity/Carcinogenicity:** SCF reports that studies are available in mice, rats and dogs. No carcinogenic potential in any species. The dog study was used for the ADI setting. No details of the studies are given [3;3].

Several studies are available: 3 studies in mouse, 1 study in hamster, 5 studies in rats, and 2 studies in dog. No colour-related significant adverse toxic effects in any of these studies. In one of the two studies in dogs 5% in diet was moderately toxic causing weight loss and diarrhoea as major effects. The reference to this study is not given, but it might be the same as the first study in the dogs [5].

**Reproduction toxicity:** One study published since the committees’ evaluations [21] reports that reproductive functions and neurobehaviour were affected. No teratogenic potential. Single and multi-generation studies are available in rats and dogs. Reproductive functions were not affected. No teratogenic potential. No details reported by SCF [3].

Mice were given 0, 0.15, 0.30, or 0.60% in diet from 5 weeks of age in the F0 generation to nine weeks of age in the F1 generation. Selected reproductive and neurobehavioral parameters were measured. There were few adverse effects on litter size, weight, or sex ratio. Average body weight of offspring during the late lactation period was significantly increased in the low- and middle-dose groups of each sex. In the neurobehavioral parameters, swimming direction was significantly affected in a dose-related manner in male and female offspring during the early lactation period. Also in the early lactation period, surface righting and negative geotaxis were significantly affected in male offspring in the middle-dose group, and swimming head angle was significantly affected in female offspring in a dose-related manner [21].

**Allergy/Intolerance:** The prevalence of intolerance has been reviewed. The mechanism is not mediated by an immunological reaction and there is no *in vivo* or *in vitro* confirmatory test [22]. In 90 patients with chronic or chronic relapsing urticaria 4% was found to be caused by food additives (benzoates, sorbic acid, and sunset yellow) [23].

In a skin test performed on patients sensitive to p-phenylene-diamine the colour produced eczematous hypersensitivity. No sensitisation activity in guinea-pig [7].

**Effect in humans:**

**Childhood behaviour:** 19 of 39 children whose behaviour by their parents was found to be reversibly improved on artificial food additive free diet completed a double-blind study. In these 19 children food colour challenge was found to have an adverse effect on a daily Conners’ rating of behaviour, but most parents could not detect these changes [24]. Azorubine (25 mg), tartrazine (50 mg), sunset yellow (25 mg), and amaranth (25 mg) were studied in combination.

**Other:** *Biochemical aspects:* Sunset yellow is azo-reduced in the gut. Some breakdown products are absorbed. Metabolites are excreted via bile and urine [3;3].
Studies are available in rats and rabbits. Only about 4% of a p.o. dose was absorbed in rats. Azo-reduction via intestinal bacteria is documented. Some breakdown products and the parent compound are absorbed and excreted via urine during 48 hr (% of total excreted by rabbits): Sunset yellow (2%), sulfanilic acid (54%), p-acetamido-sulfonic acid (23%), 1-amino-2-naphthol-6-sulfonic acid (55%) Studies are performed in rabbit (1 study), rat (3 studies) [7].

Conclusion: The toxicological data reported by SCF include what would normally be required for an ADI to be set for a food additive. The reporting, however, does not allow for a full review of the background. The basis behind the size of the ADI is unclear.

One study published later than the SCF and JECFA evaluations [21] reports that reproductive functions and neurobehaviour were affected. The potential impact of this should be evaluated.

Sunset yellow FCF as defined by the specifications seems to be covered by the toxicological evaluation.

References:


4. [1982, TRS 683-JECFA 26]


7. [1982, FAS 17-JECFA 26]


COCHINEAL CARMINIC ACID CARMINES

E number: E 120

Recommendation: A re-evaluation is recommended due to new data concerning allergic reactions to cochineal. As the allergic responses presumably are due to the protein content of the carmine preparation, a restriction of the protein level in E 120 should be considered. As new data on reproduction has accrued after the latest evaluation an update of the ADI is warranted. Further information on metabolism is also desirable. The difference, if any, between the effect of the aluminium salt and the lithium salt should be elucidated.

Chemical name/synonyms: 7-β-D-glucopyranosyl-3,5,6,8-tetrahydroxy-1-methyl-9,10-dioxaanthracene-2-carboxylic acid (carminic acid; carmine is the hydrated aluminium chelate of this acid).

Chemical formula: C_{22}H_{20}O_{13} (carminic acid)

Class: Anthraquinone.

EINECS number:
- Cochineal: 215-680-6
- Carminic acid: 215-023-3
- Carmine: 215-724-4

CAS number:
- Cochineal: 215-680-6
- Carminic acid: 1260-17-9
- Carmine: 1390-65-4

Functional Class: Colour.

Specification:
- Manufacture: Cochineal extract, Carminic acid and carmines are obtained by aqueous, aqueous alcoholic or alcoholic extraction of cochineal, which consists of the dried bodies of the female insect *Dactylopius coccus* Costa.

Definition: Carminic acid is a well-defined chemical compound of the class anthraquinone. Carmines are hydrated aluminium chelates of carminic acid in which aluminium and carminic acid is thought to be present in the molar ratio 1:2. In commercial products the colouring principle is present in association with ammonium, calcium, potassium or sodium cations, singly or in combination, and these cations may also be present in excess. Commercial products may also contain proteinaceous material derived from the source insect, and may also contain free carminate or a small excess of aluminium cations. Cochineal extract is the concentrated solution obtained after removing the alcohol from the alcoholic extract.
**EC specifications:** E 120 Cochineal, carminic acid, carmines [1].
Assay: Not less than 2.0% carminic acid in the extracts containing carminic acid and not less than 50% of carminic acid in the hydrated aluminium chelate of this acid.
The specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Carmines [2].
Assay: Not less than 50% of carminic acid on the anhydrous basis.
Protein: Not more than 25%.
In addition the specification includes purity criteria on Loss on drying, Total ash, Matter insoluble in ammonia, Arsenic, Lead, Heavy metals and microbiological criteria.

**JECFA specifications:** Cochineal extract [2].
Assay: Not less than 2.0% of carminic acid.
Protein: Not more than 2.2%
In addition the specification includes purity criteria on Methanol, Lead and microbiological criteria.

**Exposure:** Permitted in all “colourable” foods and in some of those with only limited number of permitted colours. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods

In the EU monitoring system the substance was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 3-22% of ADI, while the calculated intake by young children is reported by one member state as 80%. It was concluded that no further examination was needed at this stage.

**SCF/JECFA evaluation:**
**SCF-status:** Latest evaluation: July 1983. ADI 5 mg/kg bw [3].

**JECFA status:** Latest evaluation: 1982. ADI 5 mg/kg bw [4].

**Background data:**
**Subacute/subchronic toxicity:** Cochineal incorporated in the diet at 0.75, 1.5 or 3% was administered to 5-week-old male and female Wistar rats for 13 weeks. No toxic symptoms or death occurred in any treatment groups and no histopathological changes attributed to cochineal were observed [5]. Studies performed between 1931 and 1962 in mice, rats and rabbits at doses up to 4% of an aqueous solution of lithium carmine likewise did not adversely affect growth, hematology or other clinical parameters when administered for up to 90 days. The only abnormality observed was in mice where an increased rate of proliferation in the spleen was observed following exposure to 2% lithium carmine for 60 days.

**Genotoxicity:** *In vitro:* Carminic acid was negative in the Bacillus subtilis rec. assay [6] and in Ames mutagenicity assay using several different strains in the presence of rat microsomes or rat caecal microflora [7]. Carminic acid likewise did not induce sister chromatide exchanges *in vitro* in Chinese hamster ovary cells [8].
In vivo: No evidence for in vivo genotoxic effects of carminic acid using the mouse micronucleus test [8].

Chronic toxicity/Carcinogenicity: Carmine fed continuously to female and male rats at dietary levels providing 50, 150 or 500 mg/kg bw/day for up to 109 weeks did not induce carcinogenesis in any organ [9]. The carcinogenicity of cochineal was studied in a 2-year bioassay in B6C3F1 mice at a dietary concentration of 0, 3 or 6 % [10]. No evidence for a carcinogenic effect of cochineal was observed.

Reproduction toxicity: Carmine administered in the diet throughout all phases of mating, gestation, lactation, weaning and adult life over three successive generations at doses up to 500 mg/kg bw/day had no effects on growth or fertility of adult rats [11]. Increased number of retarded foetuses seen in mice subcutaneously administered lithium carmine at 150 mg/kg bw on day 8 of pregnancy [12]. A teratogenic effect was observed following intraperitoneal administration of lithium carmine at 150 mg/kg bw at day 6, 8 or 10 [12] of pregnancy. Studies by Grant et al. [11] revealed adverse effects on embryo development, such as body weights, pregnancy rates, pre-implantation losses, the average number of live young, litter weight or foetal weights in rats given doses of 0, 200, 500 or 1000 mg carmine/kg bw, by oral intubation throughout pregnancy. In a reproduction study conducted in mice no adverse effects of cochineal at dietary levels of 0.5-2% was observed when administered from 5 weeks of age in the F0 generation to nine weeks of age in the F1 generation. The recent data by Grant et al. [11] has accrued after the latest JECFA and SCF evaluations in 1982 and 1983, respectively, and a re-evaluation of E 120 is thus warranted taking these new findings into account.

Allergy/Intolerance: Several reports have become available during the past 5 years on the allergenic potential of cochineal and carmine[13-17] presumably due to the inherent present of foreign protein. Carmine has thus been found to induce IgE-mediated food allergy and occupational asthma in workers in the dye industry and in workers using products where its presence could easily be overlooked such as in the manufacturing of spices [13;16]. Additionally, several cases have been reported of anaphylactic reactions following ingestion of carmine-containing products [14;17]. In one case the triggering dose of carmine was as low as 1 mg [14].

Others: Carminic acid has been found to redox cycle to produce free radicals. These radicals in the presence of trace amounts of iron salts readily cause damage to membrane lipids [14;18].

Conclusion: The recent findings on adverse effects of cochineal with regard to teratogenicity and reproduction and the recent data on the allergenic potential of carmine and cochineal of which neither were included in the latest SCF and JECFA evaluations, strongly warrants a re-evaluation of this additive. Furthermore the limited information on the metabolism of cochineal and carmine warrants further studies in this regard.

While the specifications for cochineal, carminic acid and carmines as defined by the specifications defines aluminium chelates many of the tests performed on the substances have been performed on the lithium salt. The significance of this is not clear.
References:


4. [1982, TRS 683-JECFA 26]


12. [1977, FAS 12-JECFA 21]


**E 122 Azorubine**

**azorubine, carmoisine**

**E number:** E 122

**Recommendation:** No re-evaluation is necessary.

**Chemical name/synonyms:** Disodium 4-hydroxy-3- (4-sulfonato-1-naphthylazo) naphthalene-1-sulfonate/ CI Food Red 3; CI Acid Red 14; Ext. D&C Red No. 10; Food Red 5.

**Chemical formula:** \( \text{C}_{20}\text{H}_{12}\text{N}_{2}\text{Na}_{2}\text{O}_{7}\text{S}_{2} \)

**Class:** Monoazo.

**EINECS number:** 222-657-4

**CAS number:** 3567-69-9

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Azorubine is manufactured by chemical synthesis.

**Definition:** Azorubine consists essentially of disodium 4-hydroxy-3- (4-sulfonato-1-naphthylazo) naphthalene-1-sulfonate and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Disodium 4-hydroxy-3- (4-sulfonato-1-naphthylazo) naphthalene-1-sulfonate is described as the sodium salt. The calcium and the potassium salts are also permitted.

**EC specifications:** E 122 Azorubine [5].

- **Assay:** Not less than 85% total colouring matters calculated as the sodium salt.
- **Subsidiary colouring matters:** Not more than 2.0%.

  In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Azorubine [4].

- **Assay:** Not less than 85% total colouring matters.
- **Subsidiary colouring matters:** Not more than 1%.

  In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.
**Exposure:** Permitted in all “colourable” foods and in a few of those with only limited number of permitted colours. Maximum level in soft drinks 50 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system azorubine was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 3-16% of ADI, while the calculated intake by young children is reported by one member state as 50%. It was concluded that no further examination was needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** An ADI of 4 mg/kg bw was established by SCF in 1983 [3] on the basis of the no-effect-level determined in a long-term study in rats. No specification of NOAEL or safety-factor was given. No details of the study were reported in [3]. However see “Chronic toxicity/carcinogenicity”.

**JECFA status:** An ADI of 4 mg/kg bw was established by JECFA in 1983 [2]. The basis was the levels causing no toxicological effects in mice, rats, and mini-pigs:
- In a study in mice NEL was 0.25% in the diet equivalent to 375 mg/kg bw [16]. The levels in diet were 0, 0.01, 0.05, 0.25, and 1.25%. The 1.25% level lowered female haemoglobin and induced mild anaemia.
- In a study in rats NEL was 0.8% in the diet equivalent to 400 mg/kg bw [14]. The levels in diet were 0, 0.35, 0.8, and 2.0%. The 2.0% level induced bronchitis and tracheal irritation in the male rats.
- In a study in mini-pigs NEL was 0.1% in the diet corresponding to 400 mg/kg bw [12]. This was the highest level in the study. The safety factor for the ADI was 100.

**Background data:**

**Subacute/subchronic toxicity:** No adverse toxic effects.

A 28-day study in rats and a 90-day study in mini-pig showed no toxic effects including induction of tumours. NEL was 1000 mg/kg bw/day (highest doses) in the mini-pig study [12].

Azorubine (and other synthetic colors) showed different effects in rats on body weight, clinical biochemical parameters, liver and kidney functions after 30-60 days of administration. These effects were not regarded as serious effects by the authors [6].

**Genotoxicity:**

No genotoxic activity demonstrated.

*In vitro:* Several studies exist. No evidence of genotoxicity was documented [1]. Several studies on the genotoxicity in vitro have been published since the SCF and JECFA evaluations were done including salmonella microsome test, mouse lymphoma test, SCE and hepatocyte, overall these studies provide no evidence for genotoxicity[7-9;13;15;17;18;22;24;25;26;28].

*In vivo:* The cytogenetic activity of azorubine (and other colours) when given orally during 5 days to mice has been studied. The dose interval was 1-10 mg/kg. No increase in the level of cells with chromosomal damage was found [10].
**Chronic toxicity/Carcinogenicity:** No carcinogenic potential demonstrated.

Several studies in mouse and rats showed no adverse effects, including tumour induction [1].

A “new” long-term study in rats using in utero exposure has been published after the SCF and JECFA evaluations [11]. Rats were treated with 0, 100, 400, or 1200 mg/kg bw/day for 110-115 weeks. This study also included in utero exposure. The 1200 mg/kg bw group had reduced body-weight gain despite slightly higher food and water intakes. Azorubine was not carcinogenic and the no-untoward-effect level was set to 400 mg/kg bw/day. This study was used for setting the ADI.

**Reproduction toxicity:** No adverse effect on reproductive function was demonstrated. No teratogenic potential or embryotoxicity was found.

A multi-generation study showed no adverse effect on reproductive function. No teratogenic potential was demonstrated. No data was presented [3].

Studies in rats and rabbits failed to demonstrate any adverse effects including deleterious effects on reproductive parameters. No embryotoxic or teratogenic effects were associated with the colour [1].

**Allergy/Intolerance:** No sensitising activity was found in a study in guinea-pigs [1].

In a double-blind cross-over study in 14 selected children, challenged with either 50 mg tartrazine or 50 mg azorubine, 2 reactors were identified [21].

**Effect in humans:**

**Hyperactivity:**

*Childhood behaviour:* 19 of 39 children whose behaviour by their parents was found to be reversibly improved on artificial food additive free diet completed a double-blind study. In these 19 children food colour challenge was found to have an adverse effect on a daily Conners’rating of behaviour, but most parents could not detect these changes [20]. Azorubine (25 mg), tartrazine (50 mg), sunset yellow (25 mg), and amaranth (25 mg) were studied in combination.

**Other:** Biochemical studies are available in three species. There is azo-reduction in the gut to naphthionic acid and aminonaphthol sulphonate. Most of the absorbed fraction is excreted within 24-72 hr. after administration. If any, there is only minimal transplacental passage. There is no marked accumulation in any tissue [3].

Absorption, distribution, excretion and metabolism were intensively studied in rat, mouse and guinea pig. There is moderate absorption after oral administration (about 10% of dose) and rapid distribution. Following p.o. or i.v. administration radioactivity is excreted via urine and faeces, most via faeces. No specific accumulation of the colour in any organ. There is one study in rats of placental transfer. Here, no evidence for transplacental transfer of azorubine or its metabolites was documented. 2-amino-1-naphthol-4-sulfonic acid and 1,2-naphthoquinone-4-sulfonate are identified in urine. *In vitro* rat liver studies indicate that the colour inhibits the succinic oxidase system [1].

Since azorubine was evaluated by SCF and JECFA, some “new” biochemical studies have been published:
The absorption, metabolism, and excretion of $^{14}$C-labelled azorubine have been studied in rat, mouse, and guinea-pig [19]. The placental transfer and detection of metabolites of azorubine administered orally has been studied in male and pregnant female rats. No evidence for transplacental transfer of azorubine or its metabolites was obtained. Pregnancy did not affect the kinetic and the metabolic profile at different days of gestation [27].

The azoreductase activity has been studied in a recent investigation [23;27].

**Conclusion:** The toxicological data include what would normally be required for an ADI to be set for a food additive and are sufficient for the setting of ADI. No new data, that would necessitate a re-evaluation of the ADI, has been found.

Azorubine as defined by the specifications seems to be covered by the toxicological evaluation.

**References:**


faecal metabolites of 14C-carmoisine in male and pregnant female rats after oral

AMARANTH

E number: E 123

Recommendation: According to the available database and the low exposure there is no immediate need for a re-evaluation. However, if reviewed at a later stage the studies by Tanaka [26,27] should be included and the apparent discrepancy between the SCF and the JECFA ADI’s clarified.

Chemical name/synonyms: Trisodium 2-hydroxy-1- (4-sulfonato-1-naphthylazo) naphthalene-3,6-disulfonate/ CI Food Red 9; CI Acid Red 27; Naphtol Rot S; FD&C Red No. 2; Red Dye No. 2.

Chemical formula: C$_{20}$H$_{11}$N$_2$Na$_3$O$_{10}$S$_3$

Class: Monoazo.

EINECS number: 213-022-2

CAS number: 915-67-3

Functional Class: Colour.

Specification:

Manufacture: Amaranth is manufactured by chemical synthesis.

Definition: Amaranth consists essentially of trisodium 2-hydroxy-1- (4-sulfonato-1-naphthylazo) naphthalene-3,6-disulfonate and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Trisodium 2-hydroxy-1- (4-sulfonato-1-naphthylazo) naphthalene-3,6-disulfonate is described as the sodium salt. The calcium and the potassium salt are also permitted.

EC specifications: E 123 Amaranth [7].
Assay: Not less than 85% total colouring matters calculated as the sodium salt.
Subsidiary colouring matters: Not more than 3.0%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Amaranth [6].
Assay: Not less than 85% total colouring matters.
Subsidiary colouring matters: Not more than 3%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate.
calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.

Exposure: Permitted uses limited to “Americano”, Bitter Soda, Bitter Vino (100 mg/l), aperitif wine (30 mg/l) and fish roe (30 mg/l) so normal exposure will be well below the ADI’s and amaranth was therefore not included in the EU monitoring system (tier 0).

SCF/JECFA evaluation:
SCF status: An ADI of 0.8 mg/kg bw was established by SCF in 1983 [5] on the basis of a no-effect level for the renal effects established in a 90-day study. The data, NEL, and the safety-factor were not specified in the report so the background for the ADI cannot be elucidated. The safety-factor cannot be calculated on the basis of information reported [5].

JECFA status: The present JECFA ADI of 0.5 mg/kg bw was allocated in 1984 [1]. The basis was a NEL with respect to renal calcification and hyperplasia corresponding to 50 mg/kg bw/day in a long-term rat study including in utero exposure [4]. The safety-factor was 100. In this long-term study rats were provided a daily intake of 0, 50, 250, or 1250 mg/kg bw via the diet. There were no consistent findings on haematological or clinical biochemical parameters or on mortality. No carcinogenicity was demonstrated. [11]. A further histopathological examination of tissue from this very study revealed a dose-related trend for increased calcification and epithelial hyperplasia in the renal pelvis of the female F1 rats. These effects were not statistically different from the controls at the 50 mg/kg bw/day level. A NEL of 50 mg/kg bw/day was therefore concluded in this re-evaluation [3].

Background data:
Subacute/subchronic toxicity: Studies are available in rats (3-21 days administration). No toxic effects were reported [2;3].

Genotoxicity: No genotoxic potential.

In vitro: JECFA notes that studies are available in bacteria and yeast. No mutagenic effect [2]. Amaranth was non-genotoxic in somatic and germ line cells of Drosophila [29]. In bacteria tests no mutagenic activity was reported [30]. Other studies investigated the mutagenicity without publishing any abstract [15;21;23]. One study indicates the presence of low levels of ether-extractable impurities [21]. One paper may report evidence for direct-acting oxidative genotoxicity by reaction products of azo-dyes (including amaranth). No data are presented [26].

In vivo: Host mediated assays and dominant lethal tests are available. No mutagenic or dominant lethal response found [2;3].
**Chronic toxicity/Carcinogenicity:** No carcinogenic potential was demonstrated.

Numerous long-term studies are available in mice, rats, and dog [2] [3] two of which indicated a carcinogenic potential not seen in any other study. JECFA concluded that because of the uncertainty about the impurity content of amaranth used in these two studies, the carcinogenicity could not be evaluated in these two studies [3]. The overall conclusion is that amaranth is not tumourgenic.

One long-term oral toxicity study (0, 50, 250, 1250 mg/kg bw for 111-112 weeks) in rats showed no carcinogenic effect in doses up to 1250 mg/kg/day, but renal calcification and pelvic epithelial hyperplasia in females. Because of these effects it was not possible to establish a no-untoward-effect level in this study [11;26]. This seems to be the same data as those reported in the unpublished report by Clode et al., 1981 as quoted by JECFA [4].

**Reproduction toxicity:** No consistent adverse effects on reproduction or parameters for teratogenicity.

Reproductive toxicity studies and special studies on embryotoxicity and teratogenicity are available in mice, rats, rabbits, hamster, cat, dog, and chicken embryo. Some of these studies reported conflicting results with regard to foetotoxicity although none produced evidence of teratogenicity. An extensive comparative teratogenicity study in three laboratories using two strains of rats revealed no adverse effects when amaranth was administered at 200 mg/kg bw/day by gavage or in the drinking water. Similarly, no teratogenic response was observed when cats received dietary levels of up to 264 mg/kg bw/day [3].

**Studies published after the SCF and JECFA evaluations:**
Amaranth did not affect embryogenesis in rat postimplementation whole embryo culture [18] and in embryo cell culture obtained after *in vivo* administration [14]. Other *in vitro* studies did not specify data in the abstract [9;10;12;13;17;20;22;24;25].

Male and female rats were given doses at 0, 50, 250, 1250 mg/kg bw from 60 days before mating. Litter was also exposed in utero without any effect on reproductive or teratogenic parameters [11]. One study investigated the teratogenic and reproductive effects of amaranth. No abstract was published [17]. In the Frog Embryo Teratogenesis Assay amaranth showed no teratogenic potential [8].

When 0, 0.03, 0.09, or 0.27% was given in diet to mice from five weeks of age of F0 to the F1 generation was nine weeks of age minor effects on reproductive, developmental and behavioural parameters were reported. Specifically, swimming direction and olfactory orientation were affected in the F1 generation even at the lowest dose corresponding to a dose of about 50 mg/kg/day. It was not possible to establish a NEL on these parameters [27].

In another study when 0, 0.025, 0.075, or 0.225% was administered in drinking water to mice from five weeks of age of F0 to the F1 generation was weaned minor effects on behavioural development were indicated [28].

At a future re-evaluation these studies by Tanaka [27;28] should be considered.

**Allergy/Intolerance:** One of 7 patients suspected to be sensitive to azo-dyes reacted with urticaria after provocation [3]. A study by Koutsogeorgopoulou et al., 1998 showed immunosuppressive effects of amaranth [16].
Effect in humans:

Childhood behaviour: 19 of 39 children whose behaviour by their parents was found to be reversibly improved on artificial food additive free diet completed a double-blind study. In these 19 children food colour challenge was found to have an adverse effect on a daily Conners’rating of behaviour, but most parents could not detect these changes [19]. Azorubine (25 mg), tartrazine (50 mg), Sunset Yellow (25 mg), and Amaranth (25 mg) were studied in combination.

Other: Biochemical aspects are thoroughly studied in rats: 2.8% of an oral dose was absorbed in GI-tract [2]. The predominant metabolites in urine, bile, and faeces after oral adm are azo-reduction products of intestinal flora activity i.e. 1-amino-4-naphthalene sulfonic acid and 1-amino-2-hydroxy-3,6-naphthalene disulfonic acid. Following oral administration of 1-amino-4-naphthalene sulfonic acid, only a little fraction is metabolised by the liver azo-reductase system. After an i.v. injection, rapid serum clearance and fast elimination via urine (42%) and faeces (11%) was observed. After prolonged administration, liver vit-A content decreased 3-4-fold and the liver and spleen glutathione content increased [2].

Conclusion: The use as a food additive is very limited. The toxicological data reported by SCF include what would normally be required for an ADI to be set for a food additive.

Previously there were some indications on carcinogenicity and teratogenicity of amaranth. These uncertainties have now been elucidated:

Ad. Carcinogenicity: Many long-term studies have been carried out in rats, mice, and dogs. Only 2 studies indicated a carcinogenic potential not seen in any other study. JECFA and SCF have concluded that because of the uncertainty about the impurity content of amaranth used in these two studies, the apparent carcinogenicity in these two studies could not be evaluated. The overall conclusion was that amaranth is not tumorigenic [4;5].

Ad. Reproduction and teratology: Several studies are available some of which gave birth to conflicting results with regard to foetotoxicity although none produced evidence of teratogenicity. An extensive comparative study has failed to reproduce these effects [4]. At a future re-evaluation, the studies by Tanaka [27;28] should be considered.

Amaranth as defined by the specifications seems to be covered by the toxicological evaluation.

References:


3. [1978, FAS 13-JECFA 22]

4. [1984, FAS 19-JECFA 28]


**PONCEAU 4R (COCHINEAL RED A)**

**E number:** E 124

**Recommendation:** There is some uncertainty with respect to the background for setting the ADI. It is therefore recommended that the background for the evaluation is reviewed.

**Chemical name/synonyms:** Trisodium 2-hydroxy-1- (4-sulfonato-1-naphthylazo) naphthalene-6,8-disulfonate/ CI Food Red 7; CI Acid Red 18; New coccine.

**Chemical formula:** \( \text{C}_{20}\text{H}_{11}\text{N}_{2}\text{Na}_{3}\text{O}_{10}\text{S}_{3} \)

**Class:** Monoazo.

**EINECS number:** 220-036-2

**CAS number:** 2611-82-7

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Ponceau 4R is manufactured by chemical synthesis.

**Definition:** Ponceau 4R consists essentially of trisodium 2-hydroxy-1- (4-sulfonato-1-naphthylazo) naphthalene-6,8-disulfonate and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Ponceau 4R is described as the sodium salt. The calcium and the potassium salts are also permitted.

**EC specifications:** E 124 Ponceau 4R [5].
- Assay: Not less than 80% total colouring matters calculated as the sodium salt.
- Subsidiary colouring matters: Not more than 1.0%.
- In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Ponceau 4R [4].
- Assay: Not less than 85% total colouring matters.
- Subsidiary colouring matters: Not more than 1%
- In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.
**Exposure:** Permitted in all “colourable” foods and in some of those with only limited number of permitted colours. Maximum level in soft drinks 50 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system Ponceau 4R was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 3-16% of ADI, while the calculated intake by young children is reported by one member state as 50%. It was concluded that no further examination was needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** The 4 mg/kg bw ADI was established by SCF in 1983 [3] allegedly on the basis of a no-adverse level in a long-term study in mice of 500 mg/kg bw. The safety factor can thus be calculated to 125. Nephrotoxicity was demonstrated at the high doses. No details about the study, no reference, or any reason for the safety factor were presented by SCF [3].

**JECFA status:** The present JECFA ADI of 4 mg/kg bw was allocated in 1983 [1]. The basis was a long-term study in mice administered 0, 0.01, 0.05, 0.25, or 1.25% in the diet. Critical effects were increased incidence of reticuloendothelial cells in the liver at the 1.25% level and episodes of glomerulonephrosis in the kidneys at the 0.25% and 1.25% level. The no-untoward-effect level was claimed in the text to be 0.05% corresponding to 75 mg/kg bw/day while in the conclusion the level of 0.25 is claimed which corresponds to a dietary level of 375 mg/kg bw, which, by applying a safety factor of 100 and rounding gives the ADI of 4 mg. There is no explanation to this discrepancy in the evaluation [2].

**Background data:**

**Subacute/subchronic toxicity:** No significant toxic effects.

A 90-days oral study has been performed in rats. No adverse effects on appearance, behaviour, growth, food consumption, haematological, or clinical biochemical parameters were found. Renal function and organ weights were normal. No gross pathological or histopathological effects appeared. In a three-months oral study in pigs, no effects on growth, urine, serum, organ weight or histopathology were demonstrated [2].

**Genotoxicity:** No mutagenic potential was demonstrated.

*In vitro:* No mutagenic effect was seen in bacteria tests [2].

No mutagenic activity of Ponceau 4R was revealed in the *S. typhimurium* test [12]. Other studies investigated the mutagenicity of Ponceau 4R without presenting any abstract [9-11;13;14].

*In vivo:* One reference indicates clastogenic activity (chromosome aberrations) at a minimum effective dose of 4 mg Ponceau 4R in *in vivo* cytogenetic studies in bone marrow cells of male mice [6].

**Chronic toxicity/Carcinogenicity:** No carcinogenic potential.

In a long-term study in mice, 0, 0.01, 0.05, 0.25, or 1.25% was administered in the diet. There was no adverse effect on mortality, body weight gain, organ weight, or tumour incidence. An increased incidence of reticuloendothelial cells was revealed in the liver at the 1.25% level and episodes of
glomerulonephrosis were seen in the kidneys at the 0.25% and 1.25% level. In several long-term study in rats, no adverse effects including tumour induction was demonstrated [2].

A long-term toxicity study in rats reported no findings of tumour incidence at 1250 mg/kg/day [8]. A three-generation reproduction study [7] demonstrated a no-adverse-effect level of 1250 mg/kg/day corresponding to highest dose.

**Reproduction toxicity:** No adverse effects on reproductive function. No teratogenic potential was detected.

A multigeneration study and teratogenic studies in 3 species were available to SCF, which notes that no adverse effects were reported, but no details were presented [3].

Reproductive studies and studies on embryotoxicity and teratogenicity are available in mice and rats. No adverse effects were reported on biological, pathological, reproductive, or teratological parameters. No embryotoxicity was demonstrated [2].

A three-generation reproduction study [7] demonstrated a no-adverse-effect level of 1250 mg/kg/day corresponding to highest dose.

**Allergy/Intolerance:** No sensitisation was observed in guinea-pigs. In one study, 16% of 51 patients showing signs of allergy reacted on an oral dose. The colour was not a sensitisier. One patch test on patients with a presumptive diagnosis of possible allergic contact dermatitis to colour dyes demonstrated no sensitisation to Ponceau 4R [2].

The hypersensitivity to Ponceau 4R has been studied, but no data are given in the abstract [15].

**Other:** **Biochemical aspects:** Reports show in vitro azo-reduction by rat caecal content. The colour undergoes extensive metabolism with formation of naphthionic acid (major urinary metabolite) and 7-hydroxy-8-amino-naphthalene-1,3-disulfonic acid in mouse, rat, guinea-pig. The parent compound and reduction products are rapidly absorbed from the g-i-tract. No significant accumulation occurs in any tissue of mouse, rat, guinea-pig. Some 30-45% of a dose is excreted unchanged by bile following i.v. injection of rats. There is faecal and urinary excretion of naphthionic acid, 7-hydroxy-8-amino-naphthalene-1,3-disulfonic acid, and unchanged colour after oral dosing of mouse, rat, guinea-pig. Substantially all of a single oral dose, 0.5 mg/kg bw, was excreted in urine and faeces within 72 hr by rats, the majority via faeces. Pregnant rats eliminate a single oral dose at a similar rate as non-pregnant rats. Only a small fraction of the colour seems to penetrate the placenta. No significant enzyme induction seems to occur: 28-days pretreatment of rats had no effect on route and time of excretion. [2].

Azoreductase has also been studied in other investigations [15].

**Conclusion:** The available toxicological data include what would normally be required for an ADI to be set for a food additive. It is, however, unclear from the reports what were the details for the setting of the ADI.

**References:**


ERYTHROSINE

**E number:** E 127

**Recommendation:** A re-evaluation is not necessary at the present stage of knowledge combined with the very low potential exposure.

**Chemical name/synonyms:** Disodium 2-(2,4,5,7-tetraiodo-3-oxido-6-oxoxanthen-9-yl) benzoate monohydrate/ CI Acid Red 51; CI Food Red 14; D&C Red No. 3; FD & C Red No. 3; Erythrosine B or BS.

**Chemical formula:** C\(_{20}\)H\(_6\)I\(_4\)Na\(_2\)O\(_5\) \cdot \text{H}_2\text{O}

**Class:** Xanthene.

**EINECS number:** 240-474-8

**CAS number:** 16423-68-0

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Erythrosine is manufactured by chemical synthesis.

**Definition:** Erythrosine consists essentially of disodium 2-(2,4,5,7-tetraiodo-3-oxido-6-oxoxanthen-9-yl) benzoate monohydrate and subsidiary colouring matters together with water, sodium chloride and/or sodium sulphate as the principal uncoloured components. Erythrosine is described as the sodium salt. The calcium and the potassium salt are also permitted.

**EC specifications:** E 127 Erythrosine [1].

Assay: Not less than 87% total colouring matters calculated as the anhydrous sodium salt.
Subsidiary colouring matters (except fluorescein): Not more than 4.0%.
Fluorescein: Not more than 20 mg/kg.
Inorganic iodides: Not more than 0.1% calculated as sodium iodide.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Erythrosine [2].

Assay: Not less than 87% total colouring matters calculated.
Subsidiary colouring matters (except fluorescein): Not more than 4.0%.
Fluorescein: Not more than 20 mg/kg.
Inorganic iodides: Not more than 0.1% calculated as sodium iodide.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the
specification), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead, Zinc and Heavy metals.

**Exposure:** The permitted uses of erythrosine are restricted to cocktail cherries and candied cherries 200 mg/kg and Bigarreaux cherries in syrup and in cocktails 150 mg/kg. The ADI of 0.1 mg/kg bw can be reached by consuming 30 g cocktail cherries with the permitted level.

In the EU monitoring system erythrosine was examined at tier 2 level. The calculated intake by adults and the whole population is reported as 0% of ADI. The calculated intake by young children is reported by one member state as 0%. The investigators concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** Erythrosine has been evaluated many times and in 1987 an ADI of 0.1 mg/kg bw was established [3]. It was based on a no-effect level of endocrine/hormonal effects on 60 mg/day equivalent to 1 mg/kg bw/day obtained in a 14-day study in human volunteers. The applied safety-factor was 10. In 1990 at its 75th meeting, when addressing the results of new mutagenicity studies, the Committee noted that the available adequate and well reported studies on oral *in vivo* activity are negative, although clastogenicity has been demonstrated by the i.p. route. The Committee reaffirmed their view that the weight of the evidence showed that the tumorigenic effects of erythrosine are secondary to its effects on thyroid function and not related to any genotoxic activity. The ADI of 0.1 mg/kg bw was maintained. No additional report was issued.

**JECFA status:** The present JECFA ADI of 0.1 mg/kg bw was allocated in 1990 [4]. The basis was a no-observed-effect level in humans of 60 mg/person/day for 14 days (equivalent to 1 mg/kg bw/day) [5]. A small statistical significant increase in thyrotropin responsiveness to thyrotropin releasing hormone was seen at a dose of 200 mg daily. The safety-factor was 10 [6]. The observed changes in rat thyroid hormone metabolism and regulation are consistent with the hypothesis that erythrosine inhibits hepatic conversion of circulating T₄ to T₃ and that the resulting decrease in the T₃ concentration stimulates the serial release of thyrotropin-releasing hormone from hypothalamus and then thyrotropin from the pituitary. The sustained levels of thyrotropin produce hyperstimulation of the thyroid, which may be associated with the tumourigenic effects noticed in the studies [6]

**Background data:**

**Subacute/subchronic toxicity:** No significant and consistent toxic effects. Overall, there are indications on an increased thyroid weight without pathological changes.

SCF reported that short-term studies were available in rats and pigs. No significant toxic effects were seen. No results were specified [7].

Several studies were available to JECFA in rat, gerbil, dog and pig. Administration of 0, 0.25, 0.5, 1, 2% in the diet to rats had no effect on biological parameters, haematology or blood and urine analyses. Dose-related caecal enlargement, pigment disposition (protein-bound erythrosine) in renal tubules, total PBI, protein-bound erythrosine, non-protein bound iodine were noticed [8]. When rats were dosed with 2% in diet an increased absolute and relative thyroid weight at 2% was seen. T₄ was unchanged and ^13¹I uptake reduced [8]. In a study, 0,
0.25, 0.5, 1, or 2% was given to rats via diet. No effect on biological parameters, haematology or serum parameters or renal function test. T₄ was unchanged. No thyroid effects were reported [8]. Gerbils were administered 0, 200, 750, 900, or 1200 mg/kg in the diet for 19 months. An elevated PBI due to erythrosine interference with analysis was noticed. No adverse effects were reported [8]. Dogs were given 0, 0.5, 1.0, or 2.0% in diet for 2 years. No adverse effects were noticed [8]. Pigs were dosed with 0, 167, 500, or 1500 mg/kg bw/day for 14 weeks. A decreased serum T₄ level was reported. Dose-related increase in PBI, non-protein-bound iodine, and protein-bound erythrosine were seen. Dose-related increased thyroid weight without pathological changes was demonstrated [8].

**Special studies on thyroid function:**
In a 60-days feeding study of 0, 0.25, or 4% in diet to rats the pituitary weight was reduced in males at 4%. No gross pathological changes in thyroid and pituitaries were reported. Rapid and sustained onset of hormonal changes were seen (Increased serum levels of TSH at 0.25 and 4%, thyroxine, T₄, at 0.25 and 4%, and of 3,3’,5’-triiodothyronine, rT₃, at 0.25 and 4%. Decreased serum level of 3,5,3’-triiodothyronine, T₃, after ingestion of 4%) [6].

**Genotoxicity:** In 1990 at the 75th SCF-meeting, the Committee noticed that the available adequate and well reported studies on oral *in vivo* activity were negative, although clastogenicity has been demonstrated by the i.p. route. Conflicting results exist in *in vitro* and *in vivo* studies. However, at the 75th SCF meeting, the Committee reaffirmed its view that the weight of the evidence showed that the tumorigenic effects of erythrosine are secondary to its effects on thyroid function and not related to genotoxic activity.

*In vitro:* Studies were available to SCF. No genotoxic activity was demonstrated. No results were specified. Earlier studies based mainly on bacterial assays were largely negative. Newer mutagenicity studies are available showing negative results in assays for point mutations in bacteria, and for gene mutations in cultured mammalian cells [3].

To JECFA studies were available in E. coli. A very slight but statistically-significant mutagenic activity was shown to be due to the xanthene molecule itself [8]. Other studies show no mutagenic activity [8]. Studies are also available in 5 strains of S. typhimurium. No mutagenic effect was demonstrated. [8]. In a study in rat hepatocytes no induction of DNA repair was noticed [6]. In the mouse lymphoma assay (2 studies) positive response was noticed both with and without addition of S9 [8]. Additional studies in Chinese hamster lung cells, in the mouse micronucleus test, and chromosome aberration in hamster cells were not possible to evaluate [6].

Several *in vitro* studies have been performed. One study suggests that erythrosine, which exhibits non-mutagenicity in Ames test, can interact with DNA repair enzymes and/or with DNA [9]. One other study showed that erythrosine was mutagenic in the Bacillus subtilis multigene sporulation assay [9]. The non-mutagenicity was demonstrated to V79 cells at concentrations of 100, 200, or 300 µg/ml [10].

*In vivo:* Negative results were also obtained in tests for clastogenic effects *in vivo* [3]. In 1990 at its 75th SCF-meeting, the Committee reported that the available adequate and well reported studies on oral *in vivo* activity are negative, although clastogenicity has been demonstrated by the i.p. route.
No cell transformation was noticed in rat embryo cells in vitro or in vivo [8]. In rat hepatocytes no induction of DNA repair was reported [6]. In the host-mediated assay in mouse (2 studies) the colour was inactive [8].

One in vivo study demonstrated that erythrosine was not genotoxic [11].

**Chronic toxicity/Carcinogenicity:** Several studies have shown that erythrosine has an oncogenic effect in the thyroid gland of several species of laboratory animals. At the present stage of knowledge this effect is shown to be a secondary effect to affected thyroid and pituitary function and not related to any genotoxic activity. It is not possible to establish a no-effect level for the tumourigenic effect in the rat.

SCF notes that several long-term studies are available in mice, rats, gerbils, and dogs. However, the studies in gerbils and dogs cannot be evaluated as essential information is missing. No other data or results were specified [7]. New long-term studies were available to SCF in 1988 showing increased incidence of thyroid follicular adenomas in male rats and some equivocal evidence of increased incidence of thyroid carcinoma [3]. The effect of erythrosine on the thyroid and pituitary function show a generally consistent picture: Erythrosine-inhibited conversion of T4 to T3 reduce the plasma and tissue levels of T3, which reduce the inhibitory effect of T3 on TSH secretion. The increased TSH concentration stimulates the thyroid leading to hyper trophy, adenoma and possibly malignant changes [3].

JECFA notes four studies available in mice. No consistent adverse effect including tumour induction was seen [8]. Numerous studies are available in rats. Some show no adverse effects including tumour induction [8]. Elevated PBI due to interference on the analysis has been demonstrated without any effect on T4 [8].

In a study by Brewer quoted by JECFA rats were given 0, 0.5 or 1% in diet for 30 months including in utero exposure. No effect was demonstrated on physical performance, behaviour, mortality, food consumption, haematology, clinical chemistry, urinanalysis, or ophthalmological findings. Statistically-significant increased incidence of benign thyroid tumours (6/68 at highest dose (1%) versus 0/140 for the control group). No increased incidence in malignant tumours was demonstrated [6].

In another study [6] rats were administered 0 or 4% in diet for approximately 29 months including in utero exposure. No effects on physical performance, behaviour, mortality, food consumption, haematology, clinical chemistry, urinanalysis, or ophthalmological findings were seen. The mean absolute and relative thyroid weight was twice that of controls. Thyroid hyperplasia significantly increased in treated males. A statistically-significant increased incidence of follicular adenoma of the thyroid in treated males (16/68 versus 0/69 for the control group). No increased incidence in malignant tumours was demonstrated.

Rats were fed 0, 1.2, or 2.5% in diet for 18 months. Only histopathological parameters were reported. No adverse effects or pathological changes in the thyroid gland were seen [8]. In a special study, rats were fed 0, 80 µg NaI, 4% purified erythrosine, 80 µg NaI + 4% purified erythrosine, 160 µg NaI + 4% purified erythrosine, or 4% commercial erythrosine. Commercial and purified erythrosine both produced hyperthyroidism, elevated TSH and T4, and decreased T3. Changes in
clinical parameters, body weight, and food consumption were indicative of hyperthyroidism. No effect of Nal was reported [8].

Borzelleca and co-authors [12;13] have performed thorough statistical analyses of the studies by Brewer mentioned above [6]. If the adenomas and carcinoma were treated statistically separate the authors conclude that erythrosine at a level of 4% in diet for 128 weeks induced an increased incidence of thyroid follicular cell adenomas in male rats 15/69 compared to 1/69 in controls. The incidence of thyroid cell carcinomas (3/69) was not statistically significantly different from controls (2/69). The numerical increase in adenomas was not statistical significant in females. If the adenomas and carcinoma were treated statistically together, an increased incidence of combined adenomas and carcinoma in male rats fed 0.1, 0.5, 1.0, and 4% for 122 weeks and in females fed 1% was revealed were revealed. It was not possible to establish a no-effect level for the tumourigenic effect in the rat [6]. The Committee considered that the occurrence of thyroid tumours in rats was most likely secondary to hormonal effects and concluded that it would be possible to establish an ADI from the no-effect level for effects on thyroid function in man [6].

Studies are also available in gerbils. When fed 0.1, 2, or 4% in diet for 105 weeks [8] a dose-related decreased body-weight gain was seen. Inconsistent isolated statistically-significant changes in haematocrit, haemoglobin and leucocyte and reticulocyte counts were reported. Statistically-significant decreased relative weight of heart, liver, and spleen at 2% and 4% was seen. A dose-related enlargement of follicles and in some cases focal hyperplasia were observed in the thyroids. Histopathology did not reveal any treatment-related effects [8]. When dosed by gavage with doses of 0, 200, 750, or 900 mg/kg twice weekly for 97 weeks no treatment related adverse effects on clinical performance, mortality, body-weight gain, haematology, organ weight, gross pathology, or histopathology were seen.

Some special studies in rats on thyroid morphology and function: Rats were fed 0 or 4% in diet [8]. Hypertrophy of follicular cells with increased development of synthetic and secretory organelles (rough endoplasmatic reticulum, Golgi apparatuses, long microvilli) were seen which is consistent with elevated serum T4.

Rats were fed 0, 0.25, 0.5, or 4% for 7 months [8]. Thyroid follicular cells from rats fed erythrosine displayed ultra-structural features (i.e. hypertrophy of follicular cells with increased development of secretory organelles) of a dose-dependent stimulation of synthetic and secretory activity, most marked in rats fed 4%. The changes were consistent with a response to long-standing TSH stimulation. The ultrastructural changes were reversible by administration of T3. In a 7-months feeding study in rats given 0, 0.25, 0.50, 1.0, 2.0, or 4.0% in diet [8] after 6 months one-third of the animals in each group received 15 µg T3/kg bw/day sc, another third received saline, and the last subgroup had no injections. There was no effect on serum TSH, whereas T4 was elevated in the 4% group. Serum T3 decreased significantly with time, the 4% group showed the decrease in T3. RT3 increased 7-fold in the 4% group.

In in vitro liver homogenate from 4% fed animals, the metabolism of T4 was reduced. No effect on pituitary T4 in vitro metabolism [8].
**Relevant studies found in the data-base search:** Two studies review the mechanisms of chemical induced injury of thyroid gland [14;15].

In another study, rats were fed 0, 0.5, 1.0, or 4.0% in diet for 30 months. The study suggests that erythrosine increases the pituitary’s conversion of TSH to TRH by altering thyrotroph cell conversion of T₄ to T₃. Chronic ingestion may promote thyroid tumour formation in rats via chronic stimulation of the thyroid by TSH [16].

Effects on TSH of oral doses to humans of erythrosine have been studied. No abstract or results were available [17].

Erythrosine given at 4% in diet for 19 weeks showed promoting effects on thyroid tumours [18].

It is not clear to see whether these studies are included among the unpublished studies referred to by JECFA. They seem not to reveal important new information and they are included for information.

**Reproduction toxicity:** No consistent effects on reproduction or parameters for teratogenicity in the studies presented to the Committees [7;8].

Rats were administered 0, 0.25, 1.0, or 4% in diet for 3 consecutive generations [8]. No consistent compound-related effects on reproductive performance of male and females and on pub survival at any dose level in any generation were reported.

In two studies, rats were administered 0, 0.25, 0.5, or 1.0% in diet [8]. This revealed increased pre-weaning offspring mortality at 0.5 and 1.0% in diet in the first experiment, but not in the second. Litter size was not affected. No consistent effect on behaviour was revealed. No psychotoxic effect on developing rats was reported.

One study indicates that erythrosine at po doses of 68 or 136 mg/kg bw/day for 21 days to male mice may affect testicular function (spermatogenesis, sperm abnormalities) and reproductive performance [19].

In a study doses (by gavage) of 0, 15, 30, 100, 200, 400, or 800 mg/kg on day 0-19 of gestation of rats showed that erythrosine was neither foetotoxic nor teratogenic [20].

Dosing rats with 0, 0.05, 0.1, 0.2, or 0.4% in drinking water (0, 64, 121, 248, or 472 mg/kg/day) showed that erythrosine was neither foetotoxic nor teratogenic [20].

**Allergy/Intolerance:** SCF notes that hypersensitivity reactions are reported in certain individuals. No details were specified [21].

Erythrosine has been reported to induce hyperactivity in children, but this has not been sufficiently documented. *In vitro* studies have shown that high concentrations of erythrosine can inhibit brain tissue ATPases and active reuptake of neurotransmitters. This has been postulated to be the underlying mechanisms for hyperactivity. However, erythrosine has not been documented to penetrate the blood brain barrier to give rise to significant brain concentrations. So also taking into consideration the very low level of exposure this effect on behaviour seems to be of only academic interest.

**Effect in humans:** SCF notes that available clinical studies have shown that erythrosine has minimal effects in humans at a dose of 200 mg daily over 14 days, while a dose of 60 mg daily equivalent to a dose of 1 mg/kg bw/day was without effect [3].
JECFA quotes several studies. Oral dosing with 1.68 mg erythrosine/day/person of 6 persons for 10 days did not affect plasma inorganic iodine, urinary iodine, thyroid function, thyroid radioiodine uptake, or levels of thyroxine (T₄) or PBI [8]. When administered 0, 5, 10, or 25 mg/day for 3 weeks the levels of total serum iodine and PBI increased. Serum concentrations of T₄, T₃, TSH, erythrosine, and urinary iodine erythrosine excretion were unchanged throughout the 3 weeks [8]. After a single oral dose of 75-80 mg ¹³¹I-labelled erythrosine [8] the faecal ¹³¹I excretion was 80-100% of the dose. Urinary 48 hr excretion was less than 0.38%. The whole body half-life of distributed erythrosine was 8.4±2.1 days. No effects on thyroid hormone levels were revealed. Normal euthyroid humans received 0, 250, 500, or 1500 µg iodine daily for 14 days [22]. The 1500 µg/day dose decreased serum T₄ and T₃ followed by a small compensatory increase in the TSH concentration and the TSH response to TRH. However, all values were within the normal range. No effect of 250 or 500 µg I₂ was seen. In conclusion: it appeared that inorganic iodide per se was the causative agent [22].

Normal men were given 0, 20, 60, or 200 mg/day for 14 days. No effect was seen on serum T₃, T₄, rT₃ levels or T₃-uptake. TSH in serum increased from day 1 to 15 at 200 mg/day and a dose-related increase in total iodine, PBI, and iodine excretion was demonstrated. The no-observed-effect level was 60 mg per person per day for 14 days (equivalent to 1 mg/kg bw/day) [5] quoted in [22]. A small statistical significant increase in thyrotropin responsiveness to thyrotropin releasing hormone was seen at a dose of 200 mg daily. This study was used by SCF and JECFA to establish the ADI.

Other: Animal and human studies are available on hormonal effects [3].

Biochemical aspects: Metabolic studies are available. In vitro studies show that erythrosine inhibits the conversion of T₄ to T₃ in liver. No other data are reported. No results were specified [7].

No detectable amounts of iodine were liberated i.e. erythrosine seems to be metabolically stable in rats [8]. It is poorly absorbed from the g-i-tract of rat and man and predominantly excreted by faeces [22]. After intravenous injection 55% of the dose was found in bile and 1.3% in urine [8]. Erythrosine may inhibit iodine uptake in thyroids of rats [8]. After oral dosing of rats blood and plasma levels peaked after 1 h, while levels in liver and kidneys peaked after 4-12 h. Levels of ¹⁴C and ¹²⁵I in thyroids were at trace levels. The thyroid ¹²⁵I level was that low that it was impossible to conclude whether it resulted from iodine impurities or deiodination. No ¹⁴C or ¹²⁵I was detectable in brain or pituitary [8].

Many records found in the data-base search concern the relation between erythrosine (an ATPase inhibitor) and the structure and function of different ATPases, Na⁺/K⁺, Ca²⁺, H⁺-ATPases. These special aspects will not be regarded in this re-evaluation.

Erythrosine 100% inhibited the respiration (State III respiration, uncoupled, supported by α-ketogluterate or succinate) in mitochondria isolated from rat liver and kidney at a concentration of 0.1 mg/mitochondrial protein [23].
Neurophysiological studies: Studies are available. The significance of in vitro studies to man is not clear. No results were specified [7].

It has previously been proposed that erythrosine was a neurotoxicant because it interrupted neurotransmitter reuptake in vitro. In the studies by Mailman & Lewis [24], data suggested that this inhibition was an artefact of the methodology.

Conclusion: For many years there has been an intense debate about the tumourigenic effects of erythrosine in the thyroid gland. At the present stage of knowledge, the weight of evidence shows that the tumourigenic effects are secondary to effects on thyroid and pituitary functions and not related to genotoxic activity.

Besides the various studies on the tumourigenic effect the toxicological data reported by SCF are comprehensive and include what would normally be required for an ADI to be set for a food additive. The use as a food additive is very limited. No need for a re-evaluation

Erythrosine as defined by the specifications is covered by the toxicological evaluation.

References:


Red 2G

**E number:** E 128

**Recommendation:** Although exposure is very low, an update of the SCF evaluation is desirable.

**Chemical name/synonyms:** Disodium 8-acetamido-1-hydroxy-2-phenylazo-naphthalene-3,6-disulfonate/ CI Acid Red I; CI Food Red 10; Ext. D&C Red No. 11; Azogeranine.

**Chemical formula:** $\text{C}_{18}\text{H}_{13}\text{N}_3\text{Na}_2\text{O}_8\text{S}_2$

**Class:** Monoazo.

**EINECS number:** 223-098-9

**CAS number:** 3734-67-6

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Red 2G is manufactured by chemical synthesis.

**Definition:** Red 2G consists essentially of disodium 8-acetamido-1-hydroxy-2-phenylazo-naphthalene-3,6-disulfonate and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Red 2G is described as the sodium salt. The calcium and the potassium salt are also permitted.

**EC specifications:** E 128 Red 2G [1].

- Assay: Not less than 80% total colouring matters calculated as the sodium salt.
- Subsidiary colouring matters: Not more than 2.0%.
- In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulphonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Red 2G [2].

- Assay: Not less than 80% total colouring matters.
- Subsidiary colouring matters: Not more than 2%.
- In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted uses limited to breakfast sausages and certain burger-meat up to 20 mg/kg. The ADI can be reached by consuming 300 g of product with maximum amount.
In the EU monitoring system Red 2G was examined at tier 2 and the calculated intake by adults and the whole population is reported in the range of 2 - 20% of ADI. The calculated intake by young children is reported by one member state as 40%. The investigators concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** An ADI of 0.1 mg/kg bw was established by SCF in 1975 with the restriction that Red 2G should not be used under conditions in which significant hydrolysis to Red 10B occurs (in acid solution). The basis was not specified [3].

**JECFA status:** The present JECFA ADI of 0.1 mg/kg bw was allocated in 1981 [4]. The ADI was based on levels causing no toxicological effect in rat (0.016% in the diet, equivalent to 8 mg/kg/day for 2 years and a safety factor of and rounding up).

There has been some debate and several specific studies have been performed in relation to the toxic effects of Red 2G on erythropoiesis. In the long-term studies used by JECFA, NEL for these effects was established in mouse and rat.

**Background data:**

**Subacute/subchronic toxicity:** Following studies were reviewed by JECFA [5]: Administration to mice of 0, 0.01, 0.1, 1.0, or 2.0% in the diet for 26, 55, or 96 days induced no effect on biological parameters. Heinz bodies and hemosiderin increased in spleen in a dose- and time-related manner. Another oral study in mice dosed for 6 weeks of 0, 0.02, 0.1, 0.5, or 1.0%, showed induction of Heinz bodies, methaemoglobinemia, splenic enlargement, and accelerated splenic macrophages. Oral administration to rats of 0, 0.05, 0.1, 0.5, 1.0, or 2% in the diet for 3 weeks or 2 months reduced growth, food consumption, macrocytosis, reticulocytosis, and polychromas. Heinz bodies were present and increased erythropoiesis, splenomegaly, kidney weight, haemosiderin in the Kupffer cells were noticed. Rats administered 0, 0.1, or 0.5% in drinking water for 100 days showed Heinz bodies after 10 days. Spleen enlargement, increased haemosiderin in Kupffer cells, and increased erythropoietic activity was demonstrated. Oral administration to rats of 100x and 600x the assumed average daily dietary intake increased erythropoiesis, and splenic red pulp haemosiderin.

**Genotoxicity:** In microbial assays, red 2G was shown to possess weak mutagenic activity at very high concentrations (10 mg/ml), including DNA damage and base-substitution mutations. There was no activity at 1 mg/ml. One study in bacteria suggest that Red 2G induces repairable DNA damage and base substitution mutation but only in the presence of rat liver microsomal activation [5].

The genotoxicity of red 2G was studied in another investigation, [6]. The genotoxicity of urine and faecal extracts from rats treated orally with red 2G (800 mg/kg bw) has been studied in S. typhimurium TA 98 and TA100 with/without activation. No mutagenic activity was observed [7]. Other genotoxicity studies have been performed in S. typhimurium [6], and in E. coli [8], in the drosophila somatic eye mutation test [9], in CHO cells [10], and in other cell cultures [11].
**Chronic toxicity/Carcinogenicity:** One study is available in mice, two in rats. When administered 0, 0.005, 0.025, 0.125, or 0.625% in diet to mice for 20 months splenic enlargement (0.125 and 0.625%) and accelerated red blood cell formation were revealed with NEL corresponding to 0.025%. No evidence for carcinogenicity [5]. Rats were administered 0, 0.004, 0.016, 0.064, or 0.16% in diet for 2 years. At 0.064 and 0.16% splenic enlargement including necrosis of splenic elastica were seen, NEL corresponding to 0.016%. No evidence for carcinogenicity was revealed [5]. Rats were administered 0 or 0.5% for 2 years. Enlargement and darkening of the spleen were reported. Accelerated splenic erythropoiesis, increased splenic haemosiderin and degeneration of splenic elastica were revealed. No effect on liver or kidneys. No results on carcinogenicity was reported [5].

**Reproduction toxicity:** Studies in rats are available to JECFA. No effect on reproduction was revealed. There was no teratogenic or foeto-toxic activity. Specifically, there was no effect on foetal spleen [5].

**Other:** **Biochemical aspects:** Red 2G is substantially reduced by the gut microflora prior to absorption. There seems to be no binding to serum proteins [5]. Six hours after a single iv injection, 64% was recovered in bile. After oral administration the excretion in urine was 61.8% / 71.5% (male/female) of the dose. Metabolites in urine are identified: 42.2% / 56.4% (48 h) was p-aminophenol, 9.2% / 2% (48 h) aniline, and 3% / 2.6% (24 h) was unreduced dye. In faeces 6.3% / 8.6% (48 h) was p-aminophenol, 1.0% / 0.3% (48 h) aniline, and 0.1% / 1.6 (24 h) unreduced dye [5]. Other studies show that 48.2% of the sulphur derived from red 2G was excreted by faeces after oral administration of rats [5].

48 h after oral administration of rabbits, the following metabolites were found: total p-aminophenol (46%), p-aminophenylglucuronide (37%), aniline (0.6%), and o-aminophenol (9%) [25]. Some in vitro studies are performed. After incubation of rat caecum content with a solution of Red 2G at 37 °C, two metabolites were identified: 2-amino-8-acetamido-1-naphtho-3,6-disulfonic acid and aniline [5]. After of rat liver homogenate two metabolites were identified: 2-amino-8-acetamido-1-naphtho-3,6-disulfonic acid and aniline [5].

Azoreduction by intestinal microflora has been studied in Red 2G [12].

Special studies on aniline have been performed in rats, dog and man:

Rats were administered by iv injection or orally. The no-effect dose in blood (parameter not specified) was 20 mg/kg bw (oral) or 10 mg/kg bw (iv) [5]. After oral administration of aniline, p-aminophenol, or phenylhydroxylamine to rats aniline and phenylhydroxylamine induced methaemoglobinemia, Heinz bodies, and splenic enlargement. The no-effect dose of aniline was 20 mg/kg bw [5].

When dosed to dogs, phenylhydroxylamine (an N-hydroxylated aniline metabolite) increased the methaemoglobin concentration [5].

Oral administration of aniline to man for 5 days induced no effects on urine or blood parameters including blood haemoglobin, methaemoglobin and Heinz bodies [5]. Methaemoglobin and Heinz body formation have been reported in three cases of acute aniline poisoning of man [5].
**Special studies on haemotoxicity and haemopoiesis:** Oral administration of red 2G for 1-1.5 g/Kg/day for 75 day to rats induced Heinz body formation. Pronounced reticulocytosis and splenomegaly were noticed [5]. In another study, the effect of oral administration for 13 days of aniline, p-aminophenol, or phenylhydroxylamine at a level of 0.1% in the diet have been studied in rats. The spleen weight was increased by aniline and henzylhydroxylamine [5].

In two studies, phenylhydroxylamine administered orally to rats increased Heinz bodies (2 studies), spleen weight (1 study), and methaemoglobin (1 study) [5].

Oral administration of Red 2G (0.5% in diet) or aniline (0.093% in diet) for 19 days both increased spleen weight and accelerated erythropoiesis and haemosiderin content. [5].

Red 2G (0.5% in diet) for 2 weeks increased methaemoglobinemia, Heinz bodies, reticulocytosis, spleen weight, erythropoiesis (in liver and spleen) and decreased haemoglobin, PCV, and red cell count (1 study) [5].

In a teratogenicity study, red 2G in diet (0, 0.004, 0.02, or 0.2%) increased spleen weight (highest dose) and erythropoietic activity (highest dose) in dams; no effects on foetal spleen were observed [5].

**Conclusion:** There has been a debate and several specific studies have been performed in relation to the toxic effects of red 2G on erythropoiesis. In the long-term studies used by JECFA, NOEL for these effects was established in mouse (0.025% in diet) and rat (0.016% in diet, equivalent to 8 mg/kg bw/day).

The evaluation performed by SCF is old and poorly reported. The use is very restricted and exposure must therefore be expected to be very low. However, considering the results seen in some studies, an update of the SCF evaluation, including all existing data is desirable.

**References:**


ALLURA RED AC

E number: E 129

Recommendation: The existing data do not suggest a need for changing the present ADI. However, new studies have been published, which should be considered and included in an updated evaluation.

Chemical name/synonyms: Disodium 2-hydroxy-1-(2-methoxy-5-methyl-4-sulfonatophenylazo) naphthalene-6-sulfonate/ CI Food Red 17; FD & C No 40.

Chemical formula: $C_{18}H_{14}N_2Na_2O_8S_2$

Class: Monoazo.

EINECS number: 247-368-0

CAS number: 25956-17-6

Functional Class: Colour.

Specification:

Manufacture: Allura Red AC is manufactured by chemical synthesis.

Definition: Allura Red AC consists essentially of disodium 2-hydroxy-1-(2-methoxy-5-methyl-4-sulfonatophenylazo) naphthalene-6-sulfonate and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Allura Red AC is described as the sodium salt. The calcium and the potassium salts are also permitted.

EC specifications: E 129 Allura Red AC [1].

Assay: Not less than 85% total colouring matters calculated as the sodium salt.

Subsidiary colouring matters: Not more than 3.0%.

In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulphonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Allura Red AC [2].

Assay: Not less than 85% total colouring matters.

Subsidiary colouring matters: Not more than 3%.

In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulphonated primary aromatic amines), Loss on drying, chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.
**Exposure:** Permitted in all “colourable” foods and in a few of those with only limited number of permitted colours. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system Allura Red AC was examined at tier 1 level. As the calculation for children suggested the possibility for exceeding the ADI the EU monitoring system examined the intake at tier 2 level. The calculated intake by young children was thus reported by one member state as 55% of the ADI and it was concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**
**SCF status:** An ADI of 7 mg/kg bw was established by SCF in 1987 [3]. The basis was not specified but SCF agreed with the JECFA evaluation from 1981.

**JECFA status:** The present JECFA ADI of 7 mg/kg bw was allocated in 1981 [4] replacing the temporary ADI allocated in 1980. The basis was the level causing no toxicological effect in rats on 1.39% in the diet equivalent to 695 mg/kg bw and a safety-factor of 100 [5;6].

**Background data:**
**Subacute/subchronic toxicity:** Studies are available in rats, dogs, and pigs. Rats were administered the colour in the diet for 6 weeks. No effects were revealed on biological parameters, on gross pathological and microscopic pathology, on blood or urine analyses. No Heinz body formation [5]. Oral administration was performed in two studies in dogs (duration not specified in one study, 104 weeks in the other study). No effects were reported on biological parameters, on gross pathological and microscopic pathology, on haematology or clinical chemistry [5]. Pigs were dosed by gavage for 75 days. No effect on clinical, haematological, or pathological parameters [5].

**Genotoxicity:** *In vitro:* Studies are available in yeast and *S. typhimurium*. No genotoxic activity was reported [5].

*In vivo:* Studies are available in Drosophila melanogaster and mice. No genotoxic potential [5].

**Chronic toxicity/Carcinogenicity:** No evidence of carcinogenicity.

Five unpublished studies were available to JECFA and are reported [7]. These included studies in mouse (3 studies) and rats (2 studies). Mice were administered dermally twice weekly for 20 months (1 study) or orally in two studies a level of 0, 0.37, 1.39, or 5.19% in diet. No increase in tumour incidence. No adverse effects were observed [5]. In a study in mice published in 1991, but presumably identical to one of the studies reported by JECFA [5], the no-observable-adverse effect-levels in male and female mice was 7300 and 8300 mg/kg/day, respectively [7]. In two studies in rats animals were administered 0, 0.37, 1.39, or 5.19% in diet (1 study: 92 weeks; 2nd study 118/121 weeks, male/females also including perinatal exposure). These studies revealed moderate growth depression at 5.19%. No other consistent effects on biological or clinical parameters, appearance, behaviour, gross- or histopathology. No Heinz body formation. In one study an increased incidence of renal calculi and focal epithelial proliferation in the high-dose rats were noticed [6]. Study 2 reported a no-adverse-effect-levels in male on 5,19% corresponding to
2829 mg/kg/day and 1.39% corresponding to 901 mg/kg/day in females where a reduced body weight was seen at the highest dose [8].

**Reproduction toxicity:** Rats were fed 0, 0.37, 1.39, or 5.19% in diet. No consistent reproductive effects or pathological changes. No evidence of teratogenic or embryotoxic effects. In another study rats were fed 0, 15, 30, 100, or 200 mg/kg by gavage. No effect on early or late death, resorptions per litter, pre-implantation loss, number of foetuses per litter, or average foetus weight. In a third study, rabbits were administered 0, 200, or 700 mg/kg by gavage. No adverse effects on reproductive or teratogenic parameters were revealed [5].

A reproductive and neurobehavioral study in mice given Allura Red in the diet at 0, 0.42, 0.84, or 1.68% from 5 weeks of age of the F0 generation to 9 weeks of age of the F1 generation indicates that there might be some effects on litter size, weight, sex ratio, and behaviour [9].

Developmental toxicity was studied in rats. Animals were fed the colour (0, 2.5, 5.0, or 10.0% in diet) 2 weeks before breeding, during gestation, lactation and thereafter. Parents and offspring were examined. There was reduced reproductive success, parental and offspring weight, brain weight, survival, and female vaginal patency development. There was decreased running wheel activity [10]. The study was considered by SCF, which noted that the effects were only seen in doses much higher than the doses on which the ADI was derived [3].

Other teratogenic studies reported no adverse effects on reproductive or teratological parameters: Rats were given Allura Red in the drinking water throughout gestation at levels of 0, 0.2, 0.4, or 0.7%, corresponding to 273.6, 545.7, or 939.3 mg/kg/day in the females. Sacrifice at gestation day 20. No adverse reproductive or teratogenic effects [11].

Other teratogenic studies reported no adverse effects on reproductive or teratological parameters: Rats were given Allura Red in the drinking water throughout gestation at levels of 0, 0.2, 0.4, or 0.7%, corresponding to 273.6, 545.7, or 939.3 mg/kg/day in the females. Sacrifice at gestation day 20. No adverse reproductive or teratogenic effects [11].

Rats were given 0, 30, 75, 150, 300, 600, or 1000 mg/kg bw/day by gavage on days 0-19 of gestation. No adverse reproductive or teratogenic effects [12].

**Allergy/Intolerance:** No skin irritation, contact dermatitis, photosensitisation, or sensitisation. However, in a challenge study, a positive reaction was reported in 15% (8) of 52 patients suffering from urticaria or angioedema [5].

Chronic cutaneous small vessel vasculitis (LCV) is proposed to be related to circulating immune complexes. One patient is reported with chronic cutaneous LCV which were presumed to be caused by some dyes in the capsules. Allura Red and sunset yellow are mentioned in that connection [13].

**Other:** Biochemical aspects: A number of studies were available to SCF and JECFA. It appears that negligible/limited quantities of intact Allura Red are absorbed. There are indications that Allura Red might adhere to the intestinal wall. After oral administration of rats, 0.1% and 29% of the dose was excreted by urine and faeces, respectively. Following oral administration of rat and dog faeces was the major route of excretion after 72 hours (rat: 76-92% of the dose; dog: 92-95% of the dose). Rats excreted 5.7-19.8% of the dose and dogs 2.7-3.6% via urine. It has been postulated that azo-reduction by gut flora of the dye will yield the two parent compounds. Cresidesulfonic acid was the major urinary and faecal metabolite in rat and dog, whereas the parent compound was not measurable urine, but was present in faeces [5].

Azo-reduction of Allura Red by intestinal microflora and mutagenicity were studied but no details are given in the abstract [14].
Conclusion: Allura Red AC has been thoroughly studied and the ADI seems well founded. However, the studies by Tanaka [9] and Vorhees et al. [10] should be thoroughly considered in a coming re-evaluation.

Allura Red AC as defined by the specifications is covered by the toxicological evaluation.

References:


**PATENT BLUE V**

**E number:** E 131

**Recommendation:** The basis for the ADI as allocated by SCF in 1983 should be investigated and all existing data re-evaluated and fully reported, especially as JECFA has not been able to allocate an ADI.

**Chemical name/synonyms:** The calcium or sodium compound of (4-(α-(4-diethylaminophenyl)-5-hydroxy-2,4-disulfophenyl-methylidene) 2,5-cyclohexadien-1-ylidene) diethyl-ammonium hydroxide inner salt/ CI Acid Blue 1; CI Acid Blue 3; CI Food Blue 5; Patent blue 5.

**Chemical formula:**
- Calcium compound: \( \text{C}_{27}\text{H}_{31}\text{N}_{2}\text{O}_{7}\text{S}_{2}\frac{1}{2}\text{Ca} \)
- Sodium compound: \( \text{C}_{27}\text{H}_{31}\text{N}_{2}\text{O}_{7}\text{S}_{2}\text{Na} \)

**Class:** Triarylmethane.

**EINECS number:** 222-573-8

**CAS number:** 3536-49-0

**Functional Class:** Colour.

**Specification:**
**Manufacture:** Patent Blue V is manufactured by chemical synthesis.

**Definition:** Patent Blue V consists essentially of the calcium or sodium compound of [4-(α-(4-diethylaminophenyl)-5-hydroxy-2,4-disulfophenyl-methylidene) 2,5-cyclohexadien-1-ylidene] diethyl-ammonium hydroxide inner salt and subsidiary colouring matters together with sodium chloride and/or sodium sulphate and/or calcium sulphate as the principal uncoloured components. The potassium salt is also permitted.

**EC specifications:** E 131 Patent Blue V [1].
- Assay: Not less than 85% total colouring matters calculated as the sodium salt.
- Subsidiary colouring matters: Not more than 2.0%.
- Leuco base: Not more than 4.0%.
- In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulphonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Patent Blue V [2].
- Assay: Not less than 85% total colouring matters.
- Subsidiary colouring matters: Not more than 2%.
Organic compounds other than colouring matters (defined in the specification): Not more than 0.5%.
Leuco base: Not more than 4.0%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Chromium and Heavy metals.

**Exposure:** Permitted in all “colourable” foods. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods. For a child of 20 kg 3 litres of soft drink with 100 mg/l or 600 g solid food with 500 mg/l must be consumed to reach the SCF ADI of 15 mg/kg bw. Still in the EU monitoring system the calculated intake for children suggested the possibility for exceeding the ADI. The colour was therefore examined at tier 2 level. The calculated intake by young children was thus reported by one member state as 13% of the ADI and it was concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**
**SCF status:** SCF last evaluated Patent Blue V in 1983 [3] when an ADI of 15 mg/kg bw was established on the basis of a no-adverse level corresponding to 1500 mg/kg bw/day in a long-term study in mice and a safety-factor of 100. This study, or any other, was not identified so further details of the basis for the evaluation cannot be derived.

**JECFA status:** In 1974 [4] JECFA withdrew the temporary ADI of 1 mg/kg bw allocated in 1969 based on the level causing no toxicological effect in rats on 1% (10,000 ppm) equivalent to 500 mg/kg bw/day and a safety factor of 500. The reason for withdrawing the ADI in 1974 was that the supplementary studies required in 1969 had not been submitted. When on the agenda again in 1982, these studies had still not been submitted, JECFA was again unable to allocate an ADI [5].

**BIBRA:** The toxicological data for Patent Blue V within classical endpoints including acute oral toxicity, reproduction, genotoxicity, and carcinogenicity, have been reviewed by BIBRA. No adverse effects. Specifically, no convincing evidence for carcinogenicity or genotoxic potential. Patients with a history of skin complaints or asthma suffered no recurrence of their symptoms following the ingestion of patent blue V [6].

**Background data:**
**Subacute/subchronic toxicity:** Data are available to SCF from investigations in cats and dogs. No details were presented [3].

JECFA quotes that there have been performed s.c. injections of rats twice weekly for 5 weeks. Only slight tissue reactions were produced. Following oral administration of cats daily (0, 0.25, 0.50 or 0.75 g) no abnormalities were found (duration not specified) [7].

**Genotoxicity:** *In vitro:* Data were available to SCF which quotes that there is no mutagenic effect, but no details were presented [3].
**In vivo:** The cytogenetic activity of colours given orally during 5 days to mice has been studied including patent blue V. The dose-range was 0.08-0.8 mg/kg. No dose induced any increase in the level of cells with chromosomal damage [8].

**Chronic toxicity/Carcinogenicity:** Data are available to SCF from investigations in mice and rats. No carcinogenic potential was observed. No details were presented [3]. The study in mice was used as the basis for the ADI. However, this study was not identified in the report. This study seems not to have been available to JECFA.

Two studies in rat were available to JECFA. In one study, the pure colour was administered via the diet. The level was 0 or 10,000 ppm (= 1%) life span (controls average life span was 22½ months; average life span of dosed rats was 24 months last animal died after 37½ months). The average intake was approx. 80 g. In a supplementary study, rats were given the same diet with 10,000 ppm (= 1%) and also once a week for 15-19 month a s.c. injection of 1 ml of a 1% aqueous solution. The average life span of the animals was 18 months and the last animal died at an age of 30 months. In both studies it was found that growth, blood composition, reproduction, and the three generations that were bred were not influenced. No histopathological findings. In the supplementary study, no sarcoma was found at the injection site [7].

**Reproduction toxicity:** Data from a 3-generation study were available to SCF. The studies showed no effects on reproductive function or any teratogenic potential but no details were presented [3].

In the two long-term studies in rats [7], reproduction and the three generations were not influenced.

**Effects in humans:** Patients with a history of skin complaints or asthma suffered no recurrence of their symptoms following the ingestion of patent blue V [6].

**Other:** Biochemical aspects:
Data are available to SCF. The colour is poorly absorbed in rat and dog. The nature of the metabolites was not determined after a single administration. No details were presented [3].

Following iv injection of rat and sc injection of man, rat and human urine have been reported to be coloured blue [7]. It appears that no information on metabolism were available to JECFA.

**Conclusion:** The toxicological data reported by SCF are sparse but seem to include what would normally be required for an ADI to be set for a food additive although an up-to-date metabolism study is desirable, if possible in man. The basis for the ADI allocated by SCF in 1983 should be revealed. It should be especially be clarified on what basis SCF was able to allocate an ADI when JECFA was not.

Long-term and reproduction studies did not reveal any significant toxicological effect, but a long-term study in a second species was required by JECFA as well as a short-term study in a non-rodent species. These studies have not been supplied. Consequently, the previous temporary ADI was withdrawn [7].
References:


4. [1974, NMRS 54/TRS 557-JECFA 18]

5. [1982, TRS 683-JECFA 26]


7. [1974, FAS 6/NMRS 54A-JECFA 18]

INDIGOTINE, INDIGO CARMINE

**E number:** E 132

**Recommendation:** The existing data do not suggest a need for changing the present ADI. However, considering the long time since the previous evaluation(s) and the number of new studies published since then, it is recommended to update the evaluation to include the new data.

**Chemical name/synonyms:** Disodium 3,3’-dioxo-2,2’-bi-indolylidene-5,5’-disulfonate/ CI Food Blue 1; CI Acid Blue 74; CI Natural Blue 2; FD&C Blue No. 2.

**Chemical formula:** $\text{C}_{16}\text{H}_8\text{N}_2\text{Na}_2\text{O}_8\text{S}_2$

**Class:** Indigoid

**EINECS number:** 212-728-8

**CAS number:** 860-22-0

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Indigotine is manufactured by chemical synthesis.

**Definition:** Indigotine consists essentially of a mixture of disodium 3,3’-dioxo-2,2’-bi-indolylidene-5,5’-disulfonate and disodium 3,3’-dioxo-2,2’-bi-indolylidene-5,7’-disulfonate and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Indigotine is described as the sodium salt. The calcium and the potassium salts are also permitted.

**EC specifications:** E 132 Indigotine [5].
Assay: Not less than 85% total colouring matters calculated as the sodium salt. Disodium 3,3’-dioxo-2,2’-bi-indolyldene-5,7’-disulfonate: not more than 18%.
Subsidiary colouring matters: Excluding disodium 3,3’-dioxo-2,2’-bi-indolylidene-5,7’-disulfonate: Not more than 1.0%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Indigotine [4].
Assay: Not less than 85% total colouring matters. Disodium 3,3’-dioxo-2,2’-bi-indolylidene-5,7’-disulfonate: not more than 18%.
Subsidiary colouring matters: Excluding disodium 3,3’-dioxo-2,2’-bi-indolylidene-5,7’-disulfonate: Not more than 1%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsubstituted primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury and Heavy metals.

**Exposure:** Permitted in all “colourable” foods. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system indigotine was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 2-13% of ADI, while the calculated intake by young children is reported by one member state as 40%. It was concluded that no further examination was needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** An ADI of 5 mg/kg bw was established by SCF in 1983 [3]. The basis was the no-adverse-effect level equivalent to 500 mg/kg bw/day set in a long-term study in rats and a safety-factor on 100. No details were given on this or other studies.

**JECFA status:** The present JECFA ADI of 5 mg/kg bw was allocated in 1974 [1]. The basis was the level causing no toxicological effect in rats (probably the study by Hansen et al., 1966 [17]) of 1% (equivalent to 500 mg/kg bw). The safety-factor was 100.

**BIBRA:** The toxicological data for Indigotine within classical endpoints including acute oral toxicity, reproduction, genotoxicity, and carcinogenicity, have been reviewed by BIBRA in 1996. No adverse effects. Specifically, no convincing evidence for carcinogenicity or genotoxic potential [7].

**Background data:**

**Subacute/subchronic toxicity:** Administration of 0, 1, or 2% in diet for 2 years to dogs induced no clinical signs, gross lesions or effects on microscopic pathology. Administration of 0, 150, 450, or 1350 mg/kg bw/day in diet to pigs for 90 days induced no adverse effect on growth, urine or serum analyses, or organ weight. No consistent histological findings [2]. Special studies have been performed on the major metabolite, isatin-5-sulfonic acid, which was fed to rats in diet (0, 0.25, 0.5, 1, or 2%) for 13 weeks. No effect on gross or histopathological parameters. The NEL was 2% [2].

Indigotine (and other synthetic colours) showed different effects in rats on body weight, clinical biochemical parameters, liver and kidney functions after 30-60 days of administration. These effects were not regarded as serious effects by the authors [6].

**Genotoxicity:** *In vitro* studies are available in *E. coli*. No mutagenic effect was observed [2].

A literature search revealed that several genotoxicity studies have been performed. However, no data were given in the abstracts [12;19;20;25].
SCF notes that a summary exists on *in vivo* mutagenicity studies. No data or details were presented [3].

The cytogenetic activity of Indigotine in doses of 1.4-14 mg/kg did not induce any increase in the level of cells with chromosomal damage [14]. Two studies by Giri indicated effects *in vivo* on bone marrow chromosomes of mice [16]. Furthermore, Indigotine and tartrazine have been studied in chromosomes of Allium cepa. An increased number of polyploid cells were reported [25].

**Chronic toxicity/Carcinogenicity:** Two studies are available in mice. After s.c. injection of 0 or 2.5 mg weekly for 104 weeks no tumours were induced. In another study administration of 0.2, 0.4, 0.8, or 1.6% in diet for 80 weeks induced a slight anaemia in animals fed 0.8 or 1.6%. No adverse effects were observed on biological, gross- or histopathological parameters. No tumour induction. The no-untoward-effect level was 0.4% corresponding to 550 mg/kg bw/day [2].

Four studies are available in rats. Rats were administered 0 or 1% in diet for 2 years. No adverse effects on growth, reproduction, survival, gross or microscopic pathology were observed. No tumour induction was noticed [24]. In a second study rats were fed diet containing 0, 0.5, 1.0, 2.0, or 5% for 2 years. Growth was inhibited in male animals at 2 and 5%. No effect on mortality, organ weight, haematology, gross-or microscopic pathology. The NEL was 1%. This is probably the study applied by JECFA for the ADI assessment [17]. In a third study weekly injection (route not specified) of 0 or 2% for 2 years was performed in rats. No effect on survival. Induction of fibrosarcoma was observed at the injection site (14/80 in dosed; 1/100 in controls). No other effects were observed [2]. In the fourth study rats were injected s.c. with 1 ml of 2% solution and later with 0.5% as 50 injection over a period of 7 months. No local tumours were observed [2].

No signs of carcinogenicity were observed in chronic toxicity/carcinogenicity studies in mice fed 0, 0.5, 1.5, or 5% in the diet [10] or rats fed 0, 0.5, 1.0, or 2.0% [8;11] A multigeneration study has been performed in rats. No data given in the abstract [8].

**Reproduction toxicity:** A reproduction study were available to JECFA. No adverse effect on reproduction [24]. Oral administration of 0, 25, 75, or 250 mg/kg bw/day by gavage to rats did not induce any change in behaviour, appearance or body weight gain of dams. No maternal or foetal parameter was affected. In a third study, rabbits were administered by gavage a dose of 0, 25, 75, or 250 mg/kg bw/day. No changes were observed in behaviour, appearance, or body weight gain of dams. No maternal or foetal parameter was affected [2].

Rats received Indigotine by gavage on days 6-15 of gestation. The doses were 0, 25, 75, or 250 mg/kg bw/day. Furthermore, rabbits received by gavage on days 6-18 of gestation 0, 25, 75, or 250 mg/kg bw/day. The colour did not exert any teratogenicity or other developmental toxicity in rats or rabbits [9].

**Allergy/Intolerance:** Bronchospasm and urticaria have been reported as single cases during surgery [22]. Asthma has been caused by occupational exposure in 2 of 204 animal feed mill workers [21].

These effects are not possible to extrapolate to the use as a food additive.
**Effect in humans:** Effects on the cardiovascular system:
Indigotine might be vaso-active [13]. Episodes of single-person hypotension have been reported [15;22;23;28] when administered intravenously at various kinds of surgery when used as a vasography agent. Hypertension has also been observed [18].

These effects were induced in patients during surgery and are not possible to extrapolate to the use as a food additive.

**Other:** Biochemical aspects:
SCF notes that data are available and that isatin-5-sulphonic acid is a major metabolite. The colour is poorly absorbed from the gut. No details were presented [3].

Studies suggest poor absorption of the colour from the alimentary tract. Examination of the renal excretion by rabbit shows that 15% is excreted from glumeruli and 75% by the tubules following microinjection. After i.v. injection of rats, 63% appeared after 6h in urine and 10% in bile. After oral administration 3% of the dose was found in urine after 3 days, 60-80% in faeces due to lack of absorption, no biliary excretion was documented. The metabolites isatin-5-sulfuric acid and 5-sulfoanthranilic acid has been identified in urine [2].

Azoreductase activity has also been studied [27], and the metabolism of Indigotine has been studied through caecal microflora of rats giving rise to four metabolites [26].

**Conclusion:** The toxicological data reported include what would normally be required for an ADI to be set for a food additive. However, the evaluations are old and new studies have been published, which should be included in an updated evaluation.

**References:**

1. [1974, NMRS 54/TRS 557-JECFA 18]

2. [1974, FAS 6/NMRS 54A-JECFA 18]


**BRILLIANT BLUE FCF**

**E number:** E 133

**Recommendation:** The existing data do not suggest a need for changing the present ADI. However, considering the long time since the previous evaluation(s) and the appearance of new studies published since then, it is recommended to update the evaluation to include the new data.

**Chemical name/synonyms:** Disodium α(4-(N-ethyl-3-sulfonatobenzylamino)phenyl)-α-(4-(N-ethyl-3-sulfonatobenzylamino) cyclohexa-2,5-dienyliden) toluen-2-sulfonat / CI Acid Blue 9; CI Food Blue 2; D&C Blue No 1; D&C Blue No 4; FD&C Blue No. 1.

**Chemical formula:** \(C_{37}H_{34}N_2Na_2O_9S_3\)

**Class:** Triarylmethane.

**EINECS number:** 223-339-8

**CAS number:** 3844-45-9

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Brilliant Blue FCF is manufactured by chemical synthesis.

**Definition:** Brilliant Blue FCF consists essentially of disodium α-(4-(N-ethyl-3-sulfonoatobenzylamino)phenyl)-α-(4-N-ethyl-3-sulfonatobenzylamino) cyclo-hexa-2,5-dienylidene) toluene-2-sulfonate and its isomers and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Brilliant Blue FCF is described as the sodium salt. The calcium and the potassium salts are also permitted.

**EC specifications:** E 133 Brilliant Blue FCF [5].

**Assay:** Not less than 85% total colouring matters calculated as the sodium salt.

**Subsidiary colouring matters:** Not more than 6.0%.

In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulphonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Brilliant Blue FCF [4].

**Assay:** Not less than 85% total colouring matters.

**Subsidiary colouring matters:** Not more than 6%.

In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate.
calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead, Chromium and Heavy metals.

**Exposure:** Permitted in all “colourable” foods and in a single of those with only limited number of permitted colours. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system Brilliant Blue was examined at tier 1 level. As the calculation for children suggested the possibility for exceeding the ADI the EU monitoring system examined the intake at tier 2 level. The calculated intake by young children was thus reported by one member state as 38% of the ADI and it was concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** SCF last evaluated Brilliant Blue FCF in 1983 [3] when it established an ADI of 10 mg/kg bw on the basis of a no-adverse-effect level on 2% in diet. No further details specified.

**JECFA status:** The present JECFA ADI of 12.5 mg/kg bw was allocated in 1969 [1]. The evaluation was based on the level causing no toxicological effect in the rat: 5% (highest dose) in diet equivalent to 2500 mg/kg bw/day [10]. The safety-factor was 200. The reason for this factor was not given.

**BIBRA:** The toxicological data for Brilliant Blue within classical endpoints including acute oral toxicity, reproduction, genotoxicity, and carcinogenicity, have been reviewed by BIBRA in 1996. No convincing evidence for carcinogenicity or other adverse effect [7].

**Background data:**

**Subacute/subchronic toxicity:** Daily injection of mice with 2 mg (route not specified) over 30 days induced no effects whereas a dose of 4 mg showed swelling of liver and spleen in some animals. In a study in rats, animals received s.c. injections of 1 ml 0.8% twice weekly (duration not specified). No carcinogenic potential was revealed. After feeding dogs 1 or 2% in diet for 1 year no gross or microscopic changes were induced. Injection (route not specified) of cats (dose varied) for 18 days produced no methaemoglobinemia or Heinz bodies. In a special 90-days study, rats were fed o-sulfbenz-aldehyde (a colour component) at levels of 0, 0.25, 0.5, 1, or 2% for 13 weeks. The NEL was 2%. [2].

Brilliant Blue FCF (and other synthetic colours) showed different effects in rats on body weight, clinical biochemical parameters, liver and kidney functions after 30-60 days of administration. The authors considered these effects insignificant [6].

**Genotoxicity:** No data presented by SCF or JECFA.

In a study also comprising Brilliant Blue FCF, this colour was tested in Ames Salmonella/microsome test and in the chromosomal aberration test (Chinese hamster fibroblast cell line). Conflicting results were obtained. However, no convincing evidence for mutagenicity was demonstrated [11].

Data are referred to by BIBRA. Ames tests, in general, have given no convincing evidence of mutagenicity [7].
**Chronic toxicity/Carcinogenicity:** Studies are available in mouse (2 studies) and rats (10 studies). Overall, no convincing evidence for a carcinogenic potential is presented. The high percentage production in rats of local sarcomata at the site of injection has led in the past to considerable discussion and consequently to extensive studies of this colour. The induction of these sarcomata are considered to be related to the physio-chemical properties of the colour and special condition of the experiments and does not constitute evidence of carcinogenicity by the oral route [2].

In a “new” study in rats and mice, rats were fed 0, 0.1, 1.0, or 2.0% in diet and mice were fed 0, 0.5, 1.5, or 5.0%. The NOAEL in rats was 1.0%/2.0% (female/male) and 5.0% in mice, corresponding to 631/1072 mg/kg/day (female/male rats, based on a 15% decreased body weight and decreased survival in females) and 7354/8966 mg/kg bw/day (male/female mice). The effect in female rats was decreased terminal body weight, and decreased survival. No indications of carcinogenicity [8].

**Reproduction toxicity:** SCF mentions that a reproduction and teratogenicity study is available in rats. No reproductive or other function was affected. No details reported [3].

**Other:** Biochemical aspects:
The colour is poorly absorbed and almost completely excreted in the faeces following biliary excretion if parenterally administered. No metabolism by intestinal bacteria has been reported. No details have been specified [3].

The colour is poorly absorbed. The presence of the colour after oral dosing was observed in bile of rat, rabbit, and dog. Almost the entire oral dose (dose: 200 mg/rat) administered to rats was excreted unchanged with faeces after 40 h. Some 89% of an oral dose given to dogs was excreted by faeces, nothing in urine. After s.c. dosing 77% appeared in faeces and 2.5% in urine [2].

**Eye irritation:**
No adverse effect after topical application of brilliant blue to rabbits eyes (3% in aqueous vehicle) once per day for 21 days [9].

**Conclusion:** There is nothing in the existing data suggesting toxicity within the ADI, but studies normally needed for setting an ADI are missing and new studies have been published since the evaluation [8]. An update of the evaluation is therefore recommended.

**References:**

1. [1969, NMRS 46/TRS 445-JECFA 13]

2. [1969, FAS 70.36/NMRS 46A-JECFA 13]


**CHLOROPHYLLS and CHLOROPHYLLINS**

**E number:**
Chlorophylls: E 140 (i)
Chlorophyllins: E 140 (ii)

**Recommendation:** Due to the widespread ingestion of chlorophyll-containing products by man throughout history, along with its limited absorption, further studies on these compound is not warranted despite the limited set of toxic data on the compounds. It should be investigated whether chlorophyllins are actually on the market, and if that is the case a formal evaluation of this substance should be undertaken.

**Chemical name/synonyms:**
Chlorophylls: Phytyl (13\textsuperscript{2}R, 17S,18S)-3-(8-ethyl-13\textsuperscript{2}-methoxycarbonyl-2,7,12,18-tetramethyl-13\textsuperscript{3}-oxo-3-vinyl-13\textsuperscript{4}-13\textsuperscript{2}-17,18-tetrahydrocyclopenta [at]-porphyrin-17-yl)propionate, (Phaeophytin a), or as the magnesium complex (Chlorophyll a) and Phytyl (13\textsuperscript{2}R, 17S,18S)-3-(8-ethyl-7- formyl-13\textsuperscript{2}-methoxycarbonyl-2,12,18-trimethyl-13\textsuperscript{3}-oxo-3-vinyl-13\textsuperscript{4}-13\textsuperscript{2}-17,18-tetrahydrocyclopenta [at]-porphyrin-17-yl)propionate, (Phaeophytin b), or as the magnesium complex (Chlorophyll b)/ CI Natural Green 3, Magnesium Chlorophyll, Magnesium Phaeophytin.

Chlorophyllins: 3-(10-carboxylato-4-ethyl-1,3,5,8-tetramethyl-9-oxo-2-vinylphorbin-7-y1) propionate (chlorophyllin a) and 3-(10-carboxylato-4-ethyl-3-formyl-1,5,8-trimethyl-9-oxo-2-vinylphorbin-7-y1) propionate (chlorophyllin b).

**Chemical formula:**
Chlorophylls: Chlorophyll a: C\textsubscript{55}H\textsubscript{74}N\textsubscript{4}O\textsubscript{5}
Chlorophyll a: C\textsubscript{55}H\textsubscript{72}N\textsubscript{4}O\textsubscript{5} (magnesium complex)
Chlorophyll b: C\textsubscript{55}H\textsubscript{72}N\textsubscript{4}O\textsubscript{6}
Chlorophyll b: C\textsubscript{55}H\textsubscript{70}N\textsubscript{4}O\textsubscript{6} (magnesium complex)

Chlorophyllins: Chlorophyllin a: C\textsubscript{34}H\textsubscript{34}N\textsubscript{4}O\textsubscript{5} (acid form)
Chlorophyllin b: C\textsubscript{34}H\textsubscript{32}N\textsubscript{4}O\textsubscript{6} (acid form)

**Class:** Porphyrin.

**EINECS number:**
Chlorophylls: Chlorophylls: 215-800-7
Chlorophyll a: 207-536-6
Chlorophyll b: 208-272-4

Chlorophyllins: 287-483-3
**CAS number:**

Chlorophylls:  
- Chlorophyll a: 479-61-8  
- Chlorophyll b: 519-62-0

Chlorophyllins: -

**Functional Class:** Colour.

**Specification:**

**Chlorophylls**

**Manufacture:** Chlorophylls are obtained by solvent extraction of edible plant material, grass, lucerne and nettle. During the subsequent removal of the solvent, the naturally present co-ordinated magnesium may be wholly or partially removed from the chlorophylls to give the corresponding phaeophytins. Only the following solvents may be used for the extraction: acetone, methyl ethyl ketone, dichloromethane, carbon dioxide, methanol, ethanol, propane-2-ol and hexane.

**Definition:** The principal colouring matters in chlorophylls are phaeophytins and magnesium chlorophylls. The extracted products from which the solvent has been removed contain other pigments such as carotenoids as well as oils, fats, and waxes derived from source material.

**EC specifications:** E 140 (i) Chlorophylls [4].

Assay: Content of total combined chlorophylls and their magnesium complexes is not less than 10%.

The specification includes purity criteria on Solvent residues, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Chlorophylls [3].

Assay: Content of total combined phaeophytins and their magnesium complexes is not less than 10%.

The specification includes purity criteria on Residual solvents, Arsenic and Lead.

**Chlorophyllins**

**Manufacture:** The alkali salts of chlorophyllins are obtained by the saponification of a solvent extract of edible plant material, grass, lucerne and nettle. Only the following solvents may be used for the extraction: acetone, methyl ethyl ketone, dichloromethane, carbon dioxide, methanol, ethanol, propane-2-ol and hexane.

**Definition:** By the saponification of chlorophylls the methyl and phytol ester groups are removed and the cyclopentenyl ring may partially be cleaved. The acid groups are neutralised to form the salts of potassium and/or sodium.

**EC specifications:** E 140 (ii) Chlorophyllins [4].

Assay: Content of total chlorophyllins is not less than 95% of the sample dried at ca. 100°C for 1 hour.

The specification includes purity criteria on Solvent residues, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.
**Exposure:** Permitted generally in foodstuffs except those where colours are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. No ADI has been specified and the substance was for that reason not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation in 1975. No data available, but chlorophyll was found acceptable when derived from natural foods by physical processes. Chlorophyllins were not mentioned [2].

**JECFA status:** Latest evaluation in 1969. ADI “not limited” except by good manufacturing practice. Chlorophyllins were not mentioned [1].

**Background data:**

**Subacute/subchronic toxicity:** Data not available.

**Genotoxicity:** Data not available.

**Chronic Toxicity /Carcinogenicity:** Data not available.

**Reproduction toxicity:** Data not available.

**Effects in humans:** Chlorophyll intolerance can occur due to the liberated phytol in individuals with Refsum’s disease, in which phytanic acid accumulates in the serum and other tissues due to a defect in the metabolic pathway for phytic acid.

**Other:** Only a small fraction of the ingested chlorophyll undergoes absorption in the gastrointestinal tract (1-3%).

Metabolism: The phytol side chain is cleaved and Mg is leached from the molecule upon ingestion in humans and the resulting pheophytin is excreted in the faeces. Pheophytin and pheophorbide a and b have thus been identified as chlorophyll metabolites in human subjects [5]. The full metabolic fate of chlorophyll is unknown.

**Conclusion:** Although, very limited data is available on many of the toxicological aspects of chlorophyll, the available toxicity data do not suggest any overt toxicity of chlorophyll, at doses that by far exceed a normal human intake. Chlorophyllins has not been specifically mentioned by any of the Committees.

Chlorophylls and chlorophyllins as defined by the specifications may be obtained from sources that could not be regarded as edible plant materials or foods. No JECFA specification on chlorophyllins.

**References:**

1. [1969, NMRS 46/TRS 445-JECFA 13]
   Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances


COPPER COMPLEXES OF CHLOROPHYLLS AND CHLOROPHYLLINS

E number:
Copper complexes of chlorophylls: E 141 (i)
Copper complexes of chlorophyllins: E 141 (ii)

Recommendation: As the evaluations are old, and for the sake of chlorophyllin copper complexes unclear, a re-evaluation is recommended. The issue of cancer-promoting effects of copper complexes of chlorophyllins should be addressed. Also the metabolism, especially with respect to the bioavailability and possible tissue retention of copper, should be elucidated.

Chemical name/synonyms:
Copper chlorophylls: [Phytol (13^2R, 17S,18S)-3-(8-ethyl-13^2-methoxycarbonyl-2,7,12,18-tetramethyl-13'-oxo-3-vinyl-13^1,13^2-17,18-tetrahydrocyclopenta [at]-porphyrin-17-yl) propionate] copper (II), (Copper chlorophyll a) and [Phytol (13^2R, 17S,18S)-3-(8-ethyl-7- formyl-13^2-methoxycarbonyl-2,12,18-trimethyl-13'-oxo-3-vinyl-13^1,13^2-17,18-tetrahydrocyclopenta [at]-porphyrin-17-yl) propionate], copper (II), (Copper chlorophyll b) / CI Natural Green 3, Copper chlorophyll, Copper phaeophytin.
Copper chlorophyllins: 3-(10-Carboxylato-4-ethyl-3-formyl-1,3,5,8-tetramethyl-9-oxo-2-vinylphorbin-7-yl) propionate, Copper complex (Copper chlorophyllin a) and 3-(10-carboxylato-4-ethyl-3-formyl-1,5,8-trimethyl-9-oxo-2-vinylphorbin-7-yl) propionate, copper complex (Copper chlorophyllin b).

Chemical formula:
Copper chlorophylls: Copper chlorophyll a: C_{55}H_{72}CuN_{4}O_{5}
Copper chlorophyll b: C_{55}H_{70}CuN_{4}O_{6}
Copper chlorophyllins: Copper chlorophyllin a: C_{34}H_{32}CuN_{4}O_{5} (acid form)
Copper chlorophyllin b: C_{34}H_{30}CuN_{4}O_{6} (acid form)

Class: Porphyrin.

EINECS number:
Copper chlorophylls: Copper chlorophyll a: 239-830-5
Copper chlorophyll b: 246-020-5
Copper chlorophyllins: -

CAS number:
Copper chlorophylls: 65963-40-8
Copper chlorophyllins: -

Functional Class: Colour.
**Specification:**

*Copper chlorophylls*

**Manufacture:** Copper chlorophylls are obtained by addition of a salt of copper to the substance obtained by solvent extraction of edible plant material, grass, lucerne and nettle. Only the following solvents may be used for the extraction: acetone, methyl ethyl ketone, dichloromethane, carbon dioxide, methanol, ethanol, propane-2-ol and hexane.

**Definition:** The principal colouring matters are the copper phaeophytins. The product from which the solvent has been removed contains other pigments such as carotenoids as well as oils, fats, and waxes derived from source material.

**EC specifications:** E 141 (ii) Copper complexes of chlorophylls [1].
- Assay: Content of total copper chlorophylls is not less than 10%.
- Total copper: Not more than 8.0% of the total copper phaeophytin.
- Copper ions: Not more than 200 mg/kg.
In addition the specification includes purity criteria on Solvent residues, Arsenic, Lead, Mercury and Cadmium.

**JECFA specifications:** Chlorophylls, copper complexes [2].
- Assay: Content of total copper phaeophytins is not less than 10%.
- Total copper: Not more than 8.0% of the total copper phaeophytin.
- Copper ions: Not more than 200 mg/kg.
In addition the specification includes purity criteria on Residual solvents, Arsenic and Lead.

*Copper chlorophyllins*

**Manufacture:** Copper chlorophylls are obtained addition of a salt of copper to the substance obtained by the saponification of a solvent extract of edible plant material, grass, lucerne and nettle. After addition of copper to the purified chlorophyllins, the acid groups are neutralised to form salts of potassium and/or sodium. Only the following solvents may be used for the extraction: acetone, methyl ethyl ketone, dichloromethane, carbon dioxide, methanol, ethanol, propane-2-ol and hexane.

**Definition:** By the saponification of chlorophylls the methyl and phytol ester groups are removed and the cyclopenthenyl ring may partially be cleaved. The acid groups are neutralised to form the salts of potassium and/or sodium.

**EC specifications:** E 141 (ii) Copper complexes of chlorophyllins [1].
- Assay: Content of total copper chlorophyllins is not less than 95% of the sample dried at app. 100°C for 1 hour.
- Total copper: Not more than 8.0% of the total copper chlorophyllins.
- Copper ions: Not more than 200 mg/kg.
The specification includes purity criteria on Solvent residues, Arsenic, Lead, Mercury and Cadmium.

**JECFA specifications:** Chlorophyllins, copper complexes sodium and potassium salts [2].
- Assay: Content of total copper chlorophyllins is not less than 95% of the sample dried at app. 100°C for 1 hour.
- Total copper: Not more than 8.0% of the total copper chlorophyllins.
- Copper ions: Not more than 200 mg/kg.
The specification includes purity criteria on Solvent residues, Basic dyes, Arsenic and Lead.

**Exposure:** Permitted generally in foodstuffs except those where colours are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible.

In the EU monitoring system the substances were moved to tier 3, as they have a numerical ADI, but cannot be examined at tier 1 and 2.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation in June 1975 when the JECFA ADI of 15 mg/kg was endorsed as a group for both substances. No details specified [3].

**JECFA status:** In 1969 an ADI of 15 mg/ kg bw was established for chlorophyll copper complex. A similar figure was established for the chlorophyllin copper complex, but it was made temporary [4;5]. In 1978 this latter substance was again discussed. In the summary table the ADI is now listed as full, but no explanation given in the report [6] and no toxicological monograph prepared.

**Background data:**
**Subacute/subchronic toxicity:** Oral or parenteral administration of NaKCu-chlorophyllin to 10 different species including man at oral doses ranging from 70-2500 mg/kg bw for 7 to 123 days did not produce any gross adverse effects or pathological changes [7].

**Genotoxicity:** *In vitro:* In one study NaKCu-chlorophyllin was found to potentate (2-fold) the mutagenicity of two nitrosamines detected in Ames mutagenicity assay and in the hrprt V79 point mutation assay [8].

*In vivo:* NaKCu-chlorophyllin was evaluated in mice exposed to different doses of gamma radiation with regard to sister chromatide exchange in the spermatogonias. No evidence of genotoxicity was observed [9].

**Chronic toxicity/Carcinogenicity:** Groups of 40 rats were fed diets containing 0, 0.1, 1.0 and 3.0% of NaKCu-chlorophyllin over their life span. No adverse effects on growth rate, feed efficiency, hematology or urine-composition were observed in the chlorophyllin treated animals [10]. In a long-term study conducted on rainbow trout NaKCu-Chlorophyllin was not found to act as a tumor promoter of AFB1 hepatocarcinogenesis at doses of 2000 or 4000 ppm NaKCu-chlorophyllin [11]. On the other hand NaKCu-Chlorophyllin, was a tumor promoter in a DMH colon cancer model when administered in the drinking water at a concentration of 1.5 mM [12].

**Reproduction toxicity:** NaKCu-chlorophyllin given at 1% in the rat feed was not found to affect the rate of conception or the number of young born. NaKCu-chlorophyllin, however, adversely affected the survival of the first-generation rats during the first five days following birth. This was either due to an interference with normal liveability of the young rats and/or an adverse effect on lactation measured in terms of the weight of the young rats at weaning age [7].

**Effects in humans:** NaKCu-Chlorophyllin has been used extensively in the treatment of various human ailments such as anaemia and pancreatitis and often at doses up to 1.5 g per day without noticeable toxic side effects [13].
Other: Some of the potentially adverse effects might stem from the free ionisable copper present in the preparation. PMTDI for copper is 0.005-0.5 mg/kg bw [14].

Metabolism: The phytol side chain is expected to be cleaved as is evident for native chlorophyll. The copper complex seems to be stable during digestion, although increases in plasma levels of copper have been reported. And no evidence exists for copper storage in tissues [10].

Conclusion: The findings by Nelson et al. [12] on the tumour promoting effects of the commercially available NaKCu chlorophyllin warrants a further investigation on the toxic effects of this group of compounds. Data on biotransformation, in particular tissue levels of copper and the effect on reproduction are warranted.

The copper complexes of chlorophylls and chlorophyllins as defined by the specifications may be obtained from sources that could not be regarded as edible plant materials or foods.

References:


14. [1982, TRS 683-JECFA 26]
**GREEN S**

**E number:** E 142

**Recommendation:** The existing data do not suggest a need for changing the present ADI. However, considering the long time since the previous evaluation(s) and the number of new studies published since then, it is recommended to update the evaluation to include the new data.

**Chemical name/synonyms:** Sodium N-[4-[[4-(dimethylamino)phenyl](2-hydroxy-3,6-disulfo-1-naphthalenyl)-methylene]2,5-cyclohexadien-1-ylidene]-N-methylmethanaminium / CI Acid Green 50; CI Food Green 4; Brilliant Green BS; Food green S; Wool Green S.

**Chemical formula:** C$_{27}$H$_{25}$N$_2$NaO$_7$S$_2$

**Class:** Triarylmethane.

**EINECS number:** 221-409-2

**CAS number:** 860-22-0

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Green S is manufactured by chemical synthesis.

**Definition:** Green S consists essentially of sodium N-[4-[[4-(dimethylamino)phenyl](2-hydroxy-3,6-disulfo-1-naphthalenyl)-methylene]2,5-cyclohexadien-1-ylidene]-N-methylmethanaminium and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Green S is described as the sodium salt. The calcium and the potassium salts are also permitted.

**EC specifications:** E 142 Green S [5].

Assay: Not less than 80% total colouring matters calculated as the sodium salt.

Subsidiary colouring matters: Not more than 1.0%.

In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Green S [4].

Assay: Not less than 80% total colouring matters.

Subsidiary colouring matters: Not more than 1%.

In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and Chloride and Sulfate.
calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead, Chromium and Heavy metals.

**Exposure:** Permitted in all “colourable” foods. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system Green S was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 3 - 20% of ADI. The calculated intake by young children is reported by one member state as 76%. It was concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** SCF last evaluated green S in 1983 when it established an ADI of 5 mg/kg bw on the basis of a no-adverse-effect level corresponding to 500 mg/kg bw/day in a rat study and a safety-factor of 100. No details or reference to this or any of the other studies considered were specified [3].

**JECFA status:** JECFA in 1974 withdrew the temporary ADI of 5 mg/kg bw for green S, which was established in 1969 under the name of Wool Green BS, because the then requested data had not been submitted. JECFA concluded that green S has been studied in adequate long-term studies in rats, that metabolic information is lacking, and that the short-term studies in pigs as submitted to JECFA were not adequate for evaluation. Furthermore, adequate reproduction and embryotoxicity studies including teratology were not available although requested previously [1]. In the earlier evaluation JECFA requested adequate studies in a second rodent species and in a non-rodent species, adequate reproduction and embryotoxicity including teratology studies.

**BIBRA:** The toxicological data for green S within classical endpoints including metabolic, acute oral toxicity, short-term toxicity, reproduction (teratology + embryotoxicity), genotoxicity, and carcinogenicity (multigeneration, long-term-study) studies have been reviewed by BIBRA. No adverse effects were demonstrated. No convincing evidence for carcinogenicity exists [6].

**Background data:**

**Subacute/subchronic toxicity:** Rats were given 10 ml milk daily containing 0.15 mg green S/l for 3 months or 30 mg/l for 5 weeks. No biological or pathological abnormalities were found. In another study, rats were given 50 ml 0.1% aqueous solution for 91 days. Only the faeces was discoloured not the urine. No ill-effects were observed [2].

Rats were fed 0, 250, 500, or 1500 mg/kg bw/day for 13 weeks. At the highest dose, urinary protein, protein casts, increased caecal weight, thyroid degeneration and enlargement of lymph nodes in the intestine wall were seen. The no-effect level was considered to be 500 mg/kg [10]. However, these effects were not noticed in any of the long-term studies reviewed by BIBRA [6].

**Genotoxicity:** No mutagenicity studies were available to SCF or JECFA.

*In vivo:* One study indicated that green S induced sister chromatid exchange (SCE) and chromosome aberration (CA) in mice after in vivo exposure of single doses: Administration of 50,
100 and 200 mg/kg bw increased SCE and administration of 200 and 400 mg/kg bw increased CA [11]. However, another publication re-evaluated these data and concluded that Green S was not clastogenic [8].

**Chronic toxicity/Carcinogenicity:** Studies are available in mice (1 study, s.c. injection) [2] and in rats (8 studies, 4 oral, 4 s.c. injection) [2]. None of these consistently demonstrated a carcinogenic potential of green S.

A long-term study in mice given 0, 0.033, 0.33, or 0.6% in diet for 14, 28, or 51 weeks [7] concluded a no-untoward-effect to be 530 and 660 (highest dose) of males and females, respectively.

A three-generation toxicity study in rats fed 0, 50, 500, or 1000 mg/kg bw/day concluded a no-untoward-effect level of 500 mg/kg/day. The effects at highest dose included increased spleen weight (both sexes) increased kidney weight (male), without relevant histopathological changes in any organ [12].

**Reproduction toxicity:** SCF reports that multigeneration reproduction and teratology studies in rats are available and that no effects on reproductive function were observed. Also teratology studies in rats were available to SCF which concluded that the colour was neither embryotoxic nor teratogenic. No details were reported [3].

In two of the long-term studies in rats, no effects on behaviour, growth, or reproduction were noticed. No histopathological findings were observed [2].

A teratogenicity and embryotoxicity study in rats applying daily oral doses of 0, 250, 500, or 1000 mg/kg to pregnant rats on days 0-19 of pregnancy showed no embryotoxic or teratogenic effects of doses up to 1000 mg/kg/day [9].

**Other:** Biochemical aspects:
SCF notes that the colour is practically unabsorbed from the gut. Metabolic studies are available in three species. No details are reported [3].

No absorption was found after feeding pigs and calves with colour-containing milk. After oral administration of rats, 0.2% of the dose was excreted in urine and 27% in faeces. In another study, after sc injection of 30-56 mg, 7-12 mg was excreted in urine and 2-18 mg in faeces of rats [2].

The metabolism of green S has been studied through caecal microflora of rats giving rise to three metabolites [13].

**Conclusion:** Except for the lack of mutagenetic data the toxicological data include what would normally be required for an ADI to be set for a food additive. However, carcinogenicity studies failed to demonstrate carcinogenicity. There is no indication of undesirable effects within the ADI. The reporting from SCF is not including any details of the studies reviewed, and considering that JECFA could not allocate an ADI and that new studies have been published since the SCF evaluation, an update of the evaluation is recommended.
References:


PLAIN CARAMEL

E number: E 150a

Recommendation: No need for a re-evaluation.

Chemical name/synonyms: Caustic caramel; Caramel colour, class I.

Chemical formula: -

Class: -

EINECS number: 232-435-9

CAS number: -

Functional Class: Colour.

Specification:
Manufacture: Plain caramel is obtained by the controlled heat treatment of carbohydrate (commercially available food grade nutritive sweeteners which are the monomers glucose and fructose and/or polymers thereof, e.g. glucose syrups, sucrose and/or invert syrups and dextrose). To promote caramelization, acids, alkalis and salts may be employed, with the exception of ammonium compounds and sulphites.

Definition: Plain caramel is a complex mixture of compounds, some of which are in the form of colloidal aggregates.

EC specifications: E 150a Plain caramel [1].
Assay: -
Colour bound by DEAE cellulose: Not more than 50%.
Colour bound by phosphoryl cellulose: Not more than 50%.
Colour intensity: 0.01-0.12.
Total nitrogen: Not more than 0.1%\(^1\).
Total sulphur: Not more than 0.2%\(^1\).
In addition the specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Caramel colour, class I [2].
Assay: -
Colour bound by DEAE cellulose: Not more than 50%.
Colour bound by phosphoryl cellulose: Not more than 50%.
Colour intensity: 0.01-0.12.
Total nitrogen: Not more than 0.1% expressed on the equivalent solid basis.

\(^1\) In contrast to the other caramels these limits are not expressed on the equivalent color basis. Is that the intention?
Total sulphur: Not more than 0.3% expressed on the equivalent solid basis. 
In addition the specification includes purity criteria on Solid content, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in “colourable” foodstuffs including some of those where colours are normally not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. No ADI has been specified and the substance was for that reason not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation in December 1987 when the Committee confirmed its previous opinion that it finds plain caramel acceptable and that no numerical ADI is necessary [3].

**JECFA status:** Latest evaluation in 1985. ADI “not specified” [4].

**Background data:**
**Subacute/subchronic toxicity:** Administration of caramel colour I to groups of weanling female rats at dietary levels of 0, 15 or 30% for 8 weeks did not affect growth rate or induced gross or microscopic pathological changes [5].

**Genotoxicity:** In vitro: No evidence for mutagenic activity of Caramel Colour I in several strains of *S. typhimurium*. No evidence for clastogenic effects [6-8]. Some genotoxic activity at very high doses observed in the absence of S-9 [9].

In vivo: In the mouse micronucleus test no evidence for genotoxicity was observed [9].

**Chronic toxicity/Carcinogenicity:** No data available.

**Reproduction toxicity:** No data available.

**Conclusion:** Only limited data is available on the toxicology of Caramel Colour I. However, as this colour can be considered a natural part of the diet and as the presented data do not suggest any untoward effects, there is no need for further testing.

Plain caramel as defined by the specifications seems to be covered by the toxicological evaluation.

**References:**


CAUSTIC SULPHITE CARAMEL

E number: E 150b

Recommendation: No need for a re-evaluation of this colour.

Chemical name/synonyms: Caramel colour, class II.

Chemical formula: -

Class: -

EINECS number: 232-435-9

CAS number: -

Functional Class: Colour.

Specification:
Manufacture: Caustic sulphite caramel is obtained by the controlled heat treatment of carbohydrate (commercially available food grade nutritive sweeteners which are the monomers glucose and fructose and/or polymers thereof, e.g. glucose syrups, sucrose and/or invert syrups and dextrose) with or without acids or alkalis, in the presence of sulphite compounds (sulphurous acid, potassium sulphite, potassium bisulphite, sodium sulphite and/or sodium bisulphite). No ammonium compounds are used.

Definition: Caustic sulphite caramel is a complex mixture of compounds, some of which are in the form of colloidal aggregates.

EC specifications: E 150b Caustic sulphite caramel [1].
Assay: -
Colour bound by DEAE cellulose: More than 50%.
Colour intensity: 0.05-0.13.
Total nitrogen: Not more than 0.3% expressed on the equivalent colour basis.
Total sulphur: 0.3-3.5% expressed on the equivalent colour basis.
Sulphur dioxide: Not more than 0.2% expressed on the equivalent colour basis.
Sulphur bound by DEAE cellulose: More than 40%.
Absorbance ratio of colour bound by DEAE cellulose: 19-34.
In addition the specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Caramel colour, class II [2].
Assay: -
Colour bound by DEAE cellulose: More than 50%.
Colour intensity: 0.06-0.10.
Total nitrogen: Not more than 0.2% expressed on the equivalent solid basis.
Total sulphur: 1.3-2.5% expressed on the equivalent solid basis.
Sulphur dioxide: Not more than 0.2% expressed on the equivalent solid basis.
In addition the specification includes purity criteria on Solid content, Arsenic and Lead.

**Exposure:** Permitted generally in foodstuffs including some of those where colours are normally not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. As the colour has a numerical ADI the EU monitoring system moved it to tier 3.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1990: Group ADI 200 mg/kg bw for caustic sulphite caramel and sulphite ammonia caramel. At the 76th meeting on December 1990 the Committee concluded that the chemical composition of this colour is similar and intermediate to that of caramel colour I and IV. It was therefore satisfied that the existing toxicity data on caustic sulphite caramel and ammonium sulphite caramel provide adequate documentation for the safety in use for both these classes of caramel. No report was issued.

**JECFA status:** Latest evaluation: 2000. ADI 160 mg/kg bw. [3]. This is based on the highest dose in the subacute study mentioned below and a safety factor of 100.

**Background data:**
**Subacute/subchronic toxicity:** The toxicity of Caramel colour II was evaluated in a 13-week study in rats (F344), 20 rats per sex at levels of 0, 4, 8 and 16 g/kg and did not reveal any important toxicological or pathological findings [4].

**Genotoxicity:** In vitro: No evidence of mutagenic or clastogenic effects [5-7].
*In vivo:* No data available.

**Chronic toxicity/Carcinogenicity:** No data available.

**Reproduction toxicity:** No data available.

**Conclusion:** Only few toxicity tests have been performed on this colour. However the chemical composition as presented to the SCF justify the inclusion of the ADI of sulphite ammonia caramel. Thus there is no need for further testing.

There are significant differences between the EU and the JECFA specifications.

**References:**


AMMONIA CARAMEL

E number: E 150c

Recommendation: The factor(s) causing lymphocyte suppressing activity may need a review.

Chemical name/synonyms: Caramel colour, class III.

Chemical formula: -

Class: -

EINECS number: 232-435-9

CAS number: -

Functional Class: Colour.

Specification:
Manufacture: Ammonia caramel is obtained by the controlled heat treatment of carbohydrate (commercially available food grade nutritive sweeteners which are the monomers glucose and fructose and/or polymers thereof, e.g. glucose syrups, sucrose and/or invert syrups and dextrose) with or without acids or alkalis, in the presence of ammonium compounds (ammonium hydroxide, ammonium carbonate, ammonium hydrogen carbonate and ammonium phosphate). No sulphite compounds are used.

Definition: Ammonia caramel is a complex mixture of compounds, some of which are in the form of colloidal aggregates.

EC specifications: E 150c Ammonia caramel [1].
Assay: -
Colour bound by DEAE cellulose: Not more than 50%.
Colour bound by phosphoryl cellulose: More than 50%.
Colour intensity: 0.08-0.36.
Total nitrogen: 0.7-3.3% expressed on the equivalent colour basis.
Total sulphur: Not more than 0.2% expressed on the equivalent colour basis.
Absorbance ratio of colour bound by phosphoryl cellulose: 13-35.
4-methylimidazole: Not more than 250 mg/kg expressed on the equivalent colour basis.
2-acetyl-4-tetrahydroxy-butylimidazole: Not more than 10 mg/kg expressed on the equivalent colour basis.
In addition the specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Caramel colour, class III [2].
Assay: -
Colour bound by DEAE cellulose: Not more than 50%.
Colour bound by phosphoryl cellulose: More than 50%
Colour intensity: 0.08-0.36.
Total nitrogen: 0.7-3.3% expressed on the equivalent solid basis.
Total sulphur: Not more than 0.3% expressed on the equivalent solid basis.
4- methylimidazole: Not more than 200 mg/kg expressed on the equivalent colour basis.
2-acetyl-4-tetrahydroxy-butylimidazole: Not more than 25 mg/kg expressed on the equivalent colour basis.
In addition the specification includes purity criteria on Solid content, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs including some of those where colours are normally not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. As the colour has a numerical ADI the EU monitoring system moved it to tier 3.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation: December 1996. ADI 200 mg/kg bw. [3].

**JECFA status:** Latest evaluation: 1985. ADI 200 mg/kg bw. [4]

**Background data:**
**Subacute/subchronic toxicity:** Several short-term studies conducted in rats and mice have been conducted with Caramel colour III. The decrease in lymphocyte counts were found to be largely, if not solely, due to the presence of 4-methylimidazole and 2-acetyl-4(5)-tetrahydroxybutylimidazole (THI) [5]. A newer subchronic study, however, revealed, depressed immunological functions in mice exposed to 2% caramel colour III that meets the JECFA specification of less than 25 mg THI/kg [6].

**Genotoxicity in vitro:** The newest report on mutagenicity of Caramel colour III do not support a mutagenic potential [7;8] whereas contradictory results exist in the older literature (for a review see JECFA 1985, 29th series[5], presumably due to different levels of impurities). The most likely compound a to induce a toxic response is THI.

**in vivo:** Caramel colour III did not increase the incidence of micronuclei in mice administered doses up to 3.5 g/kg bw.

**Chronic toxicity/Carcinogenicity:** Caramel colour III was not found to be carcinogenic at dose levels up to 4% in drinking water [9].

**Reproduction toxicity:** Caramel colour III at doses ranging from 0-1600 ppm had no clearly discernible effects on nidation or fetal survival in rabbits, mice or rats [10].

**Effects in humans:** In a pilot study in 9 human volunteers 1.5 g of Caramel colour III was not found to alter clinical chemical parameters including lymphocyte count [11;12].

**Other:** The evaluation is based on caramel colour containing 15 ppm THI on a solid basis.
**Conclusion:** As long as the THI (2-acetyl-4(5)-tetrahydroxybutylimidazole) level is kept at a minimum, caramel colour III does not seem to cause a toxicological problem. However, the effect described above under subacute studies may indicate a need to review the level of THI causing immunosuppressive effect or the possibility of other factors involved in this effect.

Ammonia sulphite caramel as defined by the specifications seems to be covered by the toxicological evaluation. There are significant differences between the EU and the JECFA specifications.

**References:**


SULPHITE AMMONIA CARAMEL

**E number:** E 150d

**Recommendation:** No need to re-evaluate this caramel preparation.

**Chemical name/synonyms:** Caramel colour, class IV.

**Chemical formula:** -

**Class:** -

**EINECS number:** 232-435-9

**CAS number:** -

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Sulphite ammonia caramel is obtained by the controlled heat treatment of carbohydrate (commercially available food grade nutritive sweeteners which are the monomers glucose and fructose and/or polymers thereof, e.g. glucose syrups, sucrose and/or invert syrups and dextrose) with or without acids or alkalis, in the presence of both sulphite and ammonia compounds (sulphurous acid, potassium sulphite, potassium bisulphite, sodium sulphite, sodium bisulphite, ammonium hydroxide, ammonium carbonate, ammonium hydrogen carbonate, ammonium phosphate, ammonium sulphate, ammonium sulphite and ammonium hydrogen sulphite).

**Definition:** Sulphite ammonia caramel is a complex mixture of compounds, some of which are in the form of colloidal aggregates.

**EC specifications:** E 150c Ammonia caramel [1].

**Assay:** -

- Colour bound by DEAE cellulose: More than 50%.
- Absorbance ratio (A280/560): Not more than 50.
- Colour intensity: 0.10-0.60.
- Total nitrogen: 0.3-1.7% expressed on the equivalent colour basis.
- Total sulphur: 0.8-2.5% expressed on the equivalent colour basis.
- Ammoniacal nitrogen: Not more than 0.6% expressed on the equivalent colour basis.
- Sulphur dioxide: Not more than 0.2% expressed on the equivalent colour basis.
- Nitrogen sulphur ratio of alcohol precipitate: 0.7-2.7.
- Absorbance ratio of alcohol precipitate: 8-14.
- 4- methylimidazole: Not more than 250 mg/kg expressed on the equivalent colour basis.

In addition the specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.
**JECFA specifications:** Caramel colour, class IV [2].

Assay: -

Colour bound by DEAE cellulose: More than 50%.

Absorbance ratio (A280/560): Not more than 50.

Colour intensity: 0.10-0.60.

Total nitrogen: 0.5-7.5% expressed on the equivalent solid basis.

Total sulphur: 1.4-10.0% expressed on the equivalent solid basis.

Ammoniacal nitrogen: Not more than 2.8% expressed on the equivalent solid basis.

Sulphur dioxide: Not more than 0.5% expressed on the equivalent solid basis.

4-methylimidazole: Not more than 250 mg/kg expressed on the equivalent colour basis.

In addition the specification includes purity criteria on Solid content, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs including some of those where colours are normally not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. As the colour has a numerical ADI the EU monitoring system moved it to tier 3.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation: 1985. 200 mg/kg bw based on long-term studies, re-examination of a short-term study and mutagenic data [3].

**JECFA status:** Latest evaluation: December 1985. ADI 200 mg/kg bw (150 mg/kg bw on solids basis) based long-term and carcinogenic studies and a safety of 50. The safety factor was set to 50 because the human data show no other adverse effects than laxation [4].

**Background data:**

**Subacute/subchronic toxicity:** No overt toxic effects were observed after administration of up to 30% Caramel colour IV to mice in the drinking water [5]. Lack of toxic effects were also evident in several rats studies with administration of Caramel colour IV at 20 g/kg bw/day for 127 days [5].

**Genotoxicity:** Caramel colour IV was not found to be mutagenic in various test systems [6;7], which abrogates earlier studies presented in JECFA 1985, 29th report [5].

**Chronic Toxicity /Carcinogenicity:** Administration of Caramel colour IV to rats and mice (groups of 50 male and 50 female) at dietary levels up to 10g/kg for 104 weeks did not reveal any associated carcinogenicity [8].

**Reproduction toxicity:** Three reproduction studies conducted in rats did not reveal any gross reproductive or teratogenic effects [5], however dose-related depression of body weight gain was observed at very high doses of Caramel colour IV ranging from 8-28 g/kg bw. Absolute and relative weights of liver, caecum and kidney were also increased as compared to the control and the mesenteric lymph nodes were coloured. Special studies conducted with respect to teratogenicity were conducted in mice, rats and rabbits but did not reveal any abnormalities in the treatment groups receiving doses up to 1600 ppm Caramel colour IV [5].
Effects in humans: Tolerance studies have been conducted in men and women involving test doses up to 18 g/day. The major side effect observed was increased bowel movement and softening of faeces [5].

Other: Metabolism: Animals receiving 2.5 g/kg bw excreted close to 100% of Caramel colour within 96 hours, predominantly in the faeces. Less than 3% of the dose was recovered in the urine [5]. Pigmentation of the mesenteric lymph nodes and caecal enlargement was considered to be non-specific effects of no toxicological significance. No metabolism studies per se have been performed.

Conclusion: No overt toxic effects were observed following ingestion of very high doses of Caramel colour IV in humans or in experimental animals and thus the toxic effects to human is regarded as negligible.

Sulphite ammonia sulphite caramel as defined by the specifications seems to be covered by the toxicological evaluation. There are significant differences between the EU and the JECFA specifications.

References:


3. [1985, TRS 733-JECFA 29]


5. [1985, FAS 20-JECFA 29]


**BRILLIANT BLACK BN (BLACK PN)**

**E number:** E 151

**Recommendation:** The discrepancy between the SCF and the JECFA ADIs should be clarified and potential exposure for children possibly investigated further.

**Chemical name/synonyms:** Tetrasodium 4-acetamido-5-hydroxy-6-[7-sulfonato-4-(4-sulfonatophenylazo)-1-naphthylazo] naphthalene-1,7-disulfonate/ CI Food Black 1.

**Chemical formula:** $C_{28}H_{17}N_{5}Na_{4}O_{14}S_{4}$

**Class:** Bisazo.

**EINECS number:** 219-746-5

**CAS number:** 2519-30-4

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Brilliant black BN is manufactured by chemical synthesis.

**Definition:** Brilliant black BN consists essentially of tetrasodium 4-acetamido-5-hydroxy-6-[7-sulfonato-4-(4-sulfonatophenylazo)-1-naphthylazo] naphthalene-1,7-disulfonate and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Brilliant black BN is described as the sodium salt. The calcium and the potassium salts are also permitted.

**EC specifications:** E 151 Brilliant black BN [1].
Assay: Not less than 80% total colouring matters calculated as the sodium salt. Subsidiary colouring matters: Not more than 10% (expressed on the dye content).
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulphonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Brilliant black BN [2].
Assay: Not less than 80% total colouring matters. Subsidiary colouring matters: Not more than 4%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.
**Exposure:** Permitted in all “colourable” foods. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system Brilliant Black PN was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 3 - 20% of the SCF ADI of 5 mg/kg bw. The calculated intake by young children is reported by one member state as 76%. It was concluded that no further examination is needed at this stage, however as the JECFA ADI is one fifth of the SCF ADI that ADI may be exceeded by children. The significance of this should be clarified.

**SCF/JECFA evaluation:**

**SCF status:** SCF last evaluated brilliant black PN in 1983 [3] when it established an ADI of 5 mg/kg bw on the basis of a no-adverse-effect level corresponding to 500 mg/kg bw/day in a long-term study in rats without specifying more about that study. The safety factor was 100. SCF report the existence of a short-term study in pigs without specifying reference, results or anything else. However, the Committee stated that the studies available agree with the ADI established by JECFA in 1981, but that ADI was 1 mg/kg bw and based on the study in pigs.

**JECFA status:** The present JECFA ADI of 1 mg/kg bw was allocated in 1981 on the basis of an NEL of 100 mg/kg bw in a 90-days study in pigs [4] and a safety-factor of 100. The critical effect was cysts containing mucus and fibrin found in ileum mucosa of 4/6 pigs at 900 mg/kg bw and 1/6 at 300 mg/kg bw. It was suggested that these cysts might be due to an irritant effect of local high colour concentrations, but still the safety factor of 100 was chosen [5].

**BIBRA:**
The toxicological data for brilliant black PN within classical endpoints including acute oral toxicity, reproduction, genotoxicity, and carcinogenicity, have been reviewed by BIBRA. No adverse effects were observed. No convincing evidence for carcinogenicity [6].

**Background data:**

**Subacute/subchronic toxicity:** Rats were given 0, 0.3, 1.0, or 3.0% in the diet for 90 days. No effect was found on haematology, liver or kidney function tests. Weight of testes and kidneys increased at 3%. No untoward histopathological findings were demonstrated. A NEL was established on 1% corresponding to 500 mg/kg/day [7].

Pigs were administered 0, 100, 300, or 900 mg/kg bw/day for 90 days. No adverse effects were revealed on growth, haematology, urine analyses, serum transaminases, or organ weight. Cysts containing mucus and fibrin were found in ileum mucosa of 4/6 pigs at 900 mg/kg bw and 1/6 at 300 mg/kg bw. It was suggested that these cysts might be due to an irritative effect of local high colour concentrations. No further work was available on the ethiology and pathology of the cysts. The NEL was 100 mg/kg bw/day [4].

**Genotoxicity:** *In vitro:* SCF notes that studies are available. No evidence of mutagenicity has been demonstrated. No details were reported [3].

Two studies are available in E. coli. No mutagenic activity was demonstrated [7].
**Chronic toxicity/Carcinogenicity:** SCF notes that studies are available in mice and rats. No carcinogenic potential was demonstrated. No details were reported [3].

Six long-term studies including a reproduction study are available in rats. Rats were administered via diet (3 studies; dose range 0-3%), drinking water (2 studies; dose range 0-0.5%) and by sc injection (1 study). In these studies, no effect was found on mortality, food intake, body weight gain, haematology, blood serum chemistry, renal concentration tests, organ weights or incidence of pathological findings including tumours.

**Reproduction toxicity:** Three studies are available in rats. In a multi-generation study for 3 successive generations rats were administered 0, 0.1, 1.0, or 3% in diet. No adverse effect was revealed on fertility, litter size, weight, general condition, male/female ratio, growth, survival or maturation. No effect was found after gross or microscopic pathological examinations. No teratogenic effect was found. In two similar studies rats were dosed with 0, 250, 500, or 2500 mg/kg bw by gavage. No abnormalities were revealed on condition or behaviour of the dams. No signs of embryotoxicity or teratogenicity were demonstrated. The NEL was 2500 mg/kg bw [7].

**Other:** Biochemical aspects: Studies on the metabolism in rat and man are available [3;5]. The gut flora readily degrades the colour into metabolites containing the Cleve’s acid moiety. The colour is poorly absorbed.

It is indicated that both azo-linkages are cleaved by gut flora of rats, whereas rat-liver azo-reductase preferentially attacks the azo group linked to the two naphthalene rings. After oral administration of rats it was concluded that the colour was virtually completely degraded by gut flora and that metabolites containing the Cleve’s acid moiety were only poorly absorbed from the GI-tract. After oral administration of the colour, sulfanilic acid (SA), 4-acetamido-1-naphthylamine-6-sulfonic acid, and –7-sulfonic acid were (ANSA) detected in urine. These metabolites and unchanged brilliant black PN (trace), 1,4-diaminonaphthalene-6-sulfonic (DSA) acid and 8-acetamido-1-hydroxy-2-naphthylamine-3,5-disulfonic acid (AHNDA) were detected in faeces. Following i.p. injection of rats unchanged brilliant black PN (trace), 1-(4’-sulfophenylazo)-4-naphthyleamine-6-sulfonic acid, SA, DSA, ANSA, and AHNDA were excreted in urine and all but Black PN and SNSA in faeces [7]. After oral administration only sulfanilic acid was detected in urine of man. Faeces was not examined [7].

**Conclusion:** The toxicological data reported by SCF include what would normally be required for an ADI to be set for a food additive. However the reasons behind the differences in ADI between SCF and JECFA should be clarified.

Brilliant black BN as defined by the specifications seems to be covered by the toxicological evaluation.

**References:**


5. [1981, TRS 669-JECFA 25]


7. [1981, FAS 16-JECFA 25]
VEGETABLE CARBON

E number: E 153

Recommendation: No need for a re-evaluation.

Chemical name/synonyms: Vegetable black.

Chemical formula: C

Class: -

EINECS number: 215-609-9

CAS number: -

Functional Class: Colour.

Specification:
Manufacture: Vegetable carbon is obtained by carbonisation of vegetable material such as wood, cellulose residues, peat and coconut and other shells. The raw material is carbonised at high temperatures.

Definition: Vegetable carbon consists essentially of finely divided carbon. It may contain minor amounts of nitrogen, hydrogen and oxygen. Some moisture may be absorbed on the product after manufacture.

EC specifications: E 153 Vegetable carbon [1].
Assay: Not less than 95% of carbon on the anhydrous and ash-free basis.
Polyaromatic hydrocarbons: Passes test.
In addition the specification includes purity criteria on Loss on drying, Ash, Alkali soluble matters, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECSA specifications: Vegetable carbon [2].
Assay: Not less than 95% of carbon on the anhydrous and ash-free basis.
Polyaromatic hydrocarbons: Passes test.
In addition the specification includes purity criteria on Loss on drying, Ash, Acidity and alkalinity, Alkali soluble matters, Arsenic and Lead.

Exposure: Permitted generally in foodstuffs except those where colours are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. No ADI has been specified and the substance was for that reason not included in the EU monitoring system (tier 0).
SCF/JECFA evaluation:
SCF status: Latest evaluation September 1977. The Committee found vegetable carbon (but not carbon derived from mineral hydrocarbons) acceptable as a food colour considering its long use as therapeutic agent [3].

JECFA status: Latest evaluation in 1987 when the Committee stressed that the ADI “not limited” previously allocated covered the use as a clarifying agent when good manufacturing practices will be followed. The use as food colour was not covered in this evaluation [4].

Background data:
Subacute/subchronic toxicity: Data not available.

Genotoxicity: In vitro: The closely-related pigment carbon black, which is not included in the specification, is not mutagenic but the adsorbed polynuclear hydrocarbons show limited toxicity but no mutagenicity in several test systems [5]. No genotoxicity data is available with regard to vegetable black.
In vivo: Data not available.

Chronic toxicity/Carcinogenicity: Data not available.

Reproduction toxicity: Data not available.

Other: The ability of polynuclear aromatic hydrocarbons to adsorb to the carbon matrix is the major concern of the use of carbon black as food additive. The data on the carbon pigment are not based on vegetable carbon from vegetable sources.

Conclusion: Limited information on the toxicity of this compound. However, as carbon itself is inert and as carbon from vegetable sources has been used as a therapeutic agent in large doses without giving rise to concern, there is no reason to expect that the use of vegetable carbon, when complying with the specification, as a food colour should pose any risk.

References:


Brown FK

**E number:** E 154

**Recommendation:** Although the use of Brown FK is very limited and exposure thus very small, SCF is proposed to consider a re-evaluation to clarify the discrepancies between the SCF and JECFA evaluations. Furthermore, the existing specification for Brown FK was prepared in 1986 and it is therefore uncertain whether the evaluation by SCF in 1983 was based on a substance of the same composition as defined by these specifications.

**Chemical name/synonyms:** Brown FK is a mixture of six different components:

I. Sodium 4-(2,4-diaminophenylazo) benzenesulfonate.
II. Sodium 4-(4,6-diamino-m-tolylazo) benzenesulfonate.
III. Disodium 4,4’-(4,6-diamino-1,3-phenylenebisazo) di(benzenesulfonate).
IV. Disodium 4,4’-(2,4-diamino-1,3-phenylenebisazo) di(benzenesulfonate).
V. Disodium 4,4’-(2,4-diamino-5-methyl-1,3-phenylenebisazo) di(benzenesulfonate).
VI. Trisodium 4,4’,4’’-(2,4-diaminobenzene-1,3,5-trisazo) tri(benzenesulfonate) / CI Food Brown 1.

**Chemical formula:**

<table>
<thead>
<tr>
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<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C₁₂H₁₁N₄NaO₃S</td>
</tr>
<tr>
<td>II</td>
<td>C₁₃H₁₃N₄NaO₃S</td>
</tr>
<tr>
<td>III</td>
<td>C₁₄H₁₄N₆Na₂O₂S₂</td>
</tr>
<tr>
<td>IV</td>
<td>C₁₃H₁₄N₆Na₂O₂S₂</td>
</tr>
<tr>
<td>V</td>
<td>C₁₉H₁₆N₆Na₂O₂S₂</td>
</tr>
<tr>
<td>VI</td>
<td>C₂₄H₁₇N₈Na₃O₉S₃</td>
</tr>
</tbody>
</table>

**Class:** Azo (a mixture of mono-, bis- and trisazo colours).

**EINECS number:** -

**CAS number:** 8062-14-4

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Brown FK is manufactured by chemical synthesis.

**Definition:** Brown FK consists essentially of six different chemical components (defined above as I, II, III, IV, V and VI) and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Brown FK is described as the sodium salt. The calcium and the potassium salt are also permitted.

**EC specifications:** E 154 Brown FK [2].

Assay: Not less than 70% total colouring matters.
Of total colouring matters present the proportions of the components shall not exceed:
I  26%
II 17%
III 17%
IV 16%
V  20%
VI 16%
Subsidiary colouring matters: Not more than 3.5%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Brown FK [3].
Assay: Not less than 78% total colouring matters.
Of total colouring matters present the proportions of the components shall not exceed:
I  26%
II 17%
III 17%
IV 16%
V  20%
VI 16%
Subsidiary colouring matters: Not more than 3.5%.
In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.

**Exposure:** Brown FK is only permitted to kippers, 20 mg/kg. This means that 450 g kippers with the maximum level must be consumed before the present SCF ADI of 0.15 mg/kg bw can be reached.

**SCF/JECFA evaluation:**
**SCF status:** SCF last evaluated Brown FK in 1983 [4] when it established an ADI of 0.15 mg/kg bw on the basis of the no-adverse-effect level of 15 mg/kg in a long-term rat study. No details were specified.

**JECFA status:** At the twenty-ninth meeting held in 1985 [5] a temporary ADI of 0.075 mg/kg bw was allocated until 1986 pending the results of a complete histological examination of the low- and intermediate-dose groups in a long-term study in rats in order to adequately establish a NEL. At the 30th meeting held in 1986 these data were not submitted. Therefore, the temporary ADI was not extended i.e. no ADI was allocated [6].
The previous temporary ADI 0-0.075 mg/kg bw was based on a NEL of 0.03% equivalent to 15 mg/kg bw/day (with respect to pigment deposition) in a long-term study in rats [7]. The safety-factor was 200.
**Background data:**

**Subacute/subchronic toxicity:** Several studies are available in mice, rats, and pigs. Brown staining of tissues and effect on the heart, skeletal muscles, and other organs are reported [1].

**Genotoxicity:** Studies are available to JECFA in 3 strains of *S. typhimurium* [1].

**Chronic toxicity/Carcinogenicity:** SCF reports that studies are available in mice and rats. Reduced body weight and tissue pigmentation of the highest test dose were revealed, but no carcinogenic potential was documented. No details were presented [4].

JECFA reviews studies in mice and rats [1]. The carcinogenicity studies did not reveal increased tumour incidence.

**Reproduction toxicity:** A multigeneration study using only one dose level (15 mg/kg bw) i.e. about 100 times the expected human intake showed no effects on reproductive function and no pigment deposition in the F3a generation. In a carcinogenicity study, no reproductive effects or pigment deposition was found in F1 weaning pubs (3 doses used). Teratology studies are available. No teratogenic effects were noted. No details were presented [4].

No adverse effect were seen in the available rats studies [1].

**Other:** Biochemical aspects:

This colour is intensively studied in relation metabolism in broad. The studies available to JECFA (and SCF) include metabolic studies (absorption/distribution/biotransformation/excretion), special studies on pigmentation of tissues, special studies on Brown FK component I and II, special studies on the amine metabolites of Brown FK, and effects on oxidative phosphorylation [1].

**Conclusion:** When SCF last evaluated Brown FK [4] it established an ADI of 0.15 mg/kg bw on the basis of the information provided. This basis was not specified, but probably not very different from the one reviewed by JECFA. However, JECA withdrew its temporary ADI in 1986 [6]. Although this was more because requested data were not submitted than because of new data questioning the safety, this discrepancy should be clarified.

The existing specification for Brown FK was prepared in 1986. It is therefore uncertain whether the evaluation by SCF in 1983 was based on a substance of the same composition.

**References:**


5. [1985, TRS 733-JECFA 29]

6. [1986, TRS 751-JECFA 30]

**Brown HT**

**E number:** E 155

**Recommendation:** It is unclear on which basis the SCF ADI is derived. It is therefore recommended that Brown HT is subject to a re-evaluation to clarify this question and better to specify the questions on deposition in various organs and on the content of other components in the colour.

**Chemical name/synonyms:** Disodium 4,4’-(2,4-dihydroxy-5-hydroxymethyl-1,3-phenylene bisazo)-di-(naphthalene-1-sulfonate) / CI Food Brown 3; Chocolate Brown HT.

**Chemical formula:** C_{27}H_{18}N_{4}Na_{2}O_{9}S_{2}

**Class:** Bisazo.

**EINECS number:** 224-924-0

**CAS number:** 4553-89-3

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Brown HT is manufactured by chemical synthesis.

**Definition:** Brown HT consists essentially of disodium 4,4’-(2,4-dihydroxy-5-hydroxymethyl-1,3-phenylene bisazo)-di-(naphthalene-1-sulfonate) and subsidiary colouring matters together with sodium chloride and/or sodium sulphate as the principal uncoloured components. Brown HT is described as the sodium salt. The calcium and the potassium salts are also permitted.

**EC specifications:** E 155 Brown HT [1].

Assay: Not less than 70% total colouring matters calculated as the sodium salt.

Subsidiary colouring matters: Not more than 10%.

In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Brown HT [2].

Assay: Not less than 70% total colouring matters.

Subsidiary colouring matters: Not more than 10%.

In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying and chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.
**Exposure:** Permitted in all “colourable” foods. Maximum level in soft drinks 50 mg/l and 50-500 mg/kg in solid foods.

In the EU monitoring system Brown HT was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 3-22% of ADI, while the calculated intake by young children is reported by one member state as 67%. It was concluded that no further examination was needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** SCF last evaluated Brown HT in 1983 [3] when it established an ADI of 3 mg/kg bw on the basis of the no-adverse-effect level in a long-term study in mice. Neither the study, the NEL, its basis nor the safety-factor was specified.

**JECFA status:** The present JECFA ADI of 1.5 mg/kg bw was allocated in 1984 [4]. The basis was the level causing no toxicological effects in a long-term study in mice (0.1% in the diet, equivalent to 150 mg/kg bw/day) [4]. The safety-factor was 100.

The critical effects were: Reduced body weight gain and lower heart weight in males at 0.5%, a reduced haematocrit and leucocyte count in females at 0.5%, and increased incidence of leucocyte infiltration in liver of females at 0.5%.

**BIBRA:** The toxicological data for Brown HT within classical endpoints have been thoroughly reviewed. Specifically, no conclusive evidence was found on reproductive toxicity or carcinogenicity in mice and rats treated orally. A number of bacterial assays, including Ames’ mutagenicity test, gave no evidence of genotoxicity [5].

**Background data:**

**Subacute/subchronic toxicity:** SCF observes that studies are available in rats and pigs and that no significant toxic effects were observed. No data or details were presented [3].

JECFA reviews studies in rats (2 studies) and pigs (1 study). In one study, rats were administered 0, 0.5, 1.0, or 2.0% in the diet for 21 weeks. No effect was observed on appearance or condition. Growth retardation was noticed without diminished food intake at 1 and 2%. No effect on haematological parameters was revealed. A mild renal dysfunction was measured at 1 and 2%. Increased relative weight of brain, adrenals, spleen, kidneys, and ovaries. Brown pigmentation of liver Kupffer cells, kidneys, and lymph nodes was observed. No pathological findings [6]. In another study, rats were administered 0, 0.02, 0.06, 0.20, 0.60, 1.0, or 2% in diet for 90 days. No effect on appearance, behaviour, or survival was observed. Growth retardation on 1 and 2% was noticed. Decreased haemoglobin, red cell count and haematocrit at 2%. No pathological damage. Pigmentation of intestinal cells, lymph nodes, and in kidneys at 2% [6].

Pigs were administered 0, 5, 20, or 100 mg/kg bw/day for 13 weeks (route not specified). No adverse effect on mortality, growth, organ weight, and urine composition was observed. The haemoglobin concentration was reduced in males at all three levels. No histopathological findings [6].
Brown HT (and other synthetic colours) showed different effects in rats on body weight, clinical biochemical parameters, liver, and kidney functions after 30-60 days of administration. These effects were not regarded as serious effects according to the authors [7].

**Genotoxicity:** SCF notes that studies are available in prokaryotic systems and that no mutagenic activity was observed. No details were presented [3].

BIBRA notes that a number of bacterial assays, including Ames’ mutagenicity test, gave no evidence of genotoxicity [5].

**Chronic toxicity/Carcinogenicity:** SCF notes that studies are available in mouse and rat. Tissue staining was observed at the highest levels, but no carcinogenic potential was revealed. No details were presented [3].

JECFA reviews studies in mice and rats. Mice were administered 0, 0.01, 0.1, or 0.5% in diet for 80 weeks. Reduced body weight gain and lower heart weight were observed in males at 0.5%. A reduced haematocrit and leucocyte count were noticed in females at 0.5%. No difference in mortality was noticed. Brown colouring of internal organs at 0.5%. Increased incidence of leucocyte infiltration in liver of females at 0.5%. No carcinogenic effect [6;8].

Rats were administered diet containing 0, 500, 2000, or 10000 ppm for 2 years. No adverse effect was observed on body weight gain, food or water consumption, haematology, renal function, serum constituents, or organ weights or histopathology. No tumour induction [6].

**Reproduction toxicity:** SCF notes that a multi-generation reproduction and teratology study is available and that no effects on reproductive function were reported. A small proportion of the colour was observed in the kidney and mesenteric lymph nodes on prolonged ingestion. No other details were specified [3].

JECFA reviews a multi-generation study where rats were dosed with 0, 50, 250, or 500 mg/kg bw/day in diet for three generations. Gross pathological and histological examinations were performed in several organs: Brown colouring of GI-tract and lymph nodes was observed in some animals. No histological findings. Caecal enlargement and increased kidney weight at the highest dose in females. No effect on reproduction or teratological parameters. No effect on postnatal development. NEL with respect to reproduction was 500 mg/kg bw/day, on the basis of changed kidney weight the no-untoward-effect level was 250 mg/kg bw/day [9;10].

In another study rats were orally dosed with 0, 250, 500, or 1000 mg/kg bw/day from day 0 to day 19 of pregnancy. No effect was seen on reproduction, skeletal preparations or gross sections. No foetotoxic or teratogenic effect. It was concluded that doses up to 1000 mg/kg/day were without [10].

**Other:** **Biochemical aspects:** SCF notes that studies on metabolism are available. A small proportion of the colour was observed in the kidney and mesenteric lymph nodes on prolonged ingestion (observed in the multigeneration and teratogenesisity studies). No other details or data were specified [3].
Studies reviewed by JECFA:

*In vitro* studies showed that no significant absorption took place in loops of small intestine from mice, rats, or guinea-pigs.

In mice, rats, and guinea pigs most of the oral dose (80-90%) was excreted in faeces and 7-16.5% in urine. Only trace amounts remained in the body of rats. Trace level amounts were excreted via the bile of rats. The major urine component in these three species was naphthionic acid. The faeces contained small amounts of unchanged Brown HT together with naphthionic acid and two unidentified metabolites. Pre-treatment of male rats for 21 days or pregnancy did not influence the excretion. About 0.2% of the dose was found in the foetus. Special studies on pigment deposition of mesenteric lymph nodes and kidneys have been performed as part of the multigeneration study: No evidence of pigment deposition in any of the many different tissues examined. In conclusion, Brown HT did not survive normal tissue processing of the dye. In extensive studies the accumulation of Brown HT in tissues was investigated. It was concluded that either Brown HT and/or metabolites accumulated in significant amounts during repeated daily oral administration of doses of 250 mg/kg bw [10].

**Conclusion:** There are conflicting results in relation to the accumulation of Brown HT in different organs. The studies are difficult to interpret. No adverse effects have been demonstrated following systemic administration. So if accumulated, an accumulation seems not to cause adverse effects.

It is unclear on which basis SCF has allocated its ADI, which is higher than that of JECFA.

A significant part, about 20%, of the preparation may be unidentified components in some of the toxicological tests performed. In the specifications the amount of unidentified substances have now been reduced to max. 10%.

It should be clarified whether Brown HT as defined by the specifications is covered by the toxicological evaluation.

**References:**


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**MIXED CAROTENES AND ß-CAROTENE**

**E number:**
Mixed carotenes: E 160a (i)
ß-carotene: E 160a (ii)

**Recommendation:** Beta-carotene has recently been evaluated by SCF, which withdrew the previous ADI, but found the continued use as food additive acceptable assuming low exposure levels. SCF expressed the wish to review the advise within the next 3 years in the light of new studies. Exposure monitoring to confirm the low exposure is recommended.

**Chemical name/synonyms:** CI Food Orange 5.

**Chemical formula:** C_{40}H_{56} (ß-carotene).

**Class:** Carotenoid.

**EINECS number:** 230-636-6 (ß-carotene).

**CAS number:** 7235-40-7 (ß-carotene).

**Functional Class:** Colour.

**Specification:**

**Mixed carotenes**

**Manufacture:** Mixed carotenes are produced as two different products, plant carotenes and algal carotenes.

*Plant carotenes* are obtained by solvent extraction of edible plants, carrots, vegetable oils, grass, alfalfa (lucerne) or nettles. Only the following solvents may be used in the extraction: acetone, methyl ethyl ketone, methanol, ethanol, propan-2-ol, hexane, dichloromethane and carbon dioxide. *Algal carotenes* are obtained from the algae *Dunaliella salina*, grown in large saline lakes located in Whyalla, South Australia. ß-carotene is extracted using an essential oil. The preparation is 20-30% suspension in soy bean oil containing natural tocopherols (up to 0.3%). The ratio of trans-cis isomers is in the range of 50/50 – 71/29.

*Plant carotenes*

**Definition:** The main colouring principle of plant carotenes consists of carotenoids of which ß-carotene accounts for the major part. α-, γ-carotene and other pigments may be present. Besides the colour pigments, this substance may contain oils, fats and waxes naturally occurring in the source material.

**EC specifications:** E 160a (i) Mixed carotenes, plant carotenes [2].

**Assay:** Content of carotenes (calculated as ß-carotene) is not less than 5% For products obtained by extraction of vegetable oils: not less than 0.2 in edible fats.

The specification includes purity criteria on Solvent residues, Arsenic, Lead, Mercury, Cadmium and Heavy metals.
JECFA specifications: Carotenes (vegetable) [3].
Assay: Content of carotenes (calculated as β-carotene) is not less than declared.
The specification includes purity criteria on Residual solvents and Lead.

Algal carotenes
Definition: The main colouring principle of plant carotenes consists of carotenoids of which β-carotene accounts for the major part. α-, lutein, zeaxanthin and β-cryptoxanthin may be present. Besides the colour pigments, this substance may contain oils, fats and waxes naturally occurring in the source material.

EC specifications: E 160a (i) Mixed carotenes, algal carotenes [2].
Assay: Content of carotenes (calculated as β-carotene) is not less than 20%.
The specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Carotenes (algae) [3]. The product specified by JECFA is not identical to that specified by EU.
Assay: Content of carotenes (calculated as β-carotene) is not less than declared.
The specification includes purity criteria on Residual solvents, tocopherols and Lead.

β-carotene
Manufacture: β-carotene is obtained by chemical synthesis.

Definition: β-carotene is specified as the predominantly all trans isomer together with minor amounts of other carotenoids. Diluted and stabilised preparations may have different cis/trans isomer ratios.

EC specifications: E 160a (ii) β-carotene [1].
Assay: Not less than 96% total colouring matters (expressed as β-carotene).
The specification includes purity criteria on Subsidiary colouring matters, Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: β-carotene [4].
Assay: Not less than 96% total colouring matters (expressed as β-carotene).
The specification includes purity criteria on Subsidiary colouring matters, Sulphated ash, Arsenic, Lead and Heavy metals.

Exposure: Permitted generally in foodstuffs including some of those where colours are normally not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. As the colour has a numerical ADI the EU monitoring system moved it to tier 3. This is especially important since the ADI has been withdrawn by SCF and the continued acceptance is linked to an assumed low exposure.

SCF/JECFA evaluation:
SCF status: In 1975 SCF endorsed the JECFA ADI of 0-5 mg/kg bodyweight (bw.) expressed as a sum of beta-apo-8’-carotenal (AC), beta-carotene and beta-apo-8’-carotenoic acid, ethyl ester (EAC) [5]. In September 2000, however, SCF decided to withdraw the ADI because of the adverse
effects of β-carotene observed on smokers in human studies, and because the ADI was based on animal studies which had been shown to be irrelevant for the safety evaluation of these substances [6]. In 1997 algal beta-carotene from *Dunaliella salina* grown in South Australia was accepted without ADI but on the basis of an assumed maximal use of around 10 ppm beta-carotene in foods [7].

**JECFA status:** Latest evaluation 1974 (ADI 0-5 mg/kg bodyweight (bw.) expressed as a sum of beta-apo-8’-carotenal, synthetic beta-carotene, beta-apo-8’-carotenoid acid ethyl ester, and beta-apo-8’-carotenoid acid methyl ester [8]. This ADI was based on results from a range of animal studies, the pivotal one being a 4-generation study in rats fed 1000 ppm in the diet, equivalent to 50 mg/kg bw/day, in which no adverse effects were seen. At that time, because of the low toxicity of carotenoids in animal studies and because of their natural occurrence in the human diet, a lower safety factor of 10 was used to derive the ADI. JECFA has not allocated an ADI to algal beta-carotene [9].

**Background data:**

**Subacute/subchronic toxicity:** Synthetic beta-carotene has been tested in rats, rabbits and dogs at doses up to 100 mg/kg for 13 weeks without side effects [10]. Beta-carotene given for four weeks at a dose level of 500 mg/kg bw/day, but not at 375 mg/kg bw/day, increased relative kidney and liver weights. This treatment effect disappeared within two weeks after discontinuation of feeding with beta-carotene. In a subsequent 90-day feeding study with up to 1000 mg/kg bw/day no effects were observed. No adverse effect was observed in rats or chicken exposed to 0.1% algal beta-carotene (about 60 mg/kg bw/day) for up to 8 weeks [7].

**Genotoxicity:** In vitro: Synthetic beta-carotene was not mutagenic in the Ames test using *S. typhimurium*. No genotoxicity was seen for beta-carotene in cultured Chinese hamster ovary cells, in cultured mouse mammary glands, in or in human hep G2 cells exposed to beta-carotene [10]. Algal beta-carotene was not mutagenic in the Ames test using *S. typhimurium* or in a chromosome aberration test with human lymphocytes.

*In vivo:* No genotoxic effects were observed in the mouse bone-marrow micronucleus test at doses up to 234 mg/kg bw/day [11].

**Chronic toxicity/Carcinogenicity:** No adverse effects. In a chronic toxicity study (104 weeks) with groups of 100 male and 100 female CD mice no effects were observed in a range of organs, in clinical chemistry or in ophthalmoscopy.

**Reproduction toxicity:** In a three-generation study with rats dosed with 0, 100, 250, 500 and 1000 mg/kg bw beta-carotene no adverse effects were observed in any generation [10;11]. Algal beta-carotene at 0.2 % in the diet (around 120 mg/kg bw/day) was reported to have no toxicity or any reproductive effects in a rat multigeneration study [7].

**Effects in humans:** There seems to be no sensitisation or intolerance. One of 135 with urticaria or atopic dermatitis reacted positively, and another had an equivocal response, when given oral doses of 100 mg apo-carotenal together with 100 mg β-carotene. None of 123 contact dermatitis patients showed this response. One patient from the contact dermatitis group and one from the urticaria group reacted when tested with placebo [12]. Two long-term studies with doses of 20-30 mg/day given to male smokers or asbestos exposed workers through 2-6 years have shown a significant
increase in the lung cancer incidence and also an increased risk of heart disease [13;14] such effects were observed in non-smokers or in ex-smokers.

**Other:** Metabolism: Beta-carotene is absorbed from the gut. The absorption fraction varies from 8-50% depending on the food matrix. Conversion to vitamin A may take place, depending on the current vitamin A status. In animals most of the dietary beta-carotene is immediately converted to retinol.

**Conclusion:** Beta-carotene is in general not toxic to animals or humans except for a co-carcinogenic effect in heavy smokers. As SCF has withdrawn the ADI it should be investigated what is the likely exposure from additive uses. Toxicological studies on species relevant for the safety evaluation are desirable to establish an ADI.

**References:**


6. Opinion of the Scientific Committee on Food the safety of use of beta-carotene from all dietary sources (expressed on 7 September 2000).  
   [http://europa.eu.int/comm/food/fs/sc/scf/out71_en.pdf](http://europa.eu.int/comm/food/fs/sc/scf/out71_en.pdf)


8. [1974, NMRS 54/TRS 557-JECFA 18]  

9. [1993, TRS 837-JECFA 41]  


ANNATTO (BIXIN, NORBIXIN)

E number: E 160b

Recommendation: Considering that the existing toxicological data are old and performed on colours whose composition significantly differs from what is used to day a re-evaluation should be considered.

Chemical name/synonyms:
Bixin: 6’-Mthylhydrogen-9’-cis-6,6’-diapocarotene-6,6’dioate and 6’-methylhydrogen-9’-trans-6,6’-diapocarotene-6,6’dioate/ CI Natural orange 4.
Norbixin: 9’-Cis-6,6’-diapocarotene-6,6’dioic acid and 9’-trans-6,6’-diapocarotene-6,6’dioic acid / CI Natural orange 4.

Chemical formula:
Bixin: C_{25}H_{30}O_{4}
Norbixin: C_{24}H_{28}O_{4}

Class: Carotenoid.

EINECS number:
215-735-4 (annatto)
289-561-2 (annatto seed extract)
230-248-7 (bixin)

CAS number: 1393-63-1

Functional Class: Colour.

Specification: EC specifies the following three annatto products: Solvent extracted bixin and norbixin, alkali extracted annatto and oil extracted annatto.

Solvent extracted bixin and norbixin

Manufacture: Bixin is prepared by the extraction of the outer coating of the seeds of the annatto tree (Bixa orellana L.) with one or more of the following solvents: acetone, methanol, hexane, dichloromethane or carbon dioxide, followed by removal of the solvent. Norbixin is prepared by hydrolysis by aqueous alkali of the extracted bixin. Bixin and norbixin may contain other materials extracted from the source material.

Definition: Bixin powder contains several coloured components, the major single one being bixin, which may be present in both cis- and trans- forms. Thermal degradation products of bixin may also be present. Bixin is soluble in ethanol and acetone. The norbixin powder contains the hydrolysis product of bixin, in the form of sodium and potassium salts as the major colouring principle. Both cis- and trans- forms may be present. Norbixin is soluble in water and dilute alkali.
EC specifications: E 160b (i) Solvent extracted bixin and norbixin [1]. Assay: Content of bixin powders not less than 75% total carotenoids calculated as bixin. Content of norbixin powders not less than 25% of total carotenoids calculated as norbixin. The specification includes purity criteria on Solvent residues, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Annatto extracts (solvent extracted) [2]. Assay: Content of bixin preparations not less than 75% total carotenoids calculated as bixin. Content of norbixin preparations not less than 25% of total carotenoids calculated as norbixin. The specification includes purity criteria on Residual solvents, Arsenic and Heavy metals.

Alkali extracted annatto

Manufacture: Alkali extracted annatto is prepared by the extraction of the outer coating of the seeds of the annatto tree (Bixa orellana L.) with aqueous alkali (sodium or potassium hydroxide). Alkali extracted annatto may contain other materials extracted from the source material.

Definition: Alkali extracted annatto contains norbixin, the hydrolysis product of bixin, in the form of sodium or potassium salts, as the major colouring principle. Both cis- and trans- forms may be present. Alkali extracted annatto is soluble in water and slightly soluble in ethanol.

EC specifications: E 160b (ii) Alkali extracted annatto [1]. Assay: Not less than 0.1% total carotenoids expressed as norbixin. The specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Alkali extracted annatto is defined together with oil extracted annatto in one combined specification. See below.

Oil extracted annatto

Manufacture: Oil extracted annatto in oil, as solution or suspension is prepared by the extraction of the outer coating of the seeds of the annatto tree (Bixa orellana L.) with edible vegetable oils. Oil extracted annatto may contain other materials extracted from the source material.

Definition: Oil extracted annatto contains several coloured components, the major single one being bixin, which may be present in both cis- and trans- forms. Thermal degradation products of bixin may also be present. Oil extracted annatto is insoluble in water and slightly soluble in ethanol.

EC specifications: E 160b (ii) Alkali extracted annatto [1]. Assay: Not less than 0.1% total carotenoids expressed as bixin. The specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Annatto extracts (oil and alkali-extracted) [2]. Assay: Oil extracted annatto: Not less than the percentage of total carotenoids (expressed as bixin) stated by the vendor. Alkali extracted annatto: Not less than the percentage of total carotenoids (expressed as norbixin) stated by the vendor. The specification includes purity criteria on Arsenic and Heavy metals.

Exposure: The permitted uses of annatto is restricted to a few commodities of which can be mentioned margarine, fine bakery wares desserts and smoked fish 10 mg/kg, decorations and
coatings, edible ices and some snacks 20 mg/kg and in red Leicester cheese 50 mg/kg. Not permitted in beverages except liqueurs (10 mg/l).

In the EU monitoring system annatto was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 0-62% of ADI, while the calculated intake by young children is reported in the range of 108-170%. The investigators concluded that examination at tier 3 of intakes by young children is needed.

In 1999 JECFA reported that intake estimates based on levels proposed in the draft General Standard for Food Additives and the range of foods in which use is allowed integrated with national food consumption data exceeded the ADI of 0-0.065 mg/kg bw, expressed as bixin [3].

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation in 1979 when an ADI of 2.5 mg/kg bw was allocated to an extract containing 2.6% carotenoids expressed as bixin. The Committee notes that the ADI is based on a long-term study with an extract with 2.6% bixin, but no details were specified. Based on the content of bixin in the extract tested an ADI of 0.065 mg/kg bw was calculated expressed as bixin [4].

**JECFA status:** Latest evaluation in 1982 when an ADI of 0-0.065 mg/kg bw expressed as bixin was allocated [5]. Based on the long-term and reproduction rat study mentioned below [6].

**Background data:**

**Subacute/subchronic toxicity:** Three groups of 10 male and 10 female rats were fed 2% fat-soluble annatto, 2% water-soluble annatto, or no extract for 13 weeks. There were no abnormalities on food intake, growth, body weight gain or histopathology of the major organs [6]. Other animal studies confirm this.

**Genotoxicity:** *In vitro:* Annatto extracts were not genotoxic in an investigation of its ability to induce DNA damage in an E. coli rec [6]. No genotoxicity was evident in Ames test [7].

**Chronic toxicity/Carcinogenicity:** Two groups of fifty male and fifty female mice were fed either 0.5% corn oil or 0.5% fat-soluble annatto for their life span. The animals also received 0.1 ml s.c. three times a week for 17 month. Two other groups of 25 male and 24 female mice were fed 0 and 0.05% concentrated fat-soluble annatto for there life span an injected with 0. 001 ml s.c. for 10½ month. Most animals died between 15 and 21 month due to intercurrent infection. No statistically significant increase in tumour incidence in any of these groups [6].

**Reproduction toxicity:** Ten male and 10 female rats received corn oil containing 0, 0.05% fat-soluble annatto or 0.5% water-soluble annatto for their life span (bixin content between 0.2 and 2.6%). A further generation and the offspring of this generation were fed similar diets for 7 and 8½ months. No deleterious effects were seen on growth, reproduction or mortality. No teratogenic effects were seen [6].

**Effect in humans:** when a group of 56 patient suffering from chronic urticaria and/or angioneurotic oedema were orally 25µl of annatto extract 15 patients reacted with flare up of symptoms [6] Skin reactions were produced in 11 of 112 urticaria patient given oral doses of up to 10 mg of annatto extract [8].
Other: There is evidence for intestinal absorption of annatto pigments. The excretions for oil-soluble as well as water-soluble annatto extracts were investigated in a study where 5 groups of rats (4 male and 4 female) were given 1. A undiluted water-soluble preparation, mainly norbixin (10 ml/kg). 2. A vegetable oil solution, mainly bixin (2 ml/kg) 3. A vegetable oil solution containing bixin and thermal degradation product (2 ml/kg) 4. Sunflower oil (2 mg/kg) 5. Water (10 ml/kg) The excretion from blood was fastest for the water-soluble extract, presumable because the oil-soluble extract is metabolised to water-soluble pigments before being further metabolised. After 24 hours almost all water-soluble extract were absorbed and [6].

The depletion of adipose tissue stored pigments is fast. In four male and four female rats fed oil-soluble extract for 2 weeks and then fed a normal diet for 2 weeks there was a clear difference in the coloration of the adipose tissue between week 2 and 4 [6]. After ingestion of 1 ml commercial Annatto Food Colour, bixin and norbixin were detected in blood plasma. Complete clearance from plasma was seen after 8 hours for bixin and after 24 hours for norbixin [9].

Conclusion: Data are old, but within the ADI sufficient except for genotoxicity in vivo. Data on genotoxicity are desirable. Some data indicate the possibility that the extract or components can cause allergy-like symptoms and this should be taken into consideration in the next evaluation.

The manufacturing procedures of annatto, bixin, norbixin has been developed significantly since the toxicological evaluation carried out by SCF and JECFA. Especially the solvent extracted bixin and norbixin have been introduced on the market after the evaluations. A re-evaluation to reflect the present days products is desirable.

References:


3. [1999, TRS 896-JECFA 53]


5. [1982, TRS 683-JECFA 26]

6. [1982, FAS 17-JECFA 26]


PAPRIKA EXTRACT (CAPSANTHIN, CAPSORUBIN)

E number: E 160c

Recommendation: Paprika extract has not formally been evaluated by SCF. Although there is no reason to expect any adverse effect if exposure lies within what can normally be expected from the use of paprika as a spice in food, the colour should be evaluated.

Chemical name/synonyms:
Capsanthin: (3R, 3’S, 5’R)-3,3’-dihydroxy-β,κ-carotene-6-one.
Capsorubin: (3S, 3’S, 5R, 5’R)-3,3’-dihydroxy-κ,κ-carotene-6,6’-dione.

Chemical formula:
Capsanthin: C_{40}H_{56}O_{3}
Capsorubin: C_{40}H_{56}O_{4}

Class: Carotenoid.

EINECS number:
Capsanthin: 207-364-1
Capsorubin: 207-425-2

CAS number: 68917-78-2

Functional Class: Colour.

Specification:
Manufacture: Paprika extract is obtained by solvent extraction of paprika, which consists of the ground fruit pods, with or without seeds, of Capsicum annuum L. Only methanol, ethanol, acetone, hexane, dichloromethane, ethyl acetate and carbon dioxide may be used as solvents in the extraction. The JECFA specification also allows for the use of trichloroethylene.

Definition: Paprika extract consists contains capsanthin and capsorubin as the major colouring principles. A wide variety of other coloured compounds are known to be present together with other substances extracted from the source material.

EC specifications: E 160c Paprika extract, capsanthin, capsorubin [1].
Assay: Paprika extract: not less than 7.0% carotenoids. Capsanthin/capsorubin: not less than 30% of total carotenoids.
Capsaicin: not more than 250 mg/kg.
In addition the specification includes purity criteria on Solvent residues, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Paprika Oleoresin [2].
Assay: Not less than 500 ASTA Color Value units.
Capsaicin: not more than 0.5%
In addition the specification includes purity criteria on Residual solvents, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where colours are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. Not included in the EU monitoring system.

**SCF/JECFA evaluation:**
**SCF status:** Not evaluated by SCF.

**JECFA status:** In 1989 JECFA stated that the use of paprika oleoresin is “self limiting as a spice extract” and therefore it did not allocate an ADI [3]. In 2000, when asked to clarify this statement, JECFA specified that this only covered the use as spice and that the use as colour thus has not been evaluated [4].

**Background data:**
**Subacute/subchronic toxicity:** No data available.

**Genotoxicity:** No data available.

**Chronic toxicity/Carcinogenicity:** No data available.

**Reproduction toxicity:** No data available.

**Allergy/Intolerance:** A low incidence of local reactions were seen in skin tests with paprika in dermatitis patients [5]. One case have been reported on the development of IgE antibodies specific to paprika in a person who previously has been diagnosed as having food allergy one year after starting to prepare a certain kind of sausage, but no cases have been reported after intake of food containing paprika extract [6].

**Conclusion:** The use of paprika extract as a food colour has not been evaluated by SCF or JECFA and no toxicological data exists on this colour. However, as paprika is a normal constituent of food as a spice, there is no reason to expect undesirable side effects from its use as a food colour. Especially so as the specifications exclude the content of capsaicin (EU max 250 mg/kg paprika extract and JECFA max 5 g/kg). Capsaicin is the constituent, which gives strong paprika its pungent taste and which has been reported to possess toxic properties.

There are significant differences between the EC specification and the JECFA specification, the former being the most restrictive. The EU specification defines the preparations sold and used as a food additive.

**References:**


3. [1989, TRS 789-JECFA 35]

4. [2000, TRS 901-JECFA 55]


LYCOPENE

E number: E 160d

Recommendation: No need for a re-evaluation, but a monitoring of present exposure is desirable to assess whether the SCF assumption on exposure is still valid.

Chemical name/synonyms: Lycopene, ψ,ψ-carotene/carotene/ Natural yellow 27.

Chemical formula: C₄₀H₅₆

Class: Carotenoid.

Functional Class: Colour.

Specification:
Manufacture: Lycopene is obtained by solvent extraction of red tomatoes (Lycopersicon esculentum L.) with subsequent removal of the solvent. Only dichloromethane, carbon dioxide, ethyl acetate, acetone, propan-2-ol, methanol, ethanol and hexane may be used as solvents in the extraction.

Definition: The major colouring principle of the lycopene preparations is the carotenoid lycopene. Minor amounts of other carotenoid pigments may be present. The preparations may contain oils, fats, waxes and flavour components naturally occurring in the source material.

EC specifications: E 160d Lycopene [1].
Assay: -
The specification includes purity criteria on Solvent residues, Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: No JECFA specification has been prepared.

Exposure: Permitted in all “colourable” foods. Maximum level in soft drinks 100 mg/l and 50-500 mg/kg in solid foods. This means that if the colour is used to the maximum permitted exposure will far exceed the intake from natural sources.

No ADI has been specified and the substance was for that reason not included in the EU monitoring system (tier 0) notwithstanding that the SCF evaluation is specifically linked to potential exposure.

SCF/JECFA evaluation:
SCF status: Latest evaluation: 1987. Acceptable from natural foods when derived from natural processes [2]. In accordance with the 1987 evaluation SCF in 1999 was asked to advise on the safety in use of synthetic lycopene as a food colour. However, the Committee requested further information before synthetic lycopene can be fully evaluated [3].

Background data:

**Subacute/subchronic toxicity:** A daily dose of 500 mg/kg bw/day to the rat only induced slight variations in diverse toxicological parameters, that was not found to exceed the physiological norm. Older studies conducted showed the same lack of toxic effects [3].

**Genotoxicity in vitro:** Lycopene has been found not to be mutagenic in several strains of *S. typhimurium*. Upon exposure to light weak mutagenic activity was observed in Ames strains TA100 and TA97. The presence of S-9 reduced the mutagenicity [3]

**Chronic toxicity/Carcinogenicity:** No data available on experimental animals. Most reports suggest that lycopene is protective against a wide range of cancers [5].

**Reproduction toxicity:** No reproductive toxicity was observed in rats fed 1-20 mg lycopene/kg bw/day for 200 days [6].

**Effects in humans:** Single cases have been reported in which individuals consumed high doses of lycopene through natural food stuffs. The intake of 2 litres of tomato juice daily for several years (2.7 mg/kg bw/day) resulted in orange/yellow discolouration of the skin and histological analysis of the liver revealed deposition of the pigment [7]. Discomforts such as nausea, vomiting and diarrhoea were also observed. No discolouration was observed in males administered 180 g tomato juice (0.2 mg/kg bw/day) for 42 days [8].

**Other:** Metabolism: In average 8-9% of an initial dose of 14C-labeled-lycopene was absorbed, with maximal plasma levels after 2 hours [9], with 87-97 recovered in the faeces. One major lycopene metabolite has been found in humans, 5,6-dihydroxy-5,6-dihydrolycopene, which apparently results from oxidation of lycopene to an intermediate, lycopene epoxide. Comparison of the tissue uptake and accumulation of natural and synthetic lycopene revealed a 2.5 fold increase in the level of lycopene in the latter [9], which presumably stems from the fact that the synthetic preparation contains more of the cis-form which presumably is more bioavailable than the trans-isomer [10].

**Conclusion:** If present uses of lycopene from natural sources do not result in intakes which differ significantly from what can be consumed through normal food there is no need for further safety testing or a re-evaluation of this pigment due to its general low toxicity. However the present permitted levels can result in intakes, which vastly exceeds what can be consumed from natural sources. The actual use levels should therefore be monitored.

In line with the SCF opinion the issues regarding synthetic lycopene should be treated separately from natural lycopene. Synthetic lycopene has a chemical composition different from that of natural sources. Thus synthetic lycopene contains significantly more of the cis-isomers as compared to natural lycopene and the cis-forms seem to be absorbed to a greater extent than the trans-isomers [10].

On the assumption that solvent extraction is regarded as a natural process, lycopene as defined by the specifications is covered by the toxicological evaluation.
References:


   http://europa.eu.int/comm/food/fs/sc/scf/out47_en.pdf

4. [1977, TRS 617-JECFA 21]


**β-apo-8’-Carotenal (C30) and Ethyl Ester of β-apo-8’-carotenoic Acid (C30)**

**E number:**
- β-apo-8’-Carotenal (C30): E 160e
- Ethyl ester of β-apo-8’-carotenoic acid (C30): E 160f

**Recommendation:** As SCF has decided to withdraw also the ADI for β-apo-8’-Carotenal (C30) and ethyl ester of β-apo-8’-carotenoic acid (C30) when the previous ADI for β-carotene was deleted, also these substances should be included in the review foreseen by SCF for β-carotene.

**Chemical name/synonyms:**
- Ethyl ester of β-apo-8’-carotenoic acid (C30): β-apo-8’-carotenoic acid ethyl ester, ethyl 8’-apo-β-caroten-8’oate/ CI Food Orange 7.

**Chemical formula:**
- β-apo-8’-Carotenal (C30): C_{30}H_{40}O
- Ethyl ester of β-apo-8’-carotenoic acid (C30): C_{32}H_{44}O_{2}

**Class:** Carotenoid.

**EINECS number:**
- β-apo-8’-Carotenal (C30): 214-171-6
- Ethyl ester of β-apo-8’-carotenoic acid (C30): 214-173-7

**CAS number:**
- β-apo-8’-Carotenal (C30): 1107-26-2
- Ethyl ester of β-apo-8’-carotenoic acid (C30): 1109-11-1

**Functional Class:** Colour.

**Specification:**
*Manufacture:* β-apo-8’-Carotenal (C30) and ethyl ester of β-apo-8’-carotenoic acid (C30) are obtained by chemical synthesis.

**β-apo-8’-Carotenal (C30)**

**Definition:** β-apo-8’-Carotenal (C30) as specified is the predominantly all trans isomer of β-apo-8’-carotenal together with minor amounts of other carotenoids. Diluted or stabilised forms are prepared from β-apo-8’-carotenal meeting the specification and include solutions or suspensions of β-apo-8’-carotenal in edible fats or oils, emulsions and water dispersible powders. These preparations may have different cis/trans isomer ratios.
E 160e β-apo-8’-Carotenal (C30) and E 160f ethyl ester of β-apo-8’-carotenoic acid (C30).

**EC specifications:** E 160e β-apo-8’-Carotenal (C30) [1].  
Assay: Not less than 96% of total colouring matters.  
The specification includes purity criteria on Subsidiary colouring matters, Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** β-apo-8’-Carotenal [2].  
Assay: Not less than 96% of total colouring matters.  
The specification includes purity criteria on Subsidiary colouring matters, Sulfated ash, Arsenic, Lead and Heavy metals.

*Ethyl ester of β-apo-8’-carotenoic acid (C30)*  
**Definition:** Ethyl ester of β-apo-8’-carotenoic acid (C30) as specified is the predominantly all trans isomer of β-apo-8’-carotenoic acid ethyl ester together with minor amounts of other carotenoids. Diluted or stabilised forms are prepared from β-apo-8’-carotenoic acid ethyl ester meeting the specification and include solutions or suspensions of β-apo-8’-carotenoic acid ethyl ester in edible fats or oils, emulsions and water dispersible powders. These preparations may have different cis/trans isomer ratios.

**EC specifications:** E 160f Ethyl ester of β-apo-8’-carotenoic acid (C30) [1].  
Assay: Not less than 96% of total colouring matters.  
The specification includes purity criteria on Subsidiary colouring matters, Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** β-apo-8’-Carotenoic acid ethyl ester [2].  
Assay: Not less than 96% of total colouring matters.  
The specification includes purity criteria on Subsidiary colouring matters, Sulfated ash, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted in all “colourable” food. Maximum level in soft drinks 50 mg/l and 50-500 mg/kg in solid foods. Although the permitted uses are restricted and had a numerical ADI the colours were not included in the first tiers of the EU monitoring system but moved to tier 3 together with beta-carotene.

**SCF/JECFA evaluation:**  
**SCF status:** In 1975 the JECFA ADI of 5 mg/kg bw was endorsed. It was expressed as the sum of beta-apo-8’-carotenal and beta-apo-8’-carotenoic acid, ethyl ester together with β-carotene (E-160a) [3]. After the general deadline for inclusion of new data into the present review SCF decided to withdraw the previous ADI for β-carotene and, as they were included in the group ADI, also β-apo-8’-carotenal and β-apo-8’-carotenoic acid ethyl ester. This decision was based on the adverse effects of β-carotene observed in human studies conducted in male smokers, and because the ADI was based on animal studies where the model had been shown to lack relevance with regard to human risk assessment (see also the monograph on 160a) [4].
**JECFA status:** Latest evaluation in 1974 when an ADI of 0-5 mg/kg bw was allocated. It was expressed as the sum of beta-apo-8’-carotenal and beta-apo-8’-carotenoic acid ethyl and methyl ester together with \(\beta\) carotene [5].

**Background data:**

**Subacute/subchronic toxicity:** No adverse effects on rats. Groups of 16 male rats received intragastrically doses of 0, 100 or 500 mg/kg beta-apo-8’-carotenal (AC) or \(\beta\)-apo-8’-carotenoic acid ethyl ester (EAC) five days a week for 34 weeks without adverse effect on bodyweight gain, general health, survival, liver and kidney function and organ weight. Testicular weights of the 500 mg/kg group were significant lower than control group. Fertility was not affected [6].

**Genotoxicity:** *In vitro:* AC was not mutagenic in the Ames test using *S. typhimurium*. No genotoxicity was seen for AC in cultured hamster lymphocytes exposed for AC in 48 hours (quoted in [7]). No data available *in vivo*.

**Chronic toxicity/Carcinogenicity:** A three-generation study from 1966 in rats at 0 ppm, 1000 ppm, 2000 ppm and 5000 ppm AC for 2 years showed no adverse effect in any generation [6]. 15 male rats were fed diet containing 1% EAC for 2 years without adverse effect on mortality, weight, fertility and general health.

**Reproduction toxicity:** A three-generation study in rats at 0 ppm, 1000 ppm, 2000 ppm and 5000 ppm AC for 2 years showed no adverse effect in any generation [6].

**Effect in humans:** There seem to be no sensitisation or intolerance. One of 135 persons with urticaria or atopic dermatitis reacted positively, and another had an equivocal response, when given oral doses of 100 mg AC with 100 mg \(\beta\)-carotene. None of 123 persons with contact dermatitis showed this response. One patient from the contact dermatitis group and one from the urticaria group reacted when tested with placebo (quoted in [7]).

**Other:** If administrated to rats, as the only dietary carotene there is some accumulation of AC in the liver. If excessive dose is given almost all is excreted in faeces indicating low absorption. After oral administration of AC to monkeys there was an orange discoloration of liver and fat [6]. In vitamin A-deficient rats, 4% of dietary AC is converted to vitamin A in the gut. *In vivo* AC is oxidized to carotenoic acids but less readily reduced to alcohols. AC given to human as one oral dose was extensively metabolised to mainly the corresponding acid, alcohol and palmitate ester [6]. Without giving further information JECFA mention that EAC is eliminated very rapid from the blood of human infant.

**Conclusion:** Although none of the available data indicate any reason for concern there are too few data to make a full conclusion about these pro vitamin A compounds. As SCF has decided to withdraw also the ADI for \(\beta\)-apo-8’-Carotenal (C30) and ethyl ester of \(\beta\)-apo-8’-carotenoic acid (C30) when the previous ADI for \(\beta\) carotene was deleted, also these substances should be included in the review foreseen by SCF for \(\beta\)-carotene [4].

\(\beta\)-apo-8’-Carotenal (C30) and ethyl ester of \(\beta\)-apo-8’-carotenoic acid (C30) as defined by the specifications seems to be covered by the toxicological evaluation.
E 160e β-apo-8’-Carotenal (C30) and E 160f ethyl ester of β-apo-8’-carotenoic acid (C30).

References:


5. *[1974, NMRS 54/TRS 557-JECFA 18]*

6. *[1974, FAS 6/NMRS 54A-JECFA 18]*

LUTEIN

E number: E 161b

Recommendation: No need for an evaluation, but an estimate of present exposure is desirable. Specification differ from SCF evaluation with respect to permitted sources.

Chemical name/synonyms: 3,3’-dihydroxy-d-carotene/ mixed carotenoids, xanthophylls.

Chemical formula: \(C_{40}H_{56}O_{2}\)

Class: Carotenoid.

EINECS number: 204-840-0

CAS number: 127-40-2

Functional Class: Colour.

Specification:

Manufacture: Lutein is obtained by solvent extraction of edible fruits, plants, grass, lucerne (alfalfa) and Tagetes erecta. Only methanol, ethanol, propane-2-ol, hexane, acetone, methyl ethyl ketone, dichloromethane and carbon dioxide may be used as solvents in the extraction.

Definition: The main colouring principle of preparations of lutein consists of carotenoids of which lutein and its fatty acid esters account for the major part. Variable amounts of carotenes will also be present. The product may contain fats, oils and waxes naturally occurring in the source material. It is insoluble in water and soluble in hexane.

EC specifications: E 161b Lutein [1].
Assay: Not less than 4% of total colouring matter calculated as lutein.
In addition the specification includes purity criteria on Solvent residues, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Mixed carotenoids [2].
Assay: Content of total colouring matter calculated as lutein not less than declared.
In addition the specification includes purity criteria on Residual solvents, synthetic colours and Lead.

Exposure: Permitted in all colourable food. Maximum level in soft drinks 50 mg/l and 50-500 mg/kg in solid foods, but if used as permitted exposure from this source could considerably exceed normal exposure.

Based on the concentration of lutein in different vegetables and a household budget survey of vegetables and fruits the daily intake of lutein from natural sources in Denmark is estimated to less than 1 mg/day with big individual variations [3].
**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1974. Without giving an ADI SCF stated that although there are no biological data available, xanthophylls prepared from natural foods by physical processes could be accepted for use as colouring matter in food without further investigation [4]. However, in the same report, as in several later reports, the Committee stresses that the use of colours derived from natural sources are only acceptable as food colours provided the quantities ingested from this use do not differ substantially from the amounts likely to be ingested as a result of the normal consumption of the foods in which they occur naturally.

In 1977 SCF expressed that antheraxanthin from Aztec marigold (tagetes) should not be used to colour food [6]

**JECFA status:** Not evaluated.

**Background data:**

**Subacute/subchronic toxicity:** No data available.

**Genotoxicity:** No data available.

**Chronic toxicity/Carcinogenicity:** No data available.

**Reproduction toxicity:** No data available.

**Other:** The toxicity of carotenoids was evaluated in two recent publications one from the Nordic Council of ministers [3] and another from WHO [5]. None of them gave any data about the toxicity of lutein, but concentrated on the potential beneficial effects.

**Conclusion:** Although there are no toxicological data available there are no evidence suggesting that there is any problems using lutein as a food colour provided it is prepared from natural foods and that the quantities ingested do not differ substantially from the amounts likely to be ingested in a normal diet. The uncertainty about the daily intake makes it impossible to make any recommendation concerning the amount, which can be considered as safe.

Lutein as defined by the specifications includes source materials as lucerne and tagetes that could not be regarded as natural foods.

**References:**


**CANTHAXANTHIN**

**E number:** E 161g

**Recommendation:** A re-evaluation is not needed.

**Chemical name/synonyms:** β-Carotene-4,4’-dione, 4,4’-dioxo-β-carotene/ CI Food Orange 8.

**Chemical formula:** $C_{40}H_{52}O_2$

**Class:** Carotenoid.

**EINECS number:** 208-187-2

**CAS number:** 514-78-3

**Functional Class:** Colour.

**Specification:**
**Manufacture:** Canthaxanthin is obtained by chemical synthesis.

**Definition:** Canthaxanthin consists predominantly of trans-β-Carotene-4,4’-dione together with minor amounts of other isomers. Diluted and stabilised preparations are prepared from canthaxanthin meeting the specification and include solutions or suspensions of canthaxanthin in edible fats or oils, emulsions and water dispersible powders. These preparations may have different cis/trans isomer ratios.

**EC specifications:** E 161g Canthaxanthin [1].
Assay: Not less than 96% of total colouring matters (expressed as canthaxanthin).
The specification includes purity criteria on Subsidiary colouring matters, Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Canthaxanthin [2].
Assay: Not less than 96% of total colouring matters (expressed as canthaxanthin).
The specification includes purity criteria on Subsidiary colouring matters, Sulphated ash and Lead.

**Exposure:** Canthaxanthin is permitted only as an additive in Saucisse de Strasbourg 15 mg/kg, which means that exposure from the use as direct additive is negligible. Besides the occurrence in some wild mushrooms canthaxanthin is used as a feed additive for poultry and fish. Reliable intake estimates are not available but the Scientific Committee on Food has estimated a residue level of 0.2 mg/egg and 0.1 mg/100g fish [3].

In the EU monitoring system canthaxanthin was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 0% of ADI, while
the calculated intake by young children is reported by one member state as 0%. It was concluded that no further examination was needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** When evaluated first time in 1983 canthaxanthin was allocated an ADI of 25 mg/kg bw based on studies in rats [4]. Because of the effects seen in the human eye the ADI was reduced to 0.05 mg/kg bw in 1989 [5]. The substance was latest evaluated in 1997 when an ADI 0.03 mg/kg bw was allocated (rounded up from 0.025) [3].

**JECFA status:** The previous ADI of 25 mg/kg bw was reduced in 1987 and latest in 1995 an ADI of 0-0.03 mg/kg bw was allocated based on the NOEL of 0.25 mg/kg bw per day in humans and a safety factor of 10 [6].

**Background data:**

**Subacute/subchronic toxicity:** There was no adverse effect in a study where groups of three male and three female dogs receive 0, 100 and 400 mg/kg bw of canthaxanthin for 15 weeks [7].

**Genotoxicity:** *In vitro*: Canthaxanthin did not induce mutation in *S. typhimurium* nor in *Saccharomyces cerevisiae* [8]. *In vivo*: There was no evidence of chromosomal damage in the form of micronuclei in mice after “two- fold application” (route unspecified) at doses up to 222 mg/kg bw [9].

**Chronic toxicity/Carcinogenicity:** Groups of 50 male CD Sprague-Dawley rats were given canthaxanthin as microencapsulated water soluble beads containing 10% canthaxanthin in their food for up to 104 weeks in doses up to 250 mg/kg bw/day. There was no effect on survival of the rats or on organ weights. There was a discoloration of GI tract and adipose tissue at all dose levels. In animals treated 75 mg/kg bw/day or 250 mg/kg bw/day there was a hepatocyte enlargement in the liver, a higher incidence of and/or grade of fat accumulation. In animals receiving 25 mg/kg bw/day or more there was increased incidence of vacuolation in the liver [9]. In a similar study groups of 80 to 105 female CD Sprague-Dawley rats were given the same doses. In this study there was a significant increase in liver weight in animals receiving 75 or 250 mg/kg bw other effects were similar to the effects on male rats [9].

Some studies in monkeys indicate that with canthaxanthin is tolerated in high doses for 2-3 years. In these studies special attention was made to retinal crystalline deposition and crystals were observed in 8/18 animals at 200 mg/kg bw/day or higher doses [9].

**Reproduction toxicity:** In a three generation study male and female rats were fed doses of 0, 0(placebo) 250, 500 and 1000 mg/kg bw/day in form of beadsles in the diet throughout the study. There were no adverse effects related to the reproductive performance. Groups of 40 pregnant FU-Albino rats were given canthaxanthin in the diet at dose levels of 0, 250, 500 or 1000 mg/kg bw/day on day 7 to 16 of pregnancy. There was no treatment-related effect [8].

**Effect in humans:** The major concern for the use of canthaxanthin is the formation of retinal crystalline deposit. In a retrospective biostatistical investigation in humans who had taken canthaxanthin for either medical or cosmetic reason 95 out of 411 person had retinal crystalline deposition. The daily intake was 15-240 mg/person and the total dose was 0.6-201g over a period of 1 to 14. There was a strong dose-response relationship between formation of retinal crystalline
deposit and the use of canthaxanthin suggesting a NOEL below 30 mg/person/day or a total intake of less than 3000 mg [9]. In 14 patients treated with cumulative doses of canthaxanthin up to 178 g for up to 12 years the retinal crystalline deposit was reduced up to 70% 5 years after discontinuation of treatment [9]. The effect on the visual function was studied by threshold static perimetry in 19 patients who had ingested canthaxanthin (amount not given). It was shown that patients with retinal deposits presented lower retinal sensitivity than both controls (patient with no history of canthaxanthin intake) and treated patient without retinal deposit. This led to the conclusion that canthaxanthin retinopathy adversely affect the neurosensory retina [9].

The effect of canthaxanthin on the ERG scotopic b-wave amplitude was investigated in a study of 27 humans suffering from porphyria. They were treated with doses of 15 mg/day for 5 weeks, increasing to 60 mg/day for 5 week and subsequently 90 to 120 mg/day during the summer month. No treatment was given during winter. While one month dosage of 15 mg/day produced no systemic change an additional month on a dose of 60 mg/day produced a reduction in ERG scotopic b-wave amplitude. The effect was reversible, during the winter the reduction disappeared. The NOEL in this study was 15 mg/day, equivalent to 0.25mg/kg bw/day [9].

The canthaxanthin concentration in retina in 7 monkeys given 49 mg/kg bw/day for 36 to 83 weeks (total intake up to 54 g canthaxanthin) was compared with a person who had taken sun-tanning pills (16 in total). The concentration in retina of the reference person was 100 times higher than concentration in retina in the monkeys. This has led to the assumption that humans have a higher susceptibility to canthaxanthin deposition in the retina than monkeys [9].

No hepatotoxicity was seen in 11 patients treated for up to 12 years with cumulative doses up to 150g.

Other: A study with single doses of radio labelled doses of canthaxanthin administered to male and female Cynomolgus monkeys showed that about 3% to 7% of the dose was absorbed. The highest concentration was found in the adrenal gland. There were moderate concentrations in the spleen liver, bone marrow, skin and fat. Low concentrations were found in parts of the eye and brain [9].

In a study where 5 SPF Wistar rats were administrated canthaxanthin in the diet (300 mg canthaxanthin/kg diet) for 15 days there was a strong induction of P450 dependent hepatic enzymes particularly EROD and MROD [10]. These results were confirmed by a later study where also some of the P450 enzymes in liver and kidney were induced [11].

Conclusion: The major concern is the possible formation of retinal deposit and the JECFA as well as the SCF ADI of 0-0.03 mg/kg bw/day was based on the study concerning reduction of the b-scutopic wave. This ADI is unlikely to be exceeded from its use as food additive.

Canthaxanthin as defined by the specifications seems to be covered by the toxicological evaluation.
References:


**BEETROOT RED (BETANIN)**

**E number:** E 162

**Recommendation:** Clarify the significance of tumourigenesis induced by AFB1. Also studies to describe the current use of E 162 and the associated concentration of nitrate are desirable.

**Chemical name/synonyms:** (S-(R’,R’)-4-(2-(2-Carboxy-5(β-D-glucopyranosyloxy)-2,3-dihydro-6-hydroxy-1H-indol-1-y1)ethenyl)-2,3-dihydro-2,6-pyridine-dicarboxylic acid, 1-(2-(2,6-dicarboxy-1,2,3,4-tetrahydro-4-pyridylidene)ethylidene)-5-β-D-glucopyranosyloxy)-6-hydroxyindolium-2-carboxylate/ beet red.

**Chemical formula:** C_{24}H_{26}N_{2}O_{13}

**Class:** Betalaine.

**EINECS number:** 231-628-5

**CAS number:** 7659-95-2

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Beetroot red is obtained from the roots of red beets (*Beta vulgaris* L. var. rubra) by pressing crushed beet as press juice or by aqueous extraction of shredded beetroots and subsequent enrichment in the active principle. The products may be concentrated and some products may be refined in order to remove most of the sugars, salts and proteins.

**Definition:** The colouring principle of beetroot red is composed of different pigments all belonging to the class betalaine. The main colouring principle consists of betacyanins (red) of which betanin accounts for 75-95%. Minor amounts of betaxanthin (yellow) and degradation products of betalains (light brown) may be present. Besides the colour pigments beetroot red may contain sugars, salts and/or protein naturally occurring in the source material.

**EC specifications:** E 162 Beetroot red, betanin [4].
Assay: Not less than 0.4% of red colour (expressed as betanin).
Nitrate: Not more than 2 g nitrate anion/g red colour (as calculated from the assay).
In addition the specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Beet red [3].
Assay: Not less than 0.4% of red colour (expressed as betanine).
Nitrate: Not more than 2 g nitrate anion/ g red colour (as calculated from the assay).
In addition the specification includes purity criteria on Basic colouring matters, Other acidic colouring matters, Arsenic, Lead and Heavy metals.
Exposure: Permitted generally in foodstuffs except those where colours are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. No ADI is allocated and the colour was for that reason not included in the EU monitoring system (tier 0).

SCF/JECFA evaluation:
SCF status: Latest evaluation 1975 when the use as food colour was found acceptable. The Committee stressed that toxicological studies will be needed if considerable extension of the use in food is contemplated at some future date [2].

JECFA status: Latest evaluation in 1987 when an ADI “not specified” was allocated for beet red when used as a colouring The Committee stressed that careful specifications need to be established as nitrate is a component of the beet extract and it is thus necessary to ensure that the levels of nitrate do not exceed acceptable levels. When used to enhance the colour of beet products, beet red is considered as a food. The Committee was not able to allocate an ADI for betanine as such [1].

Background data:
Subacute/subchronic toxicity: Data not available.

Genotoxicity: In vitro: Beet red extract caused chromosome damage in human cells in culture and was found positive in Ames Bacterial tests in S. typhimurium [8]. In another experimental setting beet root red (purity not specified) did not induce a detectable genotoxic effect in the E.coli rec. assay or in Ames mutagenicity assay. Both assay were conducted with and without metabolic activation using caecal extracts and rat liver microsomes [7].
In vivo: Beet root extracts did not cause chromosomal damages in rats treated orally [6].

Chronic toxicity/Carcinogenicity: Lifetime treatment with beet root pigments (betanine in pure and degraded form) in the drinking water did not initiate or promote hepatocarcinogenesis induced by N-Nitrosodiethylamine in rat liver when administered at doses between 50 and 2000 ppm [10], whereas in another study freeze-dried beet root enhanced liver tumorigenesis induced by AFB1 [5].

Reproduction toxicity: -

Other: Metabolism: The uptake, metabolism and excretion of betanine from beet root revealed that betanine is poorly absorbed from the gastrointestinal tract, and furthermore is not biotransformed in the liver [9]. Major transformations, however, occur in the gastrointestinal wall, verified by the loss of the characteristic beetroot colour [9].

Conclusion: The study in which freeze-dried beet root enhanced liver tumorigenesis induced by AFB1 [5], do suggest that beet root red do exhibit adverse activities that needs to be further investigated. This effect should be addressed and it should be ascertained whether exposure is still kept within what was assumed by SCF.

Beetroot red as defined by the specifications may not have been on the market when SCF evaluated the substance. The specified product is covered by the JECFA evaluation.
References:


**ANTHOCYANINS**

**E number:** E 163

**Recommendation:** Studies to confirm that exposures lie within what was envisaged by SCF is desirable.

**Chemical name/synonyms:**
- Cyanidin: \(3,3',4',5,7\)-Pentahydroxy-flavylium chloride.
- Peonidin: \(3,4',5,7\)-Tetrahydroxy-3'-methoxyflavylium chloride.
- Malvidin: \(3,4',5,7\)-Pentahydroxy-3',5'-dimethoxyflavylium chloride.
- Delphinidin: \(3,5,7\)-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-1-benzopyrylium chloride.
- Petunidin: \(3,3',4',5,7\)-Pentahydroxy-5'-methoxyflavylium chloride.
- Pelargonidin: \(3,5,7\)-Trihydroxy-2-(4-hydroxyphenyl)-1-benzopyrylium chloride.

**Chemical formula:**
- Cyanidin: \(C_{15}H_{11}O_6Cl\)
- Peonidin: \(C_{16}H_{13}O_6Cl\)
- Malvidin: \(C_{17}H_{15}O_7Cl\)
- Delphinidin: \(C_{15}H_{11}O_7Cl\)
- Petunidin: \(C_{16}H_{15}O_7Cl\)
- Pelargonidin: \(C_{15}H_{11}O_5Cl\)

**Class:** Anthocyanin.

**EINECS number:**
- Cyanidin: 208-438-6
- Peonidin: 205-125-6
- Malvidin: 211-403-8
- Delphinidin: 208-437-0
- Petunidin: -
- Pelargonidin: 205-127-7

**CAS number:** -

**Functional Class:** Colour.

**Specification:**
**Manufacture:** Anthocyanins are obtained by extraction with sulphited water, acidified water, carbon dioxide, methanol or ethanol from vegetables and edible fruits.

**Definition:** Anthocyanins contain anthocyanins representative for the source material. They may also contain other common components of the source material, namely, organic acids, tannins, sugars, minerals etc., but not necessarily in the same proportion as found in the source material. The JECFA specifications define anthocyanins from different source materials individually. Actually Grape skin extract and Blackcurrant extract have been specified.
**EC specifications:** E 163 Anthocyanins [1].
Assay: -
The specification includes purity criteria on Solvent residues, Sulphur dioxide, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Grape skin extract [2].
Assay: Not less than declared.
The specification includes purity criteria on Sulphur dioxide, Basic colouring matters, Other acidic colouring matters, Arsenic, Lead and Heavy metals.

**JECFA specifications:** Blackcurrant extract [3].
Assay: Not less than declared.
The specification includes purity criteria on Sulphur dioxide, Basic colouring matters, Other acidic colouring matters, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where colours are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. No ADI is allocated and the colour was for that reason not included in the EU monitoring system (tier 0). It is thus not clear whether the assumptions expressed by SCF are still valid.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1975, acceptable from natural foods [4]. However, in the same report, as in several later reports, the Committee stresses that the use of colours derived from natural sources are only acceptable as food colours provided the quantities ingested from this use do not differ substantially from the amounts likely to be ingested as a result of the normal consumption of the foods in which they occur naturally.

**JECFA status:** Latest evaluation 1982, ADI 2.5 mg/kg bw for anthocyanins from grape skin [5].

**Background data:**
**Subacute/subchronic toxicity:** An adequate 90-day study in rats has been performed with anthocyanin extract at 3 and 6g/kg bw/day without any evidence of adverse clinical, biochemical, or pathological effects as compared to a control group [6]. A 90-day study in beagle dogs has also been performed with no evidence of adverse effects at doses up to 0.36% in the diet [6].

**Genotoxicity:** in vitro: Some anthocyanins have been adequately in bacterial and yeast mutagenicity tests and found to be inactive [6-8].

**Chronic toxicity/Carcinogenicity:** No data available.

**Reproduction and teratogenicity:** An adequate two-generation study has been performed with a grape skin extract equivalent to 0.225% and 0.45% in rats. A decreased weight gain and decreased organ weights were observed in the high dose group, which also experienced a decreased food intake. No effects on reproduction or pup viability were observed in comparison with the control group [6].
**Effects in humans:** There is a considerable current interest in the possible positive health effects of anthocyanins in humans, due to their potent antioxidant effects, and their reported positive effects on the vessel walls and on night vision. None of the presently available studies have been concerned with possible toxicity.

**Other:** The complicated chemistry of the anthocyanins which exist in several stable chemical forms at different pH values has precluded good studies with pure anthocyanins. Improved analytical methodology may have overcome these problems so that adequate studies on anthocyanin metabolism and disposition should now be possible. Several studies indicate that anthocyanins can inhibit various enzymes *in vitro* [9;10]

*Metabolism:* Anthocyanins are believed to be poorly absorbed [6]. However, recent data show that anthocyanins are indeed absorbed in humans [11] and up to a few percent of the dose are excreted unchanged with the urine. Since hydrolysis of conjugates was not attempted in any of these studies, absorption might be higher. The anthocyanin ring system is apparently not cleaved by bacteria in the gut. In the rat, detailed data exist regarding metabolism, kinetics and disposition of anthocyanins [6].

**Conclusion:** Data on possible long-term effects are missing for a complete dossier, however, none of the available data point to adverse effects of anthocyanins or to a need for such studies. Studies on the potential effects of anthocyanins on antioxidant effects, on fragility of vessel walls and on the arachidonate pathway *in vivo* could add useful new knowledge on the effects of these substances.

The EU specifications only allows for the use of vegetables and edible fruits as sources of anthocyanins, which is in compliance with the SCF evaluation.

**References:**


5. *[1982, TRS 683-JECFA 26]*


CALCIUM CARBONATES

E Number: E 170

See: E 500 Carbonates.
TITANIUM DIOXIDE

E number: E 171

Recommendation: No need for a re-evaluation.

Chemical name/synonyms: Titanium dioxide/ CI Pigment white 6.

Chemical formula: TiO₂

Class: Inorganic.

EINECS number: 236-675-5

CAS number: 13463-67-7

Functional Class: Colour.

Specification:
Manufacture: No information on the manufacturing process used for food grade titanium dioxide.

Definition: Titanium dioxide consists essentially of pure anatase titanium dioxide which may be coated with small amounts of alumina and/or silica to improve the technological properties of the product.

EC specifications: E 171 Titanium dioxide [1].
Assay: Not less than99% on an alumina and silica free basis.
In addition the specification includes purity criteria on Loss on drying, Loss on ignition, Aluminium oxide and/or silicon dioxide, Matter soluble in 0.5 N HCl, Water soluble matters, Antimony, Arsenic, Lead, Mercury, Cadmium and Zinc.

JECFA specifications: Titanium dioxide [2].
Assay: Not less than99% on an alumina and silica free basis.
In addition the specification includes purity criteria on Loss on drying, Loss on ignition, Aluminium oxide and/or silicon dioxide, Matter soluble in 0.5 N HCl, Water soluble matters, Antimony, Arsenic, Lead, Mercury and Zinc.

Exposure: Permitted generally in foodstuffs except those where colours are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. No ADI is allocated and the colour was for that reason not included in the EU monitoring system (tier 0).

SCF/JECFA evaluation:
SCF status: Titanium dioxide was first evaluated in June 1975 when the Committee in contrast to JECFA did not allocate an ADI but found the colour acceptable for use on confectionary. No toxicological background given [3]. In 1977 the acceptance was extended to cover the use as food colour in general [4].
**JECFA status:** Latest evaluation: 1969. ADI “not limited” except for good manufacturing practice [5].

**Background data:**

**Subacute/subchronic toxicity:** No adverse effects have been observed in rats and dog administered up to 2 g/kg bw for up to 2 months [6].

**Genotoxicity:** -

**Chronic toxicity/Carcinogenicity:** Titanium dioxide administered for 390 days to guinea-pigs, rabbits, cats and dogs at a dietary level of 0.6-9 g/day did not reveal any adverse effects. Less than 5 microgram of titanium was found in bile, heart, spleen and skeletal muscle [7].

**Reproduction toxicity:** Data not available.

**Conclusion:** The available data do not meet currently requirements. However the inertness of the substance and the lack of absorption and tissue storage does not warrant further testing or a re-evaluation of the safety in use of this compound. Titanium dioxide as defined by the specifications is representative for products sold as food colours.

**References:**


5. [1969, NMRS 46/TRS 445-JECFA 13]

6. [1969, FAS 70.36/NMRS 46A-JECFA 13]
   Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances. *FAO Nutrition Meetings Report Series*, No. 46A; WHO/Food Add/70.36.

IRON OXIDES AND IRON HYDROXIDES

E number: E 172

Recommendation: Basis for the evaluation is unclear, should be clarified.

Chemical name/synonyms:
Iron oxide yellow: Hydrated ferric oxide, hydrated iron (III) oxide/ CI Pigment yellow 42 and 43.
Iron oxide red: Anhydrous ferric oxide, anhydrous iron (III) oxide/ CI Pigment 101 and 102.
Iron oxide black: Ferroso ferric oxide, iron (II, III) oxide/ CI Pigment 11

Chemical formula:
Iron oxide yellow: FeO(OH)\(\cdot\)xH\(_2\)O
Iron oxide red: Fe\(_2\)O\(_3\)
Iron oxide black: FeO\(\cdot\)Fe\(_2\)O\(_3\)

Class: Inorganic

EINECS number:
Iron oxide yellow: 257-098-5
Iron oxide black: 235-442-5

CAS number:
Iron oxide yellow: 51274-00-1
Iron oxide red: 1309-37-1
Iron oxide black: 1317-61-9

Functional Class: Colour.

Specification:
Manufacture: Iron oxides and iron hydroxides are produced synthetically. The food grade material is obtained by specific selection and control of the source iron and/or by the extent of chemical purification during the manufacturing process.

Definition: Iron oxides and iron hydroxides consist essentially of anhydrous and/or hydrated iron oxides. The range of hues includes yellows, reds, browns and blacks. Food grad iron oxides are primarily distinguished from technical grades by the comparatively low levels of contamination by other metals. Iron oxides and iron hydroxides are insoluble in water and soluble in concentrated mineral acids.

EC specifications: E 172 Iron oxides and iron hydroxides [4].
Assay: Iron oxide yellow: not less than 60%, iron oxide red and iron oxide black: not less than 68% total iron expressed as iron.
The specification includes purity criteria on Water-soluble matters, Arsenic, Barium, Chromium, Copper, Nickel, Zinc, Lead, Mercury and Cadmium.

**JECFA specifications:** Iron oxides [3].
Assay: Iron oxide yellow: not less than 60% iron expressed as iron.
The specification includes purity criteria on Water-soluble matters, Arsenic, Barium, Chromium, Copper, Nickel, Zinc, Lead, Mercury and Cadmium.

**Exposure:** Permitted generally in foodstuffs except those where colours are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. SCF has allocated an ADI “not specified” and the colour was for that reason not included in the EU monitoring system (tier 0). JECFA has allocated a numerical ADI.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation in June 1975 when an ADI “not specified” was allocated [2].

**JECFA status:** Latest evaluation in 1979 when the previous temporary ADI “not specified”, as established at its 18th meeting was changed to an ADI of 0.5 mg/kg. No explanation of the reasons for that figure and no toxicological monograph prepared at that occasion [1].

**Background data:**
**Subacute/subchronic toxicity:** Data not available.

**Genotoxicity:** Data not available.

**Chronic toxicity/Carcinogenicity:** No studies available based on dietary exposures.

**Reproduction:** -

**Other:** -

**Conclusion:** There is no reason to expect that the use of iron oxides and iron hydroxide will cause any undesirable side effects as the bioavailability of iron is likely to be much less than from iron salts. However the basis for the evaluations are unclear and need being better described.

**References:**

1. [1979, TRS 648-JECFA 23]


ALUMINIUM

**E number:** E 173

**Recommendation:** Exposure from metallic aluminium used according to the restricted uses is likely to be very small and of no toxicological concern. Still it is recommended that aluminium from all sources, including the use as colour and as a component in colour lakes, is evaluated in general.

**Chemical name/synonyms:** Aluminium/ CI Pigment Metal.

**Chemical formula:** Al

**EINECS number:** 231-072-3

**CAS number:** 7429-90-5

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Aluminium as a food colour is obtained by grinding aluminium in the presence of edible vegetable oils and/or food grade fatty acids.

**Definition:** Aluminium as a food colour is composed of finely divided particles of aluminium. It is free from admixture with substances other than edible vegetable oils and/or food additive quality of fatty acids.

**EC specifications:** E 173 Aluminium [1].

Assay: Not less than 99% as Al on an oil-free basis.

The specification includes purity criteria on Loss on drying, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Aluminium powder [2].

Assay: Not less than 99.0%.

The specification includes purity criteria on Loss on drying, Arsenic and Lead.

**Exposure:** Metallic aluminium is authorised only for use as external coating of sugar confectionery for the decoration of cakes and pastries, q.s. This use of aluminium was not included in the EU-monitoring system (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** Metallic aluminium for use as a surface colouring was accepted by SCF in 1975 without giving any details on the toxicological background [3], In 1990 SCF (25th report) endorsed the PTWI of 7 mg/kg bw from all sources as established by JECFA in 1988, when the Committee evaluated aluminium containing additives (See also E 520-3, 541 and 554-9). The Committee did not indicate whether the contribution from metallic aluminium should be included in this PTWI.
**JECFA status:** Metallic aluminium was evaluated in 1977. JECFA did not allocate an ADI, but concluded that the very limited use as a silvering decoration for certain items of confectionery was not considered to present a hazard [4]. In 1988 a PTWI of 7 mg/kg bw was allocated for aluminium from all sources based on the level of aluminium phosphate causing no effect in dogs, but it was not specified whether metallic aluminium should be considered within this PTWI [5;6].

**Background data:** Aluminium is allocated a group PTWI for all aluminium containing food additives based on the evaluation of aluminium phosphate (E 541). The background data the aluminium containing food additives covered by PTWI are presented in this monograph.

**Conclusion:** There has been an intensive work in the investigation of the role of aluminium in Alzheimer’s disease and other mental impairments. WHO concludes that there is not a relation between Alzheimer disease and the intake of aluminium from drinking water (see aluminium phosphate). However the whole question on aluminium toxicity and the significance of aluminium containing food additives seems unclear an a re-evaluation is therefore warranted.

**References:**


SILVER

**E number:** E 174

**Recommendation:** Re-evaluation is not needed.

**Chemical name/synonyms:** Silver/ Argentum.

**Chemical formula:** Ag

**EINECS number:** 231-131-3

**CAS number:** 7440-22-4

**Functional Class:** Colour.

**Specification:**

**Manufacture:** No information on manufacturing processes for Silver as a food additive.

**Definition:** Silver as a food additive consists of finely divided particles of silver or tiny sheets.

**EC specifications:** E 174 Silver [1].
Assay: Not less than 99.5% Ag.
The specification includes no other criteria.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** External coating of confectionery, decoration of chocolates and liqueurs only. Q.s.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1975. The Committee had inadequate data available, but felt that the limited use as external coating was acceptable (but the use in liqueurs was not mentioned) [2].

**JECFA status:** Latest evaluation 1977. Decision postponed [3]. A toxicological monograph was prepared [4].

**Other:** US-EPA has calculated an ADI of 182 µg/day/person and estimated the average daily dietary intake to be 10-88 µg/d [5].

**Background data:**

**Subacute/subchronic toxicity:** No data on metallic silver

**Genotoxicity:** No mutagenicity of AgI was observed in Ames test with or without activation [6]. AgI did not induce sister chromatide in the SCE test *in vitro* as well as *in vivo* [6].
**Chronic toxicity/Carcinogenicity:** Implants of foil, platelets and pellets have induced local fibrocarcinomas [3]. No information available after oral administration.

**Reproduction toxicity:**

**Effect in humans:** Repeated exposure to silver salts or colloidal silver leads to effects classically described as argyria. This clinical condition is characterised by a grey-blue discoloration of skin which is most pronounced in areas exposed to light. The dose needed to develop argyria is large. Hundreds of patients have received up to 1.7 g Ag without adverse effects [3]. The exposure condition giving rise to argyria is not well defined but the total dose required seems to be between 1 to 30 g of soluble silver salts [7].

**Other:** Studies on radiolabelled silver indicate that less about 10% of a dose given orally are absorbed and whole body retention in rats, mice and monkeys was less than 1% after 1 week [3].

**Conclusion:** The use of metallic silver as a food colour is limited. The intake from food additives is small and the uptake is considered to be low after ingestion. Therefore, at the present level the use of silver can be considered acceptable although the toxicological data are limited. The available data on the dose-relationship for silver induced development of argyria are conflicting and of limited quality in terms of setting health based ADI.

**References:**


**GOLD**

**E number:** E 175

**Recommendation:** Further evaluation is not needed.

**Chemical name/synonyms:** Gold/ Pigment metal 3, Aurum.

**Chemical formula:** Au

**EINECS number:** 231-165-9

**CAS number:** 7440-57-5

**Functional Class:** Colour.

**Specification:**
**Manufacture:** No information on manufacturing processes for Gold as a food additive.

**Definition:** Gold as a food additive is a finely divided powder or tiny sheets.

**EC specifications:** E 175 Gold [3].
**Assay:** Not less than 90% Au.
The specification includes purity criteria on Copper and Silver.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** External coating of sugar confectionery, decoration of chocolates and liqueurs only.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1975. The Committee had inadequate data available, but felt that the limited use as external coating was acceptable (but the use in liqueurs was not mentioned) [2].

**JECFA status:** Latest evaluation 1977. No ADI was allocated but JECFA did not consider it to present a hazard due to the very limited use [1].

**Subacute toxicity:** No data available.

**Genotoxicity:** No data available.

**Chronic toxicity/carcinogenicity:** No data available.

**Reproduction toxicity:** No data available.
**Conclusion:** Very little data exists on toxicological data on oral intake of metallic gold, but considering the inertness of metallic gold and the expected very limited use as a food additive there is no reason to expect a toxic effect and no further evaluation is necessary.

**References:**


**LITHOLRUBINE BK**

**E number:** E 180

**Recommendation:** Albeit exposure is likely to be very low compared with the SCF ADI, an update of the evaluation is recommended as the full basis behind this ADI is not clear and JECFA has not been able to allocate an ADI.

**Chemical name/synonyms:** Calcium 3-hydroxy-4-(4-methyl-2-sulfonatophenylazo)-2-naphthalencarboxylate/ CI Pigment Red 57; Carmine 6B; D&C Red No. 7; Rubinpigment BK; Brilliant carmine 6B; Carmine 6B; Litholrubintoner BLK; Permanent Rubine L6B.

**Chemical formula:** C_{18}H_{12}CaN_{2}O_{6}S

**Class:** Monoazo.

**EINECS number:** 226-109-5

**CAS number:** 5284-04-9

**Functional Class:** Colour.

**Specification:**

**Manufacture:** Litholrubine BK is manufactured by chemical synthesis.

**Definition:** Litholrubine BK consists essentially of calcium 3-hydroxy-4- (4-methyl-2-sulfonatophenylazo)-2-naphthalencarboxylate and subsidiary colouring matters together with calcium chloride and/or calcium sulphate as the principal uncoloured components.

**EC specifications:** E 180 Litholrubine BK [1].
- Assay: Not less than 90% total colouring matters calculated as the sodium salt.
- Subsidiary colouring matters: Not more than 0.5%.
- In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulphonated primary aromatic amines), Water insoluble matter, Ether extractable matter, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Lithol Rubine BK [2]
- Assay: Not less than 90% total colouring matters.
- Subsidiary colouring matters: Not more than 0.5%.
- In addition the specification includes purity criteria on Organic compounds other than colouring matters (including organic impurities related to the manufacturing process - as defined in the specification and Unsulfonated primary aromatic amines), Loss on drying, chloride and sulfate calculated as sodium salts, Water insoluble matter, Ether extractable matter, Arsenic, Lead and Heavy metals.
Exposure: Litholrubine BK may only be used in edible cheese rind, so the exposure is likely to be very limited.

SCF/JECFA evaluation:

SCF status: SCF last evaluated Litholrubine BK in 1983 [3] when it established an ADI of 1.5 mg/kg bw on the basis of a no-adverse-effect level corresponding to 150 mg/kg bw/day in a long-term study in rats. The safety-factor was 100. No details were specified.

JECFA status: JECFA in 1986 [4] was not able to establish an ADI because it was not possible to determine an unequivocal no-effect level in the two long-term studies. The following data were required by JECFA:
- Results of a complete histopathological examination of all dose-groups in the long-term mouse study.
- Results of a new long-term study in rats.
- An adequate reproduction/teratology study.

These studies have not been submitted.

BIBRA: The toxicological data for Litholrubine within classical endpoints were reviewed. Specifically, no conclusive evidence of reproductive toxicity or carcinogenicity was demonstrated. A number of bacterial assays (Ames mutagenicity test) gave no evidence of genotoxicity [5].

Background data:

Subacute/subchronic toxicity: SCF notes that studies are available in rat and dog. No details or data were presented [3].

No information was available to JECFA [6].

Genotoxicity:

In vitro studies were available to SCF. No genotoxic potential was reported. No details were presented [3].

Chronic toxicity/Carcinogenicity: SCF notes that studies are available in mouse and rat on the disodium-salt and in rat and dog on the calcium-salt. The NEL in the rat study was said to be 150 mg/kg bw, but no other details or data were presented. [3].

To JECFA studies in mouse and rat were available: Mice were administered 0, 0.05, 1.0, or 5% in diet for 104 weeks. No effect was revealed on food consumption, bw gain, or haematological parameters except depressed reticulocyte count in the 5% group. There was an increased mortality in males and reduced survival in males in the 5% group. No effect was seen on organ weight or gross morphology. Degenerative renal changes in males and higher incidence (considered of dubious significance) of alveolar adenomas were revealed in high-dosed males. No increase in tumour or neoplastic lesions was found. In conclusion, this study revealed a dose-related increase in mortality and renal pathology, but detailed histopathology was not conducted on the low- and intermediate-dose groups. Furthermore, it was not possible to determine an unequivocal no-effect level [6].

Rats were administered 0, 0.05, 0.3, or 2% in the diet. There was also in utero exposure. In the in utero phase no effects on body weight, food consumption, ophthalmoscopic examination, fertility,
gestation, or lactation were seen. In the long-term phase no effect on food consumption despite that a decreased bw gain was revealed. Accelerated mortality in males in the 5% group. No effects on haematological, clinical biochemical parameters, and urine analyses were demonstrated. No macroscopic changes. Histopathological examinations revealed higher incidence of chronic nephritis, renal tubular epithelial hyperplasia, myocardial fibrosis, reticular hyperplasia, and pigment deposition in the spleen. Only limited histopathological examinations were conducted. It was not possible to determine an unequivocal no-effect level [6].

**Reproduction toxicity:** SCF reports that a reproduction study is available on the Ca- and the disodium-salt and a teratogenicity study on the Ca-salt. The Committee notes that there are no effects on reproductive function and no teratological effects were observed, but no details is given on the studies [3].

No data were available to JECFA.

**Conclusion:** The use is restricted and the intake thus very limited. However the basis for the SCF ADI is unclear and as JECFA was not able to allocate an ADI it is proposed to update the evaluation.

Litholrubine BK as defined by the specifications seems to be covered by the toxicological evaluation.

**References:**


4. [1986, TRS 751-JECFA 30]


6. [1986, FAS 21-JECFA 30]
SORBIC ACID, POTASSIUM SORBATE AND CALCIUM SORBATE

**E number:**
- Sorbic acid: E 200
- Potassium sorbate: E 202
- Calcium sorbate: E 203

**Recommendation:** No need for a re-evaluation.

**Chemical name/synonyms:**
- Sorbic acid: Trans, trans-2,4hexadienoic acid/ 2-propenylacrylic acid.
- Potassium sorbate: Potassium salt of trans, trans-2,4hexadienoic acid.
- Calcium sorbate: Calcium salt of trans, trans-2,4hexadienoic acid.

**Chemical formula:**
- Sorbic acid: C₆H₈O₂
- Potassium sorbate: C₆H₇KO₂
- Calcium sorbate: C₁₂CaH₁₄O₄

**EINECS number:**
- Sorbic acid: 203-768-7
- Potassium sorbate: 246-376-1
- Calcium sorbate: 231-321-6

**CAS number:**
- Sorbic acid: 110-44-1
- Potassium sorbate: 24634-61-5
- Calcium sorbate: 7492-55-9

**Functional Class:** Preservative.

**Specification:**
**Manufacture:** Sorbic acid as defined in the specification is manufactured by chemical synthesis.

**Sorbic acid**
**Definition:** Sorbic acid is a naturally occurring organic acid. It is slightly soluble in water and soluble in ethanol.

**EC specifications:** E 200 Sorbic acid [1].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Water, Sulphated ash, Aldehydes, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sorbic acid [2].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Water, Sulphated ash, Aldehydes, Arsenic and Heavy
Potassium sorbate

Definition: Potassium sorbate is the potassium salt of sorbic acid. It is freely soluble in water and solubile in ethanol.

EC specifications: E 202 Potassium sorbate [2].
Assay: Not less than 99% on the dried basis.
The specification includes purity criteria on Loss on drying, Acidity and alkalinity, Aldehydes, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Potassium sorbate [3].
Assay: Not less than 98% and not more than 102% on the dried basis.
The specification includes purity criteria on Loss on drying, Acidity and alkalinity, Aldehydes and Heavy metals.

Calcium sorbate

Definition: Calcium sorbate is the calcium salt of sorbic acid. It is soluble in water and and practically insoluble in ethanol.

EC specifications: E 203 Calcium sorbate [2].
Assay: Not less than 98% on the dried basis.
The specification includes purity criteria on Loss on drying, Aldehydes, Fluoride, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Calcium sorbate [3].
Assay: Not less than 98% and not more than 102% on the dried basis.
The specification includes purity criteria on Loss on drying, Aldehydes, Fluoride and Heavy metals.

Exposure: Sorbates are used in a variety of foods, only in marginal products exceeding 2 g/kg. In beverages 300 mg/litre is permitted. They are also used in wine as a substitute for sulphites.

In the EU monitoring system the sorbates were examined at tier 1 level. As the calculation suggested a possibility for children exceeding the ADI, the intake was examined at tier 2 level. The calculated intake by young children was reported by one member state as 76% of the ADI and it was concluded that no further examination is needed at this stage.

SCF/JECFA evaluation:

SCF status: Latest evaluation 1996, ADI 25 mg/kg bw [6]. No toxicological studies have been performed with calcium sorbate [6].

JECFA status: Latest evaluation 1973 ADI 25 mg/kg bw [4]. The ADI is based on an old long-term study in rats. In this study the NOAEL was 2500 mg/kg bw.

Background data:

Subacute/subchronic toxicity: Short-term studies have been performed on mice, rats, rabbits and dogs with sorbic acid and potassium sorbate. Reduced growth was seen in mice given 80 mg/kg bw
of sorbic acid for three months. In rats, increased liver weight has been noted down to 2 % sorbic acid in the diet for 80 days. 10 % sorbic acid in the diet raised the blood cholesterol level, depressed the leukocyte number and partially impaired the cholinesterase activity in a 4-month study. Rats fed potassium sorbate for 3 months at 5 and 10 % of the diet had increased kidney weights, probably due to the high potassium load [5].

**Genotoxicity:** Sorbic acid and potassium sorbate have been tested for genotoxicity activity *in vitro* and *in vivo* in various test systems. Most of the *in vitro* results have been negative. Some *in vivo* tests have yielded positive results for sorbic acid, but it should be noted that in these experiments the control values were unusually low. Calcium sorbate has not been tested for genotoxicity [6].

**Chronic toxicity/Carcinogenicity:** Long-term carcinogenicity studies with sorbic acid up to 10 % in the animal feed have been conducted in mice and rats without showing any carcinogenic effect. The NOEL for potassium sorbate and sorbic acid is 5 % in both species which is equivalent to 2500 mg/kg bw per day in rats. At higher doses changes in organ weight were noted. One poorly reported study showed a carcinogenic effect on the liver of mice eating a diet containing 15 % sorbic acid. This finding may be explained by that sorbic acid in high doses may reduce the level of lipid peroxides and glutathione in the liver and induce hepatic paroxysmal enzyme activities. Calcium sorbate has not been tested in a long-term study [6].

In a long-term study rats were fed 750 mg/kg bw and 5000 mg/kg bw. At 5000 mg/kg changes in the relative weights of some organs occurred [6].

In a long-term study in mouse changes in organ weights were observed at the two highest dose levels of 7000 and 14000 mg/kg bw [6].

**Reproduction toxicity:** Potassium sorbate caused no teratogenic effects after dosing mice with up to 460 mg/kg bw and rats with up to 340 mg/kg bw [6].

**Allergy/Intolerance:** Sorbic acid and potassium sorbate have caused hypersensitivity reactions; particularly contact urticaria, in certain population subgroups [6].

**Other:** The safety in use of the combination of sorbates and nitrites has been questioned (possible mutagenic or DNA-damaging reaction products) but SCF concludes that under normal conditions of use no hazard to human health arises [6].

**Conclusion:** Although the ADI is based on an old long-term study in rats there is no reason for requiring new tests. No toxicological studies have been carried out with calcium sorbate but its toxicological profile is not likely to be much different from potassium sorbate and sorbic acid. The main problem with the sorbates is likely to be the hypersensitivity that they may induce in certain population subgroups.

Sorbic acid and sorbates as defined by the specifications seems to be covered by the toxicological evaluation. The JECFA specifications for these substances are old. It may therefore be appropriate to revise the specifications for this group of substances at a future JECFA meeting.
References:


**BENZOIC ACID, SODIUM BENZOATE, POTASSIUM BENZOATE AND CALCIUM BENZOATE**

**E number:**
- Benzoic acid: E 210
- Sodium benzoate: E 211
- Potassium benzoate: E 212
- Calcium benzoate: E 213

**Recommendation:** Is on the agenda of SCF for re-evaluation. Further effort to estimate exposure is desirable as ADI may be exceeded by sections of the population.

**Chemical name/synonyms:**
- Benzoic acid: Benzoic acid, benzenecarboxylic acid, phenylcarboxylic acid.
- Sodium benzoate: Sodium benzoate, sodium salt of benzenecarboxylic acid, sodium salt of phenylcarboxylic acid.
- Potassium benzoate: Potassium benzoate, potassium salt of benzenecarboxylic acid, potassium salt of phenylcarboxylic acid.
- Calcium benzoate: Calcium benzoate, calcium salt of benzenecarboxylic acid, calcium salt of phenylcarboxylic acid/ monocalcium benzoate.

**Chemical formula:**
- Benzoic acid: \(C_7H_6O_2\)
- Sodium benzoate: \(C_7H_5NaO_2\)
- Potassium benzoate: \(C_7H_5KO_2\cdot3HO_2\)
- Calcium benzoate: Anhydrous: \(C_{14}H_{10}CaO_4\)
  Monohydrate: \(C_{14}H_{10}CaO_4\cdotHO_2\)
  Trihydrate: \(C_{14}H_{10}CaO_4\cdot3HO_2\)

**EINECS number:**
- Benzoic acid: 200-618-2
- Sodium benzoate: 208-534-8
- Potassium benzoate: 209-481-3
- Calcium benzoate: 218-235-4

**CAS number:**
- Benzoic acid: 65-85-10
- Sodium benzoate: 532-32-1
- Potassium benzoate: 582-25-2 (anhydrous)
- Calcium benzoate: 2090-05-3

**Functional Class:** Preservative.

**Specification:**
**Manufacture:** Benzoic acid as defined in the specification is manufactured by chemical synthesis.
**Benzoic acid**

**Definition:** Benzoic acid is a naturally occurring organic acid. It is slightly soluble in water and freely soluble in ethanol.

**EC specifications:** E 210 - Benzoic acid [2].
Assay: Not less than 99.5% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, pH, Sulphated ash, Chlorinated organic compounds, Readily oxidisable substances, Readily carbonisable substances, Polycyclic acids, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Benzoic acid [1].
Assay: Not less than 99.5% on the dried basis.
The specification includes purity criteria on Sublimation test, Loss on drying, Sulphated ash, Chlorinated organic compounds, Readily oxidisable substances, Readily carbonisable substances, Polycyclic acids and Heavy metals.

**Sodium benzoate**

**Definition:** Sodium benzoate is the sodium salt of benzoic acid. It is freely soluble in water and sparingly soluble in ethanol.

**EC specifications:** E 211 - Sodium benzoate [2].
Assay: Not less than 99% on the dried basis.
The specification includes purity criteria on Loss on drying, Chlorinated organic compounds, Readily oxidisable substances, Readily carbonisable substances, Degree of acidity and alkalinity, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium benzoate [1].
Assay: Not less than 99.0% on the dried basis.
The specification includes purity criteria on Acidity and alkalinity, Loss on drying, Chlorinated organic compounds, Readily oxidisable substances, Readily carbonisable substances and Heavy metals.

**Potassium benzoate**

**Definition:** Potassium benzoate is the potassium salt of benzoic acid. It is freely soluble in water and sparingly soluble in ethanol.

**EC specifications:** E 212 - Potassium benzoate [2].
Assay: Not less than 99% on the dried basis.
The specification includes purity criteria on Loss on drying, Chlorinated organic compounds, Readily oxidisable substances, Readily carbonisable substances, Degree of acidity and alkalinity, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Potassium benzoate [1].
Assay: Not less than 99.0% on the dried basis.
The specification includes purity criteria on Acidity and alkalinity, Loss on drying, Chlorinated organic compounds, Readily oxidisable substances, Readily carbonisable substances and Heavy metals.
Calcium benzoate

**Definition:** Calcium benzoate is the calcium salt of benzoic acid. It is sparingly soluble in water.

**EC specifications:** E 213 - Calcium benzoate [2].
Assay: Not less than 99% on the dried basis.
The specification includes purity criteria on Loss on drying, Water insoluble matter, Chlorinated organic compounds, Readily oxidisable substances, Readily carbonisable substances, Degree of acidity and alkalinity, Fluoride and Heavy metals.

**JECFA specifications:** Calcium benzoate [1].
Assay: Not less than 99.0% on the dried basis.
The specification includes purity criteria on Water-insoluble matter, Acidity and alkalinity, Loss on drying, Chlorinated organic compounds, Readily oxidisable substances, Readily carbonisable substances, Polycyclic acids, Fluoride and Heavy metals.

**Exposure:** Benzoates are used in limited number of foods, only in marginal products exceeding 2 g/kg. In beverages 150-200 mg/litre is permitted.

In the EU monitoring system a tier 1 calculation indicated the possibility of exceeding the ADI. In tier 2 the calculated intake by adults and the whole population is reported in the range of 6 - 84% of ADI. The calculated intake by young children is reported in the range of 17 - 96%. Taking into account the possible high intake by young children and that the intake calculation is based on average consumer data, examination at tier 3 of the intake by young children is needed.

**Additional information:** A Finnish study done at tier 3 level and targeted especially on 1 – 6 year old children has been reported. Estimations for intake were based on individual food consumption and analysed food additive levels in products consumed in Finland. The intake of benzoate by high level consumers (95th percentile) was 101 - 160% of the ADI.

**SCF/JECFA:**
**SCF status:** Latest evaluation 1994, ADI 5 mg/kg bw (temporary) [6]. The current temporary ADI is based on a NOEL of 500 mg/kg bw. This NOEL is not from one study but from a combination of the long-term and the multigeneration studies. The SCF expressed the wish to review the situation at a later stage because they were concerned about glycin metabolism regarding benzoate-induced depletion of glycin in humans and animals. They would like to see a teratogenicity study with oral administration. In addition, an in vivo test for clastogenic activity is desirable since benzoic acid is clastogenic in vitro. [6].

**JECFA status:** Latest evaluation 1996, group ADI of 5 mg/kg bw together with the alcohol, aldehyde and ester [4].

**Background data:**
**Subacute/subchronic toxicity:** Many short-term studies (5-42 days) have been performed on mice, rats, cats and dogs between 1933 and 1993. Administration of benzoic acid or sodium benzoate at levels higher than about 1 % in the diet for rodents (600 mg/kg per day), 0.5 % for cats (400 mg/kg per day) and 1000 mg/kg per day for dogs resulted in adverse effects (increased mortality, changes in body and organ weight, damage to liver and kidney, neurological disorders). [7].
Genotoxicity: Benzoic acid/sodium benzoate was found without mutagenic effect in \textit{in vitro} mutagenicity tests. However, with respect to sodium benzoate - but not benzoic acid - positive or ambiguous results were obtained in some of the \textit{in vitro} chromosomal aberration tests and tests for effects on DNA. Negative results were seen in two \textit{in vivo} chromosomal aberration tests with sodium benzoate [7]. SCF is stating that benzoic acid was positive in tests for chromosomal aberrations and tests for effects on DNA. [6].

Chronic toxicity/Carcinogenicity: Reduced food intake, growth retardation and increased mortality was observed in rats fed a diet containing 1.5 % benzoic acid (approx. 1125 mg/kg bw per day) for 18 months in a study from 1960. No pathological data were recorded. In another study from 1984, only reported as a short communication, sodium benzoate administered as a 2 % solution in drinking water (approx. 4000 mg/kg per day) to mice for their life span, showed a higher incidence and earlier onset of mammary gland tumours in dosed females (8 %) compared to controls (2 %). In a third study from 1980, rats were fed 0, 1 or 2 % sodium benzoate in the diet (approx. 500-1000 mg/kg per day) for 18-24 months. No differences in mortality or tumour occurrence were observed. [6;7].

Reproduction toxicity: In a four generation feeding experiment from 1960 benzoic acid in doses up to 1 % (approx. 600 mg/kg bw per day) did not lead to any effect on fertility and litter size. In another study from 1978, up to 2 % of sodium benzoate in the diet during the whole gestation period (approx. 1180 mg benzoic acid/kg bw per day) was without adverse effect. At higher levels maternal toxicity, prenatal death and foetal abnormalities of organs and the skeletal system were found. In a third study from 1992, maternal toxicity and severe adverse effects on foetal development has been reported when benzoic acid was given rats in doses of 450 mg/kg bw per day in day 7-16 of gestation, however, details were not specified (EPA/OTS abstract only). The NOEL for maternal and foetal toxicity in this study was 30 mg/kg per day. Studies in mice, rabbits and hamsters did not show any signs of benzoic acid induced maternal or foetal toxicity. However, only dose levels up to 150-250 mg/kg per day were tested. [7]. It is claimed that benzoic acid posses estrogenic properties in uterotrophic assay but more recent studies including uterotrophic assay performed on mice and rats and \textit{in vitro} test have not been able to confirm this [3].

Allergy/Intolerance: Benzoic acid is able to induce hypersensitivity reactions. Oral doses corresponding to less than 4 mg benzoic acid/kg bw has been shown able to cause skin reactions in sensitive persons. Anaphylaxis has been induced in sensitive persons after ingestion of a meal containing sodium benzoate as preservative and a following provocation test with oral administration of 160 mg sodium benzoate (corresponding to 2.5 mg benzoic acid/kg bw) induced localised urticaria. [7]

Effects in human: Benzoic acid has been reported to cause gastro-intestinal disorders after single oral or short term administration of 1-5 g, corresponding to approx. 14-70 mg /kg bw. However, doses below 14 mg/kg bw/day for 88-92 days were without visible effect. [7] (see allergy).

Other: Depletion of glycine, due to the formation of the main metabolite glycine conjugate (hippuric acid), may explain some of the adverse effects seen in experimental animals and man. Increased concentrations of benzoic acid in the organism may lead to disturbances in the acid/base balance [7]. Benzoic acid at high doses interferes with intermediary metabolism, including the urea
cycle, gluconeogenesis, fatty acid metabolism, and the tricarboxylic acid cycle, probably by sequestering coenzyme A prior to its conjugation with glycine [5].

**Conclusion:** No pathological data except neoplastic ones have been recorded. As reproductive studies, SCF is only mentioning the 4-generation study from 1960 and an intraperitoneal study. Two oral reproductive studies from 1978 and 1992 are mentioned in the report from the Danish EPA. Exposure to levels of benzoic acid that does not induce maternal toxicity probably does not cause developmental/foetal toxicity. In all the studies but the newest one from 1992, the doses causing reproductive effects are above 500 mg/kg bw per day. However, in the newest study, which is only reported as an abstract, the NOEL for maternal and foetal toxicity was only 30 mg/kg per day.

Regarding genotoxicity, it is not clear whether benzoic acid is clastogenic *in vivo*. However, studies has shown that sodium benzoate is not clastogenic *in vivo*. The main problem with the benzoates is most likely to be the hypersensitivity that they may induce when sensitive people are exposed.

Benzoic acid and benzoates as defined by the specifications seem to be covered by the toxicological evaluation.

**References:**


2. Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, 1996.


4. [1996, TRS 868-JECFA 46]

5. [1996, FAS 39-JECFA 46]


**ETHYL-P-HYDROXYBENZOATE, SODIUM ETHYL-P-HYDROXYBENZOATE, PROPYL-P-HYDROXYBENZOATE, SODIUM PROPYL-P-HYDROXYBENZOATE, METHYL-P-HYDROXYBENZOATE, SODIUM METHYL-P-HYDROXYBENZOATE**

**E number:**
- Ethyl-p-hydroxybenzoate: E 214
- Sodium ethyl-p-hydroxybenzoate: E 215
- Propyl-p-hydroxybenzoate: E 216
- Sodium propyl-p-hydroxybenzoate: E 217
- Methyl-p-hydroxybenzoate: E 218
- Sodium methyl-p-hydroxybenzoate: E 219

**Recommendation:** On the agenda of SCF for a re-evaluation.

**Chemical name/synonyms:**
- Sodium ethyl-p-hydroxybenzoate: Sodium ethyl-p-hydroxybenzoate, sodium compound of ethylsester of p-hydroxybenzoic acid.
- Propyl-p-hydroxybenzoate: Propyl-p-hydroxybenzoate, propylsester of p-hydroxybenzoic acid/ propylparaben, propyl p-oxobenzoate.
- Sodium propyl-p-hydroxybenzoate: Sodium propyl-p-hydroxybenzoate, sodium compound of propylsester of p-hydroxybenzoic acid.
- Methyl-p-hydroxybenzoate: Methyl-p-hydroxybenzoate, methylsester of p-hydroxybenzoic acid/ methylparaben, methyl p-oxobenzoate.
- Sodium methyl-p-hydroxybenzoate: Sodium methyl-p-hydroxybenzoate, sodium compound of methylsester of p-hydroxybenzoic acid.

**Chemical formula:**
- Ethyl-p-hydroxybenzoate: C₉H₁₀O₃
- Sodium ethyl-p-hydroxybenzoate: C₉H₉O₃Na
- Propyl-p-hydroxybenzoate: C₁₀H₁₂O₃
- Sodium propyl-p-hydroxybenzoate: C₁₀H₁₁O₃Na
- Methyl-p-hydroxybenzoate: C₈H₈O₃
- Sodium methyl-p-hydroxybenzoate: C₈H₇O₃Na

**EINECS number:**
- Ethyl-p-hydroxybenzoate: 204-399-4
- Sodium ethyl-p-hydroxybenzoate: 252-487-6
- Propyl-p-hydroxybenzoate: 202-307-7
- Sodium propyl-p-hydroxybenzoate: 252-488-1
- Methyl-p-hydroxybenzoate: 243-171-5
- Sodium methyl-p-hydroxybenzoate: -

**CAS number:**
- Ethyl-p-hydroxybenzoate: 120-47-8
- Sodium ethyl-p-hydroxybenzoate: 35285-68-8
Propyl-p-hydroxybenzoate: 94-13-3  
Sodium propyl-p-hydroxybenzoate: 35285-69-9  
Methyl-p-hydroxybenzoate: 99-76-3  
Sodium methyl-p-hydroxybenzoate: 5026-62-0

**Functional Class:** Preservative.

**Specification:**

**Manufacture:** The p-hydroxybenzoates as defined by the specifications are obtained by chemical synthesis.

*Ethyl-p-hydroxybenzoate*

**Definition:** Ethyl-p-hydroxybenzoate is the ethyl ester of p-hydroxybenzoic acid. It is freely soluble in ethanol.

**EC specifications:** E 214 - Ethyl-p-hydroxybenzoate [2].  
Assay: Not less than 99.5% on the dried basis.  
The specification includes purity criteria on Loss on drying, Sulphated ash, p-Hydroxybenzoic acid and salicylic acid, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Ethyl-p-hydroxybenzoate [1].  
Assay: Not less than 99.0% on the dried basis.  
The specification includes purity criteria on Loss on drying, Sulphated ash, Acidity, p-Hydroxybenzoic acid and salicylic acid and Lead.

*Sodium ethyl-p-hydroxybenzoate*

**Definition:** Sodium ethyl-p-hydroxybenzoate is the sodium compound of ethyl-p-hydroxybenzoate.

**EC specifications:** E 215 - Sodium ethyl-p-hydroxybenzoate [2].  
Assay: content of ethyl-p-hydroxybenzoic acid is not less than 83% on the dried basis.  
The specification includes purity criteria on Loss on drying, Sulphated ash, p-Hydroxybenzoic acid and salicylic acid, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

*Propyl-p-hydroxybenzoate*

**Definition:** Propyl-p-hydroxybenzoate is the propyl ester of p-hydroxybenzoic acid. It is freely soluble in ethanol.

**EC specifications:** E 216 - Propyl-p-hydroxybenzoate [2].  
Assay: Not less than 99.5% on the dried basis.  
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, p-Hydroxybenzoic acid and salicylic acid, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Propyl-p-hydroxybenzoate [1].  
Assay: Not less than 99.0% on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Acidity, p-Hydroxybenzoic acid and salicylic acid and Lead.

**Sodium propyl-p-hydroxybenzoate**  
**Definition:** Sodium propyl-p-hydroxybenzoate is the sodium compound of propyl-p-hydroxybenzoate.

**EC specifications:** E 217 - Sodium propyl-p-hydroxybenzoate [2].  
Assay: content of propyl-p-hydroxybenzoic acid is not less than 85% on the dried basis.  
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, p-Hydroxybenzoic acid and salicylic acid, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

**Methyl-p-hydroxybenzoate**  
**Definition:** Methyl-p-hydroxybenzoate is the methyl ester of p-hydroxybenzoic acid. It is slightly soluble in water and freely soluble in ethanol.

**EC specifications:** E 218 - Methyl-p-hydroxybenzoate [2].  
Assay: Not less than 99% on the dried basis.  
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, p-Hydroxybenzoic acid and salicylic acid, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Methyl-p-hydroxybenzoate [1].  
Assay: Not less than 99.0% on the dried basis.  
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Acidity, p-Hydroxybenzoic acid and salicylic acid and Lead.

**Sodium methyl-p-hydroxybenzoate**  
**Definition:** Sodium methyl-p-hydroxybenzoate is the sodium compound of methyl-p-hydroxybenzoate.

**EC specifications:** E 219 - Sodium methyl-p-hydroxybenzoate [2].  
Assay: Not less than 99.5% on the dried basis.  
In addition the specification includes purity criteria on Water, Sulphated ash, P-Hydroxybenzoic acid and salicylic acid, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** The methyl-, ethyl- and propyl-hydroxybenzoates are only permitted in jelly coating of meat products and pate 1000 mg/kg, surface treatment of dried meat products q.s., cereal or potato based snacks and coated nuts and confectionery 300 mg/kg, liquid dietary supplements 2000 mg/kg. Not permitted in beverages. The ADI for a 60 kg person can only be reached after consuming 600 g jelly coated meat products or 2 kg snack or confectionery. Exposure of additive passed tier 1 with adults and children in the EU intake evaluation and do not require further examination at this stage.
SCF/JECFA:

**SCF status:** Latest evaluation 1994. ADI is 10 mg/kg bw (temporary) and is based on a no effect level of 1000 mg/kg of body weight per day for reduction in body weight gain observed in a long-term rat study. The SCF expressed its wish to review the situation at a later stage. They would like to see a cell proliferation study in the rat with a solution of propyl-p-hydroxybenzoate and a new oral teratogenicity study in the rat with p-hydroxybenzoic acid or one of its esters. [8]

**JECFA status:** Latest evaluation 1973, ADI=10 mg/kg bw [4].

Background data:

**Subacute/subchronic toxicity:** In a twelve-week feeding experiment in rats 2 % of the methyl or propyl esters were without adverse effect but at 8 % there was reduced growth rate. 1000 mg/kg bw per day of the methyl or propyl esters was the NOEL in a study with two dogs given doses of 500 or 1000 mg/kg bw per day for approximately a year. ([6] Quoted from SCF and JECFA.)

**Genotoxicity:** Several *in vitro* studies covering both point mutations and chromosome aberrations, and an *in vivo* host mediated assay and dominant lethal assay provided no evidence of genotoxicity of methylparaben. Propylparaben was not mutagenic *in vitro*. No mutagenicity data are available for ethylparaben. [8].

**Chronic toxicity/Carcinogenicity:** Several old (1940-1968) long-term studies on the parabens have been conducted in rats [5;8]. The NOEL for the methyl-, ethyl- and propylparabens was 2 % in the diet, equivalent to 900-1200 mg/kg bw per day in two rat studies. At 8 % decreased weight gain was observed. Macroscopic and microscopic examination was performed on all animals but no significant changes were observed in the organs. [6]–(Quoted from SCF and JECFA.)

**Reproduction toxicity:** One study in the rat using ethylparaben at levels up to 10 % in the diet found no adverse effects on reproductive performance but the finding with respect to foetal anomalies were equivocal, the reported anomalies showing no clear dose-response relationship [8]. Parabens have been shown to be weakly estrogenic *in vitro* [7]. An *in vivo* uterotrophic assay showed no estrogenic effect [3].

**Allergy/Intolerance:** Allergic responses to the ethyl and methyl esters have been reported [5].

**Effects in human:** See Allergy.

**Other:** A number of studies on cell proliferation in the forestomach and glandular stomach have been carried out in rats fed for 9 days at 4 % of finely ground-powdered parabens in the diet. Methylparaben was without activity. Ethylparaben showed minimal activity. Propylparaben induced cell proliferation in the pre-fundic region of the forestomach [8].

**Conclusion:** Although the permitted parabens seems not to have any estrogenic effect *in vivo* this question should be addressed when these substances are reviewed.
Ethyl-p-hydroxybenzoic acid, propyl-p-hydroxybenzoic acid and methyl-p-hydroxybenzoic acid and their sodium compounds as defined by the specifications seem to be covered by the toxicological evaluation.

References:


2. Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, 1996.


SULPHUR DIOXIDE, SODIUM SULPHITE, SODIUM BISULPHITE, SODIUM METABISULPHITE, POTASSIUM METABISULPHITE, CALCIUM SULPHITE, CALCIUM BISULPHITE, POTASSIUM BISULPHITE

E Number:
Sulphur dioxide: E 220
Sodium sulphite: E 221
Sodium bisulphite: E 222
Sodium metabisulphite: E 223
Potassium metabisulphite: E 224
Calcium sulphite: E 226
Calcium bisulphite: E 227
Potassium bisulphite: E 228

Recommendation: No need for a toxicological re-evaluation, but because of the severe allergic reactions in sensitive persons and the possibility to exceed the ADI considerably a reduction in use should be considered.

Chemical name/synonyms:
Sulphur dioxide: Sulphur dioxide, sulphurous acid anhydride.
Sodium sulphite: Sodium sulphite (anhydrous or heptahydrate).
Sodium bisulphite: Sodium bisulphite, sodium hydrogen sulphite.
Sodium metabisulphite: Sodium disulphite, disodium pentaoxodisulphate/ sodium pyrosulphite.
Potassium metabisulphite: Potassium disulphite, potassium pentaoxodisulphate/ potassium pyrosulphate.
Calcium sulphite: Calcium sulphite.
Calcium bisulphite: Calcium bisulphite, calcium hydrogen sulphite.
Potassium bisulphite: Potassium bisulphite, potassium hydrogen sulphite.

Chemical formula:
Sulphur dioxide: \( \text{SO}_2 \)
Sodium sulphite: \( \text{Na}_2\text{SO}_3 \) (anhydrous)
\( \text{Na}_2\text{SO}_3 \cdot 7\text{H}_2\text{O} \) (heptahydrate)
Sodium bisulphite: \( \text{NaHSO}_3 \)
Sodium metabisulphite: \( \text{Na}_2\text{S}_2\text{O}_5 \)
Potassium metabisulphite: \( \text{K}_2\text{S}_2\text{O}_5 \)
Calcium sulphite: \( \text{CaSO}_3 \cdot 2\text{H}_2\text{O} \)
Calcium bisulphite: \( \text{Ca}((\text{HSO}_3))_2 \)
Potassium bisulphite: \( \text{KHSO}_3 \)

EINECS number:
Sulphur dioxide: 231-195-2
Sodium sulphite: 231-821-4
Sodium bisulphite: 231-921-4
Sodium metabisulphite: 231-673-0
Potassium metabisulphite: 240-795-3
Calcium sulphite: 218-235-4
Calcium bisulphite: 237-423-7
Potassium bisulphite: -

**CAS Number:**
- Sulphur dioxide: 7446-09-5
- Sodium sulphite: 7757-83-7
- Sodium bisulphite: 7631-90-5
- Sodium metabisulphite: 7681-57-4
- Calcium sulphite: 10257-55-3
- Calcium bisulphite: 13780-03-5
- Potassium bisulphite: -

**Functional Class:** Preservative.

**Specification:**

**Manufacture:** No information on manufacturing processes of food grade sulphur dioxide and the sulphites defined by the specifications.

**Sulphur dioxide**

**Definition:** Sulphur dioxide is a non-flammable gas normally supplied under pressure. It is soluble in water.

**EC specifications:** E 220 - Sulphur dioxide [2].
Assay: Not less than 99%.
The specification includes purity criteria on Water, Non-volatile residue, Sulphur trioxide, Selenium, Other gases not normally present in air, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sulfur dioxide [1].
Assay: Not less than 99.9%.
The specification includes purity criteria on Water, Non-volatile residue, Selenium and Lead.

**Sodium sulphite**

**Definition:** Sodium sulphite is the sodium salt of sulphurous acid. It is freely soluble in water and sparingly soluble in ethanol.

**EC specifications:** E 221 - Sodium sulphite [2].
Assay: Anhydrous: not less than 95% of Na₂SO₃ and not less than 48% of SO₂. Heptahydrate: not less than 48% of Na₂SO₃ and not less than 24% of SO₂.
The specification includes purity criteria on Thiosulphate, Iron, Selenium, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium sulfite [1].
Assay: Not less than 95% of Na₂SO₃
The specification includes purity criteria on pH, Thiosulfate, Iron and Lead.
Sodium bisulphite
Definition: Sodium bisulphite is defined by the EC specification as a solution, while the JECFA specification defines the substance as white crystals or granular powder. It is freely soluble in water and slightly soluble in ethanol.

EC specifications: E 222 - Sodium bisulphite [2].
Assay: Not less than 32% w/w of NaHSO₃.
The specification includes purity criteria on Iron, Selenium, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Sodium bisulfite [1].
Assay: Not less than 58.5% and not more than 67.4% of SO₂
The specification includes purity criteria on Water insolubles, pH, Iron and Lead.

Sodium metabisulphite
Definition: Sodium metabisulphite is freely soluble in water and slightly soluble in ethanol.

EC specifications: E 223 - Sodium metabisulphite [2].
Assay: Not less than 95% of Na₂S₂O₅ and not less than 64% of SO₂.
The specification includes purity criteria on Thiosulphate, Iron, Selenium, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Sodium metabisulfite [1].
Assay: Not less than 90.0% and not more than 100.5% of Na₂S₂O₅
The specification includes purity criteria on Water insolubles, pH, Thiosulfate, Iron and Lead.

Potassium metabisulphite
Definition: Potassium metabisulphite is soluble in water and insoluble in ethanol.

EC specifications: E 224 - Potassium metabisulphite [2].
Assay: Not less than 90% of K₂S₂O₅ and not less than 51.8% of SO₂, the remainder being composed almost entirely of potassium sulphate.
The specification includes purity criteria on Thiosulphate, Iron, Selenium, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Potassium metabisulfite [1].
Assay: Not less than 90.0% of K₂S₂O₅
The specification includes purity criteria on Water insolubles, pH, Thiosulfate, Iron and Lead.

Calcium sulphite
Definition: Calcium sulphite is the calcium salt of sulphurous acid.

EC specifications: E 226 - Calcium sulphite [2].
Assay: Not less than 95% of CaSO₃·2H₂O and not less than 39% of SO₂.
The specification includes purity criteria on Iron, Selenium, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

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**Calcium bisulphite**

**Definition:** Calcium bisulphite is defined by the specifications as an aqueous solution.

**EC specifications:** E 227 - Calcium bisulphite [2].
Assay: 6 to 8% (w/v) of SO₂ and 2.5 to 3.5% (w/v) of CaO.
The specification includes purity criteria on Iron, Selenium, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Calcium bisulfite [1].
Assay: Not less than 6% and not more than 8% of SO₂.
The specification includes purity criteria on Iron, Selenium, Arsenic and Heavy metals.

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**Potassium bisulphite**

**Definition:** Potassium bisulphite is defined by the specifications as an aqueous solution.

**EC specifications:** E 228 - Potassium bisulphite [2].
Assay: Not less than 280 g KHSO₃ per litre (or 150 g SO₂ per litre).
The specification includes purity criteria on Iron, Selenium, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

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**Exposure:** Sulphites may be added to a wide variety of foods among which burger meat and breakfast sausages 450 mg/kg, dehydrated granulated potatoes 400 mg/kg, dried fruits 500-2000 mg/kg and wines 16-400 ml/litre. The later may contribute most to the intake. In non-alcoholic beverages and beer 20-50 mg/litre. The ADI for a 60 kg person can be reached by consuming 20 g dried apricot (or peach, grape, prune, or fig), or about 100 g burger/ sausage or potato, or 200 ml wine (with 200 mg/litre) or 0.8-2 litre beer or non-alcoholic drink. In the EU monitoring system the sulphites were examined in tier 2 and the calculated intake by adults is reported in the range of 20-266%. The calculated intake by young children is reported in the range of 83-1227 % of ADI. These sulphite intake estimates are conservative and based on the assumption that the additive is used in the widest possible range of foods and at maximum permitted levels. Work is in progress to refine intake estimates using actual usage data, which will considerably reduce the degree of overestimation in the current figure (tier 3).

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**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1994. The ADI is 0.7 mg/kg bw [3] and is based on a NOEL of 70 mg/kg bw per day for gastric irritation in long-term feeding studies in both rats and pigs. SCF recommend that the use of sulphites should be limited where possible to those foods where there is a sound technological justification for their inclusion. In addition, and all food and beverages containing added sulphites should be labelled irrespective of the final amount present as a help and warning for sensitive individuals.
**JECFA status:** Latest evaluation 1998, the previous group ADI of 0.7 mg/kg bw [5] was confirmed and maintained [7].

**Background data:**

**Subacute/subchronic toxicity:** No evidence of any systemic effects attributable to sulphites has been reported in short term studies in rats with an induced deficiency in sulphite metabolism [3].

**Genotoxicity:** Sulphites are genotoxic *in vitro* but not *in vivo* [6].

**Chronic toxicity/Carcinogenicity:** Sulphites are not carcinogenic in animals. The only treatment-related effects in animals attributable to sulphites are reversible changes localised in the stomach (hyperplasia and inflammation). These changes showed dose-related severity, which have been noted in several species and at very high doses decreases in growth rate and food consumption and anaemia secondary to severe haemorrhage from stomach erosions. [3]. The NOEL for gastric irritation in long-term feeding studies in both rats and pigs was 70 mg/kg bw per day. No evidence of any systemic effects was seen at doses up to 8 times the NOAEL. ( [3;4] - quoted from SCF 35th series). Acetaldehyde hydroxysulphonate, which is a major bound form of sulphite in wines and other fermented foods and beverages, caused hepatic lesions in rats but it is not clear what the role of acetaldehyde might be in this effect [7].

**Reproduction toxicity:** Sulphites are not reproductive toxicants in animals [3].

**Allergy/Intolerance:** Severe asthmatic reactions, including deaths, have been recorded following the use of sulphites in proprietary salad fresheners on vegetables. Dose-related respiratory hyper-reactivity has also been documented following consumption of potassium bisulphite-treated red wine and wine which contained smaller amounts of sulphites naturally formed as products of fermentation. [3].

**Effects in human:** Exposure of human volunteers to high doses of sulphites caused gastric reactions such as abdominal pain and vomiting. [3](see allergy).

**Conclusion:** The main problem with the sulphites is the severe asthmatic reactions that they may cause. The best solution is as SCF suggest to limit the use of sulphites as much as possible and to label products containing added sulphites. In addition, it is a quite important issue that the ADI can easily be reached by consuming small amount of food containing sulphites. Liver lesions have been observed in rats treated with acetaldehyde hydroxysulphonate (one of the reasons JECFA maintained the ADI).

Sulphur dioxide and the sulphites as defined by the specifications are covered by the toxicological evaluation. However the specifications for the sulphites are tentative. Therefore this group of substances should be revised at a future JECFA meeting. Furthermore EC specifies sodium sulphite as a solution regardless of the fact that this substance exists as fairly stable and chemically well-defined solid compound. EC should consider a revision of the specification for sodium sulphite in order to define the solid compound.
References:


2. Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, 1996.


5. [1986, TRS 751-JECFA 30]

6. [1986, FAS 21-JECFA 30]

7. [1998, FAS 42-JECFA 51]
**BIPHENYL**

**E number:** E 230

**Recommendation:** In contrast to the provisions in the directive on food additives this additive has never been evaluated by the SCF. As the data base seems limited an evaluation is desirable as well as an estimate of exposure. The JECFA specification may need a revision.

**Chemical name/synonyms:** 1,1'-Biphenyl, phenylbenzene/ diphenyl.

**Chemical formula:** C\(_{12}\)H\(_{10}\)

**EINECS number:** 202-163-5

**CAS number:** 92-52-4

**Functional Class:** Preservative.

**Specification:**

**Manufacture:** Biphenyl is obtained by chemical synthesis.

**Definition:** Biphenyl is a synthetic organic compound. It is insoluble in water and soluble in ethanol.

**EC specifications:** E 230 - Biphenyl [2].
- Assay: Not less than 99.8%.
- Polycyclic aromatic hydrocarbons: Absent.
- In addition the specification includes purity criteria on Benzene, Aromatic amines, Phenol derivatives, Readily carbonisable substances, Terphenyl and higher polyphenyl derivatives, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Diphenyl [1].
- Assay: -
- Polycyclic aromatic hydrocarbons: Absent.
- The specification includes purity criteria on Distillation range, Solidification point, Arsenic and Lead.

**Exposure:** Permitted only to surface treatment of citrus fruits. Maximum level is 70 mg/kg. The substance was not part of the EU monitoring as the substance has not been evaluated by the SCF.

**SCF/JECFA:**

**SCF status:** Not evaluated.

**JECFA status:** Latest evaluation 1964, ADI 0.05 mg/kg bw (or conditional 0.05 – 0.25 mg/kg bw). The animal studies that JECFA used in their evaluation was old and not available [3,4].
**JMPR status:** An ADI of 0.125 mg/kg bw was allocated in 1966 and confirmed in 1967 [5,6]. The ADI was based on the NOEL of 25 mg/kg bw in rat and dog and a 50 mg/kg bw in monkey. The safety factor was higher than usual since children and people suffering from diseases may consume large amounts of citrus fruit.

**Background data:**

**Subacute/subchronic toxicity:** *No data found.*

**Genotoxicity:** 1,1-Biphenyl did not induce chromosomal aberrations in Chinese hamster cells [7]. Biphenyl was not mutagenic in several strains of *S. typhimurium*, but caused genetic effects in yeast with or without activating systems and mitotic abnormalities in sea urchins. These effects were seen at concentrations that also gave general toxic effects [14]. Another article reported biphenyl to be non mutagenic in *S. typhimurium*, but was found to be mutagenic in hamster V79 cells with liver homogenate [11]. Biphenyl was also found to induce DNA damage *in vivo* in several organs in CD-1 mice. The dose used in the treatment was, however, very high (2000 mg/kg) [15].

**Chronic toxicity/Carcinogenicity:** Fifteen weanling albino rats of each sex were placed in each of eight experimental groups: 0.0, 0.001, 0.005, 0.01, 0.05, 0.10, 0.50 and 1.0% biphenyl in the diet. Dietary levels of 0.5% biphenyl and greater were associated with kidney damage, reduced haemoglobin levels, decreased food intake, and decreased longevity. One animal in each of the lower dose groups and control group had detectable blood in the pelvis. Several malignant and benign tumours were found in both treated and control rats, but were not considered to be related to treatment with biphenyl. A NOAEL of 0.1% biphenyl in the diet was chosen because of the uncertainty of the significance of the effect at lower doses [8].

B6AKF1 and B6C3F1 mice (18/sex/strain) were treated with daily gavage doses of 215 mg/kg biphenyl in gelatine from days 7 to 28 of age. The mice were then given a diet containing 517 ppm biphenyl for the subsequent 18 months. No increase in tumours was found in any of the treated groups compared with negative and vehicle controls [9].

F344 rats (18/male) were treated with 0.05% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) in the drinking water for 4 weeks followed by either a basal diet of diet containing 0.5% 1,1-biphenyl for 32 weeks. A group of five rats received the 1,1-biphenyl-containing diet without pretreatment with BBN. A significant increase in the incidence of hyperplasia, papillomas and carcinomas in the urinary bladder was found for the BBN and 1,1-biphenyl treated rats, while no such effects were seen in rats treated only with 1,1-biphenyl. Thus, 1,1-Biphenyl appeared to be a tumour promoter in this experiment [13].

**Reproduction toxicity:** No foetal or maternal toxicity resulted from pregnant Wister rat dams receiving 125, 250, or 500 mg/kg bw biphenyl by gavage on days 6-15 of gestation. Some evidence (not significant) of foetotoxicity was observed at 1000 mg/kg, but maternal mortality occurred at this dose as well [12]. No significant effects were reported when giving 0, 0.1, and 0.5% biphenyl in the diet to weanling rats 60 days before mating through weaning of their offspring [8]. Diphenyl (>100µM) resulted in developmental defects in sea urchins by exposure of the embryos or sperm/egg. However, these concentrations gave also general toxic effects in this species [14].
**Effect in humans:** Chronic persistent hepatitis was reported in a 46-year-old woman poisoned with diphenyl. The woman was exposed from biphenyl containing paper used to pack citrus fruit for 25 years [10].

**Conclusion:** Both the studies on reproduction and carcinogenicity are insufficient, and do not fulfill the requirements for such studies. The carcinogenicity studies indicate, however, that biphenyl is not carcinogenic, but may function as a tumour promoter. This should be further investigated. Biphenyl is probably not genotoxic, since the concentrations used in the experiment are in the range where biphenyl induces general toxicity.

The JECFA specification is old. If this substance is still regarded as a food additive it is suggested to re-evaluate the specification at a future JECFA meeting.

**References:**


2. Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, 1996.

3. [1964, NMRS 38/TRS 309-JECFA 8]

4. [1964, FAS 66.25/NMRS 38B-JECFA 8]


ORTHOPHENYL PHENOL AND SODIUM ORTHOPHENYL PHENOL

**E number:**
Orthophenyl phenol: E 231
Sodium orthophenyl phenol: E 232

**Recommendation:** Should be evaluated by SCF. An exposure survey is desirable.

**Chemical name/synonyms:**
Orthophenyl phenol: (1,1’-Biphenyl)-2-ol, 2-hydroxydiphenyl, o-hydroxydiphenyl/orthoxenol, o-phenylphenol, orthophenylphenol.
Sodium orthophenyl phenol: Sodium orthophenylphenol/ sodium orthophenylphenate, sodium salt of o-phenylphenol.

**Chemical formula:**
Orthophenyl phenol: C_{12}H_{10}O
Sodium orthophenyl phenol: C_{12}H_{9}ONa\cdot4H_{2}O

**EINECS number:**
Orthophenylphenol: 201-993-5
Sodium orthophenylphenol: 205-055-6

**CAS number:**
Orthophenylphenol: 90-43-7
Sodium orthophenylphenol: 132-27-4

**Functional Class:** Preservative.

**Specification:**
**Manufacture:** No information on manufacturing processes for orthophenylphenols used as food additives.

*Orthophenylphenol*
**Definition:** Orthophenylphenol is a synthetic organic substance; it is practically insoluble in water and very soluble in ethanol.

**EC specifications:** E 231 - Orthophenylphenol [2].
Assay: Not less than 99%.
The specification includes purity criteria on Sulphated ash, Diphenyl ether, p-Phenylphenol, 1-Naphthol, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** o-Phenylphenol [1].
Assay: Not less than 98%.
The specification includes purity criteria on Total ash, Arsenic and Lead.
**Sodium orthophenylphenol**

**Definition:** Sodium orthophenylphenol is the sodium compound of orthophenylphenol. It is very soluble in water and in ethanol.

**EC specifications:** E 232 - Sodium orthophenylphenol [2].
Assay: Not less than 97% of C₁₂H₉ONa⋅4H₂O.
The specification includes purity criteria on Diphenyl ether, p-Phenylphenol, 1-Naphthol, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium o-phenylphenol [1].
Assay: Not less than 97.0%.
The specification includes purity criteria on Excess alkalinity, Arsenic and Lead.

**Exposure:** Orthophenylphenols are used as surface treatment of citrus fruits, max. 12 mg/kg. The substance has not been part of the EU monitoring system, as it was not evaluated by SCF.

**SCF/JECFA evaluation:**

- **SCF status:** Not evaluated by SCF.
- **JECFA status:** Latest evaluation 1964, ADI 0.2 mg/kg bw [6]. In 1999, JMPR established an ADI of 0-0.4 mg/kg bw for o-phenylphenol on the basis of the NOAEL of 39 mg/kg per day in a two-year study of toxicity and carcinogenicity in rats and a safety factor of 100. The toxicological data for Na-o-phenylphenol was not used to establish the ADI, since it does not exist as a plant residue but dissociates to 2-phenylphenol.

**Background data:**

- **Subacute/subchronic toxicity:** In four 90 days feeding studies with orthophenylphenol and/or sodium orthophenylphenol performed on mice and rats between 1979 and 1985, the NOEL of 180-760 mg/kg bw per day was based on reduced body weight. At higher doses changes in organ weights and kidney and urinary bladder pathology were observed in some of the studies. In a 1-year study with dogs from 1990 the highest dose tested 300 mg/kg bw per day was the NOEL. [3].

- **Genotoxicity:** Ortho-phenylphenol has been more extensively tested for genotoxic activity than its sodium salt. Within that limitation, the results for the two compounds were similar. Data were conflicting regarding covalent binding to DNA in the urinary bladder of rats dosed with either compound. Orthophenylphenol induced chromosomal aberrations in cultured mammalian cells but negative results were obtained for chromosomal aberrations in vivo. [3].

- **Chronic toxicity/Carcinogenicity:** In six 22-24 months feeding studies with ortho-phenylphenol or sodium ortho-phenylphenol performed on mice and rats between 1981 and 1996, decreased survival reduced body weight, increased liver weight, liver pathology, hepatocellular adenomas, increased alkaline phosphatase activity, transitional cell carcinomas of the kidneys, urinary bladder lesions and urinary bladder tumours was observed in some of the studies at doses above 39 mg/kg bw per day [3]. The ADI value established by JMPR is based on a NOEL of
39 mg/kg bw per day in a two-year study of toxicity and carcinogenicity in rats fed orthophenylphenol. At the next dose level 200 mg/kg bw per day, reduced body weight gain and an increased incidence of hyperplasia and transitional cell carcinomas in the urinary bladder was observed. ([5]– quoted from JMPR 1999.) IARC has classified sodium orthophenylphenol in Group 2 (possible carcinogenic to humans) and orthophenylphenol in Group 3 (not classifiable as to its carcinogenicity to humans) [3].

**Reproduction toxicity:** Orthophenylphenol has been studied in rats in two two-generation reproductive studies and in mice, rats and rabbits in four developmental studies. In general reproductive or developmental effects are not observed in doses which do not induce toxicity in the parents. As for the subacute and chronic studies, toxicity in the parents is in the form of decreased body weight gain, changes in organ weights and kidney and urinary bladder pathology. In addition, pathological alterations of the gastric mucosa and the intestinal tract at doses above 100 mg/kg bw per day were observed in rabbits. Reproductive and developmental effects seen at higher doses are decreased birth or foetus body weight, low average number of live foetuses, low average number of implantations and increased number of foetal resorptions [3].

**Allergy/Intolerance:** Three studies have shown that ortho-phenylphenol and sodium ortho-phenylphenol did not cause delayed contact hypersensitivity in guinea pigs [3].

**Effects in human:** In a study from 1952 on 200 volunteers ortho-phenylphenol was not found to be irritating or to cause sensitisation on human skin. Sodium ortho-phenylphenol caused irritation but not sensitisation in both 5 % and 1 % aqueous solutions [3].

**Other:** Many studies have been conducted to try to elucidate the mechanism of the carcinogenic effect seen in the rat urinary bladder. No clear mechanism has been found although raising the urinary pH and/or sodium concentration has a promoting effect. Initial irritation followed by hyperplasia might be involved in the carcinogenicity. Other studies have shown binding of orthophenylphenol and its sodium salt to DNA in the urinary bladder. [3]. Regenerative hyperplasia due to cytotoxicity of metabolites of ortho-phenylphenol and/or binding of these metabolites to protein targets may also play an important role in ortho-phenylphenol induced bladder carcinogenesis [4].

**Conclusion:** SCF has never evaluated this substance, although an evaluation is warranted. JECFA’s evaluation is from 1964 and based on quite old data. Several new studies in all areas of the toxicology of ortho-phenylphenol and its sodium salt exist and have been evaluated by JMPR recently. Establishing a new ADI by JMPR seemed to be justified since the levels of OPP that cause no toxic effect in all other studies (until 1999 and described in JMPR’s documents) are higher than 39 mg/kg per day.

The orthophenylphenols as defined by the specifications are covered by the toxicological evaluation carried out by JECFA. The JECFA specification is old as well as the evaluation. If this substance is still regarded as a food additive it is suggested that a re-evaluation of the specification and toxicology is performed at a future JECFA meeting.

**References:**

2. Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, 1996.


Nisin

**E number:** E 234

**Recommendation:** A re-evaluation is not necessary on toxicological grounds, however, the printing error concerning the SCF ADI should be corrected. This and other substances with antibiotic activity are on the agenda of the SCF to consider the possibility for induction of microbiological resistance.

**Chemical name/synonyms:** -

**Chemical formula:** \(\text{C}_{143}\text{H}_{230}\text{N}_{42}\text{O}_{37}\text{S}_{7}\)

**EINECS number:** 215-807-5

**CAS number:** 1414-45-5

**Functional Class:** Preservative.

**Specification:**

**Manufacture:** Nisin is produced by strains of *Streptococcus lactis*, Lancefield group N.

**Definition:** Nisin is a naturally occurring substance. It consists of several closely related polypeptides.

**EC specifications:** E 234 Nisin [2].

Assay: Nisin concentrate contains not less than 900 units per mg in a mixture of non-fat milk solids and a minimum sodium chloride content of 50%.

The specification includes purity criteria on Loss on drying, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Nisin [1].

Assay: -

The specification includes purity criteria on Loss on drying, Arsenic and Heavy metals.

**Exposure:** Nisin is permitted in semolina and tapioca puddings and similar products max. 3 mg/kg. Ripened cheese and processed cheese max. 12.5 mg/kg. It needs 1.3 kg semolina a day to reach ADI (30 kg child) or 600 g cheese a day (60 kg). Exposure of the additive passed tier 1 with adults and children in the EU intake evaluation and does not require further examination at this stage.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation ADI = 0.13 mg/kg bw for a product with 40.000 units/g [3]. This, however, is a printing error in the 26th series as the correct concentration is 40.000 units/mg (compare also specification).
**JECFA status:** ADI = 33.000 units/kg bw [4].

**Background data:**

**Subacute/subchronic toxicity:** Nisin had no toxicological effect on rats fed up to 2.4 x 10^6 units/kg bw per day for 12 weeks [4].

**Genotoxicity:** The available data on genotoxicity, though limited by present day standards, have not shown any adverse treatment-related effects [3].

**Chronic toxicity/Carcinogenicity:** The available data on carcinogenicity, though limited by present day standards, have not shown any adverse treatment-related effects [3]. In a study from 1962 no adverse effects were seen when rats were fed up to 3.3 x 10^6 units/kg bw per day of nisin for 2 years [4].

**Reproduction toxicity:** The ADI established by SCF is based on a reproduction study performed somewhere between 1968 and 1990 [3]. SCF has no reference to this study.

**Allergy/Intolerance:** Nisin has caused sensitisation when administered intraperitoneally or parenterally to guinea pigs or rabbits but not when administered orally. In humans there is no evidence of sensitisation [4].

**Conclusion:** The ADI for nisin is based on limited and rather old data but toxicologically nisin probably does not cause any major problems. The main concern of its use in food is the possible formation of resistant micro-organisms. This aspect is presently on the agenda of SCF.

Nisin as defined by the specifications is covered by the toxicological evaluation carried out by JECFA. The JECFA specification is old. It is therefore suggested to revise the specification at a future JECFA meeting.

**References:**


2. Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, 1996.


**NATAMYCIN**

**E number:** E 235

**Recommendation:** A re-evaluation not warranted on toxicological grounds. The question of microbiological resistance to substances with antibiotic properties is presently on the agenda of SCF.

**Chemical name/synonyms:** Pimaricin.

**Chemical formula:** $\text{C}_{33}\text{H}_{47}\text{O}_{13}\text{N}$

**EINECS number:** 231-683-5

**CAS number:** 7681-93-8

**Functional Class:** Preservative.

**Specification:**

**Manufacture:** Natamycin is produced by strains of *Streptococcus natalensis* or *Streptococcus lactis*.

**Definition:** Natamycin is a fungicide of the polyene macrolide group. It is practically insoluble in water and slightly soluble in methanol.

**EC specifications:** E 235 - Natamycin [2].
Assay: Not less than 95% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Sulphated ash, Arsenic, Lead, Mercury, Heavy metals and Microbiological criteria.

**JECFA specifications:** Natamycin [1].
Assay: Not less than 95.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Specific rotation, Sulphated ash, pH and Heavy metals.

**Exposure:** Natamycin is permitted for surface treatment of hard, semi-hard and semi-soft cheese and dried, cured sausages max. 1 mg/dm$^2$ of surface and not present deeper than 5 mm. Not included in the EU intake evaluation at this stage, but the restrictions, which are in line with the SCF recommendation should ensure intakes well below the ADI specified by JECFA.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1979. No ADI was allocated but SCF found the use of natamycin acceptable for surface treatment of whole pressed cheese (semi-hard) and on the casings of certain sausages requiring maturation before marketing provided residues do not exceed 1 mg/dm$^2$ of
surface and not present at a depth greater than 5 mm. The Committee opposed the use in other areas [3].

**JECFA status:** Latest evaluation 1976, ADI 0.3 mg/kg bw [4]. (This ADI was recently confirmed at the 57th meeting June 2001, but details not published yet).

**Background data:**

**Subacute/subchronic toxicity:** Growth inhibition and diminished food intake were the only effects observed in rats and dogs exposed to natamycin for 3 months at doses at or above 2000 ppm [5].

**Genotoxicity:** In an *in vivo* study no significantly observed abnormalities were found in metaphase chromosomes from the bone marrow [5].

**Chronic toxicity/Carcinogenicity:** In a 2-year study where in rats were given 1000 ppm of natamycin, growth inhibition and diminished food intake were the only effects observed. At lower doses no effect was seen. The number and types of tumours found were not significantly different in treated and control animals. [5].

**Reproduction toxicity:** No reproductive toxicity or teratogenicity was observed in rats (or their foetuses) fed doses up to 100 mg/kg bw per day of natamycin. Fetotoxicity in the form of reduced body weight, increased number of foetuses born dead and decreased number of pups surviving at 21 days was observed at 100 mg/kg bw per day of natamycin. [5].

**Allergy/Intolerance:** No allergic sensitisation has been reported in patients treated with natamycin or in workers engaged in the manufacture of natamycin [5].

**Effects in human:** Nausea, vomiting and diarrhoea have occasionally been caused by oral doses of about 5 mg/kg bw of natamycin daily. The ADI of JECFA is based on an estimated NOEL of 3 mg/kg bw in humans exposed to natamycin. [5].

**Conclusion:** The ADI for natamycin is based on limited data but in the sense of toxicology natamycin is unlikely to cause any major problems. The main concern of its use in food is the potential induction of microbiological resistance.

Natamycin as defined by the specifications is covered by the toxicological evaluation. Natamycin is on the agenda for the fifty-seventh JECFA.

**References:**

2. Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, 1996.

4. [1976, FNS 1/TRS 599-JECFA 20]

5. [1976, FAS 10-JECFA 20]
HEXAMETHYLENE TETRAMINE

E number: E 239

Recommendation: Only indirectly evaluated by SCF. Although use is very limited, an evaluation, as previously announced by SCF, would be desirable.

Chemical name/synonyms: 1,3,5,7-Tetraazatricyclo [3.3.1.1^3,7]-decane, hexamethylenetetramine/ hexamine, methenamine.

Chemical formula: C\textsubscript{6}H\textsubscript{12}N\textsubscript{4}

EINECS number: 202-905-8

CAS number: 100-97-0

Functional Class: Preservative.

Specification:
Manufacture: Hexamethylene tetramine is obtained by reaction between formaldehyde and ammonia.

Definition: Hexamethylene tetramine is an organic chemical substance. It is freely soluble in water and soluble in ethanol.

EC specifications: E 239 Hexamethylene tetramine [2].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Sulphated ash, Sulphates, Chlorides, Ammonium salts, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Hexamethylenetetramine [1].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Ammonium salts, Arsenic and Heavy metals.

Exposure: Hexamethylene tetramine may only be used in provolone cheese max; 25 mg/kg residual amount expressed as formaldehyde. Exposure is, therefore, very low and much lower than the JECFA ADI. Not included in the EU intake evaluation at this stage.

SCF/JECFA evaluation:
SCF status: Hexamethylene tetramine has not been directly evaluated as a food additive by SCF. In 1977 the Committee, when evaluating the use of formaldehyde in grana padano cheese, referred to hexamethylene tetramine, as it under acidic conditions or in the presence of proteins, can decompose to form formaldehyde [6]. At its 76th meeting on 13-14 December 1990 the Committee expressed some concern regarding the use of the substance, which at that time also was used to
preserve caviar like fish eggs. The Committee requested the results of a, at that time, ongoing, study of formaldehyde as well as information on the extend of formaldehyde liberation in food and after ingestion.

**JECFA status:** Latest evaluation 1973: ADI 0.15 mg/kg bw which was based on a reproductive study with a NOEL of 15 mg/kg bw per day [7].

**Background data:**

**Subacute/subchronic toxicity:** No adverse effects (except for a citrus-yellowish discoloration of the fur) were observed in rats given by gavage 400 mg of hexamethylene tetramine daily for up to 333 days or cats fed 1250 mg/kg of hexamethylene tetramine daily for two years [8].

**Genotoxicity:** Both hexamethylene tetramine and formaldehyde have been shown to act as mutagens in Drosophila [8]. Hexamethylene tetramine does not act as a clastogen on Vicia faba roots and V79 cells but it increases the frequency of sister-chromatid exchanges in V79 cells [4]. Hexamethylene tetramine was positive in Ames test both with and without metabolic activation systems. It was found to be DNA-damaging in the recessive assay on Bacillus subtilis spores. High doses induced chromosomal aberrations both in mouse lymphocyte cultures and in human HeLa cell line. Transformations were induced in baby hamster kidney cells. Mutagenic effects were absent in a dominant lethal test in C3H mice. [5].

**Chronic toxicity/Carcinogenicity:** In four old (1966-1971) long-term studies (15-30 months) in mice or rats a dietary level of 1 % hexamethylene tetramine generally caused no adverse effects (except for a yellowish discoloration of the fur of some animals). Groups receiving 5 % had reduced survival and growth rate. In one two-year study on mice a slightly increased tumour incidence was observed in female mice fed 1 % of hexamethylene tetramine but in the other studies the tumour incidence was not increased in treated animals. [8]. In chronic toxicity studies in dogs and rats receiving oral hexamethylene tetramine in a dosage of 50-200 mg/kg daily and 0.8-6.4 g/kg daily, respectively, gastric and bladder irritation occurred with some hemorrhagic sites and ulceration. (HSDB).

**Reproduction toxicity:** Several old studies in rats point to no reproduction toxicity. However, in dogs reduced birth weight and post-natal growth have been observed as well as stillborn and malformed pups. The ADI established by JECFA is based on such a reproduction study where they specified 15 mg/kg bw as NOEL value even though reduced birth weight and post-natal growth is observed at this dose level. At the higher dose of 31 mg/kg bw per day the incidence of stillbirths was slightly increased and post-natal survival to weaning was decreased. No malformations were observed in this study. [8].

**Allergy/Intolerance:** Several reports exist on the irritating and sensibilising effects of hexamethylene tetramine on the skin and the respiratory tract after occupational exposure in humans. Hexamethylene tetramine was shown to be non-sensitising to guinea pigs. However, a root canal filling substance, which contains 25 % hexamethylene tetramine, sensitised 9 out of 10 guinea pigs. [5].

**Effects in human:** Very large oral doses (1-2 g) may cause gastrointestinal irritation (vomiting and pain) with inflammatory lesions in renal tubules and pelvis. Bladder irritation, painful and frequent
micturition, albuminuria, hematuria and various rashes may result from doses of 4-8 g per day given for longer than 3-4 weeks. Repeated use may cause sensitisation with urticaria or dermatitis. (HSDB).

Other: Hexamethylene tetramine is used as an unspecific urinary disinfectant in doses of 1g twice daily [3]. In vitro formation of carcinogenic nitrosamine has been reported as a result of the interaction of nitrite with hexamethylene tetramine at pH 1-3 [8].

Conclusion: Hexamethylene tetramine is positive in several mutagenicity tests. An increased incidence of tumours was observed in one of the long-term studies. A new guideline study on chronic toxicity/carcinogenicity would therefore be valuable in assessing whether hexamethylene tetramine is carcinogenic. However, the use of hexamethylene tetramine as a food additive is limited.

Hexamethylene tetramine as defined by the specifications seems to be covered by the toxicological evaluation.

References:


2. Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, 1996.


DIMETHYL DICARBONATE

E number: E 242

Recommendation: No need for a re-evaluation.

Chemical name/synonyms: Dimethyl dicarbonate, pyrocarbonic acid demethyl ester/ DMDC, dimethyl pyrocarbonate.

Chemical formula: C₈H₆O₅

EINECS number: 224-859-8

CAS number: 004-525-33-1

Functional Class: Preservative.

Specification:
Manufacture: Dimethyl dicarbonate is obtained by chemical synthesis.

Definition: Dimethyl dicarbonate is soluble in water with decomposition yielding methanol and carbon dioxide.

EC specifications: E 242 - Dimethyl dicarbonate [2].
Assay: Not less than 99.8%.
The specification includes purity criteria on Dimethyl carbonate, Chlorine, total, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Dimethyl dicarbonate [1].
Assay: Not less than 99.8%.
The specification includes purity criteria on Dimethyl carbonate, Arsenic and Heavy metals.

Exposure: Dimethyl dicarbonate may be used for cold sterilisation in non-alcoholic aromatised beverages, alcohol free wine and liquid tea concentrates at levels of addition up to 250 mg/l. The compound disappears after hydrolysis in aqueous media and cannot be determined by analysis. The level of methanol is less than what can be found in e.g. fruit juices from natural sources. Not included in the EU intake evaluation.

SCF/JECFA evaluation:
SCF status: Latest evaluation 1997, acceptable [3]. At its 128th meeting, July 2001 the Committee extended its acceptance also to cover the cold sterilisation of wine.
(http://europa.eu.int/comm/food/fs/sc/scf/out96_en.pdf)

JECFA status: Latest evaluation 1990, acceptable [4].
Neither SCF nor JECFA have found toxicological objection to the use of dimethyl dicarbonate for cold sterilisation of the above mentioned drinks at a level of addition up to 250 mg/l since dimethyl dicarbonate is unstable in aqueous solutions and breaks down into harmless substances almost immediately after addition. Only the side product methylcarbamate might cause concern because it has produced hepatocellular carcinomas in one strain of rats at high dose levels but mutagenicity studies have shown that methylcarbamate is a non-genotoxic agent. The residues of methylcarbamate in soft drinks are less than 20 µg/l and there is a safety margin of several orders of magnitude between possible consumer intakes and the dose causing cancer. In 1997 SCF confirmed its previous decision. [3-5].

**Background data:**

**Subacute/subchronic toxicity:** Rats drinking fruit juice or alcoholic beverages treated with 4000 mg dimethyl dicarbonate per litre for 3 months tolerated it without any signs of toxicity. Dogs drinking orange juice treated with 4000 mg dimethyl dicarbonate per litre for 12 months tolerated it without any signs of toxicity. The metabolites dimethylcarbonate and methyl ethyl carbonate were tolerated by rats for 3 months without any adverse effects at concentrations up to and including 1 % in drinking water. Several short-terms studies with the metabolite methylcarbamate have been conducted in mice and rats. In three 90-days studies in rats, deaths occurred at doses at and above 800 mg/kg bw per day, reduced body weight was observed at and above 400 mg/kg bw per day, hepatotoxicity was observed at and above 200 mg/kg bw per day and lesions of the spleen, bone marrow and testis were seen at and above 400 mg/kg bw per day. [5].

**Genotoxicity:** Dimethyl dicarbonate tested negative in Ames test and in an *in vivo* micronucleus test in mouse bone marrow cells. The metabolite methylcarbonate tested negative in all but one test including Ames test, DNA damage, bacterial back mutation assay, mitotic recombination assay, gene mutation, unscheduled DNA synthesis, chromosome aberrations, sister chromatid exchange, neoplastic transformation assay, sex-linked recessive lethal mutations and dominant lethal mutations. [5].

**Chronic toxicity/Carcinogenicity:** Rats drinking orange juice or wine treated with 4000 mg dimethyl dicarbonate per litre for 30 months tolerated it without any signs of toxicity. The metabolite methylcarbamate produced hepatocellular carcinomas in Fischer 344 rats at and above 200 mg/kg bw per day in 2 year studies, but did not have such effects in Wistar rats or in mice. The NOEL for hepatic carcinogenesis was 100 mg/kg bw per day. [5].

**Reproduction toxicity:** No reproductive toxicity or embryotoxicity was observed in rats or their pups drinking orange juice treated with 4000 mg dimethyl dicarbonate per litre. The metabolite methyl ethyl carbonate at doses up to and including 1 % in the drinking water did not cause embryotoxicity in rats either. [5].

**Conclusion:** Since the compound disappears after hydrolysis in aqueous media and cannot be determined by analysis, allocating an ADI is meaningless. For the same reason the consumers are not directly exposed to the substance. The evaluation is based on sufficient toxicological data.

Dimethyl dicarbonate as defined by the specifications is covered by the toxicological evaluation.
References:


2. Commission Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners, 1996.


4. [1990, TRS 806-JECFA 37]

5. [1990, FAS 28-JECFA 37]
SODIUM NITRITE AND POTASSIUM NITRITE

E Number:
Potassium nitrite: E 249
Sodium nitrite: E 250

Recommendation: There is no need for toxicological re-evaluation. It is recommended that appropriate technological practises such as the lowering of levels of nitrate and nitrite added to foods to the minimum required to achieve the necessary preservative effect and to ensure microbiological safety be introduced.

Chemical name/synonyms:
Potassium nitrite: Potassium nitrite/
Sodium nitrite: Sodium nitrite/

Chemical formula:
Potassium nitrite: KNO₂
Sodium nitrite: NaNO₂

EINECS number:
Potassium nitrite: 231-832-4
Sodium nitrite: 231-555-9

CAS Number:
Potassium nitrite: 7758-09-0
Sodium nitrite: 7632-00-0

Functional Class: Preservative

Specification:
Potassium nitrite
Definition: Potassium nitrite is the potassium salt of nitrous acid. Is freely soluble in water and sparingly soluble in ethanol.

Manufacture: No information on manufacture of food quality of potassium nitrite at present.

EC specifications: E 249 Potassium nitrite [1]
Assay: Not less than 95% of potassium nitrite on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Potassium nitrite [2]
Assay: Not less than 95.0% of potassium nitrite on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Arsenic, Lead and Heavy metals.
Sodium nitrite

**Definition:** Sodium nitrite is the sodium salt of nitrous acid. It is soluble in water and sparingly soluble in ethanol.

**Manufacture:** No information on manufacture of food quality of sodium nitrite at present.

**EC specifications:** E 250 Sodium nitrite [1]
Assay: Not less than 97% of sodium nitrite on the dried basis.
In addition, the specification includes purity criteria on Loss on drying, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium nitrite [2]
Assay: Not less than 97.0% of sodium nitrite on the dried basis.
In addition, the specification includes purity criteria on Loss on drying, Arsenic, Lead and Heavy metals.

**Exposure:** In the EU monitoring system, nitrite was examined at tier 1 and as the calculated intake exceeds the ADI examination a tier 2 was performed and the calculated intake by adults and the whole population is reported in the range of 40 – 230% of ADI. The calculated intake by young children is reported in the range of 50 – 360%. Examination at tier 3 of the intake of these substances is therefore needed. Additional information: A Finnish study done at tier 3 level and targeted especially on 1 – 6 year old children has been reported. Estimates for intake are based on individual food consumption and analysed food additive levels in products consumed in Finland. The intake of nitrites by high-level consumers (95th percentile) was 121 – 189% of the ADI. Also, the in vivo formation of nitrite from ingested nitrate could be important. It is estimated that 5-20% of the total nitrate intake is reduced to nitrite mainly due to nitrate-reducing bacteria in the gastrointestinal tract [3]. Further, there is a significant de novo formation of nitrite in the body via nitrogen monoxide.

As there is a clear correlation between nitrite added for the curing of meat and the formation of volatile nitrosamines [4] and as the amount of added/ingoing nitrite is significantly reduced in cured meat products and the concentration of residual nitrite shows great variation it is important for the toxicological evaluation also to consider the amount of added nitrite.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation: 1995 ADI 0.06 mg/kg bw expressed as nitrite ion based on the long-term rat study mentioned below. The ADI is based on a 90-day toxicity studies in rats where the NOEL was 5.4 mg/kg bw and on a 2-year toxicity study in rats where the NOEL was 6.7 mg/kg bw. The Committee confirms that this ADI is applicable to all sources of dietary exposure. Based on the possible formation of carcinogenic N-nitroso compounds the Committee recommend that levels of nitrite added to food should be lowered to the minimum required to achieve the necessary preservative effect and to ensure microbiological safety. The Committee also recommends that further research should be carried out on the possibility of developing alternative preservatives and in the meantime, on methods of inhibiting the nitrosation reactions in foods. [3].

**JECFA status:** Latest evaluation 1996, ADI 0-0.06 mg/kg bw, expressed as nitrite ion [5]. The ADI is based on a 90 day toxicity study in rats where the NOEL was 5.4 mg/kg bw (expressed as
nitrite ion) and on a 2-year toxicity study also in rats where the NOAEL was 6.7 mg/kg bw (expressed as nitrite ion).

**BACKGROUND DATA:**

**Subacute/subchronic toxicity:**
Short-term studies with nitrite have been performed in mice, rats and rabbits [4,6]. In mice and rats methaemoglobinaemia is commonly observed as well as various adverse effects reported on the cardiovascular function and histology, on the lungs, on motor activity and hypertrophy of the adrenal zona glomerulosa. The NOEL, based on hypertrophy of the adrenal zona glomerulosa in a 90 day study in the rat, was 10 mg potassium nitrite/kg bw/day (equivalent to 5.4 mg nitrite ion/kg bw/day).

**Genotoxicity:** Nitrite is genotoxic in *in vitro* bacterial tests, but the results in *in vivo* are equivocal [4].

**Chronic toxicity/carcinogenicity:** Several studies with nitrite have been performed in mice and rats and all have failed to show carcinogenic effects [3,4,6]. All studies have used high nitrite doses, in mice up to 1000 mg/kg bw/day and in rats up to 300 mg/kg bw/day. In one of these studies, a 2-year study in rats, the NOEL was determined to 10 mg sodium nitrite/kg bw/day (equivalent to 6.7 mg nitrite ion/kg bw/day). The NOEL is based on thin and dilated coronary arteries associated with focal degeneration and fibrosis of the heart muscle, as well as on dilatation of the lung bronchi and infiltration of lymphocytes, and alveolar hyperinflation.

**Reproduction toxicity:** Studies performed with nitrite in rats, guinea-pigs and cattle have been performed and suggest that there are no adverse effects on reproductive parameters, such as fertility, abortions, litter size and birth weight [6]. However, in rats nitrite showed transplacental passage and produced methaemoglobinaemia in the foetuses [6]. Special studies on embryotoxicity/teratogenicity in mice and rats show no adverse effects, indicative of developmental toxicity, to nitrite treatment up to 500 mg/kg bw/day.

**Effect in humans:** Nitrite is more toxic to young infants than to adults, due to potentially higher nitrite exposure, increased formation of methaemoglobin and higher susceptibility in infants [5]. However, pregnant women, individuals with metabolic disorders, and adults with reduced gastric acidity (including medical treatment of diseases, such as peptic ulcer, chronic gastritis, etc) may be more sensitive and predisposed to nitrite-induced methaemoglobinaemia. The estimated minimum effective dose for man based on methaemoglobinaemia seems to be in the range of 1-8.3 mg nitrite/kg bw [3]. Especially high nitrite production has been observed in the saliva, i.e. in volunteers the average saliva nitrite formation was 8% of the nitrate dose [6]. Nitrite used in medical treatment of vasodilation and cyanide poisoning showed that 0.5-5 mg/kg bw caused no toxic effects and the no adverse effect level in humans has been estimated to be approximately 1 mg/kg bw/day [6].

**Other:** A special study on malignant transformation in mouse cells indicates that nitrite itself has cell transforming activity and that NO$_2^-$ is produced by activated macrophages [5]. A number of studies in various species have shown that nitrite intoxication induce vitamin A deficiency [5]. The explanation to this has been suggested to be due to a direct reaction of nitrite with carotene prior to absorption [5].
In combination with amines or amides, the formation of carcinogenic N-nitroso compounds has been demonstrated to occur in vivo and to lead to tumour induction in long-term studies in rodents, but only at much higher intakes than normal dietary exposure.

The addition of nitrite to food may give rise to the formation of genotoxic and carcinogenic nitrosamines, especially in cured meat products [3,4,6]. Some epidemiological studies have indicated a relationship between consumption of cured meats and childhood cancers. In a recent review by Blot et al.[7] 14 such epidemiological studies have been reviewed and they conclude that “at this time it cannot be concluded that eating cured meat has increased the risk of childhood brain cancers or any other cancers” but that “the hypothesis that eating nitrite-cured meats may influence childhood and perhaps adult brain cancers cannot be dismissed.

It has been shown, both in animals and in humans that nitrite also may be formed in vivo, partly by reduction of ingested nitrate, partly from nitrogen monoxide [4,6,]. It has also been demonstrated that N-nitroso compounds (NOC) may be formed in vivo also in humans [4,6].

In 1995 SCF concluded that “there is no direct evidence that current dietary levels of pre-formed NOC in the European Union carries a risk to human health. Moreover, whilst the potential for endogenous NOC formation in the gastrointestinal tract is generally accepted, its importance in comparison to exogenous NOC exposure is far from being settled.”

**Conclusion:** The identified major toxic effects of nitrite per se are formation of methaemoglobin, hypertrophy of the adrenal zona glomerulosa and genotoxicity. The ADI of 0.06 mg/kg bw expressed as nitrite ion is not applicable to infants under 3 months of age. Clinical studies in adults have shown that the NOAEL is in the same range as in experimental animals from which ADI is derived. However, there are several groups of individuals that can be expected to have a higher sensitivity.

As the EU monitoring system shows a high potential exposure it should be investigated to what extent the reduction in use, as recommended by SCF, could be implemented.

**References:**


5. [1995, TRS 859-JECFA 44] Evaluation of certain food additives and contaminants. (Forty-fourth report of the Joint

SODIUM NITRATE AND POTASSIUM NITRATE

E Number:
Sodium nitrate: E 251
Potassium nitrate: E 252

Recommendation: No need for a re-evaluation. However the recommendation from the SCF that “exposure to preformed nitrosamines in food should be minimised by appropriate technological practices such as the lowering of levels of nitrate and nitrite added to foods to the minimum required” should be borne in mind [4].

Chemical name/synonyms:
Sodium nitrate: Sodium nitrate/ Chile salpeter, cubic or soda nitre
Potassium nitrate: Potassium nitrate/

Chemical formula:
Sodium nitrate: NaNO₃
Potassium nitrate: KNO₃

EINECS number:
Sodium nitrate: 231-554-3
Potassium nitrate: 231-818-8

CAS Number:
Sodium nitrate: 7631-99-4
Potassium nitrate: 7757-79-1

Functional Class: Preservative

Specification:
Sodium nitrate
Definition: Sodium nitrate is the sodium salt of nitric acid. Is freely soluble in water and slightly soluble in ethanol.

Manufacture: No information on manufacture of food quality of sodium nitrate at present.

EC specifications: E 251 Sodium nitrate [1]
Assay: Not less than 99% of sodium nitrate on the dried basis.
Nitrites: Not more than 30 mg/kg expressed as sodium nitrite.
In addition the specification includes purity criteria on Loss on drying, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Sodium nitrate [2]
Assay: Not less than 99.0% of sodium nitrate on the dried basis.
Nitrites: Not more than 30 mg/kg.
In addition the specification includes purity criteria on Loss on drying, Arsenic, Lead and Heavy metals.

**Potassium nitrate**

**Definition:** Potassium nitrate is the potassium salt of nitric acid. Is soluble in water and slightly soluble in ethanol.

**Manufacture:** No information on manufacture of food quality of potassium nitrate at present.

**EC specifications:** E 252 Potassium nitrate [1]
Assay: Not less than 99% of potassium nitrate on the dried basis.
Nitrites: Not more than 20 mg/kg expressed as sodium nitrite.
In addition the specification includes purity criteria on Loss on drying, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Potassium nitrate [2]
Assay: Not less than 99.0% of potassium nitrate on the dried basis.
Nitrites: Not more than 30 mg/kg expressed as sodium nitrite.
In addition the specification includes purity criteria on Loss on drying, Arsenic, Lead and Heavy metals.

**Exposure:** The EU monitoring system shows that the estimated intake of nitrate from food additive use ranges lies well below the ADI and it is concluded that no further examination is warranted.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1995, ADI 0-3.7 mg/kg bw, expressed as nitrate ion (equivalent to 0-5.0 mg/kg bw for sodium nitrate, including intake from all sources [3,4].

**JECFA status:** Latest evaluation 1996, ADI 0-3.7 mg/kg bw, expressed as nitrate ion [5]. The ADI is based on a long-term study in rats where the NOEL was 370 mg/kg bw (expressed as nitrate ion) and on human data (5% conversion rate) using a safety factor of 50.

**BACKGROUND DATA:**

**Subacute/subchronic toxicity:** Short-term studies with nitrate have been performed in mice, rats, rabbits, dogs and cattle. Various adverse effects have been reported, such as slightly elevated methaemoglobin levels, increased relative kidney weights and reduced weight gain, as well as alterations in plasma vitamin E levels and energy conversion processes. The maximum tolerated dose of sodium nitrate in the rat was 5% in the diet. The NOEL, based on increased methaemoglobin levels, was 500 and 2500 mg sodium nitrate/kg bw/day in a 4- and 6-weeks rat study, respectively. A 4-weeks study in rabbits induced, even at the lowest dose of 200 mg potassium nitrate/kg bw/day, intoxication symptoms, including weight reduction, tachycardia, polyuria and weakness [6].

**Genotoxicity:** Nitrate has been tested for genotoxicity/mutagenicity in various in vitro and in vivo test systems [6]. When tested in bacterial in vitro systems it induced mutagenic effects only in E. coli and only under anaerobic conditions, possibly due to reduction of nitrate to nitrite. In in vitro chromosomal aberration tests inconsistent results have been obtained. Chromosome aberration tests in vivo have generated positive results in mice and rats.
**Chronic toxicity/carcinogenicity:** Several studies with nitrate have been performed in mice and rats and all have failed to show any carcinogenic effects [6]. All studies have used nitrate doses up to at least 5 % in the diet. In one 2-year study, at the 5 % dose level, a slight growth inhibition was observed, but complete histopathological examination reviled no abnormalities. The NOEL in this study was 500 mg sodium nitrate /kg bw/day, equivalent to 370 mg/kg bw/day expressed as nitrate ion.

**Reproduction toxicity:** Studies performed with nitrate in guinea-pigs, rabbits, sheep and cattle suggest that there are no adverse effects on reproductive parameters, such as fertility, abortions, litter size and birth weight [6]. However, at a very high dose (1130 mg potassium nitrate /kg bw/day) in guinea-pigs the mating behaviour was highly impaired and the number of pregnant animals was seriously reduced.

**Effect in humans:** In human intoxication, high nitrate levels in well water are frequently the cause of intoxication and children are especially vulnerable. However, no relationship between nitrate levels and late adverse pregnancy outcomes or neonatal death cases have been shown. Nitrate has been suggested to play a role in thyroid disease, i.e. a dose-dependent difference in hypertrophy between medium and high nitrate exposure groups was shown and this increase in thyroid was inversely related to serum thyroid stimulating hormone levels [6]. These effects are supported by similar findings in experimental animals. Recent data also show that the use of drinking water with high peak concentrations or great variations in nitrate concentration is correlated to sudden infant death syndrome (SIDS) [6]. A few mg nitrate/L does not seem to cause an increased risk, but peaks in the range 5-10 mg/L could be sufficient to contribute to SIDS [6].

Human lethal doses of 4-50 g nitrate (equivalent to 67-833 mg nitrate ion/kg bw) have been reported [6]. Toxicity, regarding methaemoglobin formation, has been shown to occur at doses of 2-9 g nitrate (equivalent to 33-150 mg nitrate /kg bw). In healthy infants, below 11 months of age, 50 or 100 mg nitrate/kg bw increased methaemoglobin levels to 5.3-7.5 %, but no cyanosis could be seen. Of all cases of infantile methaemoglobinaemia, 98 % occurred in areas with a nitrate content in drinking-water of more than 44-89 mg nitrate/L. Nitrate-contaminated water (23-25 mg nitrate/L) used to prepare infant formula have induced adverse reactions and the peculiar blue-gray skin syndrome [6].

Epidemiological studies in various countries show no correlation between nitrate in drinking water and stomach cancer [6]. This seems to be true even in urban areas with nitrate levels above 50 mg NO₃⁻/L drinking water. Intake from high nitrate containing drinking water in addition to the normal intake of nitrate from food may result in an estimated total intake of a few hundred mg. This is far below where adverse reactions have been reported in humans. Thus, the contribution from food additives are minor and is probably of no concern in this sense. However, a higher intake of nitrate may increase nitrite formation and its toxic effects, and this has to be considered in the evaluation of nitrate.

**Other:** In rats, doses of 40-4000 mg nitrate/L drinking water resulted in minor changes in thyroid iodine uptake, weight and histology [5]. A decrease in serum T4 has been shown in pigs after a few weeks dietary treatment with 730 mg nitrate/kg bw/day [6].
After exposure of pregnant and lactating rats and their offspring to 113 or 226 mg potassium nitrate/L drinking water, deviation in behavioural development and impairment of learning behaviour were observed [5].

**Conclusion:** It can be concluded that the toxicity of nitrate per se in humans, as well as in animals, is very low and that the adverse effects shown in some studies mainly are due to the conversion of nitrate to nitrite [4,6]. It can be estimated that 5-20% of the total nitrate intake is reduced to nitrite, mainly due to the action of nitrate-reducing bacteria in the gastrointestinal tract [5]. Thus, the effects of nitrite should also be considered in the evaluation of nitrate. The addition to meat of nitrate, which is gradually transformed to nitrite, might give rise to formation of N-nitroso compounds, especially in cured meat products, but there are no epidemiological studies which demonstrate a causal link between N-nitroso compounds, preformed in the diet and human cancer and SCF concludes that “epidemiological studies on nitrate intake and gastric cancer are inconsistent; the more reliable case-control and cohort studies, in particular, do not suggest any association” [4]

**References:**


ACETIC ACID, CALCIUM ACETATE, POTASSIUM ACETATE, SODIUM ACETATE AND SODIUM DIACETATES

E Number:
Acetic acid: E 260
Calcium acetate: E 263
Potassium acetate: E 261
Sodium acetate: E 262 (i)
Sodium diacetate: E 262 (ii)

Recommendation: No need for a re-evaluation. An update of the JECFA specification should be considered.

Chemical name/synonyms:
Acetic acid: Acetic acid, ethanoic acid.
Calcium acetate: Calcium acetate.
Potassium acetate: Potassium acetate.
Sodium acetate: Sodium acetate.
Sodium diacetate: Sodium hydrogen diacetate.

Chemical formula:
Acetic acid: C₂H₄O₂
Calcium acetate: C₄H₆O₄Ca·nH₂O (n = 0 or 1)
Potassium acetate: C₂H₃O₂K
Sodium acetates: C₂H₃O₂Na·nH₂O (n = 0 or 3)
Sodium diacetate: C₄H₇O₄Na·nH₂O (n = 0 or 3)

EINECS number:
Acetic acid: 200-580-7
Calcium acetate: 200-540-9
Potassium acetate: 204-822-2
Sodium acetates: 204-823-8
Sodium diacetate: 204-814-9

CAS Number:
Acetic acid: 64-19-7
Calcium acetate: 62-54-4
Potassium acetate: 127-08-2
Sodium acetates: 127-09-3
Sodium diacetate: -

Functional Class: Acid, base and/or salts.

Specification:
Manufacture: Acetic acid is manufactured by chemical synthesis or by fermentation.
**Acetic acid**  
**Definition:** Acetic acid is an organic acid. It is miscible with water and ethanol.

**EC specifications:** E 260 Acetic acid [7].  
Assay: Not less than 99.8%.  
The specification includes purity criteria on Non-volatile residue, Formic acid, formates and other oxidisable substances, Readily oxidisable substances, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Acetic acid, glacial [6].  
Assay: Not less than 99.0%.  
The specification includes purity criteria on Solidification point, Non-volatile residue, Readily oxidisable substances, Arsenic and Heavy metals.

**Calcium acetate**  
**Definition:** Calcium acetate is the calcium salt of acetic acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 263 Calcium acetate [7].  
Assay: Not less than 98% on the anhydrous basis.  
The specification includes purity criteria on Loss on drying, Water-insoluble matter, Formic acid, formates and other oxidisable substances, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Calcium acetate [6].  
Assay: Not less than 98% on the anhydrous basis.  
The specification includes purity criteria on Loss on drying, pH, Water-insolubles, Aldehydes, Arsenic, Lead and Heavy metals.

**Potassium acetate**  
**Definition:** Potassium acetate is the potassium salt of acetic acid. It is very soluble in water and freely soluble in ethanol.

**EC specifications:** E 261 Potassium acetate [7].  
Assay: Not less than 99% on the anhydrous basis.  
The specification includes purity criteria on Loss on drying, Formic acid, formates and other oxidisable substances, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Potassium acetate [5].  
Assay: Not less than 99% on the anhydrous basis.  
The specification includes purity criteria on Loss on drying, Alkalinity, Sodium compounds, Arsenic, Lead and Heavy metals.

**Sodium acetate**  
**Definition:** Sodium acetate is the sodium salt of acetic acid. It is very soluble in water and soluble in ethanol.

**EC specifications:** E 262 (i) Sodium acetate [7].  
Assay: Not less than 98.5% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Formic acid, formates and other oxidisable substances, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium acetate [5].
Assay: Not less than 98.5% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Alkalinity, Potassium compounds, Arsenic, Lead and Heavy metals.

**Sodium diacetate**
**Definition:** Sodium diacetate is a molecular compound of sodium acetate and acetic acid. It is freely soluble in water.

**EC specifications:** E 262 (ii) Sodium diacetate [7].
Assay: Content 39 to 41% of free acetic acid and 58 to 60% of sodium acetate.
The specification includes purity criteria on Water, Formic acid, formates and other oxidisable substances, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium diacetate [6].
Assay: Content 39 to 41% of free acetic acid and 58 to 60% of sodium acetate.
The specification includes purity criteria on Water, pH, Formic acid, formates and other oxidisable substances, Aldehydes, Arsenic and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible, or considered necessary.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1990. ADI not specified based on the fact that these substances are normal constituents of the diet and the intake from food additives is likely to be insignificant compared to the intake from natural sources [4].

**JECFA status:** Acetic acid was allocated an ADI “not limited” in 1973 [1]. In 1997 the substance was evaluated as a flavouring substance and was classified as of “no concern” [2].

Latest evaluation of calcium acetate, potassium acetate, sodium acetate and sodium diacetates 1973. ADI not limited due to the fact that these substances are natural constituents of the diet and the intake from food additives is likely to be insignificant compared to the intake from natural sources [1].

No short-term nor long-term studies has been performed, but these studies are considered not necessary [3;4].

**Conclusion:** Acetates are safe food additives. Acetic acid and its salts as defined by the specifications are covered by the toxicological evaluation. The JECFA specifications are old. It is therefore suggested to revise the specifications for this group of substances at a future JECFA meeting.
References:

1. [1973, NMRS 53/TRS 539-JECFA 17]
   Toxicological evaluation of certain food additives with a review of general principles and of
   specifications (Seventeenth report of the Joint FAO/WHO Expert Committee on Food
   539, 1974, and corrigendum.

2. [1997, TRS 884-JECFA 49]
   Evaluation of certain food additives and contaminants. (Forty-ninth report of the Joint
   1998.

   Toxicological evaluation of some food additives including anticaking agents, antimicrobials,

4. Reports from the Scientific Committee for Food (25th series). Opinion expressed 1990. *Food-
   science and techniques*, 1991.

5. Compendium of Food Additive Specifications, *FAO Food and Nutrition Paper* no. 52, FAO,

6. Compendium of Food Additive Specifications, *FAO Food and Nutrition Paper* no. 52, FAO,

7. Commission Directive 96/77/EC laying down specific purity criteria on food additives other
   than colours and sweeteners, 1996.
Lactic acid, sodium lactate, potassium lactate and calcium lactate

**E Number:**
Lactic acid: E 270  
Sodium lactate: E 325  
Potassium lactate: E 326  
Calcium lactate: E 327

**Recommendation:** No need for a re-evaluation.

**Chemical name/synonyms:**
Lactic acid: Lactic acid, 2-hydroxypropionic acid, 1-hydroxyethane-1-carboxylic acid.  
Calcium lactate: Calcium lactate, calcium dilactate, 2-hydroxypropanoic acid calcium salt.  
Potassium lactate: Potassium lactate, potassium 2-hydroxypropionic acid.  
Sodium lactate: Sodium lactate, sodium 2-hydroxypropionic acid.

**Chemical formula:**
Lactic acid: \( \text{C}_3\text{H}_6\text{O}_3 \)  
Calcium lactate: \( \text{C}_6\text{H}_{10}\text{CaO}_6\cdot n\text{H}_2\text{O} \) \( n=0 - 5 \)  
Potassium lactate: \( \text{C}_3\text{H}_5\text{KO}_3 \)  
Sodium lactate: \( \text{C}_3\text{H}_5\text{NaO}_3 \)

**EINECS number:**
Lactic acid: 200-018-0  
Calcium lactate: 212-406-7  
Potassium lactate: 213-631-3  
Sodium lactate: 200-772-0

**CAS Number:**
Lactic acid: 50-21-5 (L-: 79-33-4, D-: 10326-41-7, DL-: 598-82-3)  
Calcium lactate: 814-80-2  
Potassium lactate: 996-31-6  
Sodium lactate: 72-17-3

**Functional Class:** Antioxidant synergist, humectant, buffer.

**Specification:**
**Manufacture:** Lactic acid is obtained by the lactic fermentation of sugars or by chemical synthesis.

**Lactic acid**
**Definition:** Lactic acid is a naturally occurring organic acid. It may contain condensation products such as dilactide. Common products of commerce are 50-90% solutions. Solid products containing 100-125% of titratable lactic acid also exists. Lactic acid is sparingly soluble in water and soluble in acetone. The ratio between L- and D-isomers is not specified.

**EC specifications:** E 270 Lactic acid [4].
Lactic acid and lactates

Assay: Not less than 76% and not more than 84%. The specification includes purity criteria on Sulphated ash, Chloride, Sulphate, Iron, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Lactic acid [5].
Assay: Not less than 95.0% and not more than 105.0% of the labelled concentration. The specification includes purity criteria on Sulphated ash, Chloride, Sulphate, Cyanide, Citric, oxalic, phosphoric or tartaric acid, Sugars, Readily oxidizable substances, Iron and Heavy metals.

**Calcium lactate**
**Definition:** Calcium lactate is the calcium salt of lactic acid containing up to 5 molecules of water of crystallisation. It is soluble in water and practically insoluble in ethanol. The ratio between L- and D-isomers is not specified.

**EC specifications:** E 327 Calcium lactate [4].
Assay: Not less than 98% on the anhydrous basis. The specification includes purity criteria on Loss on drying, Acidity, Fluoride, pH, Reducing substances, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Calcium lactate [3].
Assay: Not less than 98.0% on the anhydrous basis. The specification includes purity criteria on Loss on drying, Acidity, Fluoride, pH, Magnesium and alkali salts, Arsenic, Lead and Heavy metals.

**Potassium lactate**
**Definition:** Potassium lactate is an aqueous solution of the potassium salt of lactic acid. The ratio between L- and D-isomers is not specified.

**EC specifications:** E 326 Potassium lactate [4].
Assay: Not less than 57% and not more than 66%. In addition the specification includes purity criteria on Acidity, Reducing substances, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Potassium lactate (solution) [3].
Assay: Not less than 95% and not more than 110% of the labelled concentration. In addition the specification includes purity criteria on Acidity, Reducing substances, Arsenic, Lead and Heavy metals.

**Sodium lactate**
**Definition:** Sodium lactate is an aqueous solution of the sodium salt of lactic acid. The ratio between L- and D-isomers is not specified.

**EC specifications:** E 325 Sodium lactate [4].
Assay: Not less than 57% and not more than 66%. In addition the specification includes purity criteria on Acidity, pH, Reducing substances, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium lactate (solution) [3].
Assay: Not less than 95% and not more than 110% of the labelled concentration. In addition the specification includes purity criteria on Acidity, pH, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible, but is also not considered necessary. In foods specially for children only the L(+) isomer is permitted.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990, ADI not specified due to fact that these substances are normal constituents of the diet, their metabolism is well described and the intake from food additives is likely to be insignificant compared to the intake from natural sources. For food specially prepared for small children only the L(+) isomer should be used [2].

**JECFA status:** Latest evaluation 1973. ADI not limited. The D(-)-lactic acid and (DL)-lactic acid should not be used in infant food [1].

**Other:** There is some evidence that babies have difficulties in utilizing DL- and D(-)-lactic acid.

**Conclusion:** The evaluation of these substances is based on the fact that they are natural constituents in food and the intake from food additives is likely to be insignificant compared to the intake from natural sources. Therefore, the limited toxicological data is not considered to be a problem.

The JECFA specifications for the salts of lactic acid are old. It is therefore suggested to revise the specifications for this group of substances at a future JECFA meeting.

**References:**

1. [1973, NMRS 53/TRS 539-JECFA 17]


PROPIONIC ACID, SODIUM PROPIONATE, CALCIUM PROPIONATE AND POTASSIUM PROPIONATE

E number:
Propionic acid: E 280
Sodium propionate: E 281
Calcium propionate: E 282
Potassium propionate: E 283

Recommendation: No need for a re-evaluation. However SCF should consider whether they still wish to see a comparative study with low chain fatty acids.

Chemical name/synonyms:
Propionic acid: Propionic acid, propanoic acid.
Sodium propionate: Sodium propionate, sodium propanoate.
Calcium propionate: Calcium propionate, calcium propanoate.
Potassium propionate: Potassium propionate, potassium propanoate.

Chemical formula:
Propionic acid: C₃H₆O₂
Sodium propionate: C₃H₅O₂Na
Calcium propionate: C₆H₁₀O₄Ca
Potassium propionate: C₃H₅O₂K

EINECS number:
Propionic acid: 201-176-3
Sodium propionate: 205-290-4
Calcium propionate: 223-795-8
Potassium propionate: 206-323-5

CAS number:
Propionic acid: 79-09-4
Sodium propionate: 137-40-6
Calcium propionate: 4075-81-4
Potassium propionate: 327-62-8

Functional Class: Preservative.

Specification:
Manufacture: No information on the manufacture of propionic acid as a food additive.

Propionic acid
Definition: Propionic acid is a naturally occurring organic acid. It is miscible with water and ethanol.

EC specifications: E 280 - Propionic acid [5].
Assay: Not less than 99.5%.
The specification includes purity criteria on Non-volatile residue, Aldehydes, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Propionic acid [8].
Assay: Not less than 99.5% on the dried basis.
The specification includes purity criteria on Distillation range, Non-volatile residue, Formic acid, Aldehydes and Lead.

*Sodium propionate*
**Definition:** Sodium propionate is the sodium salt of propionic acid. It is freely soluble in water and soluble in ethanol.

**EC specifications:** E 281 - Sodium propionate [5].
Assay: Not less than 99% on the dried basis.
The specification includes purity criteria on Loss on drying, Water insolubles, Iron, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium propionate [6].
Assay: Not less than 99.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble matters, pH, Iron and Lead.

**Calcium propionate**
**Definition:** Calcium propionate is the calcium salt of propionic acid. It is freely soluble in water and soluble in ethanol.

**EC specifications:** E 282 - Calcium propionate [5].
Assay: Not less than 99% on the dried basis.
The specification includes purity criteria on Loss on drying, Water insolubles, Iron, Fluoride, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Calcium propionate [8].
Assay: Not less than 98.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble matters, pH, Fluoride, Iron and Lead.

**Potassium propionate**
**Definition:** Potassium propionate is the potassium salt of propionic acid. It is freely soluble in water and soluble in ethanol.

**EC specifications:** E 283 - Potassium propionate [5].
Assay: Not less than 99% on the dried basis.
The specification includes purity criteria on Loss on drying, Water insolubles, Iron, Fluoride, Arsenic, Lead, Mercury and Heavy metals.
**JECFA specifications:** Potassium propionate [6].

Assay: Not less than 99.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble matters, pH, Iron and Lead.

**Exposure:** Propionic acid and its salts may be used in prepacked bread, fine bakery ware and Christmas pudding at a concentration of max. 1-3 g/kg. JECFA estimated the intake of propionic acid to 19 µg/kg bw per day in Europe based on production data and consumption by 10% of the population [7]. Propionic acid wax not included in the EU monitoring system as the ADI is “not specified” (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation SCF 1990; no ADI allocated, but the Committee sees no adverse health consequences from present uses of propionic acid as a food additive. However the Committee expressed its wish to see comparative studies with other short chain fatty acids and their salts [4].

**JECFA status:** Propionic acid was allocated an ADI “not limited” in 1973 [1]. In 1997 the substance was evaluated as a flavouring substance and was classified as of “no concern” [2].

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies in rats and rabbits reviewed by JECFA in 1973 showed no treatment-related toxicological findings. Since then 90-day studies with a recovery phase in rats and dogs and a 1-year study in rats have been performed. In these studies largely reversible forestomach lesions were observed. Diffuse hyperplastic mucosal changes in the oesophagus of dogs were fully reversible. [4]. In a newer study, no adverse effects on the forestomach mucosa were reported when male rats were feed a pellet diet containing 0 or 2-3 % propionic acid (about 3800-5800 mg/kg bw per day for 12 weeks [9].

**Genotoxicity:** Propionic acid was negative in Ames test, SOS chromotest, sister chromatid exchange and in vivo in micronucleus test in Chinese hamster cells. It was positive in DNA repair test (spot test) [7].

**Chronic toxicity/Carcinogenicity:** A lifespan feeding study in rats produced hyperplastic and carcinomatous lesions in the forestomach and some proliferation in the glandular stomach [4].

**Reproduction studies:** Foetal abnormalities or effects on survival were not observed when calcium propionate was fed to pregnant rodents (up to 300 mg/kg bw per day for 10 days), hamsters (up to 400 mg/kg bw per day for 5 days) and rabbits (up to 400 mg/kg bw per day for 13 days) [7].

**Effects in human:** Studies on volunteers in the fifties or earlier showed that daily oral doses of 6000 mg of sodium propionate rendered the urine faintly alkaline but had no other effect and that propionic acid is a moderate irritant of skin [3].
Conclusion: Both SCF and JECFA consider the lesions in the forestomach in animals given high doses irrelevant for humans. Besides the potential exposure from food is very low.

Propionic acid and its salts as defined by the specifications is covered by the toxicological evaluation.

References:


Boric acid and sodium tetraurate (Borax)

**E number:**
Boric acid: E 284
Sodium tetraborate: E 285

**Recommendation:** Not recommended as food additive for wider use. As the use is restricted to genuine caviar, exposure is expected to be very limited so no further action is recommended.

**Chemical name/synonyms:**
Boric acid: Boric acid/ boracic acid, orthoboric acid, borofax.
Sodium tetraborate: Sodium tetraborate, sodium biborate, sodium pyroborate/sodium borate, borax.

**Chemical formula:**
Boric acid: H₃BO₃
Sodium tetraborate: Na₂B₄O₇ (anhydrous)
Na₂B₄O₇·10 H₂O (decahydrate)

**EINECS number:**
Boric acid: 233-139-2
Sodium tetraborate: 215-540-4

**CAS number:**
Boric acid: 10043-35-3
Sodium tetraborate: 1303-96-4

**Functional Class:** Preservative.

**Specification:**
**Manufacture:** No information on manufacturing processes of boric acid and sodium tetraborate as food additives.

*Boric acid*
**Definition:** -

**EC specifications:** E 284 Boric acid [1].
Assay: Not less than 99.5%
The specification includes purity criteria on Peroxides, Arsenic, Lead, Mercury and Heavy metals.

**JEJCA specifications:** No JECFA specification has been prepared.

*Sodium tetraborate*
**Definition:** -

**EC specifications:** E 285 Sodium tetraborate [1].
Assay: -
The specification includes purity criteria on Peroxides, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** For the general population, the greatest boron exposure comes from the intake of food. The mean daily intake of boron in the diet is estimated to be about 1.2 mg. [3]. Boric acid and sodium tetraborate may only be used in sturgeons eggs (genuine caviar) at max. 4 g/kg (equivalent to about 700 mg boron/kg). This means that just about 10 g caviar, with maximum level of boron, will reach the TDI.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation as food additive in 1990, when it was found unacceptable in general as a food additive, but still acceptable for use only as a preservative for real caviar [4]. Since then SCF, in 1996, has evaluated boron as a constituent of natural mineral water and at that occasion set a TDI of 0.1 mg/kg bw [5].

**JECFA status:** Latest evaluation 1961, no ADI was allocated [2].

**WHO drinking water quality:** A tolerable daily intake (TDI) of boron was set as 0.4 mg/kg body weight based on a NOAEL for reduction foetal body weight in rats at 9.6 mg/kg bw per day and an uncertainty factor of 25 [3].

**Background data:**
**Subacute/subchronic toxicity:** Suppressed growth and testicular atrophy was observed in mice and rats given boric acid or sodium tetraborate for 1-3 months at doses of about 25 mg B/kg bw per day. At higher doses, extramedullary haematopoiesis of the spleen, decreased liver, kidney, spleen and testes weight, hyperkeratosis and acanthosis of the stomach and mortality have been observed. In rabbits dosed for 4 months elevated liver enzymes have been measured at 31 mg B/kg bw per day. In a 3 months study in dogs, reduced testis weight was observed at 4.4 mg B/kg bw per day. [3].

**Genotoxicity:** Existing data suggest that genotoxicity is not an area of concern following exposure to boron compounds in humans [3]. Chronic toxicity/Carcinogenicity: Suppressed growth and testicular atrophy and interstitial cell hyperplasia has been observed in mice and rats at doses of about 50 mg B/kg bw per day for 2 years. In mice a dose-related increase in the incidence of splenic lymphoid depletion in male was observed. No evidence of carcinogenicity of boric acid has been found. [3].

**Reproduction studies:** The data regarding developmental and reproductive toxicity show that lower foetal body weight in rats is the critical effect. The NOAEL for lower foetal body weight is 9.6 mg/kg bw per day. The LOAEL, at which rats show slight (ca. 5%) foetal body weight differences and rib anomalies, is about 13 mg/kg bw per day. As dose level increases, the effects that are seen (and the doses at which they are seen) are: a) further rib effects and testicular pathology in the rat (ca. 25 mg B/kg bw per day); b) decreased foetal body weight and increased foetal cardiovascular malformations in the rabbit, and severe testicular pathology in the rat (ca.
40 mg B/kg bw per day); c) testicular atrophy and sterility in the rat (ca. 55 mg B/kg bw per day); and d) reduced foetal body weight in the mouse (ca. 80 mg B/kg bw per day). [3].

**Effects in human:** Only few human studies have been conducted to assess health effects associated with exposure to boron compounds. The lowest lethal dose for humans exposed to boric acid is 640 mg/kg bw by oral exposure. The average dose of boric acid required to produce clinical symptoms is unclear but is presumably within the range of 0.1 g to 55 g. At toxic doses, gastrointestinal disturbances, cutaneous lesions and CNS effects have been observed. Two descriptive studies assessed fertility and secondary sex ratios in relation to exposure. Neither study reported a detrimental effect on fertility. Although an excess percentage of female birth has been suggested, the absence of statistical significance and attention to other co-variates known to affect sex ratios warrants careful interpretation of this finding. No studies have been identified that assess the spectrum of reproductive outcomes, such as time-to-pregnancy, conception delays, spontaneous abortions, and sperm analyses in males [3].

**Conclusion:** The use of boric acid and sodium tetraborate as a food additive for general use seems unjustified. However, the present permitted use as a preservative to genuine caviar is unlikely to pose any health problems as exposure can be assumed to be very low.

**References:**


CARBON DIOXIDE

E number: E 290

Recommendation: A re-evaluation is not needed.

Chemical name/synonyms:
Carbon dioxide: Carbon dioxide/ carbonic acid gas, dry ice (solid form), carbonic anhydride.

Chemical formula:
Carbon dioxide: CO₂

EINECS number:
Carbon dioxide: 204-696-9

CAS number:
Carbon dioxide: 124-38-9

Functional Class: Carbonating agent, preservative, packaging gas and propellant.

Specification:
Manufacture: No information on manufacturing processes of food grade carbon dioxide.

Definition: Carbon dioxide is a gas naturally occurring in the atmosphere.

EC specifications: E 290 Carbon dioxide [1].
Assay: Not less than 99% v/v on the gaseous basis.
The specification includes purity criteria on Acidity, Reducing substances, hydrogen phosphide and sulphide, Carbon monoxide, Oil content.

JECFA specifications: Carbon dioxide [2].
Assay: Not less than 99% v/v.
The specification includes purity criteria on Acidity, Reducing substances, hydrogen phosphide and sulphide, Carbon monoxide, Volatile hydrocarbons, Non-volatile hydrocarbons, Water.

Exposure: Permitted quantum satis to all foods. Exposure estimate not relevant.

SCF/JECFA evaluation:
SCF status: Latest evaluation 1990. Acceptable because the exposure from these sources is insignificant compared to the exposure from the atmosphere [3].

JECFA status: Latest evaluation 1985. ADI not specified [4]
A further toxicological evaluation of these substances is not necessary.
Conclusion: Due to the insignificant contribution from the intake from food additive use compared with other sources there is no need for further evaluation of these substances.

References:


MALIC ACID, SODIUM MALATES, POTASSIUM MALATE AND CALCIUM MALATES

E Number:
Malic acid: E 296
Sodium malate: E 350 (i)
Sodium hydrogen malate: E 350 (ii)
Potassium malate: E 351
Calcium malate: E 352 (i)
Calcium hydrogen malate: E 352 (ii)

Recommendation: No need for a re-evaluation.

Chemical name/synonyms:
Malic acid: DL-malic acid, hydroxybutandioic acid, hydroxsuccinic acid/ pomalous acid.
Sodium malate: Disodium DL-malate, disodium salt of hydroxybutandioic acid/ sodium salt of malic acid.
Sodium hydrogen malate: Monosodium DL-malate, monosodium salt of hydroxybutandioic acid/ monosodium salt of DL-malic acid.
Potassium malate: Dipotassium DL-malate, dipotassium salt of hydroxybutandioic acid/ potassium salt of malic acid.
Calcium malate: Calcium DL-malate, calcium salt of hydroxybutandioic acid/ calcium salt of malic acid.
Calcium hydrogen malate: Monocalcium DL-malate, monocalcium salt of hydroxybutandioic acid/ monocalcium salt of DL-malic acid.

Chemical formula:
Malic acid: C₄H₆O₅
Sodium malate: C₄H₄Na₂O₅·nH₂O (n = ½ or 3)
Sodium hydrogen malate: C₄H₅NaO₅
Potassium malate: C₄H₄K₂O₅
Calcium malate: C₄H₄CaO₅
Calcium hydrogen malate: C₈H₁₀CaO₁₀

EINECS number:
Malic acid: 230-022-8
Sodium malate: -
Sodium hydrogen malate: -
Potassium malate: -
Calcium malate: -
Calcium hydrogen malate: -

CAS Number:
Malic acid: 6915-15-7
Sodium malate: 676-46-0
Sodium hydrogen malate: 3105-51-9
Potassium malate: -
Calcium malate: -
Calcium hydrogen malate: -

**Functional Class:** Acidity regulator, flavour.

**Specification:**
*Manufacture:* No information on manufacturing processes for food grade malic acid and its salts.

**Malic acid**
**Definition:** Malic acid consists of DL-malic acid. It is very soluble in water and freely soluble in ethanol.

**EC specifications:** E 296 Malic acid [6].
Assay: Not less than 99.0%.
In addition the specification includes purity criteria on Sulphated ash, Fumaric acid, Maleic acid, Arsenic, Lead and Mercury.

**JECFA specifications:** DL-Malic acid [2].
Assay: Not less than 99.0%.
In addition the specification includes purity criteria on Sulfated ash, Fumaric and maleic acid and Lead.

**Sodium malate**
**Definition:** Sodium malate is the disodium salt of DL-malic acid. It is freely soluble in water.

**EC specifications:** E 350 (i) Sodium malate [6].
Assay: Not less than 98.0% on the anhydrous basis.
In addition the specification includes purity criteria on Loss on drying, Alkalinity, Fumaric acid, Maleic acid, Arsenic, Lead and Mercury.

**JECFA specifications:** DL-Sodium malate [5].
Assay: Not less than 98% and not more than 102% on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Sulfated ash, Alkalinity, Fumaric acid, Maleic acid, Arsenic, Lead and Heavy metals.

**Sodium hydrogen malate**
**Definition:** Sodium hydrogen malate is the monosodium salt of DL-malic acid.

**EC specifications:** E 350 (ii) Sodium hydrogen malate [6].
Assay: Not less than 99.0% on the anhydrous basis.
In addition the specification includes purity criteria on Loss on drying, Fumaric acid, Maleic acid, Arsenic, Lead and Mercury.

**JECFA specifications:** DL- Sodium hydrogen malate [3].
Assay: Not less than 99.0% on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Maleic acid, Arsenic, Lead and Heavy metals.
Potassium malate  
**Definition:** Potassium malate is an aqueous solution of the dipotassium salt of DL-malic acid.

**EC specifications:** E 351 Potassium malate [6].
Assay: Not less than 59.5%.
In addition the specification includes purity criteria on Alkalinity, Fumaric acid, Maleic acid, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

Calcium malate  
**Definition:** Calcium malate is the calcium salt of DL-malic acid. It is slightly soluble in water and insoluble in ethanol.

**EC specifications:** E 352 (i) Calcium malate [6].
Assay: Not less than 97.5% on the anhydrous basis.
In addition the specification includes purity criteria on Loss on drying, Alkalinity, Fumaric acid, Maleic acid, Fluoride, Arsenic, Lead and Mercury.

**JECFA specifications:** Calcium DL-malate [4].
Assay: Not less than 97.5% on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Maleic acid, Fluoride, Arsenic, Lead and Heavy metals.

Calcium hydrogen malate  
**Definition:** Calcium hydrogen malate is the monocalcium salt of DL-malic acid.

**EC specifications:** E 352 (ii) Calcium hydrogen malate [6].
Assay: Not less than 97.5% on the anhydrous basis.
In addition the specification includes purity criteria on Loss on drying, Fumaric acid, Maleic acid, Fluoride, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substances were thus not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**
**SCF status:** These substances are normal constituents of the diet and their metabolism is well described. This is the background for the group ADI not specified allocated by SCF [1]. Due to the fact that these substances are natural constituents of the diet and the intake from food additives is likely to be insignificant compared to the intake from natural sources there is no need for specific toxicity data.
JECFA status: group ADI not specified for malic acid and its sodium, potassium and calcium salts; in the case of D(-)-malic acid and its salts, the ADI is not applicable to very young infants [7]. The use of malic acid as flavouring agent was considered acceptable in 1999 [8].

Conclusion: Although few data exist on the toxicology of malic acid and its salts there is no need for further testing or for a re-evaluation of these compounds. Malic acid and its salts as defined by the specifications are covered by the toxicological evaluation. The JECFA specifications are mostly old and have been prepared at different JECFA meetings. It is therefore suggested to revise the specifications for this group of substances at a future JECFA meeting.

References:


7. [1969, NMRS 46/TRS 445-JECFA 13]

8. [1999, TRS 896-JECFA 53]
FUMARIC ACID

E number: E 297

Recommendation: Although limited data there is no need for further testing or a re-evaluation.

Chemical name/synonyms: Trans-butenedioic acid, trans-1,2-ethylene-dicarboxylic acid.

Chemical formula: C₄H₄O₄

EINECS number: 203-743-0

CAS number: 110-17-8

Functional Class: Acidifier, flavour.

Specification:
Manufacture: No information on manufacturing processes for food grade fumaric acid.

Definition: Fumaric acid is a naturally occurring organic acid. It is slightly soluble in water and soluble in ethanol.

EC specifications: E 297 Fumaric acid [1].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Sulphated ash, Maleic acid, Arsenic, Lead and Mercury.

JECFA specifications: Fumaric acid [2].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Melting range, Sulphated ash, Maleic acid, Arsenic and Heavy metals.

Exposure: Permitted only in fillings and toppings for fine bakery wares 2.5 g/kg, sugar confectionery 1 g/kg, some desserts 4 g/kg, chewing gum 2 g/kg, and instant powder for fruit based drinks and instant tea powder 1000 mg/litre. Also authorised in some imported wines. ADI may be reached after consumption of 360 ml drink or 90 g dessert if used to maximum.
As potential maximum intake may exceed the ADI, the EU monitoring system transferred the substance to tier 2. The calculated intake by adults and the whole population is reported in the range of 1 - 17% of ADI. The calculated intake by young children is reported in the range of 6 - 66%. The EU monitoring system concluded that no further examination is needed at this stage.

SCF/JECFA evaluation:
SCF status: Latest evaluation 1990. Fumarates are normal components in the intermediate metabolism. Early studies indicated a possible testicular atrophy after intraperitoneal administration to rabbits. No such effect was seen when doses up to 600 mg/kg bw were administrated orally to
rabbits for 150 days [3]. Based on this study SCF in 1991 allocated a group ADI of 6 mg/kg bw for fumaric acid [4].

**JECFA status:** Previously JECFA allocated an ADI of 6 mg/kg bw [5], but when evaluated as a flavour in 1989 the ADI was changed to “not specified” [6]. This was confirmed in 1999 [7]. This means that strictly speaking JECFA has not considered use as food additives.

**BACKGROUND DATA:**

**Subacute/subchronic toxicity:** No adverse effects were seen in guinea-pigs given 10 % fumaric acid in the diet for 1 year, rabbits given 6.9% sodium fumarate (equivalent to 5% fumaric acid) in the diet for 150 days and dogs given 5 % fumaric acid for 2 years [8].

**Genotoxicity:** No data found.

**Chronic toxicity/carcinogenicity:** No adverse effects were seen when groups of 14 weanling rats were kept on diets containing 0, 0.1 and 1.0% fumaric acid and 1.38% sodium fumarate for one year (half the groups) or two years [8]. groups of 12 male and 12 female rats were fed diets containing 0, 0.1, 0.5, 0.8 and 1.2% of fumaric acid for two years without toxic effects on growth or food consumption. The previous ADI was based on this study [8].

**Reproduction toxicity:** No data found.

**Effect in humans:** Seventy-five chronically disabled subjects received 500 mg fumaric acid daily for one year without any adverse effects [8].

**Conclusion:** Few toxicological data exist on fumaric acid. However, the substance is naturally occurring in food and is part of the intermediary metabolism and consequently the contribution from food additives to the total intake is insignificant. Therefore, it is unnecessary to request new studies.

Fumaric acid as defined by the specifications seems to be covered by the toxicological evaluation.

**References:**


5. [1974, NMRS 54/TRS 557-JECFA 18]

6. [1989, TRS 789-JECFA 35]

7. [1999, TRS 896-JECFA 53]

8. [1974, FAS 6/NMRS 54A-JECFA 18]
ASCORBIC ACID, SODIUM ASCORBATE and CALCIUM ASCORBATE

E number:
Ascorbic acid: E 300
Sodium ascorbate: E 301
Calcium ascorbate: E 302

Recommendation: No re-evaluation currently needed. If an update is considered the questions raised below should be clarified.

Chemical name/synonyms:
Ascorbic acid: L-ascorbic acid, 2,3-didehydro-L-threo-hexono-1,4-lactone, 3-keto-L-glucofuranolactone/ vitamin C.
Sodium ascorbate: Sodium L-ascorbate, 2,3-dihydro-L-threo-hexono-1,4-lactone sodium enolate, 3-keto-L-glucofuranolactone sodium enolate.
Calcium ascorbate: Calcium ascorbate dihydrate, calcium salt of 2,3-dihydro-L-threo-hexono-1,4-lactone dihydrate.

Chemical formula:
Ascorbic acid: C₆H₈O₆
Sodium ascorbate: C₆H₇O₆Na
Calcium ascorbate: C₁₂H₁₄O₁₂Ca·2 H₂O

EINECS number:
Ascorbic acid: 200-066-2
Sodium ascorbate: 205-126-1
Calcium ascorbate: 227-261-5

CAS number:
Ascorbic acid: 50-81-7
Sodium ascorbate: 134-03-2
Calcium ascorbate: 5743-27-1

Functional Class: Antioxidant.

Specification:
Manufacture: No information on manufacturing processes of food grade ascorbic acid and ascorbates.

Ascorbic acid
Definition: Ascorbic acid is the naturally occurring L-ascorbic acid. It is freely soluble in water and sparingly soluble in ethanol.

EC specifications: E 300 Ascorbic acid [3].
Assay: Not less than 99% of C₆H₈O₆ on the dried basis.
The specification includes purity criteria on Loss on drying, Sulphated ash, Specific rotation, pH of a
2% aqueous solution, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Ascorbic acid [1].
Assay: Not less than 99% of C₆H₈O₆ on the dried basis.
The specification includes purity criteria on Loss on drying, Sulfated ash, Specific rotation, pH of a 2% aqueous solution, Arsenic and Heavy metals.

**Sodium ascorbate**
**Definition:** Sodium ascorbate is the sodium salt of L-ascorbic acid. It is freely soluble in water and very slightly soluble in ethanol.

**EC specifications:** E 301 Sodium ascorbate [3].
Assay: Not less than 99% of C₆H₇O₆Na on the dried basis.
The specification includes purity criteria on Loss on drying, Specific rotation, pH of a 10% aqueous solution, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium ascorbate [1].
Assay: Not less than 99% of C₆H₇O₆Na on the dried basis.
The specification includes purity criteria on Loss on drying, Specific rotation, pH of a 10% aqueous solution, Arsenic and Heavy metals.

**Calcium ascorbate**
**Definition:** Calcium ascorbate is the sodium salt of L-ascorbic acid. It is freely soluble in water and very slightly soluble in ethanol.

**EC specifications:** E 302 Calcium ascorbate [3].
Assay: Not less than 99% of C₁₂H₁₄O₁₂Ca·2 H₂O.
The specification includes purity criteria on Volatile matter, Specific rotation, pH of a 10% aqueous solution, Fluoride, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Calcium ascorbate [2].
Assay: Not less than 99% of C₁₂H₁₄O₁₂Ca·2 H₂O.
The specification includes purity criteria on pH of a 10% aqueous solution, Fluoride, Arsenic and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. There is not specified an ADI and the substances were for that reason not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1981: ADI not specified (group ADI for ascorbic acid and its sodium and calcium salts). SCF underlines that ascorbate apparently does not cause in vivo mutagenicity/clastogenicity and also that additive sources of ascorbate give a relatively small contribution to the total daily intake [7].
**JECFA status:** Latest evaluation 1981: ADI not specified (group ADI for ascorbic acid and its potassium, sodium and calcium salts). They underline that ascorbate, also as its calcium salt, is unlikely to produce oxalate stones since other dietary sources of calcium are more important and no evidence of stones in humans after high ascorbate intakes have been reported [5].

**Background data:**

**Subacute/subchronic toxicity:** No effects up to 2 g/kg bw/day. At doses up to 10% in the diet to rats, there was a dose-dependent effect on weight gain and 30% (2/6) mortality in the highest dose group.

**Genotoxicity:** *In vitro,* No gene mutations in several test systems. There are indications that ascorbate can be co-mutagenic and clastogenic [9] but also many reports of antimutagenicity. *In vivo,* No mutagenic effects were observed in the host-mediated assay using *S. typhimurium* injected intrahepatically and doses of up to 5000 mg/kg bw/day [9]. Ascorbic acid at 10,000 mg/kg bw/day did not induce sister SCE’s in the bone marrow of hamsters, indicating that ascorbate has no clastogenic effects *in vivo.*

**Chronic Toxicity/Carcinogenicity:** No adverse effects of up to 2 g/kg bw/day in rats for two years. No bladder stone formation observed [6].

**Reproduction toxicity:** No teratogenic or other reproductive effects including effects on breeding behaviour and litter size in rats or mice fed up to 3340 mg/kg bw/day, whereas 48% lethality of embryos was found at the highest dose tested, 6680 mg/kg bw/day [7]. No adverse effects were observed in Although few data exist on the toxicology of citric acid and its salts there is no need for further testing or for a re-evaluation of these compounds. guinea pigs at doses up to 500 mg/kg bw/day. In a two-generation study with sodium ascorbate at doses up to 7% in the diet (approx. 3500 mg/kg bw/day) no adverse ascorbate-related effects were observed [4].

**Allergy/Intolerance:** Skin rashes have been reported in infants given extreme doses of ascorbate [6].

**Effect in humans:** No side effects at doses up to 100 mg/kg bw/day over several months in double-blind placebo controlled studies. There were no indications of oxalate stone formation [6].

**Other:** Ascorbate is found naturally in the diet at levels exceeding intakes from additive sources. The use of ascorbates as food additives will only constitute a small fraction of the total dietary intake [8]. There is a current controversy regarding the possible pro-oxidant effects of ascorbate, and conclusive data from human trials are warranted. Ascorbate is readily absorbed. At low to moderate dose levels there is little loss with the urine (about 1mg/day in humans) In rodents ascorbate is partly metabolised to carbon dioxide and a small part is metabolised into oxalate. In humans, ascorbate is excreted mainly as oxalate or unchanged and to a minor extent as diketogulonic acid. Since most mammals produce ascorbic acid in large amounts, the best animal models are those that, like humans, are unable to produce ascorbate endogenously, e.g. guinea pigs or primates.

**Conclusion:** More data related to pro-oxidant effects and allergy is desirable. The data base does not include a multigeneration study as would normally be expected, but otherwise there are
sufficient data to evaluate the effects in animals and man of repeated long- or medium-term exposures, and the use of ascorbate as an additive must be regarded as safe. However, the need for a multigeneration study should be discussed.

Ascorbic acid, sodium ascorbate and calcium ascorbate as defined by the specifications are covered by the toxicological evaluation. However the JECFA specifications are old and have in addition been prepared at two different meetings. It may be appropriate to revise the specifications for these substances as a group at a future JECFA meeting.

References:


**FATTY ACID ESTERS OF ASCORBIC ACID, ASCORBYL PALMITATE AND ASCORBYL STEARATE**

**E number:**
- Ascorbyl palmitate: E 304 (i)
- Ascorbyl stearate: E 304 (ii)

**Recommendation:** Data on metabolism and bioavailability recommended. If the substances are not hydrolysed data on reproduction toxicity may be needed. Information on potential desirable.

**Chemical name/synonyms:**
- Ascorbyl palmitate: L-ascorbyl palmitate, 2,3-didehydro-L-threo-hexono-1,4-lactone-6-palmitate, 6-palmitoyl-3-keto-L-gulofuranolactone.
- Ascorbyl stearate: L-ascorbyl stearate, 2,3-didehydro-L-threo-hexono-1,4-lactone-6-stearate, 6-stearoyl-3-keto-L-gulofuranolactone

**Chemical formula:**
- Ascorbyl palmitate: $C_{22}H_{38}O_7$
- Ascorbyl stearate: $C_{24}H_{42}O_7$

**EINECS number:**
- Ascorbyl palmitate: 205-305-4
- Ascorbyl stearate: 246-944-9

**CAS number:**
- Ascorbyl palmitate: -
- Ascorbyl stearate: 25395-66-8

**Functional Class:** Antioxidant.

**Specification:**
- **Manufacture:** No information on manufacturing processes of food grade ascorbyl palmitate and ascorbyl stearate.

*Ascorbyl palmitate*

**Definition:** Ascorbyl palmitate is the ester of palmitic acid and L-ascorbic acid (involving the hydroxyl group at the 6 position of the ascorbic acid).

**EC specifications:** E 304 (i) Ascorbyl palmitate [5].
Assay: Not less than 98% at the dried basis.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Specific rotation, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Ascorbyl palmitate INS 304 [4].
Assay: Not less than 95% at the dried basis.
In addition the specification includes purity criteria on Loss on drying, Sulfated ash, Arsenic and
Heavy metals.

**Ascorbyl stearate**

**Definition:** Ascorbyl stearate is the ester of stearic acid and L-ascorbic acid (involving the hydroxyl group at the 6 position of the ascorbic acid).

**EC specifications:** E 304 (ii) Ascorbyl stearate [5].

Assay: Not less than 98%.

In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Ascorbyl stearate INS 305 [4].

Assay: Not less than 95% of C_{24}H_{42}O_{7}.

In addition the specification includes purity criteria on Loss on drying, Sulfated ash, Arsenic and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. SCF has not specified an ADI and the substances were for that reason not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**

SCF status: Latest evaluation 1990; acceptable [3].

JECFA status: Latest evaluation 1973: ADI 1,25 mg/kg bw/day [1].

**Background data:**

**Subacute/subchronic toxicity:** Studies with up to 6.25% ascorbyl palmitate and stearate (80:20) in the feed to rats for up to 6 months had no adverse effects, whereas 5% in the feed for 9 months provoked significant growth retardation. At a level of 2% in the feed for 9 months, no adverse effects were observed [6].

**Genotoxicity:** Ascorbyl palmitate was tested in the Ames Salmonella/microsomal assay for induction of reverse mutation in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 and in Escherichia coli WP2 (uvrA). Each assay was performed in the presence and in the absence of a rat liver homogenate metabolic activation system. No excess mutagenicity was observed [7]. No data available *in vivo*.

**Chronic toxicity/Carcinogenicity:** A mixture (80:20) of ascorbyl palmitate and stearate was given in the feed (0.05-0.25%) to groups of 10 rats during two years without significant changes in mortality, growth or pathology [6]. The formation of oxalate stones in this study was considered not to be relevant for man [2], [3].

**Reproduction toxicity:** No data available.

**Other:** There are no data available on absorption and metabolism of ascorbyl esters. The esters are expected to be hydrolysed during digestion [3].
Conclusion: There are insufficient data to evaluate the effects in animals and man of ascorbyl palmitate and stearate. These additives have been accepted assuming they are fully hydrolysed to ascorbic acid and to fatty acids and thus included in the evaluation of those. Full hydrolysation has, however, not been demonstrated. Therefore data on bioavailability and biotransformation should be submitted. If full hydrolysation is not demonstrated also data on reproduction are warranted. The best data concern long- or medium-term exposures but although they do not show sign of toxic effect they do not live up to present-day standards with respect to the numbers of animals per group and there are only data for one species and one sex. To estimate the potential exposure from these additives it is recommended to include them in tier 3 in the ongoing study on dietary intake of food additives in the European Union.

Ascorbyl palmitate and stearyl palmitate as defined by the specifications seems to be covered by the toxicological evaluation.

The JECFA specifications are old. It may be appropriate to revise the specifications for these substances at a future JECFA meeting.

References:


TOCOPHEROL-RICH EXTRACT, α-TOCOPHEROL, γ-TOCOPHEROL AND δ-TOCOPHEROL

E number:
Tocopherol-rich extract: E 306
α-Tocopherol: E 307
γ-Tocopherol: E 308
δ-Tocopherol: E 309

Recommendation: It is unclear whether γ-tocopherol and δ-tocopherol are commercially available. If used as food additives they should be subject to direct toxicological testing and evaluation. No need for an immediate re-evaluation of α-tocopherol and tocopherol-rich extracts, but the question on interaction with blood clotting needs further investigation if exposure is significant. Therefore an estimate of the exposure to these additives is desirable.

Chemical name/synonyms:
Tocopherol-rich extract: -
α-Tocopherol: dl-5,7,8-trimethyltocol, dl-2,5,7,8-tetramethyl-2-(4’,8’,12’-trimethyltridecyl)-6-chromanol/ vitamin E, dl-α-Tocopherol.

Chemical formula:
Tocopherol-rich extract: -
α-Tocopherol: C_{29}H_{50}O_{2}
γ-Tocopherol: C_{28}H_{48}O_{2}
δ-Tocopherol: C_{27}H_{46}O_{2}

EINECS number:
Tocopherol-rich extract: -
α-Tocopherol: 200-412-2
γ-Tocopherol: 231-523-4
δ-Tocopherol: 204-299-0

CAS number:
Tocopherol-rich extract: -
α-Tocopherol: 59-09-9
γ-Tocopherol: -
δ-Tocopherol: -

Functional Class: Antioxidant.
**Specification:**

*Tocopherol-rich extract*

**Manufacture:** Tocopherol-rich extract is obtained by the vacuum distillation of edible vegetable oil products, comprising concentrated tocopherols and tocotrienols.

**Definition:** Tocopherol-rich extract consists of tocopherols such as d-α-, d-β-, d-γ- and d-δ-tocopherols together with components occurring in the source material. It is insoluble in water and soluble in ethanol.

**EC specifications:** E 306 Tocopherol-rich extract [6].

Assay: Not less than 34% of total tocopherols.
The specification includes purity criteria on Sulphated ash, Specific rotation, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Tocopherol concentrate, mixed [4].

Assay: Not less than 34% of total tocopherols.
The specification includes purity criteria on Sulfated ash, Specific rotation, Acidity, Arsenic, Lead and Heavy metals.

**α-Tocopherol**

**Manufacture:** α-Tocopherol is obtained by chemical synthesis.

**Definition:** α-Tocopherol is the racemic dl-α-tocopherol. It is insoluble in water and freely soluble in ethanol.

**EC specifications:** E 307 α-Tocopherol [6].

Assay: Not less than 96%.
The specification includes purity criteria on Refractive index, Sulphated ash, Specific absorption, Specific rotation, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** dl-α-Tocopherol [5].

Assay: Not less than 96% and not more than 102% of C₂₉H₅₀O₂.
The specification includes purity criteria on Specific rotation, Acidity and Lead.

**γ-Tocopherol**

**Manufacture:** γ-Tocopherol is obtained by chemical synthesis.

**Definition:** γ-Tocopherol is the racemic dl-γ-tocopherol. It is insoluble in water and freely soluble in ethanol.

**EC specifications:** E 308 γ-Tocopherol [6].

Assay: Not less than 97%.
The specification includes purity criteria on Refractive index, Sulphated ash, Specific absorption, Arsenic, Lead, Mercury and Heavy metals.
**JECA specifications**: No JECFA specification has been prepared for \( \gamma \)-Tocopherol.

**\( \delta \)-Tocopherol**

**Manufacture**: \( \delta \)-Tocopherol is obtained by chemical synthesis.

**Definition**: \( \delta \)-Tocopherol is the racemic dl-\( \gamma \)-\( \delta \)-tocopherol. It is insoluble in water and freely soluble in ethanol.

**EC specifications**: E 309 \( \delta \)-Tocopherol [6].

Assay: Not less than 97%.

The specification includes purity criteria on Refractive index, Sulphated ash, Specific absorption, Arsenic, Lead, Mercury and Heavy metals.

**JECA specifications**: No JECFA specification has been prepared for \( \delta \)-Tocopherol.

**Exposure**: Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. In contrast to JECA SCF has not specified an ADI and the substances were for that reason not included in the EU monitoring system (tier 0). However as part of the SCF evaluation was based on the assumption that exposure from food additive use is much less than exposure from natural sources, it is desirable to examine whether this is still the case.

**SCF/JECFA evaluation:**

**SCF status**: Latest evaluation in 1987 when the tocopherols were found ”acceptable” (assuming that intake from natural sources normally far will exceed that from processed foods containing tocopherol as an antioxidant). The committee noted that practically no data exists on \( \gamma \)-tocopherol and \( \delta \)-tocopherol, but nevertheless included them in the evaluation [3].

**JECA status**: Latest evaluation in 1986 when an ADI of 0.15-2mg/kg bw/day was allocated. The Committee requested further data on interactions between vitamin E and blood clotting factors [1]. \( \gamma \)-Tocopherol and \( \delta \)-tocopherol were not part of the evaluation.

**Background data:**

**Subacute/subchronic toxicity**: Data from a 90-day study in rats are available. No subchronic effects of large doses in rats were observed in a 90 day experiment. Groups of 60 rats were given food supplemented to give daily doses of 0.5 mg/kg bw., 50 mg/kg bw and 500 mg/kg bw. No toxic effects were seen as compared to controls. [8]. After eight weeks of feeding in a long-term study, bleeding was observed after blood sampling in groups dosed at 500, 1000 or 2000 mg/kg bw/day.

**Genotoxicity**: *In vitro*: Tocopherols have not been tested thoroughly in for genotoxicity *in vitro*. Several reports exist on tocopherol antimutagenicity and anticlastogenicity. There were no genotoxic effects of tocopherols in the control cultures [2]. *In vivo*: Hamsters (24) were divided into 4 groups and treated for 20 days as follows: 1. Control. 2. Vitamin E 2 mg/kg bw. 3. MeHg 2 mg /kg bw . 4. Vitamin E 2 mg/kg bw and MeHg 2 mg/kg bw. Fibroblast cultures were made from skin cells and chromosomal analyses from these cultures indicated that that there was no significant aberration in cells obtained from control and vitamin E cultures [7].
Chronic toxicity/Carcinogenicity: Data from several adequate long-term studies are available. Groups of 60 male and 60 female rats were fed with basis food and supplements calculated to give in total 500, 1000, 2000 mg/kg bw. $\alpha$-tocopheryl acetate for 104 weeks. Haemorrhages were observed in the high dose at 15 weeks, in the middle at 16 weeks and in the low-dose group at 18 weeks in the male rats only. The effects was counteracted by supplying vitamin K3 to all rats from week 24 onwards. There was no effect on the frequency of tumour-bearing animals except a trend towards lower mammary tumour incidence in females [11]. In the same study there were seen increased haemorrhages in males accompanied by prolonged prothrombin time and higher phosphatase activity. Tocopherols have been shown to be anticarcinogenic in several studies where rodents were treated with known carcinogens. There are also reports of co-carcinogenic actions with respect to dibenzanthracene-induced lung tumours in mice [2].

Reproduction toxicity: Both teratogenicity and two-generation studies have been performed on alpha-tocopherol succinate with no adverse effects found. In the two-generation study there were no differences in the reproductive index between control and treated groups even at the highest dose tested (2% in the diet). The teratogenic study revealed no toxic effect in first generation [8]. With extremely high doses, 2752 mg $\alpha$-tocopherol given during pregnancy and lactation eye abnormalities were seen in both first and second generation [10].

Allergy/Intolerance: Allergic reactions to vitamin E are known by skin contact.

Effect in humans: Studies indicate that humans tolerate large doses of tocopherols. In one study 2002 persons with a coronary arteriosclerosis was treated as follows: 546 person took 800 IU $\alpha$-tocopherol for a median of 731 days (range 3-981), 489 took 400 IU $\alpha$-tocopherol for a median of 366 days (8-961) and 967 took placebo for 494 days (9-965). This treatment was well tolerated, only 11 person left therapy due to diarrhoea, dyspepsia or rash. [9]. Hypervitaminosis is observed when the daily intake exceeds 400 mg/day [3]. The effects in question were not specified, but fatigue and increased excretion of creatinine has been reported from a small study [2]. Interactions with warfarin on blood clotting has been observed in one study and interactions with iron medication in children was observed in another [2]. Positive correlation between blood clotting time and vitamin E concentrations has been observed in cord blood after habitual intake levels of vitamin E [2]. The vitamin E quinone may be involved in the anticoagulant effects of vitamin E [2].

Other: There are sufficient data on biokinetics but data on metabolism are insufficient. Tocopherols are absorbed mainly from the medial small intestine to the lymphatic pathway. The efficiency of absorption is dose dependent in man 96.6% with a 10-mg oral dose, 81.5% with a 100-mg dose and 55.2 % with a 2000-mg dose, and it seems like the absorption rate of the different tocopherols are similar. From the lymphatic pathway it is taken up by virtually all tissues, where they are concentrated and stay in membrane-containing structures, for example mitochondria, microsomes, nucleus and plasmamembrane. Administration of rats with radioactive labelled tocopherol shows that maximum uptake was in adrenals, ovaries and liver. Almost all administered tocopherol is found unchanged in the tissues, thus in liver and kidney, less than 1% of the administrated dose was found as metabolites (oxidation products). The depletion rate is low, with biological halftime between 1 week and 1-2 month, mainly by loss to the feces [10]. Tocopherols can induce liver microsomal monooxygenases in the liver (vis. aminopyrene-N-demethylase). Tocopherols may form physiologically active quinones by oxidation.
There is some evidence for interactions between tocopherol and vitamins A, D and K. It seems that the effect of excessive intake of vitamin A can be counteracted by increased intake of vitamin E. Vitamin E in excess can decrease the availability of vitamin D. Vitamin K can reduce the prolonged prothrombin time seen when large doses of vitamin E are given [10].

**Conclusion:** Data on vitamin E are mostly sufficient but mainly related to d-alpha-tocopherol and not to γ-tocopherol and δ-tocopherol as such. The lack of *in vitro* mutagenicity data on d-alpha-tocopherol are unimportant since data on *in vivo* genotoxicity and long-term effects are sufficient. The interactions with blood clotting observed in male rats, in newborns, and in a patient treated with warfarin indicate that further studies would be needed to explain the mechanism and potential adverse consequences. Besides being a food additive, tocopherols are essential nutrients. The daily intake of α-tocopherol from food additives is estimated to be less than 0.02mg/kg bw, and thereby significantly lower than the intake from natural sources (0.07-0.28 mg/kg bw.) These intake levels are far below the levels mentioned in the studies mentioned above.

**References:**


PROPYL GALLATE, OCTYL GALLATE AND DODECYL GALLATE

E number:
Propyl gallate: E 310
Octyl gallate: E 311
Dodecyl gallate: E 312

Recommendation: It is suggested that the gallates should be re-evaluated by the SCF to clarify the discrepancy between the JECFA and SFC evaluations and the basis for setting the ADI. Besides the toxicological data base on octyl and dodecyl gallates are very limited and it should be considered whether these compounds are at all acceptable as additives by modern standards. The significance of chlorinated impurities should be addressed.

In light of the questions about the ADI it would be useful to monitor the present uses of the gallates.

Chemical name/synonyms:
Propyl gallate: n-Propyl ester of 3,4,5-trihydroxybenzoic acid, Propyl ester of gallic acid.
Octyl gallate: n-Octyl ester of 3,4,5-trihydroxybenzoic acid, octyl ester of gallic acid.
Dodecyl gallate: n-Dodecyl (or lauryl) ester of 3,4,5-trihydroxybenzoic acid, dodecyl ester of gallic acid.

Chemical formula:
Propyl gallate: C_{10}H_{12}O_{5}
Octyl gallate: C_{15}H_{22}O_{5}
Dodecyl gallate: C_{19}H_{30}O_{5}

EINECS number:
Propyl gallate: 204-498-2
Octyl gallate: 213-853-0
Dodecyl gallate: 214-620-6

CAS number:
Propyl gallate: 121-79-9
Octyl gallate: 1034-01-01
Dodecyl gallate: 1166-52-5

Functional Class: Antioxidant.

Specification:
Manufacture: No information on manufacturing processes of food grade propyl gallate, octyl gallate and dodecyl gallate.

Propyl gallate
Definition: Propyl gallate is the n-propyl ester of gallic acid. It is slightly soluble in water and freely soluble in ethanol.
EC specifications: E 310 Propyl gallate [1].
Assay: Not less than 98% on the anhydrous basis.
Chlorinated organic compounds: Not more than 100 mg/kg (as Cl).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Free acid,
Specific absorption, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Propyl gallate [2].
Assay: Not less than 98.0% and not more than 102.0% on the dried basis.
Chlorinated organic compounds: Not more than 100 mg/kg (as Cl).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Free acid and
Heavy metals.

Octyl gallate
Definition: Octyl gallate is the n-octyl ester of gallic acid. It is insoluble in water and freely soluble in ethanol.

EC specifications: E 311 Octyl gallate [1].
Assay: Not less than 98% on the anhydrous basis.
Chlorinated organic compounds: Not more than 100 mg/kg (as Cl).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Free acid,
Specific absorption, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Octyl gallate [2].
Assay: Not less than 98.5% on the dried basis.
Chlorinated organic compounds: Not more than 100 mg/kg (as Cl).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Free acid and
Heavy metals.

Dodecyl gallate
Definition: Dodecyl gallate is the n-dodecyl (or lauryl) ester of gallic acid. It is insoluble in water and freely soluble in ethanol.

EC specifications: E 312 Dodecyl gallate [3].
Assay: Not less than 98% on the anhydrous basis.
Chlorinated organic compounds: Not more than 100 mg/kg (as Cl).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Free acid,
Specific absorption, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Dodecyl gallate [2].
Assay: Not less than 98.5% on the dried basis.
Chlorinated organic compounds: Not more than 100 mg/kg (as Cl).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Free acid and
Heavy metals.

Exposure: The gallates may be used in fats and oils for the professional manufacture of heat
treated foodstuffs, frying oil and frying fat, lard, fish oil, and beef, poultry and sheep fat, and some
fat containing products. The maximum permitted level is 200 mg/kg (expressed on fat content).
Also permitted in dehydrated potatoes (25 mg/kg) and in chewing-gum and dietary supplements
This means that the SCF ADI can be reach by consuming 150 g fat (direct or indirect) or 75 g chewing gum/dietary supplement per person if the substances are present to the maximum. In the EU monitoring system the calculated intake in tier 1 exceeded the ADI. In tier 2 the calculated intake by adults and the whole population is reported in the range of 12 - 34% of ADI. The calculated intake by young children is reported in the range of 17 - 70%. It was therefore decided to perform no further examination at this stage.

SCF/JECFA evaluation:

SCF status: Group ADI of 0.5mg/kg bw/day based on a NEL of 50 mg/kg bw/day in three-generation rodent bioassays with octyl gallate and a safety factor of 100 [4]. The committee noted that despite lack of hydrolysis and metabolism data on octyl and dodecyl gallate these substances were less extensively hydrolysed and therefore presumably less toxic than propyl gallate.

JECFA status: ADI for propyl gallate, 0-1.4mg/kg bw/day, based on a NOEL of 135 mg/kg bw/day in a 90-day rat study was allocated in 1996. At the same time the ADI for the other gallates were withdrawn [5]. Data on hydrolysis and data to explain differences in their subchronic toxicity were requested. Previously group ADIs of 0-0.2 mg/kg bw/day (1980) and of 0-2.5 mg/kg bw/day (1987) were allocated. From 1993-1996 temporary ADIs for octyl gallate of 0-0.1 mg/kg bw/day and for dodecyl gallate of 0-0.05 mg/kg bw/day have been allocated [5;6].

Background data:

Subacute/subchronic toxicity: No effects were observed in rats dosed with up to 5000ppm octyl gallate for 13 weeks or in dogs fed up to 6000ppm for four weeks or 5000ppm for 13 weeks, except for a slight elevation of SGOT in dogs fed 5000ppm for 13 weeks. In a 90-day study on propyl gallate a NOEL of 1910 mg/kg feed (135 mg/kg bw/day) was observed with haematological and hepatic effects at a higher dose. A 150-day gavage study with dodecyl gallate revealed effects on spleen, liver and kidney at 50mg/kg bw/day [6].

Genotoxicity: In vitro: No mutagenicity reported.

In vivo: No mutagenicity reported in the mouse bone marrow micronucleus assay [7] or in Drosophila postmeiotic or meiotic germ cells [8].

Chronic toxicity/Carcinogenicity: Propyl gallate increased the number of aberrant crypt foci after Benzo(a)pyrene induction in the F344 rat colon [9]. A carcinogenesis bioassay of propyl gallate was conducted by feeding diets containing 6,000 or 12,000 ppm propyl gallate to groups of 50 F344/N rats and 50 B6C3F1 mice of each sex for 103 weeks. Groups of 50 untreated rats and 50 untreated mice of each sex served as controls. Although the increased incidence of malignant lymphoma in the high-dose group of male mice may have been related to the dietary administration of propyl gallate, and a significant increase in several benign tumours was observed in the low-dose group of male rats, the NTP [10] report concludes that the assay is negative for carcinogenicity of propyl gallate. More specifically, the evidence is equivocal in the case of male mice and rats and negative in the case of the females [10]. There was a significant and dose-related decrease in body weight gain in all animals dosed with propyl gallate in this study. The other gallates have not been tested in a carcinogenesis bioassay. In several studies the gallates have been observed to reduce the carcinogenic effects of model carcinogens [4;6].
**Reproduction toxicity:** Octyl gallate caused toxicity to pups during weaning when fed at 0.25-0.5% for 1-2 generations, whereas the 0.1% level was without significant effect. This effect was reproduced in a subsequent study [11], and corresponds to a NOEL of 50 mg/kg bw/day, according to the SCF [4] and JECFA [11] or to 17.5 mg/kg bw/day according to a more recent report from JECFA [6].

**Allergy:** Gallates are known to cause contact dermatitis in about 3% of the exposed. There are also data indicating an effect in or around the mouth, one of these resulting from intake of gallate containing beer [6]. Also a case of allergic stomatitis due to propyl gallate has been reported [12].

**Effect in humans:** Contact dermatitis as described above. Octyl gallate is a potent inhibitor of human liver sulphotransferases involved in steroid hormone excretion [13].

**Other:** Propyl and octyl gallates are well known to be potent lipoxygenase inhibitors. Metabolism: Gallate esters are expected to be hydrolysed in the gut and the gallate absorbed, conjugated and excreted, but bioavailability studies are lacking.

**Conclusion:** There are insufficient data to evaluate the gallates, particularly biotransformation, possible medium- and long-term effects, and allergic reactions. For several end points there are only data for one of the compounds. The allocation of an ADI for these compounds should be reconsidered individually. The effects of propyl gallate on tumour promotion should be further investigated.

Propyl gallate, octyl gallate and dodecyl gallate as defined by the specifications seems to be covered by the toxicological evaluation.

**References:**


11. \textit{[1976, FAS 10-JECFA 20]}


Erythorbic acid and sodium erythorbate

**E number:**
Erythorbic acid: E 315
Sodium erythorbate: E 316

**Recommendation:** No need for immediate action, however the need for a multigeneration guinea pig study should be considered.

**Chemical name/synonyms:**
Erythorbic acid: D-Erythro-hex-2-enoic acid γ-lactone, D-isoascorbic acid/isoascorbic acid, D-araboascorbic acid.
Sodium erythorbate: Sodium salt of D-erythro-hex-2-enoic acid γ-lactone, sodium D-isoascorbic acid, 3-keto-D-gulofuranolactone sodium enolate/ sodium isoascorbate.

**Chemical formula:**
Erythorbic acid: C₆H₈O₆
Sodium erythorbate: C₅H₇O₆Na⋅H₂O

**EINECS number:**
Erythorbic acid: 201-928-0
Sodium erythorbate: 228-973-9

**CAS number:**
Erythorbic acid: 89-65-9
Sodium erythorbate: 6381-77-7

**Functional Class:** Antioxidant.

**Specification:**
**Manufacture:** No information on manufacturing processes of food grade erythorbic acid and sodium erythorbate.

**Erythorbic acid**
**Definition:** Erythorbic acid is the D-isoascorbic acid. It is freely soluble in water and soluble in ethanol.

**EC specifications:** E 315 Erythorbic acid [1].
Assay: Not less than 98% on the anhydrous basis.
Oxalate: Passes test.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Specific rotation, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Erythorbic acid [2].
Assay: Not less than 99% on the anhydrous basis.
Oxalate: Passes test.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Specific rotation, Arsenic, Lead and Heavy metals.

**Sodium erythorbate**

**Definition:** Sodium erythorbate is the sodium salt of D-isoascorbic acid. It is freely soluble in water and very slightly soluble in ethanol.

**EC specifications:** E 316 Sodium erythorbate [1].
Assay: Not less than 98% of \( \text{C}_6\text{H}_7\text{O}_6\text{Na} \cdot \text{H}_2\text{O} \) on the dried basis.
Oxalate: Passes test.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Specific rotation, pH of a 10% aqueous solution, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium erythorbate [2].
Assay: Not less than 98% of \( \text{C}_6\text{H}_7\text{O}_6\text{Na} \cdot \text{H}_2\text{O} \) on the dried basis.
Oxalate: Passes test.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Specific rotation, pH of a 10% aqueous solution, Arsenic, Lead and Heavy metals.

**Exposure:** The use of erythorbic acid and its sodium salt is limited to semi-preserved and preserved meat products (500 mg/kg as the acid) and to preserved and semi-preserved fish products as well as frozen and deep-frozen fish with red skin (1500 mg/kg). Not permitted in beverages. Exceeding the ADI on a regular basis is unlikely, as it would take 720 g meat product or 240 g fish product with the maximum level of the substances to reach the ADI. In the EU monitoring system the calculated intake in tier 1 exceeded the ADI. In tier 2 the calculated intake by adults and the whole population is reported in the range of 1 - 24% of ADI. The calculated intake by young children is reported in the range of 1 – 19%. No further examination at this stage is needed. This is corroborated by recent calculations showing that the ADI is unlikely to be exceeded with current intakes of erythorbate in Italy [3].

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1995: ADI = 6 mg/kg bw (as erythorbate) based on growth retardation at 2.5% in the diet in a subchronic rat study [4].

**JECFA status:** Latest evaluation 1990: ADI not specified (erythorbic acid and its sodium salt) [5].

**Background data:**

**Subacute/subchronic toxicity:** In feeding experiments with groups of 10 male and 10 female rats or mice for 10 weeks (mice) or 13 weeks (rats) at doses up to 10% in the diet, the most potent effects were observed on the growth rate in rats at doses above 1.25% (approx. 600mg/kg bw/day). Maximally tolerated doses in mice were 2.5% (males) and 5% (females) in the diet. Doses above MTD caused atrophy of liver cells and renal tubules in mice. Effects in rats on anything but growth were not reported.
Genotoxicity: In vitro: Erythorbate has been repeatedly evaluated in the Ames test with negative results. Sporadic equivocal results have been observed in TA100. Negative results have also been obtained in eucaryotic cells for chromosomal aberrations.

In vivo: Erythorbate did not produce micronuclei in rat bone marrow at doses up to 1500 mg/kg bw/day in rats dosed i.p. No effects were observed in the rat dominant lethal assay after 1 or 5 doses of up to 5000mg/kg bw/day or in the mouse heritable translocation assay at doses up to 5% in the diet for 7 weeks.

Chronic toxicity/Carcinogenicity: A mouse study according to OECD guidelines has been performed with doses up to MTD. No increase in chronic toxicity or carcinogenicity was observed but at the end of the study, dosed animals had increased growth resulting in slightly different organ to body weight ratios. A rat study with 52 male and 50 female F344 rats over 104 weeks has also been performed at doses of 0, MTD and 2x MTD (2.5%) in the diet. As expected, the higher dose resulted in a decreased weight gain which was most pronounced in females in week 85. In males, no other adverse effects, including no increases in tumour rates or survival was observed. In females, there was a decreased tumour rate in the higher dose group, probably as a consequence of the growth retardation.

Reproduction toxicity: Erythorbate has been tested for reproductive effects and teratogenicity in mice at doses up to 1030mg/kg bw/day and in rats at doses up to 5% in the diet without effects on skeletal malformation, soft tissue changes, litter size, survival or post-natal development. In a chicken egg embryotoxicity test, erythorbate was found to be slightly more toxic than ascorbate. No increase in sperm abnormality or counts was observed in the rat dominant lethal assay referred above (genotoxicity in vivo). A multi-generation study with erythorbate has not been performed, and the guinea pig would be the preferred animal model for such a study.

Effect in humans: Erythorbate does not interfere with ascorbate uptake in humans even with relatively high intakes, and it may even have a small ascorbate-sparing effect. Erythorbate does not seem to be biotransformed into oxalate in humans [4].

Other: Isoascorbate has marginal anti-scorbutic effects, about 5% of the effect of ascorbic acid in guinea pigs.

Erythorbic acid competes with ascorbic acid for uptake in the mammal species dependent upon external ascorbate, e.g. humans and guinea pigs [4]. However, the affinity of erythorbate for the active transporter in the gut is lower by a factor of about 10. The same applies to the renal reabsorption transport system, resulting in relatively weak competition between the two as long as dietary ascorbate levels are much higher than those of erythorbate. High dose-level studies have been carried out in humans and several studies with radiolabelled compound have been performed in guinea pigs to substantiate this overall result [6]. A large part of orally dosed 14-C-erythorbate is excreted as CO2 in guinea pigs, whereas i.p. dosed erythorbate is mainly excreted into urine, indicating degradation by the gut flora. Human data on this are not available [4].

Conclusion: The safety of erythorbate seems to be well documented, except for the lack of a multi-generation study.
Erythorbic acid and sodium erythorbate as defined by the specifications are covered by the toxicological evaluation.

References:


5. [1990, TRS 806-JECFA 37]

6. [1990, FAS 28-JECFA 37]
**BUTYLATED HYDROXYANISOLE (BHA)**

**E number:** E 320

**Recommendation** As this additive has only a temporary SCF-ADI a re-evaluation is needed.

**Chemical name/synonyms:** 3-Tertiary-butyl-4- hydroxyanisole, a mixture of 2-tertiary-butyl-4-hydroxyanisole and 3-tertiary-butyl-4-hydroxyanisole/ BHA.

**Chemical formula:** $C_{11}H_{16}O_2$

**EINECS number:** 246-563-8

**CAS number:** 15013-16-5

**Functional Class:** Antioxidant.

**Specification:**

**Manufacture:** Butylated hydroxyanisole is manufactured by chemical synthesis.

**Definition:** Butylated hydroxyanisole is mixture of the two isomers 2-tertiary-butyl-4-hydroxyanisole and 3-tertiary-butyl-4-hydroxyanisole. It is insoluble in water and freely soluble in ethanol.

**EC specifications:** E 320 Butylated hydroxyanisole (BHA) [6].
Assay: Not less than 98.5% of $C_{11}H_{16}O_2$ and not less than 85% of 3-tertiary-butyl-4-hydroxyanisole isomer.
Phenolic impurities: Not more than 0.5%.
In addition the specification includes purity criteria on Sulphated ash, Specific absorption at 290 nm, Specific absorption at 228 nm, Arsenic, Lead and Mercury.

**JECFA specifications:** Butylated hydroxyanisole [4].
Assay: Not less than 98.5% of $C_{11}H_{16}O_2$ and not less than 85% of 3-tertiary-butyl-4-hydroxyanisole isomer.
Phenolic impurities: Not more than 0.5%.
In addition the specification includes purity criteria on Sulphated ash, Arsenic and Heavy metals.

**Exposure:** BHA may be used in fats and oils for the professional manufacture of heat-treated foodstuffs, in frying oil and frying fat, lard, fish oil, and beef, poultry and sheep fat, and some fat containing products. The maximum permitted level is 200 mg/kg (expressed on fat content). Also permitted in dehydrated potatoes (25 mg/kg) and in chewing gum and dietary supplements (400 mg/kg). This means that the SCF ADI can be reach by consuming 150 g fat (direct or indirect) or 75 g chewing gum/dietary supplement per person if the substance is present to the maximum.
In the EU monitoring system the calculated intake in tier 1 suggested that the ADI could be exceeded. In tier 2 the calculated intake by adults and the whole population is reported in the range of 12 - 37% of ADI. The calculated intake by young children is reported in the range of 17 - 62%. It was therefore decided to perform no further examination at this stage. In an evaluation of human population exposures to BHA it was concluded that ADI may be exceeded in individuals with very high intakes of fats and oils [5]. In later Dutch and Italian studies on BHA-exposure it was concluded that ADI was not likely to be exceeded [10;11].

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation in 1987: Temporary ADI = 0.5 mg/kg bw/day based on a NOEL of 62.5 mg/kg bw/day for hyperplastic effects after 90 days in the rat forestomach and an application of a safety factor of 100. This safety factor was considered sufficient since there is ample evidence to conclude that the hyperplastic effect is not due to genotoxicity and that it is not present in species without a forestomach and therefore irrelevant to man. Further data required for reproductive effects [3].

**JECFA status:** Latest evaluation at 33rd meeting 1988: ADI = 0-0.5 mg/kg bw/day based on chronic bioassay NOEL of 50 mg/kg bw/day for forestomach tumours [1].

**Background data:**

**Subacute/subchronic toxicity:** Groups of 5 male F344 rats fed 0, 0.1, 0.25, 0.5, or 2% BHA for 13 weeks were examined for forestomach hyperplasia and increased labelling index. Only the highest dose group had hyperplasia, and the labelling index was significantly increased at the 0.5% dose level or higher. In a similar study in Wistar rats, mild hyperplasia was observed already at the 0.125% dose level after 90 days [2]. No such effects were seen in some other species without a forestomach such as the guinea pig and the dog. In the pig and monkey there are indications that proliferative responses may take place in the oesophagus at dose levels considerably higher than in the rat. BHA is known to interact with a range of known carcinogens, most often to inhibit but sometimes to enhance tumourigenesis [2;3].

**Genotoxicity:** *In vitro:* BHA is not mutagenic in the Ames test (*S. typhimurium* liver microsome test) and in most other *in vitro* genotoxicity assays [8].

*In vivo:* No cytogenetic effects were observed in the bone marrow of rats dosed with BHA at 15-1500 mg/kg. Also no mutagenic effects were observed in the host-mediated assay using *S. typhimurium* G-46 and TA1530 in mice at the same dose levels [7].

**Chronic toxicity/Carcinogenicity:** Groups of 50 male F344 rats given doses of 0, 0.125, 0.25, 0.5, or 2% BHA in the diet for 104 weeks experienced a dose-dependent decrease in body weight gain, which was significant above the 0.5% dose. Histological abnormalities were observed in the forestomach only, and only at doses at or above 0.5% BHA. Tumours were only seen at the 2% dose level [2].

**Reproduction toxicity:** In several one-generation studies with mice, rats and monkeys no effects have been observed at dose levels of 50 mg/kg bw/day or higher [8]. No multigeneration study with BHA has been conducted. BHA has been shown to be weakly estrogenic *in vitro* [9].

**Allergy/Intolerance:** A few cases of contact dermatitis from BHA are known but allergy or intolerance to dietary BHA has not been described.
**Effect in humans:** A human feeding study with BHA at 0.5 mg/kg/day for 10 days has been reported. BHA at this level had no effects on clinical markers or on enzyme induction, but the kinetic behaviour of BHA in man indicates that bioaccumulation may take place [12].

**Other:** Radiolabelled BHA is well absorbed, and in the rat 47-69% is excreted with urine, 18-38% with faeces and up to 14% with expired air, depending on the position of the label in the BHA molecule. Similar results were observed in dogs. BHA is oxidised in the tert-butyl group by microsomal monoxygenases and conjugated to some extent before excretion. The methoxy group can be demethylated, and quinones and semiquinones can form and may bind covalently to proteins.

**Conclusion:** Most studies necessary for the toxicological evaluation of a food additive are available. However the studies, indicating a hyperproliferative effect in the oesophagus of pig and monkey, should be reassessed as well as the potential bioaccumulation of BHA in humans. Also a multigeneration study may be needed as was also recommended at the last SCF evaluation, leading to the temporary status when establishing the ADI [3].

Butylated hydroxyanisole as defined by the specifications seems to be covered by the toxicological evaluation.

**References:**


**BUTYLATED HYDROXYTOLUENE (BHT)**

**E number:** E 321

**Recommendation:** BHT should be re-evaluated in the light of data from a two-generation rat study published after the last SCF evaluation which might affect the over-all evaluation. This study was considered by JECFA in their evaluation and might partially explain the differences reached in the evaluations by the SCF and JECFA.

**Chemical name/synonyms:** 2,6-Ditertiary-butyl-p-cresol, 4-methyl-2,6-ditertiarybutylphenol.

**Chemical formula:** C_{15}H_{24}O

**EINECS number:** 204-881-4

**CAS number:** 128-37-0

**Functional Class:** Antioxidant.

**Specification:**

**Manufacture:** Butylated hydroxytoluene is obtained by chemical synthesis.

**Definition:** Butylated hydroxytoluene is the well defined substance 4-methyl-2,6-ditertiarybutylphenol. It is insoluble in water and freely soluble in ethanol.

**EC specifications:** E 321 Butylated hydroxytoluene (BHT) [1].
Assay: Not less than 99%.
Phenolic impurities: Not more than 0.5%.
In addition the specification includes purity criteria on Sulphated ash, Specific absorption at 278 nm, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Butylated hydroxytoluene [2].
Assay: Not less than 99.0%.
Phenolic impurities: Not more than 0.5%.
In addition the specification includes purity criteria on Solidification point, Sulphated ash, Arsenic and Heavy metals.

**Exposure:** BHT may be used in fats and oils for the professional manufacture of heat-treated foodstuffs, in frying oil and frying fat, lard, fish oil, and beef, poultry and sheep fat. The maximum permitted level is 100 mg/kg (expressed on fat content). Also permitted in chewing gum and dietary supplements (400 mg/kg). This means that the SCF ADI can be reach by consuming 30 g fat (direct or indirect) or 7.5 g chewing gum/dietary supplement per person if the substance is present to the maximum (180 g and 45 g respectively to reach the JECFA ADI).
In the EU monitoring system the calculated intake in tier 1 exceeded the SCF ADI. In tier 2 the calculated intake by adults and the whole population is reported in the range of 23-80% of ADI. The calculated intake by young children is reported in the range of 4-101%. Therefore it was concluded
that an examination at tier 3 of the intake by young children is needed. In a recent estimate the theoretical maximum daily intake of BHT in Italy was calculated to be above ADI but the loss of BHT during cooking with fats and oils and also its low availability from chewing gum probably causes the actual exposure to be below the ADI [3].

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1987: SCF concludes that the 5% reduction in pup weight seen in rats dosed *in utero* with 25 mg/kg bw/day indicates that the NOEL for this effect is even lower, probably 5 mg/kg bw/day. The acute effect on blood clotting is at a similar dose level, and with a safety factor of 100, the Committee reaches an ADI of 0-0.05 mg/kg bw/day for BHT [4].

**JECFA status:** Latest evaluation 1995: JECFA concludes that BHT is a non-genotoxic carcinogen in rats, and that liver toxicity precedes its adverse effects. Liver toxicity is related to liver enzyme induction with a well defined threshold at 100mg/kgbw/day. The NOEL for liver enzyme induction in rats is 25mg/kg bw/day in subchronic toxicity studies, and with a safety factor of 100 JECFA reaches an ADI of 0.25mg/kg bw/day, which is rounded to 0.3mg/kg bw/day [5].

**Background data:**

**Subacute/subchronic toxicity:** BHT is toxic to the liver after subchronic dosing and a NOEL of 25mg/kg bw has been found. BHT is also causing haemorrhage at high dose levels in normal and, more severely, in vitamin K-deficient rats due to a rapid decrease in the concentration of several clotting factors. Both, liver toxicity and haemorrhage is enhanced by increasing hepatic BHT metabolism and/or by decreasing the efficiency of detoxification pathways. BHT quinone methide has been implicated as the causative metabolite. No effects were observed in a dose response study at doses below 600 mg/kg bw/day in normal rats [6]. Finally, BHT is causing lung toxicity in young mice at doses above 200 mg/kg bw. In this case the metabolite hydroxylated in the tert-butyl group is implicated by having a 20-fold higher lung toxicity than the parent compound.

**Genotoxicity:** *In vitro:* BHT has been tested adequately and is not mutagenic in bacterial assays either with or without metabolic activation.

*In vivo:* BHT was not genotoxic *in vivo* in rats at doses up to 500 mg/kg bw (dominant lethal assay) or in mice at doses of 1% in the feed (dominant lethal and heritable translocation assays). There are adequate *in vivo* genotoxicity tests for BHT.

**Chronic toxicity/Carcinogenicity:** BHT increased in a dose-dependent manner the number of hepatocellular adenomas in male B6C3F1 mice treated at 1 or 2% in the diet for 104 weeks. BHT increased the total incidence of hepatic tumours in rats at doses at 100mg/kg bw and higher, however, the effect was observed in very old animals since BHT-dosed rats survived much longer than controls. There was no such effect below doses where BHT is able to induce hepatic monooxygenases. In ordinary two-year studies in rats there were no increased tumour incidence in any organ [7].

BHT causes an increase in putative preneoplastic foci in the rat liver when given after initiation with known hepatocarcinogens. In a study with N,N-diethylnitrosamine initiation and subsequent treatment with 0.5% BHT in the diet, preneoplastic lesions increased but no increase in liver tumours was observed at 22 weeks, a time point by which known tumour promoters like DDT and phenobarbital have significantly increased the number of liver tumours. In another study, BHT at a dose level of 0.7% was able to increase nitrosamine-initiated liver tumourigenesis. At similar dose
levels BHT has also been observed to increase tumourigenesis initiated by known carcinogens in the colon and oesophagus of rats and in the lungs of mice. BHT is also able to decrease 7,12-dimethylbenz[a]anthracene initiated mammary cancer in rats in a dose-dependent manner at dose levels from 0.03 – 0.6% in the diet [7].

**Reproduction toxicity:** BHT was tested in an adequate two-generation test in rats at doses up to 1000 mg/kg bw. The highest and the second highest (750 mg/kg bw) doses resulted in decreased food intake accompanied by reduced weight gain and continued poor condition among the pups. In the new born pups a weight reduction was recorded at all dose levels, including the lowest, 25 mg/kg bw/day [4]. In a subsequent three-generation study in mice, an increased pup-weight was recorded at doses from 15-400 mg/kg bw/day in all generations, an effect which was considered beneficial by the authors [8].

**Allergy/Intolerance:** In a double-blind placebo-controlled challenge test among 258 atopic patients with chronic skin conditions, none were found to respond to a challenge with BHT [7].

**Effect in humans:** The disposition of BHT has been studied in 7 males and 5 females. BHT reached comparatively higher plasma levels than in rats. About 2.8% was excreted as conjugates of BHT-COOH in urine and no residual BHT was found in faecal samples. BHT levels in human fat samples indicate a 45 times higher bioaccumulation of BHT in humans than in rats [7].

**Other:** BHT is metabolised by microsomal monooxygenases and by prostaglandin synthase. Major metabolites are hydroxylated in the 4-methyl group (BHT-OH) or in the tert-butyl group. The BHT-OH can be oxidised further to the aldehyde and the acid (BHT-COOH). Metabolites formed through radical pathways are a 4-hydroperoxymethyl derivative and a quinone methide. The latter metabolites are more toxic than the parent compound and have been implicated as causative for BHT-induced toxicity.

BHT inhibits intercellular co-operation in hamster fibroblasts, an effect shared with several known tumour promoters.

**Conclusion:** There are sufficient data to evaluate BHT. BHT is a co-carcinogen (tumour promoter) and a vitamin K antagonist only at dose levels far higher than those encountered in the human diet. New experimental data has emerged after the last SCF evaluation which might explain the apparent discrepancy between this evaluation and the later evaluation by JECFA.

Butylated hydroxytoluene as defined by the specifications is covered by the toxicological evaluation.

**References:**


5. [1995, TRS 859-JECFA 44]


7. [1995, FAS 35-JECFA 44]

LECITHINS

E number: E 322

Recommendation: There is no need for an evaluation of lecithin including hydrolysed lecithin. To help people allergic to the source materials (eggs or soya) it should be considered to make the labelling of the origin of the product used obligatory.

Chemical name/synonyms: Phosphatides, phospholipids.

EINECS number: 232-307-2

CAS number: 8002-43-5

Functional class: Emulsifier, antioxidant.

Specification:
Definition: Lecithins are complex mixtures of acetone-insoluble phosphatides including phosphatidyl-choline, phosphatidyl-ethanolamine and phosphatidyl-inositol combined with various amounts of other substances such as triglycerides, fatty acids and carbohydrates. Lecithins also include oil-free forms and partially hydrolysed products. Lecithins are only partially soluble in water, but it readily hydrates to form emulsions.

Manufacture: Lecithins are usually obtained by physical methods from oil-bearing seeds or animal sources. In the oil-free form, the preponderance of triglycerides and fatty acids is removed and the product contains 90% or more of phosphatides representing all or certain fractions of the total phosphatide complex. Partially hydrolysed lecithins are obtained by the use of a suitable lipase. Any enzymatic activity in the final product is removed by heating.

EC specifications: E 322 Lecithins [7].
Assay: Lecithins: Not less than 60.0% of acetone-insoluble matter
Hydrolysed lecithins: Not less than 56.0% of acetone-insoluble matter
In addition the specification includes purity criteria on Loss on drying, Toluene-insoluble matter, Acid value, Peroxide value, Arsenic, Lead, Mercury and Heavy metals.

JECFA specifications: Lecithin [6].
Assay: Not less than 60.0% of acetone-insoluble matter (phosphatides)
In addition the specification includes purity criteria on Loss on drying, Toluene-insoluble matter, Acid value, Peroxide value, Arsenic, Lead and Heavy metals.

Exposure: Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substance was for that reason not included in the EU monitoring system (tier 0).

The average diet provides a daily intake of several grams of lecithin from natural sources [3].
**SCF/JECFA evaluation:**

**SCF status:** SCF has not formally issued a report on lecithins, but it has indirectly been considered safe when discussed in other circumstances. Thus, when evaluating hydrolysed lecithin the Committee stated that it can be regarded metabolically and toxicologically as an alternative to lecithin and therefore acceptable [4]. Also in 1990 when its use was found acceptable to baby foods [5].

In 1999, an opinion was expressed on the safety in used as a food ingredient of phospholipids obtained from egg yolk when using a new purification process. It was concluded that two products (PL-85 and PL-100) do not lead to safety problems from the point of consumer health (http://europa.eu.int/comm/food/fs/sc/scf/out35_en.html).

**JECFA status:** An ADI “not limited” was allocated in 1973 [1]. The basis for this evaluation was: “Although fewer toxicological studies have been conducted than would normally be required for substances used as food additives, it is considered that nutritional and clinical experience with lecithin is sufficiently extensive to compensate for the incompleteness of the experimental data. Since many observations have been made in man it is not considered necessary to calculate the safe intake level from animal experiments” [3].

Hydroxylated lecithin:
No ADI was established in 1980 due to the limited available data [2].

**Background data:**

**Subacute/subchronic toxicity:** A 3-weeks study is available in rats comparing lecithin and hydrolysed lecithin: No difference with respect to body weight, food intake and growth. Levels more than 20% in diet produced effects on haematopoiesis and kidney enlargements [3].

A 90-day study is available in rats comparing lecithin and hydrolysed lecithin: Hydrolysed lecithin at levels of 5% or less in diet induced no adverse effect or any clear dose-related effect was seen up to 20%. Renal lesions were considered to be specific to Colworth rats and are therefore not significant for human health [3]

**Genotoxicity:** -

**Chronic toxicity/Carcinogenicity:** -

**Reproduction toxicity:** -

**Allergy/Intolerance:** This additive may be produced from soya beans or egg yolks. There is no limit in the specification regarding the content of protein in the preparation.

**Effect in humans:** No untoward reactions were observed in humans after daily doses (22-83 g) for two to four months [3].

**Other:** Biochemical aspects:
Hydrolysed lecithin is produced in the gut as a result of normal digestion and can be regarded metabolically and toxicologically as an alternative to lecithin [4].
Lecithin is an essential constituent of all cells of the human body. The organism is able to synthesise phosphatides and the pathways of synthesis and catabolism of lecithin are well known [3].

**Conclusion:** Lecithins have not been directly evaluated by SCF and toxicological data are fewer than would normally be required for a food additive. However, lecithins are natural constituents of all cells in the human body and can be synthesised and degraded endogenously via well-known pathways. Lecithins have been a natural component of human diet throughout evolution. Commercial lecithin is a chemically heterogeneous group of not well-defined products. Recently, partially purified lecithin fractions have been commercially available for specific technological purposes. New purified products may possess a toxic potential and should be considered individually. Especially, for the newly produced types of phospholipids (PS, PG, and PA), which are not present in egg yolk and synthesised by enzymatic conversion, additional information is needed before a final assessment of their safety as a food ingredient can be given.

There is no need for an evaluation of lecithin as such. New purified products may possess a toxic potential and should be considered individually.

**References:**


SODIUM LACTATE, POTASSIUM LACTATE AND CALCIUM LACTATE

**E Number:** E 325-327

**See:** E 270 Lactic acid and lactates.
**CITRIC ACID, CALCIUM CITRATES, POTASSIUM CITRATES, SODIUM CITRATES, TRIAMMONIUM CITRATE**

**E Number:**
- Citric acid: E 330
- Sodium citrates: E 331
- Potassium citrates: E 332
- Calcium citrates: E 333
- Triammonium citrate: E 380

**Recommendation:** No need for a re-evaluation.

**Chemical name/synonyms:**
- Citric acid: Citric acid, 2-hydroxy-1,2,3-propanetricarboxylic acid, β-hydroxytricarboxylic acid.
- Calcium citrates: Monocalcium citrate, monocalcium salt of 2-hydroxy-1,2,3-propanetricarboxylic acid/ monobasic potassium citrate.
  Dicalcium citrate, dicalcium salt of 2-hydroxy-1,2,3-propanetricarboxylic acid, dicalcium salt of citric acid/ dibasic calcium citrate.
  Tricalcium citrate.
- Potassium citrates: Monopotassium citrate, monopotassium salt of 2-hydroxy-1,2,3-propanetricarboxylic acid/ potassium dihydrogen citrate, monobasic potassium citrate.
  Tripotassium citrate, tripotassium salt of 2-hydroxy-1,2,3-propanetricarboxylic acid/ tribasic potassium citrate.
- Sodium citrates: Monosodium citrate, monosodium salt of 2-hydroxy-1,2,3-propanetricarboxylic acid/ sodium dihydrogen citrate, monobasic sodium citrate.
  Disodium citrate, disodium salt of 2-hydroxy-1,2,3-propanetricarboxylic acid, disodium salt of citric acid/ dibasic sodium citrate.
  Trisodium citrate, trisodium salt of 2-hydroxy-1,2,3-propanetricarboxylic acid/ tribasic sodium citrate.
- Triammonium citrate: Triammonium citrate, triammonium salt of 2-hydroxy-1,2,3-propanetricarboxylic acid/ tribasic ammonium citrate.

**Chemical formula:**
- Citric acid: $C_6H_8O_7$ (anhydrous)
  $C_6H_8O_7\cdot H_2O$ (monohydrate)
- Monocalcium citrate: $(C_6H_7O_7)\cdot Ca\cdot H_2O$
- Dicalcium citrate: $C_6H_6O_7\cdot Ca\cdot 3H_2O$
- Tricalcium citrate: $(C_6H_5O_7)\cdot Ca_3\cdot 4H_2O$
- Monopotassium citrate: $C_6H_7O_7\cdot K$
- Tripotassium citrate: $C_6H_5O_7\cdot K_3\cdot H_2O$
- Monosodium citrate: $C_6H_7O_7\cdot Na$ (anhydrous)
  $C_6H_7O_7\cdot Na\cdot H_2O$ (monohydrate)
- Disodium citrate: $C_6H_6O_7\cdot Na_2\cdot 1.5 H_2O$
Trisodium citrate: $C_6H_5O_7Na_3$ (anhydrous)
$C_6H_5O_7Na_3\cdot n H_2O$ (n = 2 or 5) (hydrated)

Triammonium citrate: $C_6H_{17}N_3O_7$

**EINECS number:**
- Citric acid: 201-069-1
- Monocalcium citrate: -
- Dicalcium citrate: -
- Tricalcium citrate: 212-391-7
- Monopotassium citrate: 212-753-4
- Tripotassium citrate: 212-755-5
- Monosodium citrate: -
- Disodium citrate: 205-623-3
- Trisodium citrate: 200-675-3
- Triammonium citrate: 222-394-5

**CAS Number:**
- Citric acid: 77-92-9 (anhydrous)
  5949-29-1 (monohydrate)
- Monocalcium citrate: -
- Dicalcium citrate: -
- Tricalcium citrate: 813-94-5
- Monopotassium citrate: 866-83-1
- Tripotassium citrate: 866-84-2
- Monosodium citrate: -
- Disodium citrate: -
- Trisodium citrate: 68-04-2
- Triammonium citrate: 3458-72-8

**Functional Class:** Citric acid: Acid, sequestrant, synergist for antioxidants, flavouring agent.
Citrates: Salt, sequestrant, synergist for antioxidants.

**Specification:**
**Manufacture:** Citric acid may be produced by recovery from sources such as lemon or pineapple juice or fermentation of carbohydrate solutions or other suitable media using Candida spp. or non-toxicogenic strains of Aspergillus niger.

**Citric acid**
**Definition:** Citric acid is a naturally occurring organic acid. It is very soluble in water, freely soluble in ethanol and slightly soluble in ether.

**EC specifications:** E 330 Citric acid [7].
Assay: Not less than 99.5% of $C_6H_5O_7$ on the anhydrous basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the anhydrous basis.
In addition the specification includes purity criteria on Water, Sulphated ash, Readily carbonizable substances, Arsenic, Lead, Mercury and Heavy metals (as Pb).
JECFA specifications: Citric acid [8].
Assay: Not less than 99.5% and not more than of C₆H₈O₇ on the anhydrous basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the anhydrous basis.
In addition the specification includes purity criteria on Water, Sulfated ash, Readily carbonizable substances, Sulfates and Lead.

Monocalcium citrate
Definition: It is a calcium salt of citric acid.

EC specifications: E 333 (i) Monocalcium citrate [7].
Assay: Not less than 97.5% of (C₆H₇O₇)₂Ca on the dried basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the dried basis.
In addition the specification includes purity criteria on Loss on drying, pH, Carbonates, Fluoride, Arsenic, Lead, Mercury and Heavy metals (as Pb).

JECFA specifications: No JECFA specifications have been prepared.

Dicalcium citrate
Definition: It is a calcium salt of citric acid.

EC specifications: E 333 (ii) Dicalcium citrate [7].
Assay: Not less than 97.5% of C₆H₆O₇Ca on the dried basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the dried basis.
In addition the specification includes purity criteria on Loss on drying, pH, Carbonates, Fluoride, Arsenic, Lead, Mercury and Heavy metals (as Pb).

JECFA specifications: No JECFA specifications have been prepared.

Tricalcium citrate
Definition: It is a calcium salt of citric acid. It is very slightly soluble in water and insoluble in ethanol.

EC specifications: E 333 (iii) Tricalcium citrate [7].
Assay: Not less than 97.5% of C₆H₆O₇Ca on the dried basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the dried basis.
In addition the specification includes purity criteria on Loss on drying, pH, Carbonates, Fluoride, Arsenic, Lead, Mercury and Heavy metals (as Pb).

JECFA specifications: Calcium citrate [3].
Assay: Not less than 97.5% of C₆H₆O₇Ca on the dried basis.
Oxalates: Passes test.
In addition the specification includes purity criteria on Loss on drying, free acid and alkali, Fluoride, Arsenic, Lead and Heavy metals (as Pb).

Monopotassium citrate
Definition: It is a potassium salt of citric acid. It is freely soluble in water and very slightly soluble in ethanol.
**EC specifications:** E 330-3+380 Citric acid and citrates

**Definition:** It is a potassium salt of citric acid. It is very soluble in water and insoluble in ethanol.

**EC specifications:** E 332 (i) Monopotassium citrate [7].
Assay: Not less than 99% of C₆H₇O₇K on the dried basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the dried basis.
In addition the specification includes purity criteria on Loss on drying, pH, Arsenic, Lead, Mercury and Heavy metals (as Pb).

**JECFA specifications:** Potassium dihydrogen citrate [6].
Assay: Not less than 99.0% and not more than 101.0% of C₆H₇O₇K on the dried basis.
Oxalates: Not more than 0.04%.
In addition the specification includes purity criteria on Loss on drying, Arsenic and Heavy metals (as Pb).

**Tripotassium citrate**
**Definition:** It is a potassium salt of citric acid. It is very soluble in water and insoluble in ethanol.

**EC specifications:** E 332 (ii) Tripotassium citrate [7].
Assay: Not less than 99% of C₆H₇O₇K on the dried basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the dried basis.
In addition the specification includes purity criteria on Loss on drying, pH, Arsenic, Lead, Mercury and Heavy metals (as Pb).

**JECFA specifications:** Tripotassium citrate [3].
Assay: Not less than 99.0% and not more than 101.0% of C₆H₇O₇K on the dried basis.
Oxalates: Not more than 0.04%.
In addition the specification includes purity criteria on Loss on drying, Arsenic and Heavy metals (as Pb).

**Monosodium citrate**
**Definition:** It is a sodium salt of citric acid. It is freely soluble in water and practically insoluble in ethanol.

**EC specifications:** E 331 (i) Monosodium citrate [7].
Assay: Not less than 99% of C₆H₇O₇Na on the dried basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the dried basis.
In addition the specification includes purity criteria on Loss on drying, pH, Arsenic, Lead, Mercury and Heavy metals (as Pb).

**JECFA specifications:** Sodium dihydrogen citrate [5].
Assay: Not less than 99.0% and not more than 101.0% of C₆H₆O₇Na2. Oxalates: Passes test.
In addition the specification includes purity criteria on Loss on drying, Arsenic and Heavy metals (as Pb).

**Disodium citrate**
**Definition:** Disodium citrate is a sodium salt of citric acid.

**EC specifications:** E 331 (ii) Disodium citrate [7].
Assay: Not less than 99% of C₆H₇O₇Na₂ on the dried basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the dried basis.
In addition the specification includes purity criteria on Loss on drying, pH, Arsenic, Lead, Mercury and Heavy metals (as Pb).

**JECFA specifications:** No JECFA specifications have been prepared.

**Trisodium citrate**
**Definition:** It is a sodium salt of citric acid. It is freely soluble in water and practically insoluble in ethanol. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 331 (iii) Trisodium citrate [7].
Assay: Not less than 99% of C₆H₅O₇Na₃ on the dried basis.
Oxalates: Not more than 100 mg/kg expressed as oxalic acid on the dried basis.
In addition the specification includes purity criteria on Loss on drying, pH, Arsenic, Lead, Mercury and Heavy metals (as Pb).

**JECFA specifications:** Trisodium citrate [3].
Assay: Not less than 99.0% of C₆H₅O₇Na₃ on the dried basis.
Oxalates: Passes test.
In addition the specification includes purity criteria on Loss on drying, Alkalinity, Arsenic, Lead, and Heavy metals (as Pb).

**Triammonium citrate**
**Definition:** It is an ammonium salt of citric acid. It is freely soluble in water.

**EC specifications:** E 380 Triammonium citrate [9].
Assay: Not less than 97.0% of C₆H₁₇N₃O₇.
Oxalates: Not more than 0.04% as oxalic acid.
In addition the specification includes purity criteria on arsenic, lead and mercury.

**JECFA specifications:** Triammonium citrate [4].
Assay: Not less than 97.0% of C₆H₁₇N₃O₇.
Oxalates: Not more than 0.04%.
In addition the specification includes purity criteria on arsenic, lead and Heavy metals (as Pb).

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substances were for that reason not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1990, ADI not specified because these substances are normal constituents of the diet and their metabolism is well described [2].

**JECFA status:** Latest evaluation of citric acid, triammonium citrate and calcium citrates 1973: Due to the fact that these substances are natural constituents of the diet and the intake from food additives is likely to be insignificant compared to the intake from natural sources there is no need for specific toxicity data [1].
**Conclusion:** These substances are intermediate metabolites and normal constituents of food. Although few data exist on the toxicology of citric acid and its salts there is no need for further testing or for a re-evaluation of these compounds, since intake as additives are low compared to intake from natural sources.

**References:**

1. [1973, NMRS 53/TRS 539-JECFA 17]


TARTARIC ACID, MONOSODIUM TARTRATE, DISODIUM TARTRATE, MONOPOTASSIUM TARTRATE, DIPOTASSIUM TARTRATE, SODIUM POTASSIUM TARTRATE AND CALCIUM TARTRATE

**E Number:**

<table>
<thead>
<tr>
<th>Name</th>
<th>E Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tartaric acid</td>
<td>334</td>
</tr>
<tr>
<td>Sodium tartrates</td>
<td>335 (i)</td>
</tr>
<tr>
<td>Potassium tartrates</td>
<td>336 (i)</td>
</tr>
<tr>
<td>Sodium potassium tartrate</td>
<td>337</td>
</tr>
<tr>
<td>Calcium tartrate</td>
<td>354</td>
</tr>
</tbody>
</table>

**Recommendation:** A re-evaluation is not needed if exposure is below ADI. More detailed exposure estimates (Tier 3) should be performed to make sure of this.

**Name:** L-(-)-Tartaric acid, monosodium tartrate, disodium tartrate, monopotassium tartrate, dipotassium tartrate, potassium sodium tartrate and calcium tartrate.

**E number:**

<table>
<thead>
<tr>
<th>Name</th>
<th>E Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-(+)-Tartric acid</td>
<td>E 334</td>
</tr>
<tr>
<td>Monosodium tartrate</td>
<td>E 335 (i)</td>
</tr>
<tr>
<td>Disodium tartrate</td>
<td>E 335 (ii)</td>
</tr>
<tr>
<td>Monopotassium tartrate</td>
<td>E 336 (i)</td>
</tr>
<tr>
<td>Dipotassium tartrate</td>
<td>E 336 (ii)</td>
</tr>
<tr>
<td>Potassium sodium tartrate</td>
<td>E 337</td>
</tr>
<tr>
<td>Calcium tartrate</td>
<td>E 354</td>
</tr>
</tbody>
</table>

**Chemical name/synonyms:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-(+)-Tartric acid</td>
<td>L-Tartaric acid, L-2,3-dihydroxybutanedioic acid, d-α,β-dihydroxysuccinic acid.</td>
</tr>
<tr>
<td>Monosodium tartrate</td>
<td>Monosodium salt of L-2,3-dihydroxybutanedioic acid, monohydrated monosodium salt of L-(+)-tartaric acid/ monosodium salt of L-(-)-tartaric acid.</td>
</tr>
<tr>
<td>Disodium tartrate</td>
<td>Disodium L-tartrate, disodium salt of (+)-tartrate, disodium (+)-2,3-dihydroxybutanedioic acid, dihydrated disodium salt of L-(+)-tartaric acid.</td>
</tr>
<tr>
<td>Monopotassium tartrate</td>
<td>Monopotassium salt of L-2,3-dihydroxybutanedioic acid, anhydrous monopotassium salt of L-(+)-tartaric acid/ monopotassium salt of L-(+)-tartaric acid.</td>
</tr>
<tr>
<td>Dipotassium tartrate</td>
<td>Dipotassium salt of (+)-2,3-dihydroxybutanedioic acid, dipotassium salt with half molecule of water of L-(+)-tartaric acid/ dibasic potassium tartrate.</td>
</tr>
<tr>
<td>Potassium sodium tartrate</td>
<td>Potassium sodium salt of L-2,3-dihydroxybutanedioic acid, potassium sodium salt of L-(+)-tartaric acid/potassium sodium L-(+)-tartrate, Rechelle salt, Seignette salt.</td>
</tr>
<tr>
<td>Calcium tartrate</td>
<td>Calcium L(+)2,3-dihydroxy butanedioic acid dihydrate/ L-Calcium tartrate.</td>
</tr>
</tbody>
</table>
**Chemical formula:**

<table>
<thead>
<tr>
<th></th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>L(+) - Tartaric acid</td>
<td>C₄H₆O₆</td>
</tr>
<tr>
<td>Monosodium tartrate</td>
<td>C₄H₆O₆Na⋅H₂O</td>
</tr>
<tr>
<td>Disodium tartrate</td>
<td>C₄H₆O₆Na₂⋅2H₂O</td>
</tr>
<tr>
<td>Monopotassium tartrate</td>
<td>C₄H₆O₆K</td>
</tr>
<tr>
<td>Dipotassium tartrate</td>
<td>C₄H₆O₆K₂⋅½H₂O</td>
</tr>
<tr>
<td>Potassium sodium tartrate</td>
<td>C₄H₆O₆KNa⋅4H₂O</td>
</tr>
<tr>
<td>Calcium tartrate</td>
<td>C₄H₆O₆Ca⋅2H₂O</td>
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**EINECS number:**

<table>
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<tbody>
<tr>
<td>L(+) - Tartaric acid</td>
<td>201-766-0</td>
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<td>Monosodium tartrate</td>
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<tr>
<td>Disodium tartrate</td>
<td>212-773-3</td>
</tr>
<tr>
<td>Monopotassium tartrate</td>
<td>-</td>
</tr>
<tr>
<td>Dipotassium tartrate</td>
<td>213-067-8</td>
</tr>
<tr>
<td>Potassium sodium tartrate</td>
<td>206-156-8</td>
</tr>
<tr>
<td>Calcium tartrate</td>
<td>-</td>
</tr>
</tbody>
</table>

**CAS number:**

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>L(+) - Tartaric acid</td>
<td>87-69-4</td>
</tr>
<tr>
<td>Monosodium tartrate</td>
<td>6131-98-2</td>
</tr>
<tr>
<td>Disodium tartrate</td>
<td>868-18-8</td>
</tr>
<tr>
<td>Monopotassium tartrate</td>
<td>868-14-4</td>
</tr>
<tr>
<td>Dipotassium tartrate</td>
<td>921-53-9</td>
</tr>
<tr>
<td>Potassium sodium tartrate</td>
<td>304-59-6</td>
</tr>
<tr>
<td>Calcium tartrate</td>
<td>-</td>
</tr>
</tbody>
</table>

**Functional Class:** Antioxidant synergist, acidulant (tartaric acid), buffer, sequestrant.

**Specification:**

**Manufacture:** No information on manufacturing processes of food grade tartaric acid.

**L(+) - Tartaric acid**

**Definition:** L(+)-Tartaric acid is naturally occurring organic acid. It is very soluble in water and freely soluble in ethanol.

**EC specifications:** E 334 L(+) - Tartaric acid [7].

Assay: Not less than 99.5% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Sulphated ash, Specific optical rotation, Oxalates, Lead, Mercury and Heavy metals.

**JEFCFA specifications:** L(+) - Tartaric acid [5].

Assay: Not less than 99.5% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Sulphated ash, Specific optical rotation, Sulfate and lead.
**Monosodium tartrate**

**Definition:** Monosodium tartrate is the monosodium salt of L-tartaric acid.

**EC specifications:** E 335 (i) Monosodium tartrate [7].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Oxalates, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

**Disodium tartrate**

**Definition:** Disodium tartrate is the disodium salt of L-tartaric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 335 (ii) Disodium tartrate [7].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Oxalates, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium L-(+)-tartrate [6].
Assay: Not less than 99.5% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, pH, Oxalate, Arsenic, Lead and Heavy metals.

**Monopotassium tartrate**

**Definition:** Monopotassium tartrate is the monopotassium salt of L-tartaric acid.

**EC specifications:** E 336 (i) Monopotassium tartrate [7].
Assay: Not less than 98% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, pH, Oxalates, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

**Dipotassium tartrate**

**Definition:** Dipotassium tartrate is the dipotassium salt of L-tartaric acid.

**EC specifications:** E 336 (ii) Dipotassium tartrate [7].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, pH, Oxalates, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.
**Potassium sodium tartrate**

**Definition:** Potassium sodium tartrate is the potassium and sodium salt of L-tartaric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 337 Potassium sodium tartrate [7].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, pH, Oxalates, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Potassium sodium tartrate [6].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, pH, Oxalates, Arsenic, Lead, Mercury and Heavy metals.

**Calcium tartrate**

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** Tartaric acid and its salts have been allocated a numerical group ADI. The directive allows for use of these substances by *quantum satis*. In the EU monitoring system the substances were moved to tier 3, as they cannot be examined at tier 1 and 2.

**SCF/JECFA:**

**SCF status:** Latest evaluation 1990, Group ADI 30 mg/kg bw for the L(+) tartrate. The DL-form is not acceptable due to insufficient data [4]. The ADI is based on the JECFA evaluation.

**JECFA status:** Latest evaluation for tartaric acid and sodium tartrate 1977 [2], for potassium tartrate and sodium potassium tartrate 1973 [1], group ADI 30 mg/kg bw expressed as tartaric acid.
This is based on the long-term study mentioned below, the metabolic inertness of the tartrates and the fact that they are normal constituents in food.

**BACKGROUND DATA:**

**Subacute/subchronic toxicity:** Studies with very few animals exist. No adverse effects were seen with doses below 1000 mg/kg bw [3].

**Genotoxicity:** No data available.

**Chronic toxicity/carcinogenicity:** No adverse effects were seen in a study where groups of 24 rats were feed diets containing up to 1.2% tartaric acid for two years [3].

**Reproduction toxicity:** No data available.

**Effect in humans:** Sodium tartrate in daily doses of up to 10 g or even 20 g has been used in medical practice as a laxative without any undesirable effects [3].
**Conclusion:** Although data are sparse there is no reason to expect these additives will cause any safety problems if the ADI is not exceeded. Tartaric acid and its salts as defined by the specifications are covered by the toxicological evaluation. Some of the JECFA specifications are old. It is therefore suggested to revise the specifications for this group of substances at a future JECFA meeting.

**References:**


**PHOSPHORIC ACID AND PHOSPHATES**

**E number:**

<table>
<thead>
<tr>
<th>Substance</th>
<th>E Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphoric acid</td>
<td>E 338</td>
</tr>
<tr>
<td>Monosodium phosphate</td>
<td>E 339 (i)</td>
</tr>
<tr>
<td>Disodium phosphate</td>
<td>E 339 (ii)</td>
</tr>
<tr>
<td>Trisodium phosphate</td>
<td>E 339 (iii)</td>
</tr>
<tr>
<td>Monopotassium phosphate</td>
<td>E 340 (i)</td>
</tr>
<tr>
<td>Dipotassium phosphate</td>
<td>E 340 (ii)</td>
</tr>
<tr>
<td>Tripotassium phosphate</td>
<td>E 340 (iii)</td>
</tr>
<tr>
<td>Monocalcium phosphate</td>
<td>E 341 (i)</td>
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<tr>
<td>Dicalcium phosphate</td>
<td>E 341 (ii)</td>
</tr>
<tr>
<td>Tricalcium phosphate</td>
<td>E 341 (iii)</td>
</tr>
<tr>
<td>Monomagnesium phosphate</td>
<td>E 343 (i)</td>
</tr>
<tr>
<td>Dimagnesium phosphate</td>
<td>E 343 (ii)</td>
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<tr>
<td>Disodium diphosphate</td>
<td>E 450 (i)</td>
</tr>
<tr>
<td>Trisodium diphosphate</td>
<td>E 450 (ii)</td>
</tr>
<tr>
<td>Tetrasodium diphosphate</td>
<td>E 450 (iii)</td>
</tr>
<tr>
<td>Tetrapotassium diphosphate</td>
<td>E 450 (v)</td>
</tr>
<tr>
<td>Dicalcium diphosphate</td>
<td>E 450 (vi)</td>
</tr>
<tr>
<td>Calcium dihydrogen diphosphate</td>
<td>E 450 (vii)</td>
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<tr>
<td>Pentasodium triphosphate</td>
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<td>Sodium polyphosphates</td>
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<tr>
<td>Sodium calcium polyphosphates</td>
<td>E 452 (iii)</td>
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<tr>
<td>Calcium polyphosphates</td>
<td>E 452 (iv)</td>
</tr>
</tbody>
</table>

**Recommendation:** No need for a toxicological re-evaluation. However, the possibility that the MTDI of 70 mg/kg bw from all sources is exceeded should be taken into consideration.

**Chemical name/synonyms:**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphoric acid</td>
<td>Phosphoric acid/ orthophosphoric acid, monophosphoric acid.</td>
</tr>
<tr>
<td>Monosodium phosphate</td>
<td>Sodium dihydrogen monophosphate/ monosodium monophosphate, acid monosodium monophosphate, monosodium orthophosphate, monobasic sodium phosphate.</td>
</tr>
<tr>
<td>Disodium phosphate</td>
<td>Disodium hydrogen monophosphate, disodium hydrogen orthophosphate/ disodium monophosphate, secondary sodium phosphate, disodium orthophosphate, acid disodium phosphate.</td>
</tr>
<tr>
<td>Trisodium phosphate</td>
<td>Trisodium monophosphate, trisodium phosphate / sodium phosphate, tribasic sodium phosphate, trisodium orthophosphate.</td>
</tr>
<tr>
<td>Monopotassium phosphate</td>
<td>Potassium dihydrogen phosphate, monopotassium dihydrogen orthophosphate, monopotassium dihydrogen monophosphate/ monobasic potassium phosphate, monopotassium monophosphate, potassium acid phosphate, potassium orthophosphate.</td>
</tr>
</tbody>
</table>

Tripotassium phosphate: Tripotassium monophosphate, tripotassium phosphate, tripotassium orthophosphate/ potassium phosphate, tribasic potassium phosphate.

Monocalcium phosphate: Calcium dihydrogen phosphate/ monobasic calcium phosphate, monocalcium ortho phosphate.

Dicalcium phosphate: Calcium monohydrogen phosphate, Calcium hydrogen orthophosphate, secondary calcium phosphate/ dibasic calcium phosphate, dicalcium orthophosphate.

Tricalcium phosphate: Tricalcium monophosphate/ tribasic calcium phosphate, calcium orthophosphate.

Monomagnesium phosphate: Monomagnesium dihydrogen monophosphate/ magnesium dihydrogen phosphate, monobasic magnesium phosphate, monomagnesium orthophosphate.


Disodium diphosphate: Disodium dihydrogen diphosphate/ disodium dihydrogen pyrophosphate, sodium acid pyrophosphate.

Trisodium diphosphate: Acid trisodium pyrophosphate, trisodium monohydrogen diphosphate.

Tetrasodium diphosphate: Tetrasodium diphosphate/ tetrasodium pyrophosphate, sodium pyrophosphate.

Tetrapotassium diphosphate: Tetrapotassium diphosphate, potassium pyrophosphate, tetrapotassium pyrophosphate.

Dicalcium diphosphate: Dicalcium diphosphate, dicalcium pyrophosphate/ calcium pyrophosphate.

Calcium dihydrogen diphosphate: Calcium dihydrogen diphosphate/ acid calcium pyrophosphate, monocalcium dihydrogen pyrophosphate.

Pentasodium triphosphate: Pentasodium triphosphate/ pentasodium tripolyphosphate, sodium tripolyphosphate.

Pentapotassium triphosphate: Pentapotassium triphosphate, pentapotassium tripolyphosphate/ potassium tripolyphosphate.

Sodium polyphosphates: Sodium polyphosphate/ soluble polyphosphate: sodium hexametaphosphate, sodium tetrapolyphosphate, Graham's salt, sodium polyphosphates, glassy, sodium polymetaphosphate, sodium metaphosphate; insoluble polyphosphate: insoluble sodium metaphosphate, Maddrell's salt, insoluble sodium polyphosphate, IMP.

Potassium polyphosphates: Potassium polyphosphate/ potassium metaphosphate, potassium metapolyphosphate, Korrol salt.

Sodium calcium polyphosphates: Sodium calcium polyphosphate/ sodium calcium polyphosphate, glassy.
Calcium polyphosphates: Calcium polyphosphate/ calcium metaphosphate, calcium polymetaphosphate.

**Chemical formula:**

Phosphoric acid: $\text{H}_3\text{PO}_4$
Monosodium phosphate: $\text{NaH}_2\text{PO}_4 \cdot n\text{H}_2\text{O}$ ($n = 0, 1$ or $2$)
Disodium phosphate: $\text{Na}_2\text{HPO}_4 \cdot n\text{H}_2\text{O}$ ($n = 0, 2, 7$ or $12$)
Trisodium phosphate: $\text{Na}_3\text{PO}_4 \cdot n\text{H}_2\text{O}$ ($n = 0, 0.5, 1$, or $12$)
Monopotassium phosphate: $\text{KH}_2\text{PO}_4$
Dipotassium phosphate: $\text{K}_2\text{HPO}_4$
Tripotassium phosphate: $\text{K}_3\text{PO}_4 \cdot n\text{H}_2\text{O}$ ($n = 0, 1$, or $3$)
Monocalcium phosphate: $\text{Ca(H}_2\text{PO}_4) \cdot n\text{H}_2\text{O}$ ($n = 0$ or $1$)
Dicalcium phosphate: $\text{CaHPO}_4 \cdot n\text{H}_2\text{O}$ ($n = 0$ or $2$)
Tricalcium phosphate: $\text{Ca}_3(\text{H}_2\text{PO}_4)_2$
Monomagnesium phosphate: $\text{Mg}(\text{H}_2\text{PO}_4)_2 \cdot n\text{H}_2\text{O}$ ($n = 0$ to $4$)
Dimagnesium phosphate: $\text{MgHPO}_4 \cdot n\text{H}_2\text{O}$ ($n = 0$ to $3$)
Disodium diphosphate: $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$
Trisodium diphosphate: $\text{Na}_3\text{HP}_2\text{O}_7 \cdot n\text{H}_2\text{O}$ ($n = 0$ or $1$)
Tetrasodium diphosphate: $\text{Na}_4\text{P}_2\text{O}_7 \cdot n\text{H}_2\text{O}$ ($n = 0$ or $10$)
Dicalcium diphosphate: $\text{Ca}_2\text{P}_2\text{O}_7$
Calcium dihydrogen diphosphate: $\text{CaH}_2\text{P}_2\text{O}_7$
Pentasodium triphosphate: $\text{Na}_5\text{P}_3\text{O}_{10} \cdot n\text{H}_2\text{O}$ ($n = 0$ or $6$)
Pentapotassium triphosphate: $\text{K}_5\text{P}_3\text{O}_{10}$
Sodium polyphosphates: -
Potassium polyphosphates: -
Sodium calcium polyphosphates: -
Calcium polyphosphates: -

**EINECS number:**

Phosphoric acid: 231-633-2
Monosodium phosphate: 231-449-2
Disodium phosphate: 231-448-7
Trisodium phosphate: 231-509-8
Monopotassium phosphate: 231-913-4
Dipotassium phosphate: 231-834-5
Tripotassium phosphate: 231-907-1
Monocalcium phosphate: 231-837-1
Dicalcium phosphate: 231-826-1
Tricalcium phosphate: 231-840-8
Monomagnesium phosphate: 236-004-6
Dimagnesium phosphate: 231-823-5
Disodium diphosphate: 231-835-0
Trisodium diphosphate: 238-735-6
Tetrasodium diphosphate: 231-767-1
Tetrapotassium diphosphate: 230-785-7
Dicalcium diphosphate: 232-221-5
Calculated dihydrogen diphosphate: 238-933-2
Pentasodium triphosphate: 231-838-7
Pentapotassium triphosphate: 237-574-9
Sodium polyphosphates: 272-808-3
Potassium polyphosphates: 232-212-6
Sodium calcium polyphosphates: 233-782-9
Calcium polyphosphates: 236-769-6

**CAS number:**
Phosphoric acid: 7664-38-2
Monosodium phosphate: 7558-80-7
Disodium phosphate: 7558-79-4
Trisodium phosphate: 7601-54-9
Monopotassium phosphate: 7778-77-0
Dipotassium phosphate: 7758-11-4
Tripotassium phosphate: 7778-53-2
Monocalcium phosphate: 7758-23-8 (anhydrous) 10031-30-8 (monohydrate)
Dicalcium phosphate: 7757-93-9
Tricalcium phosphate: -
Monomagnesium phosphate: -
Dimagnesium phosphate: 7757-86-0
Disodium diphasophate: 775-81-69
Trisodium dihydrogen phosphate: -
Tetrasodium diphasophate: 7722-88-5
Tetrapotassium diphasophate: 7320-34-5
Dicalcium diphasophate: 35405-51-7
Calcium dihydrogen diphosphate: -
Pentasodium triphosphate: 7758-29-4
Pentapotassium triphosphate: 13845-36-8
Sodium polyphosphates: Soluble polyphosphate: 68915-31-1, 10124-56-8, 10361-03-2;
Insoluble polyphosphates: 50813-16-6
Potassium polyphosphates: 7790-53-6
Sodium calcium polyphosphates: -
Calcium polyphosphates: -

**Functional Class:** Acidity regulator, stabiliser, sequestrant, synergist for antioxidants.

**Specification:**
**Manufacture:** No information on manufacturing processes for food grade phosphoric acid and phosphates.

**Phosphoric acid**
**Definition:** Phosphoric acid is miscible with water and ethanol.

**EC specifications:** E 338 Phosphoric acid [9].
Assay: Not less than 71% and not more than 83%.
The specification includes purity criteria on Volatile acids, Chlorides, Nitrates, Sulphates, Fluoride,
Arsenic, Lead, Mercury and Heavy metals.
**JECFA specifications:** Phosphoric acid [11].
Assay: Not less than 75% and not less than the minimum or within the range of percent claimed by the vendor.
The specification includes purity criteria on Volatile acids, Chlorides, Nitrates, Sulphates, Fluoride, Arsenic, Lead and Heavy metals.

**Monosodium phosphate**
**Definition:** Monosodium phosphate is the monosodium salt of phosphoric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 339 (i) Monosodium phosphate [9].
Assay: Not less than 97% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble substances, Fluoride, pH, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Sodium dihydrogen phosphate [8].
Assay: Not less than 97% on the dried basis.
The specification includes purity criteria on Loss on drying, Free acid and disodium phosphate, Fluoride, Arsenic, Lead and Heavy metals.

**Disodium phosphate**
**Definition:** Disodium phosphate is the disodium salt of phosphoric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 339 (ii) Disodium phosphate [9].
Assay: Not less than 98% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble substances, Fluoride, pH, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Disodium hydrogen phosphate [2].
Assay: Not less than 98.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble substances, Fluoride, Arsenic, Lead and Heavy metals.

**Trisodium phosphate**
**Definition:** Trisodium phosphate is the trisodium salt of phosphoric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 339 (iii) Trisodium phosphate [9].
Assay: Trisodium phosphate anhydrous and also hemi and monohydrates contains not less than 97.0% on the dried basis. Trisodium phosphate dodecahydrate contains not less than 92.0% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Loss on drying, Water-insoluble substances, Fluoride, pH, Arsenic, Lead, Mercury and Heavy metals.
**JECFA specifications:** Trisodium phosphate [2].
Assay: Trisodium phosphate anhydrous and also hemi and monohydrates contains not less than 97.0% on the dried basis. Trisodium phosphate dodecahydrate contains not less than 92.0% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Water-insoluble substances, Fluoride, Arsenic, Lead and Heavy metals.

*Monopotassium phosphate*
**Definition:** Monopotassium phosphate is the monopotassium salt of phosphoric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 340 (i) Monopotassium phosphate [9].
Assay: Not less than 98.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble substances, Fluoride, pH, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Potassium dihydrogen phosphate [2].
Assay: Not less than 98.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble substances, Fluoride, Arsenic, Lead and Heavy metals.

**Dipotassium phosphate**
**Definition:** Dipotassium phosphate is the dipotassium salt of phosphoric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 340 (ii) Dipotassium phosphate [9].
Assay: Not less than 98% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble substances, Fluoride, pH, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Dipotassium hydrogen phosphate [2].
Assay: Not less than 98.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Water-insoluble substances, Fluoride, Arsenic, Lead and Heavy metals.

**Tripotassium phosphate**
**Definition:** Tripotassium phosphate is the tripotassium salt of phosphoric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 340 (iii) Tripotassium phosphate [9].
Assay: Not less than 97% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Water-insoluble substances, Fluoride, pH, Arsenic, Lead, Mercury and Heavy metals.
**JECFA specifications:** Tripotassium phosphate [2].
Assay: Not less than 97.0% on the dried basis.
The specification includes purity criteria on Loss on ignition, Water-insoluble substances, Fluoride, Arsenic, Lead and Heavy metals.

*Monocalcium phosphate*
**Definition:** Monocalcium phosphate is the monocalcium salt of phosphoric acid. It is sparingly soluble in water and insoluble in ethanol.

**EC specifications:** E 341 (i) Monocalcium phosphate [9].
Assay: Not less than 95% on the dried basis.
The specification includes purity criteria on Loss on drying, Loss on ignition, Fluoride, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Calcium dihydrogen phosphate [10].
Assay: Anhydrous: not less than 16.8% and not more than 18.3% of Ca. Monohydrate: not less than 15.9% and not more than 17.7% of Ca.
The specification includes purity criteria on Loss on drying, Loss on ignition, Fluoride, Arsenic, Lead and Heavy metals.

*Dicalcium phosphate*
**Definition:** Dicalcium phosphate is the dicalcium salt of phosphoric acid. It is sparingly soluble in water and insoluble in ethanol.

**EC specifications:** E 341 (ii) Dicalcium phosphate [9].
Assay: Not less than 98% and not more than 102% on the dried basis.
The specification includes purity criteria on Loss on ignition, Fluoride, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Calcium hydrogen phosphate [2].
Assay: Not less than 98% and not more than 102% on the dried basis.
The specification includes purity criteria on Loss on drying, Fluoride, Arsenic, Lead and Heavy metals.

*Tricalcium phosphate*
**Definition:** Tricalcium phosphate is the tricalcium salt of phosphoric acid. It is practically insoluble in water and insoluble in ethanol.

**EC specifications:** E 341 (iii) Tricalcium phosphate [9].
Assay: Not less than 90% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Fluoride, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Tricalcium phosphate [1].
Assay: Not less than 90% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Fluoride, Arsenic, Lead and Heavy metals.

**Monomagnesium phosphate**
**Definition:** Monomagnesium phosphate is the monomagnesium salt of phosphoric acid.

**EC specifications:** E 343 (i) Monomagnesium phosphate [9].
Assay: Not less than 51.0% after ignition.
The specification includes purity criteria on Fluoride, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

**Dimagnesium phosphate**
**Definition:** Dimagnesium phosphate is the dimagnesium salt of phosphoric acid. It is slightly soluble in water and insoluble in ethanol.

**EC specifications:** E 343 (ii) Dimagnesium phosphate [12].
Assay: Not less than 96% after ignition.
The specification includes purity criteria on Fluoride, Arsenic, Lead and Mercury.

**JECFA specifications:** Dimagnesium phosphate [5].
Assay: Not less than 96% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Fluoride, Arsenic, Lead and Heavy metals.

**Disodium diphosphate**
**Definition:** Disodium diphosphate is the disodium salt of diphosphoric acid. It is soluble in water.

**EC specifications:** E 450 (i) Disodium diphosphate [12].
Assay: Not less than 95% of disodium diphosphate and not less than 63% and not more than 64.5% expressed as P₂O₅.
The specification includes purity criteria on pH, Loss on drying, Water-insoluble matter, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Disodium pyrophosphate [2].
Assay: Not less than 95%.
The specification includes purity criteria on Loss on drying, Water-insoluble matter, Fluoride, Arsenic, Lead and Heavy metals.

**Trisodium diphosphate**
**Definition:** Trisodium diphosphate is the trisodium salt of diphosphoric acid.

**EC specifications:** E 450 (ii) Trisodium diphosphate [12].
Assay: Not less than 95% of trisodium diphosphate on the anhydrous and not less than 57% and not more than 59% expressed as P$_2$O$_5$.
The specification includes purity criteria on pH, Loss on ignition, Loss on drying, Water-insoluble matter, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

**Tetrasodium diphosphate**
**Definition:** Tetrasodium diphosphate is the tetrasodium salt of diphosphoric acid. It is soluble in water and insoluble in ethanol.

**EC specifications:** E 450 (iii) Tetrasodium diphosphate [12].
Assay: Not less than 95% of tetrasodium diphosphate on the anhydrous and not less than 52.5% and not more than 54% expressed as P$_2$O$_5$.
The specification includes purity criteria on pH, Loss on ignition, Water-insoluble matter, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Tetrasodium pyrophosphate [21].
Assay: Not less than 95.0% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Water-insoluble matter, Fluoride, Arsenic, Lead and Heavy metals.

**Tetrapotassium diphosphate**
**Definition:** Tetrapotassium diphosphate is the tetrapotassium salt of diphosphoric acid. It is soluble in water and insoluble in ethanol.

**EC specifications:** E 450 (v) Tetrapotassium diphosphate [12].
Assay: Not less than 95% of tetrapotassium diphosphate on the anhydrous and not less than 42% and not more than 43.7% expressed as P$_2$O$_5$.
The specification includes purity criteria on pH, Loss on ignition, Water-insoluble matter, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Tetrapotassium pyrophosphate [7].
Assay: Not less than 95.0% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Water-insoluble matter, Fluoride, Arsenic, Lead and Heavy metals.

**Dicalcium diphosphate**
**Definition:** Dicalcium diphosphate is the dicalcium salt of diphosphoric acid. It is insoluble in water.

**EC specifications:** E 450 (vi) Dicalcium diphosphate [12].
Assay: Not less than 96% on the anhydrous basis and not less than 55% and not more than 56% expressed as P$_2$O$_5$.
The specification includes purity criteria on pH, Loss on ignition, Fluoride, Arsenic, Lead, Mercury,
Cadmium and Heavy metals.

**JECFA specifications:** Dicalcium pyrophosphate [4].
Assay: Not less than 96%.
The specification includes purity criteria on Loss on ignition, Fluoride, Arsenic, Lead and Heavy metals.

*Calcium dihydrogen diphosphate*
**Definition:** Calcium dihydrogen diphosphate is the monocalcium salt of diphosphoric acid.

**EC specifications:** E 450 (vii) Calcium dihydrogen diphosphate [12].
Assay: Not less than 90% on the anhydrous basis and not less than 61% and not more than 64% expressed as $P_2O_5$.
The specification includes purity criteria on Acid-insoluble matter, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

*Pentasodium triphosphate*
**Definition:** Pentasodium triphosphate is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 451 (i) Pentasodium triphosphate [12].
Assay: Not less than 85% on the anhydrous basis and not less than 56% and not more than 58% expressed as $P_2O_5$ (anhydrous) or not less than 56% and not more than 58% expressed as $P_2O_5$ (hexahydrate).
The specification includes purity criteria on Loss on drying, Water-insoluble matter, Higher polyphosphates, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Pentasodium triphosphate [22].
Assay: Not less than 85% on the anhydrous basis and not less than 56% and not more than 58% expressed as $P_2O_5$ (anhydrous).
The specification includes purity criteria on Loss on drying, Water-insoluble matter, Higher polyphosphates, Fluoride, Arsenic, Lead and Heavy metals.

*Pentapotassium triphosphate*
**Definition:** Pentapotassium triphosphate is very soluble in water.

**EC specifications:** E 451 (ii) Pentapotassium triphosphate [12].
Assay: Not less than 85% on the anhydrous basis and not less than 46.5% and not more than 48% expressed as $P_2O_5$.
The specification includes purity criteria on Loss on ignition, Water-insoluble matter, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Pentasodium triphosphate [6].
Phosphoric acid and phosphates

Assay: Not less than 85%, the remainder being principally other potassium phosphates. The specification includes purity criteria on Loss on ignition, Water-insoluble matter, P₂O₅-content, Fluoride, Arsenic and Heavy metals.

**Sodium polyphosphates - Soluble polyphosphate**

**Manufacture:** Sodium polyphosphates - Soluble polyphosphate is obtained by fusion and subsequent chilling of sodium orthophosphates.

**Definition:** Sodium polyphosphates - Soluble polyphosphate is a heterogeneous mixture of sodium salts of linear condensed polyphosphoric acids of general formula Hₙ₋₂PₙO₃n₊₁, where n is not less than 2. It is very soluble in water.

**EC specifications:** E 452 (i) Sodium polyphosphates - 1. Soluble polyphosphate [12]. Assay: Not less than 60% and not more than 71% expressed as P₂O₅. The specification includes purity criteria on Loss on ignition, Water-insoluble matter, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Sodium polyphosphates, glassy [10]. Assay: Not less than 60% and not more than 71% expressed as P₂O₅. The specification includes purity criteria on Loss on ignition, Water-insoluble matter, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**Sodium polyphosphates - Insoluble polyphosphates**

**Definition:** Sodium polyphosphates - Insoluble polyphosphate is a high molecular weight sodium polyphosphate composed of two long metaphosphate chains (NaPO₃)ₓ that spiral in opposite directions about a common axis. The Na₂O/P₂O₅ is about 1.0. The pH of 1 in 3 suspension is about 6.5. It is insoluble in water.

**EC specifications:** E 452 (i) Sodium polyphosphates - 2. Insoluble polyphosphate [12]. Assay: Not less than 68.7% and not more than 70% expressed as P₂O₅. The specification includes purity criteria on Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Sodium metaphosphates, insoluble [10]. Assay: Not less than 68.7% and not more than 70% expressed as P₂O₅. The specification includes purity criteria on Fluoride, Arsenic and Heavy metals.

**Potassium polyphosphates**

**Definition:** Potassium polyphosphates is a heterogeneous mixture of potassium salts of linear condensed polyphosphoric acids of general formula Hₙ₋₂PₙO₃n₊₁, where n is not less than 2.

**EC specifications:** E 452 (ii) Potassium polyphosphates [12]. Assay: Not less than 60% and not more than 71% expressed as P₂O₅ on the ignited basis. The specification includes purity criteria on Loss on ignition, Water-insoluble matter, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.
**JECFA specifications:** Potassium polyphosphates [5].

Assay: Not less than 53.5% and not more than 61.5% expressed as P$_2$O$_5$ on the ignited basis.

The specification includes purity criteria on Loss on ignition, Cyclic phosphate, Fluoride, Arsenic, Lead and Heavy metals.

**Sodium calcium polyphosphates**

**Definition:** Sodium calcium polyphosphates is a heterogeneous mixture of potassium and calcium salts of polyphosphoric acids.

**EC specifications:** E 452 (iii) Sodium calcium polyphosphates [12].

Assay: Not less than 61% and not more than 69% expressed as P$_2$O$_5$.

The specification includes purity criteria on Fluoride, Arsenic, Lead, Mercury and Cadmium.

**JECFA specifications:** No JECFA specification has been prepared.

**Calcium polyphosphates**

**Definition:** Calcium polyphosphates is a heterogeneous mixture of potassium salts of linear condensed polyphosphoric acids of general formula H$_{n+2}$P$_n$O$_{3n+1}$, where n is not less than 2.

**EC specifications:** E 452 (iv) Calcium polyphosphates [12].

Assay: Not less than 50% and not more than 71% expressed as P$_2$O$_5$ on the ignited basis.

The specification includes purity criteria on Loss on ignition, Cyclic phosphate, Fluoride, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Calcium polyphosphates [5].

Assay: Not less than 50.0% and not more than 71.0% expressed as P$_2$O$_5$ on the ignited basis.

The specification includes purity criteria on Loss on ignition, Cyclic phosphate, Fluoride, Arsenic, Lead and Heavy metals.

**Exposure:** Phosphates are permitted in a wide variety of foods in amounts from 1-20 g/kg. Permitted in some beverages up to 2 g/l. In vegetable protein drinks up to 20 g/l. expressed as P$_2$O$_5$.

In the EU monitoring system the substances were examined at tier 1. The calculated intake for adults does not exceed the ADI while the calculated intake for young children exceeded the ADI. In tier 2 the calculated intake by young children is reported in the range of 53 - 172%. Examination at tier 3 of the intake by young children is needed.

From the report it appears that intake calculation has only included intake of phosphate from additive use while the ADI is including all sources. It is therefore recommended that also adults are included in tier 3 and that natural sources of phosphates are included in this step.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990, MTDI 70 mg/kg bw expressed as phosphorus and including phosphate from natural sources [16]. The evaluation is based on JECFA.

**JECFA status:** Latest evaluation 1982. The maximum tolerable daily intake allocated was 70 mg/kg of body weight (expressed as phosphorus), which applies to the sum of phosphates and
polyphosphates naturally present in food and those used as additives. This figure applies to diets that are nutritionally adequate in respect of calcium. However, if the calcium intake were abnormally high, the intake of phosphates could be proportionately higher than that stated above, and the reverse relationships would also apply. The evaluation by is based on the lowest dose, which has produced nephrocalcinosis in rat. This dose is 1% P in the diet, which has been extrapolated, based on a daily intake of 2800 calories, to 6600 mg P per day as the best estimate of the lowest level that might cause nephrocalcinosis in man. The use of a safety factor was not considered suitable because phosphorous is also a nutrient [14].

BACKGROUND DATA:

Subacute/subchronic toxicity: Calcification of soft tissues has been studied in short-term studies. Many studies have been performed in order to establish a threshold for this effect but a conclusion has not been reached. This is partly because even healthy rats on a diet to which no phosphate has been added may have some small area of renal calcification, and partly because the adverse effect of phosphate are dependent of the diets content of calcium and the acidity of the food mixture as a whole [15]. The lowest dose reported to produce nephrocalcinosis in rat is 1% in the diet, this is the base for the JECFA evaluation [15]. Studies in rat indicate that nephrocalcinosis is irreversible within at least 90 days [17].

Genotoxicity: In vitro: Monocalcium phosphate, monosodium phosphates, sodium acid pyrophosphate tetrasodium pyrophosphates, sodium tripolyphosphate and sodium hexameta phosphate were tested and none of them were mutagenic with or without metabolic activation [15]. In vivo: Sodium tripolyphosphate was not mutagenic in rat bone marrow cells [15].

Chronic toxicity/carcinogenicity: No animal studies indicate any carcinogenic effects [15].

Reproduction studies: No maternal toxicity or teratogenic effects were seen in studies using rats, mice, hamsters and rabbits [15].

Effects in human: The major adverse effect of phosphate is phosphate-calcium-magnesium imbalance. High plasma levels of phosphates are regulated down on the expense of calcium. This could lead to bone resorption and calcification of soft tissues [15]. Many studies have been performed to establish a threshold dose for these effects but without success [15]. Although an optimal calcium-phosphate ratio has not been determined from animal studies FDA recommend it to be 1 [13].

There exist short time intervention studies on human. Intake of 2-4 g of phosphoric acid for 10 days revealed no observable change in urine composition [15].

The role of dietary phosphate and osteoporosis is not clear. In a recent study in young men there was no effect on bone turnover when 22 men ages 19-38 were give food supplemented with up to 2000 mg/d of phosphate for 2 weeks [20]. On the other hand there seem to be a connection between the intake of soft drinks containing phosphates and the rate of bone fracture in girls [19]. High dietary phosphate has an effect on the calcium-regulating hormones [13]. The consequences could be that adolescent do not optimise their peak bone masses, and thereby they could bee more sensitive to osteoporosis when they get older [13].
Conclusion: It is difficult to estimate a NOEL for the intake of phosphorous because it depends on the calcium intake. It is not possible to draw firm conclusions from the human studies concerning adverse effects of a high phosphorous intake, but the MTDI of 70 mg/kg bw from all sources seem a reasonable figure. As the EU monitoring system does not include natural sources of phosphate and suggest that the MTDI may be exceeded for young and adolescents from food additive uses, it is recommended to perform more detailed exposure studies including natural sources. Data from US indicate that the intake of phosphates in general is well below the tolerable upper intake level.

Phosphoric acid and the phosphates as defined by the specifications are covered by the toxicological evaluation. The JECFA specifications have been prepared at several different JECFA meetings and most of the specifications are old. It is therefore suggested to revise the specifications for this group of substances at a future JECFA meeting.

References:


14. [1982, TRS 683-JECFA 26]

15. [1982, FAS 17-JECFA 26]


SODIUM MALATES, POTASSIUM MALATE AND CALCIUM MALATES

E Number: E 350-352

See: E 296 Malic acid and malates.
**METATARTARIC ACID**

**E number:** E 353

**Recommendation:** It should be investigated to what extent the substance is actually being used. If used in any significant amount further data should be requested and an evaluation performed.

**Chemical name/synonyms:** Metatartaric acid/ ditartaric acid

**Chemical formula:** C₄H₆O₆

**EINECS number:** -

**CAS number:** -

**Functional Class:** Acidity regulator.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade metatartaric acid.

**Definition:** -

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** Metatartaric acid is only permitted in wine in levels up to 100 mg/l. As this level was accepted by SCF [1] the substance was not included in the EU monitoring system (Tier 0).

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990, No ADI allocated. However, the continued use in wine up to 100 mg/l was considered acceptable [1].

**JECFA status:** Not evaluated.

**BACKGROUND DATA:**

**Subacute/subchronic toxicity:** 15 male 15 female rats were given *ad libitum* drinking water containing 0, 0.1, 0.5 or 3.0% metatartaric acid for 18 week. The intake of food and water were decreased in the treated groups. The major findings were related to organ weights but all effects could be caused by the decrease in water and food intake although the authors could not exclude any treatment related effects on the kidney [2].

**Genotoxicity:** No data available.

**Chronic toxicity/carcinogenicity:** No data available.
Reproduction toxicity: No data available.

Other: Investigation on the stability of metatartaric acid showed that only little hydrolyses to tartaric acid in a 3% aquatic solution during an 8 hours period [2].

Conclusion: The substantial lack of data makes it impossible to make a toxicological evaluation. No information on whether it is actually used.

References:


CALCIUM TARTRATE

E Number: E 354

See: E 334 Tartaric acid and tartrates.
ADIPIC ACID, SODIUM ADIPATE AND POTASSIUM ADIPATE

E number:
Adipic acid: E 355
Sodium adipate: E 356
Potassium adipate: E 357

Recommendation: No need for a re-evaluation. Clarification of use levels in powders for homemade drinks.

Chemical name/synonyms:
Adipic acid: Hexanedioic acid, 1,4-butanedicarboxylic acid.
Sodium adipate: Sodium adipate.
Potassium adipate: Potassium adipate.

Chemical formula:
Adipic acid: C₆H₁₀O₄
Sodium adipate: C₆H₈Na₂O₄
Potassium adipate: C₆H₈K₂O₄

EINECS number:
Adipic acid: 204-673-3
Sodium adipate: 231-293-5
Potassium adipate: 242-838-1

CAS number:
Adipic acid: 124-04-9
Sodium adipate: 7486-38-6
Potassium adipate: -

Functional Class: Acidity regulator.

Specification:
Manufacture: No information on manufacturing processes for food grade adipic acid and its salts.

Adipic acid

Definition: Adipic acid is a naturally occurring organic acid. It is slightly soluble in water and freely soluble in ethanol.

EC specifications: E 355 Adipic acid [2].
Assay: Not less than 99.6%.
The specification includes purity criteria on Water, Sulphated ash, Arsenic, Lead and Mercury.

JECFA specifications: Adipic acid [1].
Assay: Not less than 99.6%.
The specification includes purity criteria on Water, Sulfated ash, and Lead.
Sodium adipate
Definition: Sodium adipate is the sodium salt of adipic acid. It is freely soluble in water.

EC specifications: An EC specification is currently in preparation.

JECFA specifications: No JECFA specification has been prepared.

Potassium adipate
Definition: Potassium adipate is the potassium salt of adipic acid. It is freely soluble in water.

EC specifications: An EC specification is currently in preparation.

JECFA specifications: No JECFA specification has been prepared.

Exposure: The use of adipic acid and the adipates is restricted to fillings and toppings for fine bakery wares: 2 g/kg. Dry powdered dessert mixes: 1 g/kg. Gel-like desserts: 6 g/kg. Fruit-flavoured desserts: 1 g/kg. In powders for home preparation of drinks the limit is 10 g/litre. All figures expressed as adipic acid

In the EU monitoring system tier 1 indicated a possible exceeding of the ADI. In the subsequent examination at tier 2 the calculated intake by adults and the whole population is reported in the range of 2 - 20% of ADI. The calculated intake by young children is reported in the range of 3 - 7%. The investigators concluded that no further examination is needed at this stage. However, if the limit for powders for home preparation of drinks is expressed as ready to drink beverage, the ADI could be reached by consuming just 30 ml.

SCF/JECFA evaluation:
SCF status: Latest evaluation 1990. ADI = 5 mg/kg bw [5] based on JECFA.

JECFA status: Latest evaluation 1977. ADI = 5 mg/kg bw based on metabolic studies, acute, short-term and long-term toxicity studies [3].

BACKGROUND DATA:
Subacute/subchronic toxicity: No adverse effects were seen in a study where rats were given up to 800 mg/day for 35 weeks. [4].

Genotoxicity: No adverse effects were seen in vitro or in vivo with or without metabolic activation [4].

Chronic toxicity/carcinogenicity: No adverse effects were seen in rats given food containing up to 5% adipic acid for 2 years [4].

Reproduction toxicity: No compound related embryotoxic or teratogenic effects were seen in mice, rats, hamsters and rabbits given up to between 205 mg/kg bw and 288 mg/kg bw [4].
**Conclusion:** These compounds can be considered as safe food additives. It should, however be clarified whether the present permitted levels of 10 g/litre in powders for home preparation of drinks is expressed as amount per litre of ready to drink beverage. If this is the case just 30 ml with this amount could reach the ADI. In this case it should be investigated whether such use levels are likely and whether consumption above the 30 ml/day is likely and thus leading to intakes above the ADI.

Adipic acid as defined by the specifications seems to be covered by the toxicological evaluation. No specifications for food grade quality of the salts have been prepared.

**References:**


3. [1977, TRS 617-JECFA 21]

4. [1977, FAS 12-JECFA 21]

**SUCCINIC ACID**

**E number:** E 363

**Recommendation:** A re-evaluation is not needed.

**Chemical name/synonyms:** Butanedioic acid, 1,2-Ethanedicarboxylic acid.

**Chemical formula:** $\text{C}_4\text{H}_6\text{O}_4$

**EINECS number:** 203-740-4

**CAS number:** 110-15-6

**Functional Class:** Acidity regulator.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade succinic acid.

**Definition:** Succinic acid is a naturally occurring organic acid. It is soluble in water and in ethanol.

**EC specifications:** E 363 Succinic acid [3].
Assay: Not less than 99.0%.
The specification includes purity criteria on Residue on ignition, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** Permitted uses are restricted to desserts 6 g/kg soups and broths 5 g/kg and powders for home preparation of drinks 3 g/l.
As succinic acid has an ADI not specified the substance was not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990: No systematic toxicity studies are available but in view of its natural occurrence and its role as an intermediate metabolite SCF allocated a group ADI “not specified” for succinate [2].

**JECFA status:** Latest evaluation 1985: JECFA evaluated a series if inorganic and organic acids and their salts. The succinate moiety was allocated an ADI not specified on the basis of its natural contend in animals and plants that are consumed. No toxicological monograph and no specifications were prepared for succinic acid or their salts. [1].

**Background data:**

**Subacute/subchronic toxicity:** No data available.
**Genotoxicity:** No data available.

**Chronic toxicity/carcinogenicity:** No data available.

**Reproduction toxicity:** No data available.

**Conclusion:** Too little information is available to provide a toxicological evaluation. However as an intermediate metabolite in the citric acid cycle and a natural occurring substance it is not likely that the limited use of succinic acid should posses any hazard.

**References:**

1. [1985, TRS 733-JECFA 29]


TRIAMMONIUM CITRATE

E Number: E 380

See: E 330 Citric acid and citrates.
CALCIUM DISODIUM ETHYLENE DIAMINE TETRAACETATE

**E number:** E 385

**Recommendation:** No need for a reevaluation.

**Chemical name/ Synonyms:** N,N’-1,2-Ethanediylbis [N-(carboxymethyl)-glycinate][[(4-)-O,O’,O N ,O N ]calcite(2)-disodium, calcium disodium ethylenediaminetetra acetate, calcium disodium (ethylenedinitrilo)tetraacetate Calcium disodium EDTA, Calcium disodium edetate.

**Chemical formula:** C\textsubscript{10}H\textsubscript{12}O\textsubscript{8}CaN\textsubscript{2} Na\textsubscript{2} ·2H\textsubscript{2}O

**EINECS:** 200-529-9

**CAS number:** 62-33-9

**Functional Class:** Sequestrant, preservative, antioxidant synergist.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade calcium disodium ethylene diamine tetraacetate.

**Definition:** Calcium disodium ethylene diamine tetraacetate is freely soluble in water and practically insoluble in ethanol.

**EC specifications:** E 385 Calcium disodium ethylenediaminetetraacetate [1]. The specification includes purity criteria on Water, Arsenic, Lead, Mercury and Heavy metals.

**JECFA specifications:** Calcium disodium ethylenediaminetetraacetate [2]. Assay: Not less than 97% and not more than 102% on the anhydrous basis. The specification includes purity criteria on pH, Magnesium chelating substances, Arsenic, Lead, Mercury and Heavy metals.

**Exposure:** Permitted uses restricted to emulsified sauces, canned and bottled fish, crustaceans and molluscs, and frozen crustaceans 75 mg/kg. Spreadable fats 100 mg/kg. Canned and bottled pulses, legumes and artichokes 250 mg/kg. Not permitted in beverages. The ADI for an adult will be contained in 2 kg fish product, 1.5 kg fat or 600 g canned pulses etc. with the maximum permitted level.

In the EU monitoring system the substance was examined at tier 1. The calculated intake does not exceed the ADI, so the investigators concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990, ADI 2.5 mg/kg bw. Based on information on metabolism, acute toxicity, short-term studies in rat and dog and a long-term study in rats [3].
**JECFA status:** Latest evaluation 1973, ADI 2.5 mg/kg bw. Based on the long-term study mentioned below [4].

**Background data:**

**Subacute/subchronic toxicity:** Small studies have been performed on rats and dogs given CaNa₂EDTA. The studies reported by JECFA contain very few animals but at doses lower than 250 mg/kg bw there were no adverse effects [5].

**Genotoxicity:** *In vitro:* Several tests, with and without activation, indicate that CaNa₂EDTA is not genotoxic *in vitro* [6]. Genotoxicity *in vivo* cannot be excluded. Na₃EDTA is able to increase the incidence of chromosomal aberration in bone marrow cells of albino mice [7].

**Chronic toxicity/carcinogenicity:** No adverse effects were seen in a 2 year study on rats where groups of 25 male and 25 female were feed diets containing 0, 50, 125 and 250 mg/kg bw of CaNa₂EDTA [5].

**Reproduction toxicity:** The study mentioned above contained a four generation study where feeding with EDTA containing food were carried on through all generations. No adverse effects were seen.

**Allergy/Intolerance:** The results are contradicting. In a human study CaNa₂EDTA caused sensitisation in 6% (3/50). In spite of this the authors concluded, “in view of its widespread use and the absence of previously reported reactions, we feel it must be a weak sensitising compound.” [8]. A study on guinea pigs with Na₃EDTA showed no sensitisation. Based on this the authors concluded that the potential for sodium salt of EDTA to produce human skin sensitisation is extremely low [9].

**Effect in humans:** No data available.

**Other:** EDTA is a very efficient chelating agent for metal ions. Therefore there have been some concern about the possibility that intake of EDTA will disturb the uptake or excretion of metal ions. Without given doses Whittaker et. Al [6]mention thay CaNa₂EDTA increases the bioavailability of Zn and Cu, enhance the excretion of Co, Hg, Mn, Ni, Pb, Yi and form EDTA chelates with Fe³⁺ and Cu²⁺, which catalyse the oxidation of vitamins and unsaturated fats and oils [6].

**Conclusion:** Calcium disodium ethylene diamine tetraacetate has been found to react with a variety of nutrients. However, the potential exposure from permitted uses is unlikely to affect mineral balance in the overall diet. A reevaluation is therefore not warranted.

**References:**


4. [1973, NMRS 53/TRS 539-JECFA 17]

5. [1973, FAS 5/NMRS 53A-JECFA 17]


ALGINIC ACID, SODIUM ALGINATE, POTASSIUM ALGINATE, AMMONIUM ALGINATE AND CALCIUM ALGINATE

E number:
Alginic acid: E 400
Sodium alginate: E 401
Potassium alginate: E 402
Ammonium alginate: E 403
Calcium alginate: E 404

Recommendation: A re-evaluation is not necessary.

Chemical name/synonyms:
Alginic acid: Alginic acid.
Sodium alginate: Sodium salt of alginic acid.
Potassium alginate: Potassium salt of alginic acid.
Ammonium alginate: Ammonium salt of alginic acid.
Calcium alginate: Calcium salt of alginic acid.

Chemical formula:
Alginic acid: \((\text{C}_6\text{H}_8\text{O}_6)_n\)
Sodium alginate: \((\text{C}_6\text{H}_7\text{NaO}_6)_n\)
Potassium alginate: \((\text{C}_6\text{H}_7\text{KO}_6)_n\)
Ammonium alginate: \((\text{C}_6\text{H}_{11}\text{NO}_6)_n\)
Calcium alginate: \((\text{C}_6\text{H}_7\text{Ca}_{\frac{1}{2}}\text{O}_6)_n\)

EINECS number:
Alginic acid: 232-680-1
Sodium alginate: -
Potassium alginate: -
Ammonium alginate: -
Calcium alginate: -

CAS number:
Alginic acid: 9005-32-7
Sodium alginate: 9005-38-3
Potassium alginate: 9005-36-1
Ammonium alginate: 9005-34-9
Calcium alginate: 9005-35-0

Functional Class: Stabiliser, thickener, gelling agent, emulsifier.

Specification:
Manufacture: Alginates are extracted by the use of diluted alkali from natural strains of various species of brown seaweeds (Phaeophyceae).
**Alginic acid**

**Definition:** Alginic acid is a linear glycoronoglycan consisting mainly of $\beta$-(1-4) linked D-mannuronic and $\alpha$-(1-4) linked L-glucuronic acid units in pyranose ring form. It is a hydrophilic colloidal carbohydrate insoluble in water and organic solvents. It dissolves slowly in solutions of sodium carbonate, sodium hydroxide and trisodium phosphate.

**EC specifications:** E 400 Alginic acid [1].
Assay: Yields, on the anhydrous basis, not less than 20 % and not more than 23 % of carbon dioxide (CO$_2$), equivalent to not less than 91 % and not more than 104.5 % of alginic acid (C$_6$H$_8$O$_6$)$_n$ (calculated on equivalent basis of 200).
In addition the specification includes purity criteria on Loss on drying, pH, Sulphated ash, Sodium hydroxide insoluble matter, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

**JECFA specifications:** Alginic acid [2].
Assay: Yields, on the dried basis, not less than 20.0 % and not more than 23.0 % of carbon dioxide (CO$_2$), equivalent to not less than 91.0 % and not more than 104.5 % of alginic acid (C$_6$H$_8$O$_6$)$_n$.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Sodium hydroxide, Arsenic, Lead and Microbiological criteria.

**Sodium alginate**

**Definition:** Sodium alginate is the sodium salt of alginic acid. It dissolves slowly in water, forming a viscous solution. It is insoluble in ethanol and ether.

**EC specifications:** E 401 Sodium alginate [1].
Assay: Yields, on the anhydrous basis, not less than 18 % and not more than 21 % of carbon dioxide (CO$_2$), equivalent to not less than 90.8 % and not more than 106.0 % of sodium alginate (C$_6$H$_7$NaO$_6$)$_n$ (calculated on equivalent basis of 222).
In addition the specification includes purity criteria on Loss on drying, Water insoluble matter, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

**JECFA specifications:** Sodium alginate [2].
Assay: Yields, on the dried basis, not less than 18.0 % and not more than 21.0 % of carbon dioxide (CO$_2$), equivalent to not less than 90.8 % and not more than 106.0 % of sodium alginate (C$_6$H$_7$NaO$_6$)$_n$.
In addition the specification includes purity criteria on Loss on drying, Water insoluble matter, Arsenic, Lead and Microbiological criteria.

**Potassium alginate**

**Definition:** Potassium alginate is the potassium salt of alginic acid. It dissolves slowly in water, forming a viscous solution. It is insoluble in ethanol and ether.

**EC specifications:** E 402 Potassium alginate [1].
Assay: Yields, on the anhydrous basis, not less than 16.5 % and not more than 19.5 % of carbon dioxide (CO$_2$), equivalent to not less than 89.2 % and not more than 105.5 % of potassium alginate (C$_6$H$_7$KO$_6$)$_n$ (calculated on equivalent basis of 238).
In addition the specification includes purity criteria on Loss on drying, Water insoluble matter, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.
**JECFA specifications:** Potassium alginate [2].
Assay: Yields, on the dried basis, not less than 16.5 % and not more than 19.5 % of carbon dioxide (CO₂), equivalent to not less than 89.2 % and not more than 105.5 % of potassium alginate (C₆H₇KO₆)ₙ.
In addition the specification includes purity criteria on Loss on drying, Water insoluble matter, Arsenic, Lead and Microbiological criteria.

**Ammonium alginate**
**Definition:** Ammonium alginate is the ammonium salt of alginic acid. It dissolves slowly in water, forming a viscous solution. It is insoluble in ethanol and ether.

**EC specifications:** E 403 Ammonium alginate [1].
Assay: Yields, on the anhydrous basis, not less than 18 % and not more than 21 % of carbon dioxide (CO₂), equivalent to not less than 88.7 % and not more than 103.6 % of ammonium alginate (C₆H₁₁NO₆)ₙ (calculated on equivalent basis of 217).
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Water insoluble matter, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

**JECFA specifications:** Ammonium alginate [2].
Assay: Yields, on the dried basis, not less than 18.0 % and not more than 21.0 % of carbon dioxide (CO₂), equivalent to not less than 88.7 % and not more than 103.6 % of ammonium alginate (C₆H₁₁NO₆)ₙ.
In addition the specification includes purity criteria on Loss on drying, Sulfated ash, Water insoluble matter, Arsenic, Lead and Microbiological criteria.

**Calcium alginate**
**Definition:** Calcium alginate is the calcium salt of alginic acid. It dissolves slowly in water, forming a viscous solution. It is insoluble in ethanol and ether.

**EC specifications:** E 404 Calcium alginate [1].
Assay: Yields, on the anhydrous basis, not less than 18 % and not more than 21 % of carbon dioxide (CO₂), equivalent to not less than 89.6 % and not more than 104.5 % of calcium alginate (C₆H₇Ca½O₆)ₙ (calculated on equivalent basis of 219).
In addition the specification includes purity criteria on Loss on drying, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

**JECFA specifications:** Calcium alginate [2].
Assay: Yields, on the dried basis, not less than 18.0 % and not more than 21.0 % of carbon dioxide (CO₂), equivalent to not less than 89.6 % and not more than 104.5 % of calcium alginate (C₆H₇Ca½O₆)ₙ.
In addition the specification includes purity criteria on Loss on drying, Arsenic, Lead and Microbiological criteria.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substances were for that reason not included in the EU monitoring system (Tier 0).
SCF/JECFA evaluation:
SCF status: An ADI “not specified” was allocated in 1990 for alginic acid and its salts (Na-, K-, Ca-salts; the ammonium salt was, of unknown reasons, not included) [3]. The basis was newly presented data together with existing data. No toxicological data were specified by SCF. The Committee stressed that the evaluation only covered the substances when used as food additives according to GMP and not special dietary or medical uses [3].

JECFA status: A group ADI “not specified” was allocated in 1992 for alginic acid and its ammonium, calcium, potassium and sodium salts. The Committee pointed out (as it had for other compounds causing this effect) that laxative effects might occur at a high level of intake [4].

Background data:
Subacute/subchronic toxicity: Studies are available in rats, guinea pigs and dogs [5]. Effects on the gastro-intestinal system have been demonstrated. No adverse effects were documented [5].

Genotoxicity: Several in vitro and in vivo studies are available, no indication of genotoxicity [5].

Chronic toxicity/Carcinogenicity: Studies are available in mice and rats. No indication for a carcinogenic activity [5]. Sodium alginate has be shown to exert inhibitory effect on the development of dimethylhydrazine induced intestinal tumours [5].

Reproduction toxicity: Studies are available in rats. No adverse effects on reproduction [5].

Allergy/Intolerance: Special studies on immunotoxicity: Studies are available in mice. No effect was reported [5].

Effect in humans: Studies are available. No untoward effects, but the action as a bulking agent in large doses.

Other: Biochemical aspects: Studies are available on absorption, distribution and excretion. The absorption, if any at all, is extremely small [5]. Special studies on the interference with minerals: Alginates have been shown to reduce absorption of Fe, Cr, Sr, and Co and increase Pb retention [5].

Conclusion: The present SCF-ADI evaluation: ADI not specified was allocated for alginic acid and its salts. Only the Na-, K-, Ca-salts were specified, not the ammonium-salt. There is no need for a special evaluation of the ammonium-salt but when convenient it should be emphasised, that this salt is also included in the ADI not specified.

Alginates as defined by the specifications seem to be covered by the JECFA evaluation.
References:


**PROPANE-1,2-DIOL ALGINATE**

**E number:** E 405

**Recommendation:** A re-evaluation of the toxicological data of propane-1,2 alginate seems unnecessary. However, the apparent discrepancy between the JECFA evaluation and the specifications, both EU and JECFA, may need a clarification.

**Chemical name/synonyms:** Propane-1,2-diol alginate/ propylene glycol alginate, 1,2-propane-diol ester of alginic acid, hydroxypropyl alginate.

**Chemical formula:** \((C_9H_{14}O_7)_n\) (esterified)

**EINECS number:** -

**CAS number:** 9005-37-2

**Functional Class:** Stabiliser, thickener, emulsifier.

**Specification:**

**Manufacture:** Propane-1,2-diol alginate is obtained by chemical reaction between alginic acid and propylene glycol.

**Definition:** Propane-1,2-diol alginate is an ester of alginic acid in which some of the carboxyl groups are esterified with propylene glycol, some neutralised with an appropriate alkali and some remains free. It is soluble in water giving a viscous, colloidal solution, soluble in up to 60% aqueous ethanol depending upon degree of esterification.

**EC specifications:** E 405 Propane-1,2-diol alginate [1].
- Assay: Yields on the anhydrous basis not less than 16% and not more than 20% of carbon dioxide (CO₂).
- Total propane-1,2-diol: Not less than 15% and not more than 45%.
- Free propane-1,2-diol: Not more than 15%.
- In addition the specification includes purity criteria on Loss on drying, Water-insoluble matter, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

**JECFA specifications:** Propylene glycol alginate [2].
- Assay: Yields on the anhydrous basis not less than 16% and not more than 20% of carbon dioxide (CO₂).
- Total propane-1,2-diol: Not less than 15% and not more than 45%.
- Free propane-1,2-diol: Not more than 15%.
- In addition the specification includes purity criteria on Loss on drying, Water-insoluble matter, Arsenic, Lead and Microbiological criteria.

**Exposure:** Propane-1,2-diol alginate is permitted in few food commodities. In solid foods 1,2-8 g/kg is permitted and in beer 100 mg/l.
In the EU monitoring system propane-1,2-diol alginate was examined at tier 1. As the calculated intake did not exceed the ADI, the investigators concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** In 1990 the Committee allocated an of ADI 0-25 mg/kg bw expressed as propane-1,2-diol [3]. No toxicological data or the basis for the evaluation was specified. (For further data on propane-1,2-diol see E 1520).

**JECFA status:** In 1993 the Committee allocated an ADI of 0-70 mg/kg bw, corrected for the propylene content corresponding to 25 mg/kg bw [4]. The basis was a NOEL of 2500 mg/kg bw/day for propylene glycol obtained in a long-term study in rats [5], a safety factor of 100, and that propylene glycol alginate contains up to 36% propylene glycol.

**Background data:**

**Subacute/subchronic toxicity:** Studies are available in rats, guinea-pig, cat, chicken, and dog. The usual gastrointestinal effects for a non absorbable macromolecular bulking agents were noticed otherwise no adverse effects were noticed [6].

**Genotoxicity:** Several *in vivo* and *in vitro* studies are available. No indication of genotoxicity [6].

**Chronic toxicity/Carcinogenicity:** Long-term studies are available in mice and rats. No indication on carcinogenicity. NOEL was 2500 mg/kg bw/day (highest dose) [5;6].

**Reproduction toxicity:** A reproduction study is available in rats. No adverse effects were observed [6]. Studies on teratogenicity are available in mice, rats, hamsters, and rabbits. No adverse effects were noticed [6].

**Allergy/Intolerance:** One very old study in humans indicates a possibility of allergic reaction. However, this could not be confirmed in a newer and expanded study [6].

**Effect in humans:** Studies are available; no untoward reactions were noticed at doses of 200 mg/kg bw/day for 23 days [6].

**Other:** *Biochemical aspects:* Studies are available on the absorption, distribution, and excretion. Only the propylene glycol moiety is absorbed and metabolised (to lactate/ pyruvic acid, acetate, or glycogen). The alginate part and the unhydrolysed parent compound are excreted unchanged in the faeces of rats and mice [6].

**Conclusion:** Although the most data are old there is nothing in the data to suggest any problems with the use of propane-1,2-diol alginate as a food additive within the ADI.

Sufficient information for elaboration of specifications for this substance has been lacking until 1997. The existing specifications (both EC and SCF) include products with contents of propylene glycol up to 45%, while the JECFA evaluation refers to a product containing up to 36%. On this basis there may be a need for addressing this aspect.
References:


AGAR

E number: E 406

Recommendation: No need for a re-evaluation of agar.

Chemical name/synonyms: Agar-agar, Gelose, Japan agar, Bengal isinglass, Ceylon isinglass, Chinese isinglass, Japanese isinglass, Layor Crang.

Chemical formula: -

EINECS number: 232-658-1

CAS number: 9002-18-0

Functional Class: Thickener, stabiliser, emulsifier.

Specification:
Manufacture: Agar is extracted from certain marine algae of the class Rhodophyceae.

Definition: Agar is a dried hydrophilic, colloidal substance. It is a polysaccharide, consisting primarily of D- and L-galactose units. About every tenth D-galactopyranose unit contains a sulphate ester group. Calcium, magnesium, potassium or sodium cations are also associated with the polysaccharide. It is insoluble in cold water and soluble in boiling water.

EC specifications: E 406 Agar [1].
Assay: The threshold gel concentration should not be higher than 0.25%.
In addition the specification includes purity criteria on Loss on drying, Ash, Acid-insoluble ash, Insoluble matter (in hot water), Starch, Gelatine and other proteins, Water absorption, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Agar [2].
Assay: Not higher than 0.25% for threshold gel concentration.
In addition the specification includes purity criteria on Loss on drying, Total ash, Acid-insoluble ash, Foreign insoluble matter, Starch and dextrins, Gelatine and other proteins, Water absorption, Arsenic, Lead and Microbiological criteria.

Exposure: Agar is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is "not specified" and the substance was for that reason not included in the EU monitoring system (Tier 0).

There is a long history of use of agar in Far Eastern countries.
SCF/JECFA evaluation:
SCF status: An ADI “not specified” was allocated in 1988 [3]. The ADI was based on the fact that agar is devoid of toxicity at the highest dose levels used. However, no details were specified. The Committee noted that the common level of use in food is generally around 1-2% [3].

JECFA status: An ADI “not limited” (= “not specified”) was allocated in 1973 [4]. The evaluation was based on human data where doses above 5 g only caused a laxative effect.

Background data:
Subacute/subchronic toxicity: Short-term studies are available in rats. No adverse effects were noticed [5].

Genotoxicity: Studies in vivo and in vitro were available to SCF. No evidence of mutagenic activity, however, no details were specified [3].

Chronic toxicity/Carcinogenicity: Studies in rats and mice with doses up to 5% in diet showed no evidence of any carcinogenic or tumourigenic or any other effect [3]. A long-term carcinogenicity study showed no histological changes indicative of tissue accumulation (this study was not specified) [3]. In a special study in mouse, 8% agar was shown to enhance the carcinogenic activity (carcinoma) of parenterally-administered dimethylhydrazine in colon. However, the Committee did not consider this study relevant to the food additive use of agar [3].

Reproduction toxicity: Studies were available to SCF. No adverse effects on reproductive performance. No evidence of any teratogenic effect. No details were specified [3].

Effect in humans: Investigations in man demonstrated that doses above 5 g only caused a laxative effect [5].

Other: Biochemical aspects: Based on a long-term study the Committee did not consider that there were any evidence of significant amount of absorption (The study not specified) [3].

Conclusion: The existing data support the safety of agar when used as a food additive.

Agar as defined by the specifications is covered by the toxicological evaluation.

References:


4. [1973, NMRS 53/TRS 539-JECFA 17]
   Toxicological evaluation of certain food additives with a review of general principles and of

CARRAGEEANAN

E number: E 407

Recommendation: The general food use of carrageenan and processed Eucheuma seaweed (see next monograph) is on the SCF agenda to clarify the question about the potential promotion of colon carcinogenesis by carrageenan. When being re-evaluated it would be desirable to review all the existing data and to clarify whether all types of carrageenan are sufficiently covered by the toxicological evaluation.

Chemical name/synonyms: Products of commerce are sold under different names often related to the source material, such as, Carrageenan, Irish moss gelose, Eucheuman (from Eucheuma spp.), Iridophycan (from Iridea spp.), Hypnean (from Hypnea spp.), Furcellaran (from Furcellaria fastigiata).

Chemical formula: -

EINECS number: 232-524-2

CAS number: 9000-07-1

Functional Class: Thickener, gelling agent, stabiliser, emulsifier.

Specification:

Manufacture: Carrageenan is obtained from seaweeds of Gigartinaceae, Solieriaceae, Hypneaceae and Furcellariceae families of the class Rhodophyceae (red seaweeds) by extraction into water or aqueous dilute alkali. It may be recovered by alcohol precipitation, by drum drying or by precipitation in aqueous potassium chloride and subsequent freezing. The alcohols used during recovery and purification are restricted to methanol, ethanol and isopropanol. Articles of commerce may include sugars, for standardisation purposes, salts to obtain specific gelling or thickening characteristics or emulsifiers carried over from drum drying processes.

Definition: Carrageenan is a hydrocolloid consisting mainly of the ammonium, calcium, magnesium, potassium and sodium sulphate esters of galactose and 3,6-anhydrogalactose polysaccharides. These hexoses are alternatively linked α-1,3 and β-1,4 in the copolymer. The relative proportions of cations existing in carrageenan may be changed during processing to the extent that one may become predominant. Depending on the source seaweed the functional components are kappa-carrageenan, iota-carrageenan or lambda-carrageenan, each of which is characterised by the content of sulphate groups and gelling properties. Carrageenan is soluble in water of about 80°C, forming a viscous, clear or slightly opalescent solution that flows readily. It is insoluble in ethanol.

EC specifications: E 407 Carrageenan [1].

Assay: -

Viscosity of a 1.5% solution at 75°C: Not less than 5 mPa.s.
In addition the specification includes purity criteria on Methanol, ethanol and propane-1-ol, Loss on drying, Sulphate, Ash, Acid-insoluble ash, Acid-insoluble matter, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

**JECFA specifications:** Carrageenan [2].
Assay: -
Viscosity of a 1,5% solution at 75°C: Not less than 5 mPa.s.
In addition the specification includes purity criteria on Residual solvent, Loss on drying, pH, Sulfate, Total ash, Acid-insoluble ash, Acid-insoluble matter, Arsenic, Lead, Mercury, Cadmium and Microbiological criteria.

**Exposure:** Carrageenan is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is limited to 75 mg/kg and was therefore moved to tier 3 in the EU monitoring system.

**SCF/JECFA evaluation:**

**SCF status:** In 1977 The Committee endorsed the ADI of 0-75 mg/kg bw as established by JECFA [3]. No detailed information was presented. In 1992 the Committee considered information on the possible degradation of carrageenan in food, gastric hydrolysis and studies on the immune system. While maintaining the ADI the Committee made clear that carrageenan should not be used in infant formula [4]. In 1994, when PES (E 407a) was included it the ADI, the Committee noted that although JECFA had at that time allocated an ADI “not specified” for carrageenan it wished to maintain the numerical ADI of 75 mg/kg bw because of the remaining uncertainty over the general immunoreactive potential of the various carrageenans now in use as food additives [5]. In 1997 the Committee stated that it was unable to offer an opinion on the acceptability of the use of carrageenan in foods for special medical purposes for infants and young children until its current review on carrageenan is completed [6].

**JECFA status:** The ADI of 75 mg/kg bw as established in 1973 [7] was changed to an ADI “not specified“ in 1984 [8]. The basis was studies including a three-generation study of reproductive toxicity, short-term and long-term studies of toxicity in rats at dietary concentrations up to 5%, and short- and long-term studies of toxicity in hamsters, guinea-pigs, and monkeys. In 1998 PES (E 407a) was included in the ADI [9]. At the same time the ADI was made temporary pending clarification of the significance of the promotion of colon cancer observed in experimental rats. The Committee required this information for review in 2001 [9].

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies on various types of carrageenan are available in mice, rat, guinea-pig, pig, and monkey. Diarrhoea was noticed. No adverse effects were reported [10;11].

**Genotoxicity:** Studies on the genotoxicity of various types of carrageenan are available in vitro and in vivo. No indication of genotoxicity [10;11].

**Chronic toxicity/Carcinogenicity:** Long-term studies on various types of carrageenan are available in mice, rat, hamster, and monkeys. Diarrhoea was noticed. No adverse effects were noticed [10;11].
Special studies on proliferation and tumour promotion are available on various types of carrageenan in rats indicating tumour promotion of carrageenan on chemically-induced tumours [10;11].

**Reproduction toxicity:** Studies on reproductive and developmental toxicity of various types of carrageenan are available in mice, rats, hamsters, rabbits, and chick embryos. No consistent adverse effects were noticed on reproduction and no teratogenic or foetotoxic effects were demonstrated of food grade carrageenan [10;11].

**Allergy/Intolerance:** Studies are available on effects on the immune system of different types of carrageenan. Various effects are reported, but a consistent pattern of changes is not possible to integrate [10;11].

**Other:**
Studies quoted by SCF:
Uptake of small amounts in certain species [4]. Increased intestinal permeability in very young infants [4]. There is a possibility that absorption by the immature gut may take place and affect the immune system [4].

Degraded carrageenan has been reported to possess an ulcerogenic effect in some species (rat, guinea pig, rabbit) but not in others (mouse, hamster, gerbil, ferret, pig, squirrel, monkey) [3].

Degraded carrageenan might be formed under certain food processing conditions [12].

Studies quoted by JECFA [10;11]:
Carrageenan has no nutritive value. Studies on various types of carrageenan are available on absorption, distribution, and excretion in rats, guinea-pigs, rabbits, and monkeys. No direct nutritive value. No tissue distribution. There may be some uptake into the intestinal wall of the iota-form, but the radiolabel with tritium is questionable.
Degradation in the intestinal tract was studied *in vitro* and *in vivo*. Although native carrageenan may be degraded in the gut, this possibility is probably of limited toxicological significance because of absence of effects in feeding studies.
There is no evidence of fermentation.

**Conclusion:** Carrageenan has been extensively studied and in most studies seems to pose no toxicological problem. However the question about the potential promotion of colon carcinogenesis by carrageenan should be clarified.
SCF has expressed the wish to review carrageenan in the light of this aspect. JECFA, however, at its 57th meeting June 2001, withdrew the temporary status and allocated a full ADI “not specified”.

It may be necessary to clarify whether all types of carrageenan are sufficiently covered by the toxicological evaluation.

**References:**


7. [1973, NMRS 53/TRS 539-JECFA 17]

8. [1984, TRS 710-JECFA 28]

9. [1998, TRS 891-JECFA 51]

10. [1998, FAS 42-JECFA 51]

11. [1984, FAS 19-JECFA 28]

PROCESSED EUCHEUMA SEAWEED

E number: E 407a

Recommendation: No need to re-evaluate PES as such, but carrageenan is currently under review (see previous monograph).

Chemical name/synonyms: PES, PNG-carrageenan, semi-refined carrageenan, alternatively refined carrageenan.

Chemical formula: -

EINECS number: -

CAS number: -

Functional Class: Thickener, gelling agent, stabiliser, emulsifier.

Specification:

Manufacture: Processed eucheuma seaweed is obtained by soaking the cleaned seaweed in alkali for a short time at elevated temperatures. The material is then thoroughly washed with water to remove residual salt followed by purification, drying and milling to a powder. Alcohols that may be used during purification are restricted to methanol, ethanol and isopropanol. Articles of commerce may include sugars, for standardisation purposes or salts to obtain specific gelling or thickening characteristics.

Definition: Processed eucheuma seaweed is a substance with hydrocolloid properties obtained from either *Eucheuma cottonii* or *Eucheuma spinosum* (from the *Rhodophyceae* class of red seaweeds). In addition to carrageenan polysaccharides, processed eucheuma seaweed may contain up to 15% of insoluble algal cellulose and minor amounts of other insoluble matter. The functional component obtained from *E. cottonii* is kappa-carrageenan and the functional component obtained from *E. spinosum* is iota-carrageenan.

EC specifications: E 407a Processed eucheuma seaweed [1].

Assay: -
Viscosity of a 1.5% solution at 75°C: Not less than 5 mPa.s.
In addition the specification includes purity criteria on Methanol, ethanol and propane-1-ol, Loss on drying, Sulphate, Ash, Acid-insoluble ash, Acid-insoluble matter, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

JECFA specifications: Processed eucheuma seaweed [2].

Assay: -
Viscosity of a 1.5% solution at 75°C: Not less than 5 mPa.s.
In addition the specification includes purity criteria on Residual solvent, Loss on drying, pH, Sulfate, Total ash, Acid-insoluble ash, Acid-insoluble matter, Arsenic, Lead, Mercury, Cadmium and Microbiological criteria.
**Exposure:** Processed eucheuma seaweed is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is limited to 75 mg/kg and therefore ought to have been moved to tier 3 in the EU monitoring system, but was excluded because it is a new additive (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** The ADI of 75 mg/kg bw, as previously established for carrageenans (see previous monograph), was in 1994 extended also to include PES (which in the report is called “alternatively refined carrageenan”). The Committee concluded that further toxicological testing is not needed specifically on PES [3].

**JECFA status:** In 1998 the Committee included PES in the ADI “not specified” previously established for carrageenans. The ADI was at the same time made temporary until 2001 to clarify the questions described in previous monograph [4].

**Background data:**

**Subacute/subchronic toxicity:** Studies are available in rats. No obvious adverse effects were reported. NOEL 5% PES in the diet (the highest level tested) [3].

A 90-day study on PES from two sources (*E. cottonii* and *E. spinosum*) is available in rats fed 0, 0.5, 1.5, or 5% in the diet. No adverse effects were noted [4].

**Genotoxicity:**

*In vitro:* Studies are available on carrageenan and PES. No genotoxic or clastogenic activity. No details were reported [4;5].

*In vivo:* Studies are available. No genotoxic activity. No details were reported [3].

**Chronic toxicity/Carcinogenicity:**

**Reproduction toxicity:**

**Other:** A cytotoxicity study is available in bone marrow mononuclear cells and in hepatocyte cultures. The interpretation of the results remains unclear. No details were specified [3].

**Conclusion:** Because of the similarities in the nature of processed eucheuma seaweed and the conventionally processed carrageenans and in the effects they caused in the recent 90-day study it can be concluded that PES can be included in the evaluation of carrageenans.

Processed eucheuma seaweed as defined by the specifications is covered by the toxicological evaluation.
References:


4. [1998, *TRS 891-JECFA 51*]

**LOCUST BEAN GUM**

**E number:** E 410

**Recommendation:** An evaluation of locust bean gum is not necessary of toxicological grounds, however an update including newer data and with a more detailed description is desirable.

**Chemical name/synonyms:** Carob bean gum, algaroba gum.

**Chemical formula:** -

**EINECS number:** 232-541-5

**CAS number:** 9000-40-2

**Functional Class:** Thickener, stabiliser, emulsifier.

**Specification:**

**Manufacture:** The seeds of *Ceratonia siliqua* (L.) Taub. (fam. *Leguminosae*) are dehusked by treating with dilute sulphuric acid at high temperature or roasting the kernels, followed by milling and screening of the peeled seeds to obtain the endosperm. The gum may be purified by washing with ethanol or isopropanol or dispersing in boiling water, followed by filtering, evaporation and drying.

**Definition:** Locust bean gum consists mainly of high molecular weight (approximately 50,000-3,000,000) polysaccharide composed of galactomannans. It is soluble in hot water and insoluble in ethanol.

**EC specifications:** E 410 Locust bean gum [1].
Assay: Galactomannan content not less than 75%.
The specification includes purity criteria on Loss on drying, Ash, Protein, Acid-insoluble matter, Starch, Ethanol and propane-2-ol, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Carob bean gum [2].
Assay: -
The specification includes purity criteria on Loss on drying, Total ash, Protein, Acid-insoluble matter, Starch, Ethanol and propane-2-ol, Lead and Microbiological criteria.

**Exposure:** Locust bean gum is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substance was for that reason not included in the EU monitoring system (tier 0).
SCF/JECFA evaluation:
SCF status: Not formally evaluated by SCF for general use. However, it was accepted for use in weaning food [3] and in infant formulas for special medical purposes [4], but not for infant food in general [4;5]. This evaluation was mainly based on the evaluation of JECFA.

JECFA status: An ADI “not specified” was allocated in 1981 [6]. The basis for the ADI was lack of adverse toxicity in the available toxicity studies that include what would be normally required for an ADI to be set for a food additive.

Background data:
Subacute/subchronic toxicity: Short-term studies are available in rats, dog, chicken, and Japanese quail. In general no adverse effects were demonstrated at levels up to 5% in diet [7]. However, growth was depressed in chickens fed 2% locust bean gum for 24 days [4;5].

Genotoxicity: In in vitro studies, carob bean gum did not exhibit genetic activity [7].

Chronic toxicity/Carcinogenicity: Long-term studies are available in mouse and rat. No carcinogenic potential was noticed [7]. In a 103-weeks feeding study with locust bean gum, no carcinogenic effects were found in rats or mice [8].

Reproduction toxicity: An unpublished 3-generation reproduction study showed significant decreases in premating body weight gain in F0 females fed 2%, and final body weight in females fed 5%. There were no significant treatment-related effects on reproduction indices or gross or microscopic pathology [5].

Studies on reproduction (rats) and teratogenicity (rats, mice, hamsters, rabbits) are available. No effects were shown on reproductive indices or gross or microscopic pathology [7]. No teratological effects were seen [7].

Allergy/Intolerance: A study reported allergy to be induced by carob bean gum in an infant [9]. Induction of rhinitis and asthma has been caused by occupational exposure [10;11]. A fourth study reported that proteins from carob are not allergenic in peanut-allergic subjects [12]. Reactions seem to be associated with inhalation exposure. In a recent study immunoblotting analyses revealed that locust bean gum specific IgE was induced in humans challenged to the gum [12].

Effect in humans: Two studies are available. No untoward effects and no allergenic reaction was noticed [7].

Other: Biochemical aspects: Locust bean gum preparations are fermented in the colon, providing a small energetic gain. They can cause abdominal pain and diarrhoea [5].

Carob bean gum is not a source of bioavailable calories to rats [7]. In vitro studies using artificial human enzyme preparations did not show evidence of significant hydrolysis [7].

Conclusion: This additive is widely used and there is a long history of safe intake of locust beans as food. There is no need, of toxicological grounds, for a re-evaluation.
References:


GUAR GUM

E number: E 412

Recommendation: No immediate re-evaluation of guar gum is necessary. However, the aspect of allergy/intolerance and purity should be included in the next evaluation and the conduction of a multigeneration study including reproduction should be considered.

Chemical name/synonyms: Gum cyamopsis, Guar flour.

Chemical formula: -

EINECS number: 232-536-0

CAS number: 9000-30-0

Functional Class: Thickener, stabiliser, emulsifier.

Specification:
Manufacture: Guar gum is obtained by grinding the endosperm of the seeds from *Cyamopsis tetragonobulus* (L.) Taub. (Fam. *Leguminosae*). It may be purified by washing with ethanol or isopropanol or dispersing in boiling water, followed by filtering, evaporation and drying.

Definition: Guar gum consists mainly of polysaccharides of high molecular weight (50,000-8,000,000), composed of galactomannans; mannose: galactose ratio is about 2:1.

EC specifications: E 412 Guar gum [1].
Assay: Galactomannan content not less than 75%.
The specification includes purity criteria on Loss on drying, Ash, Protein, Acid-insoluble matter, Starch, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Guar gum [2].
Assay: -
The specification includes purity criteria on Loss on drying, Borate, Total ash, Protein, Acid-insoluble matter, Ethanol and propane-2-ol, Lead and Microbiological criteria.

Exposure: Guar gum is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substance was for that reason not included in the EU monitoring system (tier 0).

SCF/JECFA evaluation:
SCF status: An ADI “not specified” was allocated in 1977 [3]. No detailed information was given of the basis for the evaluation. Accepted for certain baby foods [4-6]
**JECFA status:** An ADI “not specified” was allocated in 1975 [7]. The basis for the ADI was lack of adverse toxicity in the available toxicity studies [7].

**Background data:**
**Subacute/subchronic toxicity:** Short-term studies are available in rat, chicken, dog, and monkey. No adverse effects were noticed [8].

A subchronic study has been conducted in rats fed the gum for 91 days. No adverse effect was revealed [9].

**Genotoxicity:** -

**Chronic toxicity/Carcinogenicity:** An old long-term study is available in rats. No abnormalities were found [8]. This study does not fulfil present standards.

In a 103-weeks feeding study with guar gum, no carcinogenic effects were found in rats or mice [10].

**Reproduction toxicity:** A reproduction toxicity study is missing but it seems unlikely that guar gum should pose any problem.

Studies on teratogenicity are available in three species (mice, rats, and hamsters). No teratogenicity was observed [8].

In a teratology study in rats, no adverse effects were seen on parameters of teratogenicity [11].

**Allergy/Intolerance:** Guar gum products contain a significant amount of protein and true allergy to guar gum via inhalation and subsequently via the oral route has been recorded in exposed workers [6]. IgE and IgG antibodies to guar gum were measured in 133 of 162 (82%) occupationally guar gum exposed workers [12;13].

**Effect in humans:** An old study is available in five volunteers. No apparent effects were found [8]. Guar gum is consumed as food in some parts of the world as a component of guar flour without reported adverse effects.

**Other:** SCF [3] quotes a report from Feldheim and Stamm’s summarising earlier feeding trials on cattle, poultry and rats with guar seeds. The protein fractions caused toxic effects and the carbohydrate-rich fractions depressed growth. This report also mention studies in which isolated guar protein caused swelling and inflammation of rats intestines.

**Biochemical aspects:** Data on caloric value and digestibility are available. The gum may calorically be equivalent to corn starch perhaps owing to gut flora activity, although no evidence of hydrolysis was demonstrated using mammalian intestinal enzyme preparations [8].

**Conclusion:** The data reviewed by SCF are few and do not include all the data that would normally be required for an ADI to be set for a food additive. Ideally, a multi-generation study [6] or a reproduction study in which exposure to guar gum is continued through lactation and weaning
should be available [14]. Furthermore, the aspect of allergy/intolerance and purity should be included in the next evaluation.

References:


7. [1975, NMRS 55/TRS 576-JECFA 19]

8. [1975, FAS 8/NMRS 55A-JECFA 19]


TRAGACANTH

**E number:** E 413

**Recommendation:** No re-evaluation of tragacanth is necessary. However, the aspect of allergy/intolerance should be included in the next evaluation.

**Chemical name/synonyms:** Tragacanth gum, tragant.

**Chemical formula:** -

**EINECS number:** 232-252-5

**CAS number:** 9000-65-1

**Functional Class:** Emulsifier, stabiliser, thickener.

**Specification:**

**Manufacture:** Tragacanth is a dried exudation obtained from the stems and branches of *Astragalus gummifer* Labilliardiere and other Asiatic species of *Astragalus* (family *Leguminiosae*).

**Definition:** Tragacanth consists mainly of high molecular weight polysaccharides (approximately 800,000) – galactoarabans and acidic polysaccharides, which on hydrolysis yield galacturonic acid, galactose, arabinose, xylose, and fucose. Small amounts of rhamnose and of glucose (derived from traces of starch and/or cellulose) may be present.

**EC specifications:** E 413 Tragacanth [1].
Assay: -
The specification includes purity criteria on Karaya gum, Loss on drying, Total ash, Acid-insoluble ash, Acid-insoluble matter, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

**JECFA specifications:** Tragacanth gum [2].
Assay: -
The specification includes purity criteria on Karaya gum, Acacia and other soluble gums, Agar, Dextrin, Loss on drying, Sulfated ash, Acid-insoluble ash, Acid-insoluble matter, Arsenic, Lead, Heavy metals and Microbiological criteria.

**Exposure:** Tragacanth is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substance was for that reason not included in the EU monitoring system (tier 0). It is therefore not possible at present to check whether the use is still limited as supposed by SCF in its evaluation.
SCF/JECFA evaluation:
SCF status: An ADI “not specified” was allocated in 1988 [3]. The basis was the available toxicological data combined with a claimed limited use, but no details were specified.

JECFA status: An ADI “not specified” was allocated in 1985 [4]. The basis was the level causing no toxicological effect in a 13-weeks study in rats on 6000 ppm in diet, equivalent to 3000 mg/kg bw/day.

Background data:
Subacute/subchronic toxicity: Short-term studies (including 90-day studies) are available in rats, chicken, and quail. No adverse effects were shown [5].

Genotoxicity: Mutagenicity tests in vitro and in vivo showed no mutagenic activity [5].

Chronic toxicity/Carcinogenicity: No chronic toxicity or carcinogenicity studies were available to SCF [3] or JECFA [5].

Reproduction toxicity: Teratogenicity studies are available in mice, rats, guinea pigs, hamsters, rabbits, and chicken. No teratogenic activity was demonstrated [5]. No effect on reproductive performance or post-partum development at dietary levels up to 6% was shown [5].

Allergy/Intolerance: Sensitisation studies are available. These studies showed no toxic effects at the doses employed, but results were only cited, no specific data were presented [3]. Tragacanth has sensitisation potential equivalent to egg-albumin [3]. Some old studies show allergenic properties that may occur as a result of inhalation or oral ingestion [5]. Earlier reports of allergic reactions were not substantiated by more recent studies that showed no evidence of specific immune responses [3].

Effect in humans: Large doses cause no reactions in man when taken orally for 3 weeks [3]. The tragacanth gum was well tolerated by man and no adverse effect was reported in any of the 5 volunteers administered 9.9 g/day for 32 days. Bulking effects were noticed [5].

Other: Biochemical aspects: Some digestion products from intestinal organisms activity may be absorbed [3]. No enzyme induction was found [3]. Changes in liver microsomal activity and in oxidative phosphorylation of heart and liver mitochondria as reported in an earlier study could not be confirmed in more recent investigations [3].

Many different species of bacteria found in human colon fermented tragacanth [5].

Conclusion: No chronic or carcinogenicity study is available. However, no mutagenic potential was noticed in in vitro or in vivo assays, 90-days studies in several species did not show adverse effects, and the use is limited. Otherwise, the data include the data that would normally be required for an ADI to be set for a food additive although no detailed information about studies is presented. The reviewer is unaware of any information that could necessitate a re-evaluation of the SCF-ADI for tragacanth gum.
References


4. [1985, TRS 733-JECFA 29]

5. [1985, FAS 20-JECFA 29]
ACACIA GUM

E number: E 414

Recommendation: Acacia gum has not been subject to a full evaluation by SCF. It is recommended that an evaluation be undertaken. The aspect of allergy/intolerance should be included in such an evaluation. Furthermore, it is proposed to clarify whether the toxicological testing covers acacia gum obtained from Acacia seyal.

Chemical name/synonyms: Gum arabic.

Chemical formula: -

EINECS number: 232-519-5

CAS number: 9000-01-5

Functional Class: Emulsifier, thickener, stabiliser.

Specification:
Manufacture: The EU specification describes that Acacia gum is obtained from the dried exudation obtained from the stems and branches of Acacia senegal (L) Willdenow or closely related species. Originally this source material was the predominant source material. Accordingly most monographs specified that Gum arabic is levorotatory. However, during recent years the use of gums from Acacia seyal (fam. Leguminosae) as source material has been increased significantly. For this reason both botanical sources are listed in the existing JECFA specification. Gums from Acacia seyal are dextrorotatory.

Definition: Acacia gum consists mainly of high molecular weight polysaccharides and their calcium, magnesium and potassium salt, which on hydrolysis yields arabinose, galactose, rhamnose and glucuronic acid. Items of commerce may contain extraneous materials such as sand and pieces of bark, which must be removed before use in food. It is soluble in water and insoluble in ethanol.

EC specifications: E 414 Acacia gum [1].
Assay: -
Tannin: Absent by test.
In addition the specification includes purity criteria on Loss on drying, Total ash, Acid-insoluble ash, Acid-insoluble matter, Starch or dextrin, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

JECFA specifications: Gum arabic [2].
Assay: -
Tannin: Absent by test.
In addition the specification includes purity criteria on Loss on drying, Total ash, Acid-insoluble ash, Acid-insoluble matter, Starch or dextrin, Lead and Microbiological criteria.
Exposure: Acacia gum is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. The substance was not included in the EU monitoring system (tier 0).

SCF/JECFA evaluation:
SCF status: This additive has not been formally evaluated by SCF. Accepted in baby food and for the coating of vitamin tablets in 1997 [3;4].

JECFA status: In 1989, JECFA confirmed the ADI “not specified “[5] as established in 1982 [6]. The basis was lack of adverse toxicity in the available toxicity studies that include what would be normally required for an ADI to be set for a food additive. At that occasion the Committee stressed that the evaluation covered only *Acacia senegal* and closely related species, and the specification was modified accordingly. However, in 1998 (51st session) the specification was changed to cover also *Acacia seyal* without a formal explanation.

Background data:
Subacute/subchronic toxicity: No obvious adverse effects have been shown.

Short-term studies are available in mouse, rat, guinea-pig, rabbit, and dog. No adverse effects were noticed [7].

A 13-week study in rats showed no adverse effects ([8].

Genotoxicity: *In vitro* and *in vivo* studies are available. No mutagenic activity was demonstrated [7].

Chronic toxicity/Carcinogenicity: No evidence of carcinogenicity.

Studies are available in mouse and rat. No carcinogenic activity was demonstrated at levels of 5% in the diet to rats and mice [7].

In a 103-weeks feeding study with acacia gum, no carcinogenic effects were found in rats or mice [9].

Reproduction toxicity: Reproduction and teratogenicity studies in rats, mice, hamsters and rabbits indicated no adverse effects [7;10].

Allergy/Intolerance: Two old studies (both from 1955) report a true antigen-antibody reaction to acacia gum in guinea-pigs and sensitivity reactions have been reported in some other old studies in man (studies from 1941-1952), quoted in [7]. Occupational exposure have been associated with rhinitis and asthma in sensitive individuals and from use as a tablet additive [7].

Although acacia gum is a complex, proteinaceous polysaccharide it is well-tolerated when an animal encounters it by the natural route i.e. via diet [11;12]. Acacia gum elicited an immune response comparable with the specific immune response elicited by hens’egg ovalbumin and more pure preparation of acacia gum led to a significant reduction of the immune response under *in vivo* test conditions [13;14].
Two studies reported acacia gum specific IgE antibodies mainly directed against the carbohydrate fraction of this additive [15;16].

**Effect in humans:** A change in human faecal flora in response to acacia gum in the diet has been published [17].

**Other:** **Biochemical aspects:** The gum seems to have a caloric value at the level of corn starch and is almost completely digested by guinea-pigs and rats [7]. An *in vivo* study in rats indicates enzyme induction of various enzymes [7;10]. *In vivo* studies show a reversible uncoupling of oxidative phosphorylation in heart and liver mitochondria [7].

A review and studies of the caloric value are published. The value seems to be below 4 kcal/g [18-21]. The fermentation by human faecal bacteria and in animals has been studied. Some volatile fatty acids (propionate, butyrate) are formed [22;23].

**Conclusion:** SCF has not formally evaluated acacia gum. Although the existing data do not point on any toxicological concern, the aspect of allergy/intolerance should be included in a future evaluation as well as the problem of marketing gums originating from acacia species not included in the evaluation should be solved (see “JECFA evaluation”).

**References:**


**XANTHAN GUM**

**E number:** E 415

**Recommendation:** No immediate re-evaluation of xanthan gum is necessary. However, as the SCF evaluation has been linked to assumptions of normal use levels of 1-4 g/kg food, the present use levels should be monitored, e.g. through the EU monitoring system tier 3. If uses should show to have changed markedly, the conduction of an adequate long-term study in a second rodent species, as requested by JECFA, could be considered.

**Chemical name/synonyms:** -

**Chemical formula:** -

**EINECS number:** 234-394-2

**CAS number:** 11138-66-2

**Functional Class:** Thickener, stabiliser, emulsifier, foaming agent.

**Specification:**

**Manufacture:** Xanthan gum is produced by a pure-culture fermentation of a carbohydrate with *Xanthomonas campestris*, purified by recovery with ethanol or isopropanol, dried and milled.

**Definition:** Xanthan gum is a high molecular weight polysaccharide of which D-glucose and D-mannose are the dominant hexose units, along with D-glocuronic acid and pyruvic acid. It exists as the sodium, potassium or calcium salts; its solutions are neutral. It is soluble in water and insoluble in ethanol.

**EC specifications:** E 415 Xanthan gum [1].

Assay: Yields, on dried basis, not less than 4.2% and not more than 5% of CO₂ corresponding to between 91% and 108% of Xanthan gum.

The specification includes purity criteria on Loss on drying, Total ash, Pyruvic acid, Nitrogen, Propane-2-ol, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria (including *Xanthomonas campestris*).

**JECFA specifications:** Xanthan gum [2].

Assay: Yields, on dried basis, not less than 4.2% and not more than 5.4% of CO₂ corresponding to between 91% and 117% of Xanthan gum.

The specification includes purity criteria on Loss on drying, Total ash, Pyruvic acid, Nitrogen, Ethanol and isopropanol, Lead and Microbiological criteria.

**Exposure:** Xanthan gum is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substance was for that reason not included in the EU monitoring system (tier
The assumption from SCF that normal use levels are about 1-4 g/kg food has thus not been tested.

**SCF/JECFA evaluation:**

**SCF status:** SCF evaluated xanthan gum in 1978 [3] when it endorsed “ADI 10 mg/kg bw” established by JECFA in 1974. SCF did not detail the toxicological data on which its evaluation was based. In 1990 an ADI “not specified” was established. The basis was a no-effect-level corresponding to the highest possible feeding level (not specified) and the usual levels used in food (1-4 g/kg). The basis was not further specified but SCF refers that the JECFA evaluation in 1986 [4] was based on metabolism, acute toxicity, 3-generation rat study, long-term studies in rat and dog, and observations in man. However, no details were given [5].

Xanthan gum was accepted in certain kind of baby food in 1997 [6].

**JECFA status:** In 1986 the previous ADI of 10 mg/kg bw was changed to an ADI “not specified” 1986 [4]. The basis was lack of adverse toxicity in the available toxicity studies that include what would be normally required for an ADI to be set for a food additive. JECFA desired an adequate long-term study in a second rodent species, because of the potential high exposure levels and the fact that xanthan gum is prepared from a microbial source not normally used in food.

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies are available in rats, guinea pigs, rabbits, and dogs. No consistent adverse effects were demonstrated [7].

**Genotoxicity:** No reports on mutagenicity studies are available.

**Chronic toxicity/Carcinogenicity:** Long-term studies are available in rats and dogs. No adverse effects were noticed [7].

**Reproduction toxicity:** A three-generation study in rats on reproduction is available. No adverse effects were reported on reproduction or teratogenicity [7].

**Effect in humans:** Studies in over-weight patients and volunteers showed that the gum was well tolerated at levels up to 10-13/day [7].

The ingestion of xanthan gum caused no adverse dietary or physiological effects in 5 human volunteers [8].

**Other:** *Biochemical aspects:* Caloric availability and digestibility studies indicate that xanthan gum is not utilised by the body. Other studies indicate a 15% excretion of 14C-label as CO₂, probably due to microbial activity. No accumulation in the body [7].

**Conclusion:** No indication of toxic effect of xanthan gum. No reports on mutagenicity studies are available and JECFA has desired an adequate long-term study in a second rodent species. No information on actual use levels.

Xanthan gum as defined by the specifications is covered by the toxicological evaluation.
References:


4. [1986, TRS 751-JECFA 30]


7. [1986, FAS 21-JECFA 30]

**E 416 Karaya gum**

**E number:** E 416

**Recommendation:** No re-evaluation of karaya gum is necessary.

**Chemical name/synonyms:** Katilo, kadaya, gum sterculia, sterculia, karaya, gum karaya, kullo, kuterra.

**Chemical formula:** -

**EINECS number:** 232-539-4

**CAS number:** 9000-36-6

**Functional Class:** Emulsifier, stabiliser, thickener.

**Specification:**

** Manufacture:** Karaya gum is a dried exudation from the stems and branches of *Sterculia urens* Roxburgh and other species of *Sterculia* (fam. *Steculiaceae*) or from *Cochlospermum gossypium* A.P. De Candolle or other species of *Cochlospermum* (fam. *Bixaceae*).

**Definition:** Karaya gum consists mainly of high molecular weight acetylated polysaccharides, which on hydrolysis yields galactose, rhamnose and galacturonic acid together with minor amounts of glucuronic acid. It is insoluble in ethanol.

**EC specifications:** E 416 Karaya gum [6].

**Assay:** -

The specification includes purity criteria on Loss on drying, Total ash, Acid-insoluble ash, Acid-insoluble matter, Volatile acid, Starch, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

**JECFA specifications:** Karaya gum [5].

**Assay:** -

The specification includes purity criteria on Loss on drying, Total ash, Acid-insoluble ash, Acid-insoluble matter, Volatile acid, Starch, Arsenic, Lead, Heavy metals and Microbiological criteria.

**Exposure:** Karaya gum is permitted in a limited number of non-stable foods. Maximum levels are 5-10 g/kg.

In the EU monitoring system karaya gum was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 0-16% of ADI, while the calculated intake by young children is reported by one member state as 17-48%. It was concluded that no further examination was needed at this stage.
SCF/JECFA evaluation:

SCF status: In 1983 a temporary ADI of 12.5 mg/kg bw was established and the Committee requested an additional study in a non-rodent species to assess the possibility of establishing ADI not specified [2]. This additional study was performed in monkeys and was received but did not supply all the information originally requested. Therefore, when SCF in 1988 re-evaluated the substance, the ADI was not changed. [4]. The Committee used a higher than usual safety factor to take into account for the limited value of the study in monkeys. The study in monkeys, the basis for the evaluation, and the safety factor were not specified.

JECFA status: Latest evaluation in 1988 when an ADI “not specified” was allocated [1]. The basis was lack of adverse toxicity in the available toxicity studies.

Background data:

Subacute/subchronic toxicity: Short-term study in rats showed no evidence of adverse effects at the 5% level. Studies are available in mice, rats and dogs. No adverse effects were found [3].

Genotoxicity: Studies in vitro and in vivo are available. No evidence of genotoxicity was noticed [3].

Chronic toxicity/Carcinogenicity:
No study on chronic toxicity and carcinogenicity was available to SCF [4].

Long-term studies are available in rats, guinea-pigs, and rhesus monkeys. No carcinogenic response was found [3].

Reproduction toxicity: Teratology studies are available in mice. No adverse effects were noticed [3].

Allergy/Intolerance: Some special studies on the immunoresponse are available in mice. The gum produced a response comparable to hens egg ovalbumin that could be abolished by processing or purification of the gum [3].

Effect in humans: Dietary studies in man indicate that the gum is well tolerated for 21 days at dose levels of 10.5 g/day without any adverse effects [3].

No adverse incidents involving human health has been reported following ingestion of karaya gum [7;8].

Other: Biochemical aspects: Studies on absorption and metabolism are available. The gum is not degraded by strains of bacteria found in the human colon and does not undergo metabolic modification in the intestinal tract of rats and dogs. The gum seems not to be digested nor degraded in rats and man [3].

Conclusion: The available data shows no sign of toxicity and the higher than usual safety factor in the SCF evaluation reflects the more limited data than would normally be required. The present restrictions in use ensure that the ADI will not be exceeded. A re-evaluation is therefore not warranted.
E 416 Karaya gum

References:


**TARA GUM**

**E number:** E 417

**Recommendation:** No re-evaluation of tara gum is necessary. It should, however, be considered to include tara gum in tier 3 in the food monitoring system to test whether the use levels assumed by SCF are still valid.

**Chemical name/synonyms:** Peruvian carob.

**Chemical formula:** -

**EINECS number:** 254-409-6

**CAS number:** -

**Functional Class:** Thickener, stabiliser.

**Specification:**

**Manufacture:** Tara gum is obtained by grinding of the endosperm of the seeds of *Caesalpinia spinosa* (fam. *Leguminosae*).

**Definition:** Tara gum consists mainly of high molecular weight polysaccharides composed mainly of galactomannans. The principal component consists of a linear chain of (1-4)-β-D-mannopyranose units with α-D-galactopyranose units attached by (1-6) linkages. The ratio of mannose to galactose is 3:1. It is soluble in water and insoluble in ethanol.

**EC specifications:** E 417 Tara gum [5].

Assay: -

The specification includes purity criteria on Loss on drying, Ash, Acid-insoluble matter, Protein, Starch, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Tara gum [3].

Assay: -

The specification includes purity criteria on Loss on drying, Ash, Acid-insoluble matter, Protein, Starch, Arsenic and Heavy metals.

**Exposure:** Tara gum is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substance was for that reason not included in the EU monitoring system (tier 0). It was thus not tested whether the SCF assumption of use levels in the range of 0.5-1% is still the case.

**SCF/JECFA evaluation:**

**SCF status:** An ADI “not specified” was allocated in 1990 [4]. The Committee based its evaluation on the use levels presented, ranging form 0.5 to 1% and the evaluation by JECFA in 1986.
**JECFA status:** An ADI “not specified” was allocated in 1986 [1]. The basis was lack of adverse toxicity in the available toxicity studies that essentially include what would be normally required for an ADI to be set for a food additive.

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies in mice, rats, and dogs showed no evidence of adverse effects at the 5% level [2]. A 90-day study in rats showed no adverse effects at the 5% level [2].

**Genotoxicity:**

**Chronic toxicity/Carcinogenicity:** Studies are available in mice and rats at levels up to 5%. Tara gum was not found to be carcinogenic [2].

In a 103-weeks feeding study with tara gum, no carcinogenic effects were found in rats or mice [6].

**Reproduction toxicity:** A study on reproduction is available in rats. It indicated a possible effect of 5% tara gum on lactation. A newer special study on embryotoxicity in rats, however, showed no evidence of embryonic and/or teratogenic effects [2].

**Other:** Biochemical aspects: Studies on the digestibility are available. In vitro studies with human gastric juice, duodenal juice+bile, pancreatic juice, or succus entericus produced no signs of hydrolysis. Tara gum seems not to be a source of bioavailable calories [2].

**Conclusion:** The available data give no reason for concern and a re-evaluation. However, when extending the food additive monitoring system in EU it should be considered to include the gum in tier 3 to test whether the SCF assumptions on use levels is still valid.

Tara gum as defined by the specifications is covered by the toxicological evaluation.

**References:**


GELLAN GUM

E number: E 418

Recommendation: No re-evaluation of gellan gum is necessary.

Chemical name/synonyms: -

Chemical formula: -

EINECS number: 275-117-5

CAS number: 71010-52-1

Functional Class: Thickener, gelling agent, stabiliser.

Specification:
Manufacture: Gellan gum is produced by a pure culture fermentation of a carbohydrate by Pseudomonas elodea, purified by recovery with isopropyl alcohol, dried and milled.

Definition: Gellan gum is a high molecular weight polysaccharide principally composed of a tetrasaccharide repeating unit of one rhamnose, one glucuronic acid and two glucose units, and is substituted with acyl (glyceryl and acetyl) groups as the O-glycosidically-linked esters. The glucuronic acid is neutralised to a mixed potassium, sodium, calcium and magnesium salt. It usually contains a small amount of nitrogen containing compounds resulting from the fermentation procedures. It is soluble in water and insoluble in ethanol.

EC specifications: E 418 Gellan gum [5].
Assay: Yields on the dried basis not less than 3.3% and not more than 6.8% of CO₂.
The specification includes purity criteria on Loss on drying, Nitrogen, Propane-2-ol, Arsenic, Lead, Mercury, Cadmium, Heavy metals and Microbiological criteria.

JECFA specifications: Gellan gum [4].
Assay: Yields on the dried basis not less than 3.3% and not more than 6.8% of CO₂.
The specification includes purity criteria on Loss on drying, Nitrogen, Isopropyl alcohol, Lead and Microbiological criteria.

Exposure: Gellan gum is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substance was for that reason not included in the EU monitoring system (tier 0).

SCF/JECFA evaluation:
SCF status: An “ADI not specified” was established in 1990 [3]. The basis was data from the available toxicological studies mentioned below and the use levels 0.1 and 1% in food. Toxicological data available for SCF are mentioned, but no details are specified, only mentioned
that they exist. These studies include what would normally be required for an ADI to be set for a food additive, but it is not possible to perform an evaluation of the information as presented by SCF.

**JECFA status:** An ADI “not specified” was established in 1990 [1]. The basis was lack of adverse toxicity in the available toxicity studies that include what would be normally required for an ADI to be set for a food additive. The Committee pointed out that the potential laxative effect at high intakes should be taken into account when used as a food additive.

**Background data:**

**Subacute/subchronic toxicity:** In a 28-day study in monkeys at highest dose level at 3 g/kg/day, no overt signs of toxicity were observed[2]. A 90-day in rats exists at levels up to 60 g/kg. No adverse effects were observed [2].

**Genotoxicity:** The gum has been shown to be non-genotoxic in a battery of standard short-term tests [2].

**Chronic toxicity/Carcinogenicity:** In a 1-year study in dogs at levels up to 60 g/kg in diet, no adverse effects were found. Long-term carcinogenicity studies showed no adverse effects in mice or rats at the highest dose (30 and 50 g/kg respectively) [2].

**Reproduction toxicity:** In reproduction and teratogenicity studies in rats at dose levels up to 50 g/kg in diet, no effect were seen on the reproductive process. No embryotoxic or developmental effects were found [2].

**Effect in humans:** The gum is well tolerated in man at doses up to 200 mg/kg bw/day for 23 days although usual faecal bulking effects were observed [2].

No adverse incidents involving human health has been reported following ingestion of gellan gum at high doses for 23 days [6].

**Other:** *Biochemical aspects:* Studies are available on absorption, distribution, and excretion. The gum is poorly absorbed if at all. [2].

**Conclusion:** The available data as reported by JECFA covers what can be expected for a full evaluation and shows no reason for any concern. The SCF opinion contains no details of the background for the evaluation.

Gellan gum as defined by the specifications is covered by the toxicological evaluation.
References:

1. [1990, TRS 806-JECFA 37]
   Evaluation of certain food additives and contaminants (Thirty-seventh report of the Joint
   1991, and corrigenda.

2. [1990, FAS 28-JECFA 37]
   Toxicological evaluation of certain food additives and contaminants. *WHO Food Additives

3. Reports from the Scientific Committee for Food (26th series). Opinion expressed 1990. *Food-


   criteria on food additives other than colours and sweeteners, 1998.

   in humans. *Food Addit Contam*, 5, 237-249.
SORBITOL

E Number:
Sorbitol: E 420 (i)
Sorbitol syrup: E 420 (ii)

Recommendation: No need for a toxicological re-evaluation. However a monitoring of actual uses and exposure is recommended.

Chemical name/synonyms: D-glucitol.

Chemical formula: C$_6$H$_{14}$O$_6$

EINECS number: 200-061-5

CAS Number: 50-70-4

Specification:
Sorbitol
Definition: Sorbitol is a polyol. It is a bulk sweetener having about the same sweetness as sucrose. It contains minor amounts of other hydrogenated saccharides. It is very soluble in water and slightly soluble in ethanol.

Manufacture: Sorbitol is obtained by catalytic (nickel) hydrogenation of glucose.

EC specifications: E 420 (i) Sorbitol [1].
Assay: Not less than 97.0% of glycitols and not less than 91.0% of D-sorbitol on the anhydrous basis.
Nickel: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Water, Sulphated ash, Reducing sugars, Total sugars, Chlorides, Sulphates, Arsenic, Lead and Heavy metals.

JECFA specifications: Sorbitol [2].
Assay: Not less than 97.0% of glycitols and not less than 91.0% of D-sorbitol on the anhydrous basis.
Nickel: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Water, Sulfated ash, Reducing sugars, Total sugars, Chlorides, Sulfates, Lead and Heavy metals.

Sorbitol syrup
Definition: Sorbitol syrup is a mixture of polyols, consisting predominantly of D-sorbitol together with variable amounts of D-mannitol and hydrogenated oligosaccharides. It is a bulk sweetener having about the same sweetness as sucrose. It is very soluble in water and slightly soluble in ethanol.

Manufacture: Sorbitol is obtained by catalytic (nickel) hydrogenation of glucose sirup.
EC specifications: E 420 (ii) Sorbitol syrup [1].
Assay: Not less than 69% dry matter and not less than 50% of D-sorbitol on the anhydrous basis.
Nickel: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Water, Sulphated ash, Reducing sugars, Chlorides, Sulphates, Arsenic, Lead and Heavy metals.

JECFA specifications: Sorbitol syrup [2].
Assay: Not less than 99.0% of hydrogenated saccharides and not less than 50.0% of D-sorbitol on the anhydrous basis.
Nickel: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Water, Sulfated ash, Reducing sugars, Total sugars, Chlorides, Sulfates, Lead and Heavy metals.

Exposure: Sorbitol is permitted as a sweetener in a variety of foods not including beverages. No upper limit is specified. For other purposes than sweetening sorbitol is permitted quantum satis in all foods where additives may be used except beverages other than liqueurs. As no upper limits of use have been specified an exposure estimate is not possible and sorbitol was not included in the EU monitoring system (tier 0). As sorbitol, as other bulk sweeteners, has the sweetening effect close to that of sugar it could, in principle, replace all sugar in solid foods (it is not permitted in beverages). Assuming an average intake of sugar of 60 g/day and a high intake of 180 g/day and that half of this could be from solid foods a potential intake of 30 g/day (average) and 90 g/day (high) can be calculated. As this theoretically calculated exposure exceeds the laxative threshold as defined by SCF a monitoring of actual exposure is desirable. Also non-sweetener use of this and the other sugar alcohols should be taken into account.

SCF/JECFA evaluation:
SCF evaluation:
1984: The Committee considered the continued use of sorbitol acceptable provided limitations due to its laxative action were kept in mind. The committee noted that consumption in the order of 20 g/person/day of this and other polyols alone or in combination is unlikely to cause undesirable laxative symptoms [3].

JECFA evaluations:
1973: ADI “not specified” [4;5].
1978: Temporary ADI “not specified” [6]. A summary of data was prepared [7].
1980: Temporary ADI “not specified” confirmed [8].
1982: ADI not specified [9]. Specifications were revised but no new monograph was prepared.

Background data:
Subacute/subchronic toxicity: Subchronic studies were reviewed by SCF [3].
Genotoxicity: Sorbitol was not mutagenic in several studies [3].
Chronic toxicity/Carcinogenicity: In a 2-year feeding study in rats (dietary levels of 0 or 20% sorbitol or 20% sucrose, 50 males and 50 females per group for tumorigenic evaluation, 15 males
and 15 females per group for laboratory investigation, 10 male and 10 females for interim sacrifices of 5 males and 5 females per group at 26 and 52 weeks, derived from parents exposed to the respective diets) no indications were found of carcinogenic properties of sorbitol but lower absolute and relative thyroid weights, caecal enlargement and the significantly increased incidence of both unilateral and bilateral hyperplasia of adrenal medulla were recorded for both sexes at 20% sorbitol [7].

In a 2-year feeding study in beagle dogs (dietary levels of 0, or 20% sorbitol or 20% sucrose, 8 males and 8 females per group) the increase in serum protein, body weight and organ weight in the sorbitol treated animals was recorded but no other significant findings [7].

**Reproduction toxicity:** In a multigeneration study in rats (dietary levels of 20% rice starch as a control, 20% sorbitol or 20% sucrose, 20 males and 20 females per group, 3 successive generations) the mating performance and pregnancy rate were not affected. Gestation period was increased (23-24 days) in 36% of litters of the first mating versus 16% of control and 23% of second mating versus 7% of controls. Litter size was decreased (total and viable pups), as was litter weight but with increased mean pup weight. No terata were observed grossly. A statistically significantly decreased absolute thyroid weight and enlargement of caecum was noted at terminal sacrifices. In addition, two rats from F3b generation showed absence of thymic tissue, cortical lymphocyte depletion and changes in a number of other tissues – the relationship of which is unknown. Furthermore, two males and one female showed an absence of extramedullary haematopoiesis in the liver [7].

In a teratogenicity study in rats (dietary dose groups of 20% rice starch as a control, 20% sorbitol or 20% sucrose, 31-33 females per dose group exposed to the respective diets 5 weeks before mating) no major malformations were noted and no treatment related skeletal variation were recorded.

In a study on a possible teratogenic effect of sorbitol, the female rabbits were fed either 20% sorbitol or 20% sucrose (control) from day seven to day 19 of gestation (20 females per group, males untreated) no teratogenic effect was reported [7].

**Allergy/Intolerance:** No information available.

**Effect in humans:** The tolerance of humans to high oral doses of sorbitol has been investigated in numerous studies with healthy and diabetic volunteers. Transient laxation and gastrointestinal discomfort may occur after high doses of sorbitol [5;7], a side effect general observed after intake of sugar alcohols and slowly digestible carbohydrates (e.g. lactose, fruit juices).

**Other:** Short-term studies. The studies on possible irritant effect on the stomach mucosal surface in rats and dogs demonstrated that only high doses of sorbitol caused irritation / hyppearemia and this effect was less expressed for sorbitol than equivalent doses of glycerol [5].

The cariogenicity of sorbitol has been evaluated in numerous studies *in vitro* and *in vivo* (with rats and in humans). It has been concluded that, under normal conditions of use, the acidogenicity of sorbitol is negligibly small and that it is virtually non cariogenic but it does not possess specific cariostatic properties [10].
**Conclusion:** The safety of sorbitol is sufficiently documented. However, a laxative effect in man after ingestion of high amounts of this compound should be taken into account when considering its appropriate levels of use alone and in combination with other sugar alcohols.

**References:**


4. [1973, NMRS 53/TRS 539-JECFA 17]

5. [1973, FAS 5/NMRS 53A-JECFA 17]

6. [1978, TRS 631-JECFA 22]

7. [1978, FAS 13-JECFA 22]

8. [1980, TRS 653-JECFA 24]

9. [1982, TRS 683-JECFA 26]

MANNITOL

E Number: E 421

Recommendation: No need for a toxicological re-evaluation. However a monitoring of actual uses and exposure is recommended.

Chemical name/synonyms: D-mannitol/ mannite.

Chemical formula: C\textsubscript{6}H\textsubscript{14}O\textsubscript{6}

EINECS number: 200-711-8

CAS Number: 69-65-8

Functional Class: Sweetener.

Specification:
Definition: Mannitol is a naturally occurring polyol. It is a bulk sweetener having about the same sweetness as sucrose. It is soluble in water and very slightly soluble in ethanol.

Manufacture: Mannitol is manufactured either by catalytic (nickel) hydrogenation of glucose and fructose made from invert sugar or from starch or by discontinuous fermentation under aerobic conditions by a conventional strain of the yeast Zygosaccharomyces rouxii.

EC specifications: E 421 Mannitol [1].

Manufactured by hydrogenation:
Assay: Not less than 96.0% and not more than 102% on the dried basis.
Nickel: Not more than 2 mg/kg.
Purity criteria on Loss on drying, Reducing sugars, Total sugars, Sulphated ash, Chloride, Sulphate and Lead.

Manufactured by fermentation
Assay: Not less than 96.0% and not more than 102% on the dried basis.
Arabitol: Not more than 0.3%.
Purity criteria on Loss on drying, Reducing sugars, Total sugars, Sulphated ash, Chloride, Sulphate, Lead and Microbial contaminants.

JECFA specifications: Mannitol [2].
The specification does not include mannitol manufactured by fermentation.
Assay: Not less than 96.0% and not more than 102.0% on the dried basis.
Nickel: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Loss on drying, Specific rotation, pH, Reducing sugars, Total sugars, Sulfated ash, Chloride, Sulfate, Lead and Heavy metals.
**Exposure:** Mannitol is permitted as a sweetener in a variety of foods not including beverages. No upper limit is specified. For other purposes than sweetening mannitol is permitted *quantum satis* in all foods where additives may be used except beverages other than liqueurs. As no upper limits of use has been specified an exposure estimate is not possible and mannitol was not included in the EU monitoring system (tier 0). As mannitol, as other bulk sweeteners, has the sweetening effect close to that of sugar it could, in principle, replace all sugar in solid foods (it is not permitted in beverages). Assuming an average intake of sugar of 60 g/day and a high intake of 180 g/day and that half of this could be from solid foods a potential intake of 30 g/day (average) and 90 g/day (high) can be calculated. As this theoretically calculated exposure exceeds the laxative threshold as defined by SCF a monitoring of actual exposure is desirable. Also non-sweetener use of this and the other sugar alcohols should be taken into account.

**SCF/JECFA evaluation:**

**SCF status:**
1984: Acceptable. The Committee considered the continued use of mannitol acceptable provided limitations due to its laxative action were kept in mind. The committee noted that consumption in the order of 20 g/person/day of this and other polyols alone or in combination is unlikely to cause undesirable laxative symptoms[3].

1999: Mannitol manufactured by fermentation found acceptable [4].

**JECFA status:**
1974: A temporary ADI of 0-50 mg/kg bw was allocated [5].
1976: The temporary ADI was retained [6].
1985: The temporary ADI 0-50 mg/kg bw was extended to 1986 [7].
1987: An ADI “not specified” was allocated. The fact that mannitol exert a laxative effect in man should be taken into consideration [8]. A monograph was prepared [9].

**Background data:**

**Subacute/subchronic toxicity:** In a 13-week feeding mouse study (dietary levels of 0., 0.3, 0.6, 1.2, 2.5 or 5.0% mannitol; 10 males and 10 females per group) no compound related effects were observed at necropsy or on histopathological examination [9].

In a 3-month feeding study in rats (dietary levels of 35% sucrose plus 5% mannitol or 40% sucrose; 20 animals per group) the growth curves showed that mannitol was nutritionally inferior to sucrose [9].

In a 13-week study in rats (dietary levels of 0., 0.3, 0.6, 1.25, or 5.0% mannitol; 10 males and 10 females per group) no compound-related clinical signs or histopathologic effects were observed [9].

In a 3-month feeding study in rhesus monkeys (dietary levels of 0 or 3 g/day mannitol, 2 and 3 animals per group respectively) no toxic nor pathological changes were observed [9].

**Genotoxicity:** No mutagenic or cytotoxic effect was found when mannitol was tested *in vitro* and *in vivo* [9].

**Chronic toxicity/Carcinogenicity:** In a carcinogenicity study in mice (dietary levels of 0, 2.5 or 5% mannitol; 50 males and 50 females per group; duration 103 weeks) mannitol was non-
carcinogenic. Mild nephrosis (characterized by focal vacuolisation of the tubular epithelium) was observed in increased incidence in treated mice of both sexes (males: 30%, 58%, 64%, females: 2%, 6%, 29% in the controls, low- and high-dose groups respectively) [9].

In a carcinogenicity study in rats (dietary levels of 0, 2.5 or 5% mannitol; 50 males and 50 females per group; duration 103 weeks) mannitol was non-carcinogenic. Retinopathy and cataracts occurred at increased incidences in high-dose males and mild- and high-dose females. These finding were explained by the distance of animals from sources of fluorescent light, but a contributing effect could not be discounted completely [9]. However, they were not recorded in other long-term studies.

In a long-term toxicity study in Wistar rats (dietary levels of 0, 1, 5 or 10% mannitol, 40 males and 40 females per group; duration 94 weeks) an increase in the number of benign thymomas was recorded in females (2, 6, 6 and 10 in the control, low- mid- and high-dose group respectively). However, this finding was not reproduced in three other studies designed to evaluate the species specificity of this finding [9] (see below).

In a long-term toxicity study in Sprague-Dawley female rats (dietary levels of 0, 1, 5 or 10% mannitol; duration 27 months) no effects attributable to mannitol administration were recorded [9].

In a long-term toxicity study in Wistar female rats (dietary levels of 0, 1, 5 or 10% mannitol; duration 30 months, 100 animals per group) no effects attributable to mannitol administration were recorded. Slightly increased incidences of tissue masses in the cervix/and or uterus noted in the compound treated groups as compared to the control were considered of no biological importance because of their overall low incidence [9].

In the long-term toxicity study in Fischer female rats (dietary levels of 0, 1, 5 or 10% mannitol; duration 30 months, 100 animals per group) no effects of mannitol on the development of primary thymic neoplasms was observed but increased incidence of adrenal medullary hyperplasia and pheochromocytoma were recorded [9] (the lesions are known to occur in rats after long-term polyol administration).

**Reproduction toxicity:** No multigeneration study reported.

Teratogenic studies in pregnant mice and rats (doses up to 1.6 g/kg bw for 10 consecutive days) and hamsters (doses up to 1.2 g/kg bw for 5 consecutive days did not reveal any compound –related teratogenic effects [9].

**Effect in humans:** Some studies on absorption and excretion as well as the effect on blood glucose has been performed [7]. The laxative effect due to ingestion of mannitol were noted at between 10 and 20 g per single dose [7].

**Other:** Several animal studies on metabolism of mannitol are summarised in [7].

**Conclusion:** The safety of mannitol is well documented. However, a laxative effect in man after ingestion of high amounts of this compound should be taken into account when considering its appropriate levels of use alone and in combination with other sugar alcohols.
E 421 Mannitol

References:


5. [1974, NMRS 54/TRS 557-JECFA 18]

6. [1976, FNS I/TRS 599-JECFA 20]

7. [1985, TRS 733-JECFA 29]

8. [1986, TRS 751-JECFA 30]

9. [1986, FAS 21-JECFA 30]
GLYCEROL

E number: E 422

Recommendation: No need for a re-evaluation but monitoring of use is suggested.

Chemical name/synonyms: 1,2,3-propanetriol, trihydroxypropane/ Glycerin, Glycerine.

Chemical formula: C₆H₈O₃

EINECS number: 200-289-5

CAS number: 56-81-5

Functional Class: Humectant, solvent, plasticizer.

Specification:
Manufacture: No information on manufacture of food grade glycerol.

Definition: Glycerol is miscible with water and with ethanol. It is immiscible with ether.

EC specifications: E 422 Glycerol [1].
Assay: Not less than 98% of C₆H₈O₃ on the anhydrous basis.
Chlorinated compounds: Not more than 30 mg/kg (as chlorine).
In addition the specification includes purity criteria on Water, Sulphated ash, Butantriols, Acrolein, glucose and ammonium compounds, Fatty acids and esters, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Glycerol [2].
Assay: Not less than 99% of C₆H₈O₃ on the anhydrous basis.
Chlorinated compounds: Not more than 30 mg/kg (as chlorine).
In addition the specification includes purity criteria on Water, Colour, Sulfated ash, Chlorides, Butantriols, Readily carbonizable substances, Fatty acids and esters, Arsenic, and Heavy metals.

Exposure: Glycerol is permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substance was for that reason not included in the EU monitoring system (tier 0).

SCF/JECFA evaluation:
SCF status: An ADI “not specified” was allocated in 1982 [3]. In 1997 The Committee considered a request to use glycerol as a non-cariogenic substitute for sugar in juices based on vegetables and fruits, especially intended for young children. It was not accepted by the Committee because dehydrating effects occur at exposure levels which are similar to those which could be consumed as a result of the proposed levels. Furthermore the intake of glycerol may have severe consequences
for patients with diabetes and it may worsen the condition of a child already dehydrated by infection
or other diseases [4].

**JECFA status:** Latest evaluation 1976. ADI “not specified” based on the available toxicological
studies and on the assumption that the daily intake of glycerol arising from its use as a food additive
is minimal compared to the amounts consumed through its natural occurrence in fat [5]. Glycerol is
on the agenda for 2001 as a flavouring substance.

**Subacute/subchronic toxicity:** Few studies have been performed without finding serious adverse
effects [6].

**Genotoxicity:** No data available.

**Chronic toxicity/carcinogenicity:** No adverse effects were seen when groups of 48 rats were
given food containing up to 20% natural or synthetic glycerol [6].

**Reproduction toxicity:** In a seven-generation rat study 9 male and 18 female in each group were
feed synthetic food containing 40% glycerol. Besides a lower weight of the pups no adverse effects
where seen [6].

**Effects in humans:** Glycerol is absorbed and readily metabolised. It is used in doses of
0.75-1.5 g/kg bw to treat acute glaucoma in children as well as adults. The adverse effects are
primarily due to its dehydrating action, and the symptoms in otherwise healthy patients are
headache, nausea and vomiting less frequent diarrhoea, thirst, dizziness, and mental confusion can
occur and cardiac arrhythmias have been reported. Mild osmotic diuresis occurs after oral glycerol
doses of 1.0-1.3 g/kg bw [4].

In a human study 14 students of good health ingested 110g 95% glycerol per day in 3 doses for
50 days without adverse effects [6].

**Conclusion:** No new data indicate the need for a re-evaluation of glycerol. As the present
permitted use is q.s., which may lead somebody to the conclusion that all levels are acceptable, it
should be considered to monitor the use of glycerol at tier 3 level to ensure that it is not used as a
sugar replacement in contrast with the clear opinion from SCF that such use is not acceptable within
the present hazard assessment.

**References:**

1. Commission Directive 96/77/EC laying down specific purity criteria on food additives other
than colours and sweeteners, 1996.

2. Compendium of Food Additive Specifications, *FAO Food and Nutrition Paper* no. 52, FAO,

3. Reports from the Scientific Committee for Food (11th series). Opinion expressed 1981. *Food-
science and techniques*, 1981.


**KONJAC GUM (EVALUATED BY JECFA AS KONJAC FLOUR)**

**E number:** E 425 (i)

**Recommendation:** There is no need for a re-evaluation of konjac gum with the present permitted uses.

**Chemical name/synonyms:** -

**Chemical formula:** -

**EINECS number:** -

**CAS number:** -

**Functional Class:** Gelling agent, thickener, emulsifier, stabiliser.

**Specification:**

**Manufacture:** Konjac gum is obtained by aqueous extraction of Konjac flour, which is the unpurified raw product from the ground roots of the perennial plant *Amorphophallus konjac*.

**Definition:** Konjac gum is a water-soluble hydrocolloid. The main component is the high molecular weight galactomannan (200,000-2,000,000), which consists of D-mannose and D-glucose units at a molecular ratio of 1.6:1.0, connected by (1-4)-glucosidic bonds, and acetyl groups occur at random at a ratio of about 1 group per 9 to 19 sugar units. It contains not less than 75% carbohydrate.

**EC specifications:** E 425i Konjac gum [2].
Assay: Not less than 75% carbohydrate.
The specification includes purity criteria on Loss on drying, Starch, Protein, Ether soluble material, Total ash, Arsenic, Lead, Salmonella and E. coli.

**JECFA specifications:** Konjac flour [1].
Assay: Not less than 75% carbohydrate.
The specification includes purity criteria on Loss on drying, Starch, Protein, Total ash, Arsenic, Lead, and Heavy metals.

**Functional class:** Gelling agent, thickener, emulsifier, stabiliser, texturiser, glazing agent.

**Exposure:** Permitted in food in general except those where additives may not be used. Max. level 10 g/kg.

**SCF/JECFA evaluation:**

**SCF status:** Konjac gum was tested adequately in 90-day feeding study in rats and dogs. NOEL was 1.25 g/kg bw/day. A long-term study is lacking and the breakdown is not clear. Therefore, an ADI cannot be established. The existing data as well as human experience does not give reason for concern. Konjac materials have a long history as traditional food in Far East countries [3].
The use of Konjac gum as an additive at the intended levels up to 1% in food is acceptable provided that the total intake from all sources do not exceed 3 g/day [3].

**JECFA status:** In 1996 JECFA allocated “ADI “not specified” for konjac flour on the basis of the available data on toxicology, particularly from human studies, the long history of use of konjac as a food in China and Japan, and estimates of consumption in traditional and anticipated uses. The Committee stressed that its evaluation applies only to the use of konjac flour as a food additive [4]. The basis was the available toxicological data from human studies, the long history of use of konjac as a food in China and Japan, and estimates of konjac flour consumption from traditional and anticipated food additive uses.

**Background data:**

**Subacute/subchronic toxicity:** A sub-chronic (28-days) toxicity study in rats and sub-chronic (90-days) studies in rats and in dogs are available. No adverse effects noticed [3]. In the 90-day study in rats NOEL was 2.5% in diet, corresponding to 1.25 mg/kg bw/day [3].

Short-term toxicity studies are available in rats and cat. No adverse effects were reported [5]

**Genotoxicity:** Studies in vitro and in vivo are available. No indication of genotoxicity [5] [3].

**Chronic toxicity/Carcinogenicity:** Long-term toxicity studies are available in rats. No adverse effects were reported. NOAEL was 1% (highest dose) equivalent to an intake of 500 mg/kg bw/day [5].

**Reproduction toxicity:** A reproduction study in rats is available. No adverse effects [3].

Special studies on embryotoxicity:

Studies are available in cats. No adverse effects were noticed [6].

**Allergy/Intolerance:** In the data-base search one paper revealed respiratory sensitisation to konjac flour in guinea-pigs. This study indicates that respiratory hypersensitivity to food grade konjac flour can be induced in guinea-pigs following repeated inhalation exposure [7]. This is not regarded to represent potential problems when ingested via diet.

**Effect in humans:** Studies are available in man. No toxic effects were revealed [3].

Several studies are available. They report symptoms such as loose stools, flatulence, diarrhoea, and abdominal pain at doses much higher than following use as a food additive [6].

**Other:** Biochemical aspects: The main component glucomannane seems to be non-digestible by human intestinal enzymes [3]. The extent to what this additive is decomposed in the intestine is not clear [3].

Konjac flour is considered to be soluble as a result of its ability to form a solution of very high viscosity in water [5]. Studies exist on in vitro digestion in the small intestine, in vitro and in vivo fermentation in the large intestine including metabolism of fermentation end-products, the digestibility in humans, and the effect on absorption of nutrients. There may be an effect on E-
vitamin absorption at intake much higher than intake following use as a food additive. Konjac flour behaves metabolically in the intestine in a similar way to other polysaccharide gums [5].

Special studies on anti-carcinogenic effects:
Studies are available in mice and rats. No conclusive over-all effects were demonstrated [6].

Special studies on gastrointestinal effects:
Studies are available in mice and rats. No adverse effects were shown [6].

**Conclusion:** Taking into account the long history of safe use in Far Eastern countries, there is no evidence of any toxic effect. It is, however, prudent to draw attention to the need to restrict the total daily intake in order to avoid effects on the gastrointestinal tract (diarrhoea, flatulence, and slight abdominal pain) [3]. The present restrictions in use should ensure that.

**References:**


KONJAC GLUCOMANNAN

E number: E 425 (ii)

Recommendation: There is no need for an immediate re-evaluation of konjac glucomannan. If future use results in a significant increased intake, SCF should re-evaluate this additive.

Chemical name/synonyms: -

Chemical formula: -

EINECS number: -

CAS number: -

Functional Class: Gelling agent, thickener, emulsifier, stabiliser.

Specification:
Manufacture: Konjac glucomannan is obtained from Konjac flour by washing with water-containing ethanol. Konjac flour is the unpurified raw product from the ground roots of the perennial plant *Amorphophallus konjac*.

Definition: Konjac glucomannan is a water-soluble hydrocolloid. The main component is the high molecular weight (500,000-2,000,000) galactomannan, which consists of D-mannose and D-glucose units at a molecular ratio of 1.6:1.0, connected by (1-4)-glucosidic bonds with a branch at about each 50th or 60th unit. About each 19th sugar residue is acetylated. It contains not less than 95% total dietary fibre.

EC specifications: E 425i Konjac glucomannan [1]
Assay: Not less than 95% carbohydrate.
The specification includes purity criteria on Loss on drying, Starch, Protein, Ether soluble material, Sulphite, Chloride, 50% Alcohol-soluble, Total ash, Lead, Salmonella and E. coli.

JECFA specifications: No JECFA specifications have been prepared.

Exposure: Permitted in food in general except those where additives may not be used. Max. level 10 g/kg

SCF/JECFA evaluation:
SCF status: No ADI could be established in 1996 [2]. There are not sufficient data of modern standards to allow an ADI to be set. Adequate subchronic and long-term studies are lacking and a no-observed-effect-level cannot be derived. The catabolism is not clear. The existing data as well as human experience do not give reason for concern. Konjac materials have a long history as traditional food in Far East countries. Konjac glucomannan was therefore accepted as a food additive provided intake would not exceed 3 g/person/day [2].
**JECFA status:** No evaluation has been performed.

**Background data:**

**Subacute/subchronic toxicity:** Sub-acute and sub-chronic toxicity studies in rats are available. No adverse effects noticed [2].

**Genotoxicity:** *In vitro* and *in vivo* assays are available. No genotoxic potential [2].

**Chronic toxicity/Carcinogenicity:**

**Reproduction toxicity:**

**Effect in humans:** Studies are available in man. No toxic effects were revealed [2].

**Other:** *Biochemical aspects:* The main component glucomannan seems to be non-digestible by human intestinal enzymes [2]. The extent to what this additive is decomposed in the intestine is not clear [2].

**Conclusion:** Taking into account the long history of safe use in Far Eastern countries, there is no evidence of any toxic effect. It was, however, prudent to draw attention to the need to restrict the total daily intake in order to avoid effects on the gastrointestinal tract (diarrhoea, flatulence, and slight abdominal pain) [2]. Therefore, the use is restricted to 10 g/kg, which should ensure compliance.

**References:**


POLYOXYETHYLENE (40) STEARATE

**E number:** E 431

**Recommendation:** This substance has not been accepted as additive by the SCF because of lack of data. If the present permitted use in imported wine is to be prolonged, a re-evaluation is recommended.

**Chemical name/synonyms:** Polyoxyl (40) stearate, polyoxyethylene (40) monostearate

**Chemical formula:** -

**EINECS number:** -

**CAS number:** -

**Functional Class:** Emulsifier.

**Specification:**
**Manufacture:** No information on manufacture of food grade polyoxyethylene (40) stearate.

**Definition:** Polyoxyethylene (40) stearate consists of a mixture of the mono- and diesters of edible stearic acid and polyoxyethylene diols (having an average polymer length of about 40 oxyethylene units) together with free polyol.

**EC specifications:** E 431 Polyoxyethylene (40) stearate [1].
Assay: Not less than 97.5% on the anhydrous basis.
1,4-dioxane: Not more than 5 mg/kg.
Free ethylene oxide: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Water, Acid value, Saponification value, Hydroxyl value, Ethylene glycols (mono- and di-), Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Polyoxyethylene (40) stearate [2].
Assay: Not less than 84.0% and not more than 88.0% oxyethylene groups equivalent to not less than 97.5% and not more than 102.5% of polyoxyethylene (40) stearate on the anhydrous basis.
The specification includes purity criteria on Water, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

**Exposure:** Permitted in wine imported from USA until 2003 according to regulation 1873/84. No limits given so exposure estimate not possible.

**SCF/JECFA evaluation:**
**SCF status:** No ADI could be established in 1983 due to the lack of toxicological data [3].
At the 1978 evaluation [4] the Committee required a metabolic study and a 90-day study in a rodent species within 2 years. These studies have never been presented to SCF.
**JECFA status:** An ADI of 25 mg/kg bw was established in 1973 [5]. (Group ADI as the total of polyoxyethylene(8)- and -(40)sterate). The basis was the level causing no toxicological effects in rats on 50000 ppm (5%) in the diet corresponding to 2500 mg/kg bw/day. At higher levels effects were seen on weight gain, liver and kidneys. The basal study was not identified. The safety factor was 100.

**Background data:**

**Subacute/subchronic toxicity:** Short term studies are available in mouse, rat, hamster, cat, dog and monkey. No adverse effects were found up to 10% in the diet. Some unspecific effects were seen in some studies with 20% in the diet [6].

**Genotoxicity:** -

**Chronic toxicity/Carcinogenicity:** Long-term studies are available in rats. No adverse effects were found [6].

**Reproduction toxicity:** -

**Effect in humans:** One study is available. No untoward effects were found [6].

**Other:** Biochemical aspects: The polyoxyethylene (40) moiety was not well absorbed and sometimes had a laxative effect at dose levels of 5% or more.

**Conclusion:** The existing data are old and incomplete why SCF did not accept the substance as food additive. Based on the existing data there is no reason to expect that the limited use in wine should cause any reason for concern. However, if the present permission is sought prolonged new data should be submitted and a re-evaluation performed.

**References:**


5. [1973, NMRS 53/TRS 539-JECFA 17]
POLYOXYETHYLENE SORBITAN MONOLAURATE (POLYSORBATE 20),
POLYOXYETHYLENE SORBITAN MONOOLEATE (POLYSORBATE 80),
POLYOXYETHYLENE SORBITAN MONOPALMITATE (POLYSORBATE 40),
POLYOXYETHYLENE SORBITAN MONOSTEARATE (POLYSORBATE 60),
POLYOXYETHYLENE SORBITAN TRISTEARATE (POLYSORBATE 65)

E number:
Polyoxyethylene sorbitan monolaurate: E 432
Polyoxyethylene sorbitan monooleate: E 433
Polyoxyethylene sorbitan monopalmitate: E 434
Polyoxyethylene sorbitan monostearate: E 435
Polyoxyethylene sorbitan tristearate: E 436

Recommendation: No immediate re-evaluation of polysorbate 20, 40, 60, 65 or 80 is necessary. However, in the light of the age of the data and evaluations and the potential for exceeding the SCF ADI, an update of the evaluation is recommended. The question of residual ethylene oxide is presently being evaluated by SCF.

Chemical name/synonyms:
Polyoxyethylene sorbitan monolaurate: Polysorbate 20, Polyoxyethylene (20) sorbitan monolaurate.
Polyoxyethylene sorbitan monooleate: Polysorbate 80, Polyoxyethylene (20) sorbitan monooleate.
Polyoxyethylene sorbitan monopalmitate: Polysorbate 40, Polyoxyethylene (20) sorbitan monopalmitate.
Polyoxyethylene sorbitan monostearate: Polysorbate 60, Polyoxyethylene (20) sorbitan monostearate.
Polyoxyethylene sorbitan tristearate: Polysorbate 65, Polyoxyethylene (20) sorbitan tristearate

Chemical formula: -

EINECS number: -

CAS number: -

Functional Class: Emulsifier, dispersing agent.

Specification:
Manufacture: No information on manufacture of food grade polysorbates.
**Polyoxyethylene sorbitan monolaurate**

**Definition:** Polyoxyethylene sorbitan monolaurate consists of a mixture of the partial esters of sorbitol and its mono- and dianhydrides with edible commercial lauric acid and condensed with approximately 20 moles of ethylene oxide per mole of sorbitol and its anhydrides.

**EC specifications:** E 432 Polyoxyethylene sorbitan monolaurate [1].
Assay: Not less than 70% of oxyethylene groups, equivalent to not less than 97.3% of polyoxyethylene sorbitan monolaurate on the anhydrous basis.
1,4-dioxane: Not more than 5 mg/kg.
Free ethylene oxide: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Water, Acid value, Saponification value, Hydroxyl value, Ethylene glycols (mono- and di-), Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Polyoxyethylene sorbitan monolaurate [2].
Assay: Not less than 70.0% and not more than 74.0% of oxyethylene groups, equivalent to not less than 97.3% and not more than 103.0% of polyoxyethylene sorbitan monolaurate on the anhydrous basis.
The specification includes purity criteria on Water, Sulfated ash, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

**Polyoxyethylene sorbitan monooleate**

**Definition:** Polyoxyethylene sorbitan monooleate consists of a mixture of the partial esters of sorbitol and its mono- and dianhydrides with edible commercial oleic acid and condensed with approximately 20 moles of ethylene oxide per mole of sorbitol and its anhydrides.

**EC specifications:** E 433 Polyoxyethylene sorbitan monooleate [1].
Assay: Not less than 65% of oxyethylene groups, equivalent to not less than 96.5% of polyoxyethylene sorbitan monooleate on the anhydrous basis.
1,4-dioxane: Not more than 5 mg/kg.
Free ethylene oxide: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Water, Acid value, Saponification value, Hydroxyl value, Ethylene glycols (mono- and di-), Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Polyoxyethylene sorbitan monooleate [2].
Assay: Not less than 65.0% and not more than 69.5% of oxyethylene groups, equivalent to not less than 96.5% and not more than 103.5% of polyoxyethylene sorbitan monooleate on the anhydrous basis.
The specification includes purity criteria on Water, Sulfated ash, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

**Polyoxyethylene sorbitan monopalmitate**

**Definition:** Polyoxyethylene sorbitan monopalmitate consists of a mixture of the partial esters of sorbitol and its mono- and dianhydrides with edible commercial palmitic acid and condensed with approximately 20 moles of ethylene oxide per mole of sorbitol and its anhydrides.
**EC specifications:** E 434 Polyoxyethylene sorbitan monopalmitate [1].
Assay: Not less than 66% of oxyethylene groups, equivalent to not less than 97% of polyoxyethylene sorbitan monopalmitate on the anhydrous basis.

1,4-dioxane: Not more than 5 mg/kg.
Free ethylene oxide: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Water, Acid value, Saponification value, Hydroxyl value, Ethylene glycols (mono- and di-), Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Polyoxyethylene sorbitan monopalmitate [2].
Assay: Not less than 66.0% and not more than 70.5% of oxyethylene groups, equivalent to not less than 97.0% and not more than 103.0% of polyoxyethylene sorbitan monopalmitate on the anhydrous basis.
The specification includes purity criteria on Water, Sulfated ash, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

Polyoxyethylene sorbitan monostearate
**Definition:** Polyoxyethylene sorbitan monostearate consists of a mixture of the partial esters of sorbitol and its mono- and dianhydrides with edible commercial stearic acid and condensed with approximately 20 moles of ethylene oxide per mole of sorbitol and its anhydrides.

**EC specifications:** E 435 Polyoxyethylene sorbitan monostearate [1].
Assay: Not less than 65% of oxyethylene groups, equivalent to not less than 97% of polyoxyethylene sorbitan monostearate on the anhydrous basis.

1,4-dioxane: Not more than 5 mg/kg.
Free ethylene oxide: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Water, Acid value, Saponification value, Hydroxyl value, Ethylene glycols (mono- and di-), Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Polyoxyethylene sorbitan monostearate [3].
Assay: Not less than 65.0% and not more than 69.5% of oxyethylene groups, equivalent to not less than 97.0% and not more than 103.0% of polyoxyethylene sorbitan monostearate on the anhydrous basis.
The specification includes purity criteria on Water, Sulfated ash, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

Polyoxyethylene sorbitan tristearate
**Definition:** Polyoxyethylene sorbitan tristearate consists of a mixture of the partial esters of sorbitol and its mono- and dianhydrides with edible commercial stearic acid and condensed with approximately 20 moles of ethylene oxide per mole of sorbitol and its anhydrides.

**EC specifications:** E 436 Polyoxyethylene sorbitan tristearate [1].
Assay: Not less than 46% of oxyethylene groups, equivalent to not less than 96% of polyoxyethylene sorbitan tristearate on the anhydrous basis.
1,4-dioxane: Not more than 5 mg/kg.
Free ethylene oxide: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Water, Acid value, Saponification value, Hydroxyl value, Ethylene glycols (mono- and di-), Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Polyoxethylene sorbitan tristearate [3].
Assay: Not less than 46.0% and not more than 50.0% of oxyethylene groups, equivalent to not less than 96.0% and not more than 104.0% of polyoxethylene sorbitan tristearate on the anhydrous basis.
1,4-dioxane: Not more than 10 mg/kg.
In addition the specification includes purity criteria on Water, Sulfated ash, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

**Exposure:** The permitted uses of polysorbates are limited to edible ices, sugar confectionary, soups and some dietary foods 1g/kg, fine bakers wares and desserts 3 g/kg, milk and cream analogues, emulsified sauces and chewing gum 5 g/kg and in fat emulsions for baking purposes 10 g/kg. In dietary supplements they are permitted q.s. The SCF ADI can be reach by consuming 600, 200, 120, or 60 g product with 1, 3, 5 or 10 g/kg.

In the EU monitoring system the polysorbates were examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 2 - 78% of ADI, while the calculated intake by young children is reported by one member state as 47 - 107%. It was concluded that because of the possible high intakes and that the directive allows for use of this substance by quantum satis, examination at tier 3 of these substances are needed.

**SCF/JECFA evaluation:**
**SCF status:** An ADI of 10 mg/kg bw was allocated in 1983 (group ADI for polysorbate 20, 40, 60, 65 and 80) [4]. The basis was NEL 2% in the diet in the 90-day study [4]. No details from that study were presented. The safety factor was not specified. The inclusion in the group ADI was confirmed for polysorbate 80 in 1993 [5].

**JECFA status:** A group ADI 0-25 mg/kg bw was established in 1973. The basis was the level of 5% in diet to rats, equivalent to 2500 mg/kg bw found in five old long-term studies. The safety factor was 100. The basal study was not identified [6].

**Background data:**
**Subacute/subchronic toxicity:** Studies are available in mouse, rat, hamster, dog, monkey and chick. No adverse effects were reported [7].

**Genotoxicity:** Ames test results in four strains S. typhimurium with/without metabolic activation were negative [5]. Other bacterial gene mutation tests, chromosome aberration (CA) tests, sister chromatid exchange tests in mammalian cells, and CA and micronuclei bone marrow tests showed that polysorbate was not genotoxic [5]

**Chronic toxicity/Carcinogenicity:** No consistent findings on carcinogenicity.
An NTP study is available. It is not stated whether this study was a 90-day or long-term study. Increased incidence was shown of neoplastic and non-neoplastic lesions in adrenal medulla, spleen, and haemopoetic system in the high dose male F344/N rats, not in female F344/N rats, male or female B6CF1 mice [5]. These data are equivocal. Lesions of the observed type have previously been associated with poorly metabolised food additives and have been regarded of no relevance for humans. There is an adequate safety margin between NOEL and the present ADI [5].

Studies are available in rats. No compound related effects were observed when the esters were fed at 5% in diet [7]. At higher levels (10, 20, 25%) marked diarrhoea, enlargement of caecum, and effects on postnatal survival, lactation efficiency and duration, and growth efficiency were noticed [7].

**Reproduction toxicity:** No relevant studies are found.

**Effect in humans:** No relevant studies are found.

**Other:** **Biochemical aspects:** Data on the metabolism are available. Data are consistent with intestinal hydrolysis of the ester linkage and metabolism of the fatty acid by the normal pathway [7].

**Conclusion:** The toxicological data available for SCF and JECFA include what would normally be required for an ADI to be set for a food additive. Generally, these studies show no toxic effects to be induced by the polysorbates. However, an NTP study reported increased incidence of neoplastic and non-neoplastic lesions in adrenal medulla, spleen, and haemopoetic system in the high dose male F344/N rats, but not in female F344/N rats, male or female B6CF1 mice. These effects were considered equivocal in animals by SCF because similar lesions have previously been associated with other poorly metabolised food additives given to animals at high doses. The effects are regarded to be of no relevance for humans by SCF. Furthermore, Ames test results in four strains S. typhimurium with/without metabolic activation were negative. In addition, other bacterial gene mutation tests, chromosome aberration (CA) tests, sister chromatide exchange tests in mammalian cells, and CA and micronuclei bone marrow tests showed that polysorbate 80 was not genotoxic. SCF concluded, that there are no reasons for requesting further studies nor for changing the existing acceptable status for polysorbate 80 [5].

Although there thus is no reason for direct concern, an update of the evaluation is recommended in light of the old evaluations, the discrepancy between the SCF and JECFA evaluations and the potential for exceeding the SCF ADI.

Polysorbates as defined by the specifications seems to be covered by the toxicological evaluation except for the content of impurities such as ethylene oxide, which is presently being addressed by SCF. The JECFA specifications are old, prepared in 1973 and 1981 respectively. It would be desirable to revise the specifications for this group of substances in future.

**References:**


6. [1973, NMRS 53/TRS 539-JECFA 17]

PECTIN AND AMIDATED PECTIN

E number:
Pectin: E 440 (i)
Amidated pectin: E 440 (ii)

Recommendation: No re-evaluation of pectin or amidated pectin is necessary.

Chemical name/synonyms: -

Chemical formula: -

EINECS number:
Pectin: 232-553-0
Amidated pectin: -

CAS number: 9000-60-5

Functional Class: Gelling agent, thickening agent, stabiliser.

Specification:
Manufacture: Pectin is obtained by extraction in an aqueous medium of appropriate plant material, usually citrus fruits and apples. Only organic precipitants used are methanol, ethanol and propane-2-ol.

Pectin
Definition: Pectin consists mainly of the partial methyl esters of polygalacturonic acid and their ammonium, sodium, potassium and calcium salts. It is soluble in water and insoluble in ethanol. Amidated pectin is obtained by further treatment with ammonia under alkaline conditions.

EC specifications: E 440 (i) Pectin [7].
Assay: Not less than 65% galacturonic acid on the ash-free and anhydrous basis after washing with acid and alcohol.
The specification includes purity criteria on Loss on drying, Acid-insoluble ash, Sulphur dioxide, Nitrogen, Free methanol, ethanol and propane-2-ol, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Pectins [5].
Assay: -
Galacturonic acid: Not less than 65% on the ash-free and dried basis.
In addition the specification includes purity criteria on Loss on drying, Acid-insoluble ash, Sulphur dioxide, Nitrogen, Free methanol, ethanol and propane-2-ol, Degree of amidation, Arsenic, Copper, Lead, Zinc and Heavy metals.


**Amidated pectin**

**Definition:** Amidated pectin consists mainly of the partial methyl esters and amides of polygalacturonic acid and their ammonium, sodium, potassium and calcium salts. It is soluble in water and insoluble in ethanol.

**EC specifications:** E 440 (ii) Amidated pectin [7].

Assay: Not less than 65% galacturonic acid on the ash-free and anhydrous basis after washing with acid and alcohol.

The specification includes purity criteria on Loss on drying, Degree of amidation, Acid-insoluble ash, Sulphur dioxide, Nitrogen, Free methanol, ethanol and propane-2-ol, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Amidated pectin is included in the JECFA specification for Pectins.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substances were for that reason not included in the EU monitoring system (tier 0).

Pectin is a natural component of human diet.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1983: An ADI “not specified” (Group ADI for non-amidated and amidated pectin) was allocated [4]. The Committee has been presented with sufficient data on amidated and non-amidated pectin for toxicological equivalent, but these data were not specified [4].

**JECFA status:** An ADI “not specified” (Group ADI for pectin and amidated pectin) was allocated in 1981 [1]. The basis was lack of adverse toxicity in the available toxicity studies and that pectin is a normal constituent of the diet.

**Background data:**

**Subacute/subchronic toxicity:** The available short-term study (90-day study in rats) showed that at 5% dietary levels, no adverse effects were seen [3].

**Genotoxicity:** No studies are necessary

**Chronic toxicity/Carcinogenicity:** No consistent evidence of carcinogenicity.

A long-term study in rats is available studying amidated pectin [4]. It showed the absence of any dose-response relationship in the incidence of hyperkeratosis of the forestomach, a lesion noted in an earlier long-term feeding study.

A 2-years pectin feeding study is available in rats [2]. It showed no significant difference between rats fed pectin or amidated pectin at levels of 10% in diet.

Effects of prolonged oral daily administration of 100 mg/kg bw of amidated pectin to has been studied in rats [2]. There appeared to be no adverse effects.
The Committee agreed that neither of the completed long-term studies were adequate either in terms of number of animals used, levels fed, or design [2].

Long-term feeding studies in rats fed diets containing up to 18.4% amidated or up to 10% non-amidated pectin showed no significant toxicological differences between animals fed amidated and non-amidated pectin [3].

**Reproduction toxicity:** A three-generation reproduction study in mice and a teratogenicity feeding study in rats fed diets containing 2% and 5% amidated or non-amidated pectin showed no significant toxicological differences between animals fed amidated and non-amidated pectin. No adverse effects were reported [3].

**Conclusion:** Pectin has been a natural component of human diet throughout evolution. There is no indication of toxic effects to be induced by pectin or amidated pectin.

Pectins as defined by the specifications are covered by the toxicological evaluation.

**References:**


AMMONIUM PHOSPHATIDES

E number: E 442

Recommendation: A re-evaluation of ammonium phosphatides is not necessary.

Chemical name/synonyms: Ammonium salts of phosphatidic acid, mixed ammonium salts of phosphorylated glycerides.

Chemical formula: -

EINECS number: -

CAS number:

Functional Class: Emulsifier.

Specification:

Manufacture: Obtained through reaction between ammonia and phosphatidic acids derived from edible fat (usually partially hardened rapeseed oil).

Definition: Ammonium phosphatides are a mixture of the ammonium compounds of phosphatidic acid. One or two or three glyceride moieties may be attached to phosphorus. Moreover, two phosphorus esters may be linked together as phosphatidyl phosphatides.

EC specifications: E 442 Ammonium phosphatides [1].
Assay: The phosphorus content is not less than 3% and not more than 3.4% by weight; the ammonium content is not less than 1.2% and not more than1.5% (calculated as N). Petroleum ether insoluble matter: Not more than 2.5%. In addition the specification includes purity criteria on Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Ammonium salts of phosphatidic acid [2].
Assay: The phosphorous content is not less than 3.0% and not more than 3.4% by weight; the ammonium content is not less than 1.2% and not more than1.5% (calculated as N). The specification includes purity criteria on Lead.

Exposure: The permitted uses of ammonium phosphatides is limited to cocoa and chocolate products including cocoa confectionary, max 10 g/kg, which means that it takes 180 g product with maximum content to reach the ADI.

In the EU monitoring system the substances were examined at tier 2 where the calculated intake by adults and the whole population is reported in the range of 1 - 11% of ADI. The calculated intake by young children is reported in the range of 8 - 26%. The investigators concluded that no further examination is needed at this stage.
SCF/JECFA evaluation:
SCF status: An ADI of 30 mg/kg bw was established in 1978 [3]. No data on toxicity or the basis for the evaluation were specified by SCF [3].

JECFA status: An ADI of 0-30 mg/kg bw was established in 1974 [4]. The basis was the level causing no toxicological, effects in rats of 60000 ppm (6%, highest dose) in the diet corresponding to 3000 mg/kg bw/day [4]. The safety factor was 100. The committee stated that the phosphorus content is to be included in the ADI for phosphates.

Background data:
Subacute/subchronic toxicity: Short-term studies (5 weeks, 90-days, 45 weeks) are available in rats at dietary levels up to 6% [5]. No adverse effects.

Genotoxicity: No study is needed.

Chronic toxicity/Carcinogenicity: A long-term study in rats showed no adverse effects at dietary levels up to 6% (highest dose studied) [5].

Reproduction toxicity: Reproduction studies in rats showed no adverse effects at dietary levels up to 6% (highest dose studied) [5].

Other: Biochemical aspects: The biochemical studies show that the ammonium salts of phosphatidic acids break down into normal food constituents that are absorbed and metabolised by normal physiological routes [5].

Conclusion: These additives seem to break down into normal food constituents that are absorbed and metabolised as such. Man has been exposed to these constituents throughout evolution. Therefore, although the data are old, there is no reason to expect any health problems with the limited use.

Ammonium phosphatides as defined by the specifications seem to be covered by the toxicological evaluation.

References:
4. [1974, NMRS 54/TRS 557-JECFA 18]
5. [1974, FAS 6/NMRS 54A-JECFA 18]
SUCROSE ACETATE ISOBUTYRATE

E number: E 444

Recommendation: No re-evaluation of SAIB is necessary.

Chemical name/synonyms: Sucrose diacetate hexaisobutyrate/ SAIB.

Chemical formula: $\text{C}_{40}\text{H}_{63}\text{O}_{19}$

EINECS number: 204-771-6

CAS number: 34482-63-8

Functional Class: Stabiliser.

Specification:
Manufacture: Sucrose acetate isobutyrate is obtained by esterification of food grade sucrose with acetic anhydride and isobutyric anhydride, followed by distillation.

Definition: Sucrose acetate isobutyrate is a mixture of all possible combination esters of sucrose, acetate and isobutyrate in which the molar ratio of acetate to isobutyrate is about 2:6.

EC specifications: E 444 Sucrose acetate isobutyrate [1].
Assay: Not less than 98.8% and not more than 101.9% of $\text{C}_{40}\text{H}_{63}\text{O}_{19}$.
Triacetin: Not more than 0.1%.
In addition the specification includes purity criteria on Acid value, Saponification value, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Sucrose acetate isobutyrate [2].
Assay: Not less than 98.8% and not more than 101.9% of $\text{C}_{40}\text{H}_{63}\text{O}_{19}$.
Triacetin: Not more than 0.1%.
In addition the specification includes purity criteria on Acid value, Saponification value and Heavy metals.

Exposure: Sucrose acetate isobutyrate is permitted only in soft drinks in an amount up to 300 mg/l. This means that an adult can reach the SCF ADI of 10 mg/kg only after 2 litres and a child of 30 kg after 1 litre drink containing the maximum level.

In the EU monitoring system, tier 2, the intake by young children is reported by one member state as 14% of the ADI. The investigators concluded that no further examination is needed at this stage.

SCF/JECFA evaluation:
SCF status: An ADI of 10 mg/kg bw was allocated in 1992 [3]. Chronic studies in rat were used for establishing a no adverse effect level and consequently an ADI. At the highest dose level used, 2000 mg/kg bw, the Committee found that there was some evidence of an effect on bodyweight and
food consumption in both sexes. At the lower dose, 1000 mg/kg bw dose, no consistent adverse effects were noted [3]. The safety factor was 100. Previously, there has been some debate about hepatic effect of SAIB as demonstrated in dogs. Based on available studies, the dog appears to be a particularly sensitive species to such effects. In the light of the available studies SCF concluded: “it would not be unreasonable to consider the hepatic effects, noted in the dog, as having little relevance to the evaluation of the safety of SAIB in man” [3].

**JECFA status:** Latest evaluation in 1996 when the previously allocated temporary ADI of 10 mg/kg bw was made full and set at 20 mg/kg bw [4]. The basis was the same rat study as used by SCF However, in contrast to SCF, JECFA considered the highest dose administered, 2000 mg/kg bw/day, as the NOEL and used a safety factor of 100.

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies in mouse and rat are available. No adverse hepatic effect and no evidence of interference with hepatobiliary function. A one year study in monkeys revealed no adverse hepatic effects and showed no evidence of interference with hepatobiliary function [3] [4].

The liver seems to be the target organ in the dog only. The changes were reversible within 3 weeks of removal of SAIB from the diet. The NOEL was 5 mg/kg bw/day. It was concluded, that the effects represented a functional rather than a toxic effect. No study longer than 12-13 weeks of duration was available. The effect of prolonged administration is not known [5]. The Committees concluded that a 2-year study in dogs were not necessary and that the dog was an inappropriate species on which to base an ADI [5] and that these effects were not relevant for humans [3] [4].

**Genotoxicity:** SAIB was not genotoxic in various tests *in vitro* and *in vivo* [5].

**Chronic toxicity/Carcinogenicity:** The carcinogenic potential has been investigated in mice and rats in long-term studies of up to 2 and 5 g/kg bw/day. No carcinogenic potential was shown [3] [5].

**Reproduction toxicity:** A multi-generation reproduction/teratogenicity study in rats and a teratology study in rabbits were negative [5].

**Effect in humans:** Three studies in humans are available in doses up to 20 mg/kg/day. There was no effect on the liver [3] [5].

**Other:** *Biochemical aspects:* Metabolic studies in rat, dog, monkey and man are available:

Hydrolysis and absorption:
Both rat, dog, monkey, and man absorb SAIB easily [3].

Studies in rat, dog, and humans indicate that absorption is delayed for several hours but that elimination is nearly complete by 4 to 5 days after ingestion. There is a de-esterification by non-specific esterases to partially acetylated esters and sucrose. Absorbed doses are largely excreted as CO₂ [5]. The dog differs from rat and humans in its disposition of SAIB [5]. The Committee concluded that the dog was an inappropriate species on which to base an ADI [5].

Excretion via urine and faeces
In rat and man 20-30% of dose is excreted as metabolites in urine and 10-20% as SAIB and metabolites in faeces. Dog excreted about 7% as metabolites in urine and about 50% as SAIB and metabolites in faeces [3]. The dog appeared to excrete highly acetylated sucrose in urine while rat and man excrete less highly acetylated partial sucrose esters i.e. dog appears to be unable to degrade highly acetylated sucrose [3].

Excretion via exhalation:
About 50% of SAIB is expired as CO₂ in rat and man, and about 25% in dog [3].

**Conclusion:** This additive is thoroughly studied. The studies available are mostly of newer date and include what normally would be required for an ADI to be set for a food additive. Generally, when excluding the dog, which is considered an inappropriate species for evaluating risk to humans for this substance, these studies show no effects to be induced by SAIB.

Sucrose acetate isobutyrate as defined by the specifications is covered by the toxicological evaluation.

**References:**


4. [1996, TRS 868-JECFA 46]

5. [1993, FAS 32-JECFA 41]
GLYCEROL ESTERS OF WOOD ROSIN

E number: E 445

Recommendation: A re-evaluation of glycerol esters of wood rosin is not necessary.

Chemical name/synonyms: Ester gum.

Chemical formula: -

EINECS number: -

CAS number: 8050-30-4

Functional Class: Emulsifier, stabiliser.

Specification:
Manufacture: Glycerol esters of wood rosin is obtained by reaction between glycerol and wood rosin derived by solvent extraction of aged pine stumps followed by a liquid-liquid solvent refining process. Substances derived from gum rosin, exudate of living pine trees and substances derived from tall oil rosin (a by-product of kraft (paper) pulp processing) are allowed as source materials. The substance is purified by stripping or by concurrent steam distillation.

Definition: Glycerol esters of wood rosin is a complex mixture of tri- and diglycerol esters of resin acids from wood rosin. It is composed of about 90% resin acids and 10% neutral (non-acidic) compounds. The resin acid fraction is a complex mixture of isomeric diterpenoid monocarboxylic acids having the typical empirical formula of \( \text{C}_{20}\text{H}_{30}\text{O}_{2} \), of which the main component is abietic acid. It is insoluble in water and soluble in acetone.

EC specifications: E 445 Glycerol esters of wood rosin [1].
Assay: -
The specification includes purity criteria on Specific gravity of solution, Ring and ball softening range, Acid value, Hydroxyl value, Test for absence of tall oil rosin, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Glycerol esters of wood rosin [2].
Assay: -
The specification includes purity criteria on Specific gravity of solution, Ring and ball softening range, Acid value, Hydroxyl value, Test for absence of tall oil rosin, Arsenic, Lead and Heavy metals.

Exposure: The permitted use of glycerol esters of wood rosin is restricted to soft drinks, 100 mg/l, and the surface treatment of citrus fruits, 50 mg/kg. Thus the potential maximum intake will be well below the ADI of 12,5 mg/kg bw from these sources.
SCF/JECFA evaluation:

SCF status: Latest evaluation in 1992 when an ADI of 12.5 mg/kg bw was established [3]. This value replaced the previous temporary ADI of 0.5 mg/kg bw as established in 1990 [4]. The basis was a new 90-day rat study, which was requested at the previous meeting. Here the NOEL was 2500 mg/kg bw. The committee applied a safety factor of 200, taking into account that no longer term study than the 90-days study is available [3]. No details or references were given in any of the opinions.

JECFA status: Latest evaluation in 1996 when an ADI of 0-25 mg/kg bw was allocated [5]. The basis was new metabolic studies and the toxicological data. The basal investigation was a 13-weeks study in rats that demonstrated a NOEL of 2500 mg/kg bw/day (highest dose). The safety factor was 100 [5].

Background data:

Subacute/subchronic toxicity: SCF notes that a 90-day rat study is available on glycerol esters of wood rosin: It indicated a NOEL of 2500 mg/kg bw [3]. The basic resins for production of the glycerol esters, wood rosin, gum rosin, and tall oil rosin have all been tested in 90-day studies in rat and dog [4]. No data were specified by SCF. A 90-days study in rats fed Ester gum 8 D#, which is assumed to be the same product as Estergum 8BG indicates that this ester is quantitatively similar in effect to the parent rosin (wood rosin) [4]. Again no data were specified by SCF.

JECFA notes that food-grade material was less toxic than the non-food-grade material in 13-week studies [6]. Short-term toxicity studies are available in rats [7] No adverse effects were demonstrated at the highest doses: 2500 mg/kg bw [6].

Genotoxicity: No evidence of genotoxicity [4;6].

Chronic toxicity/Carcinogenicity: No long-term studies have been performed on the ester as such, but are available in rats and dogs on gum rosin, wood rosin, and tall oil rosin. No consistent adverse effects were demonstrated [4] [6]. Wood rosin at doses up to 434 mg/kg bw/day did not induce histopathological changes in a long-term study of toxicity and carcinogenicity in rats [6].

Reproduction toxicity: Although there was no reproduction/teratogenicity study available, JECFA considered that the data from previously reviewed studies and the new studies confirming non-bioavailability were adequate to establish the ADI [5].

Effect in humans: Studies are available in man [6]. No adverse effects were noticed.

Other: Biochemical aspects: In vitro (incubation with human faecal extracts) and in vivo metabolism studies in rats are available. They show that the food-grade material is quite stable in the gastrointestinal tract and that only a minor fraction (the monoglycerol fraction) undergoes partial hydrolysis if any, although the sensitivity of the analysis was questioned [7].

Conclusion: Although there are no reproduction/teratogenicity study or a long-term study on the substance as such, the overall available data, including metabolism data, and the low level of
exposure gives no reason for concern. If however, permitted levels were to be raised significantly, a reproduction/teratogenicity study should be obtained.

Glycerol esters of wood rosin as defined by the specifications is covered by the toxicological evaluation.

**References:**


**Di-, Tri- and Polypophosphates**

**E number:**

<table>
<thead>
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<th>Compound</th>
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<td>Disodium diphosphate</td>
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<td>Pentasodium tripolyphosphate</td>
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**See:** E 338 Phosphoric acid.
**β-CYCDODEXTRIN**

**E Number:** E 459

**Recommendation:** No re-evaluation of β-cyclodextrin is necessary.

**Chemical name/synonyms:** Cycloheptaamylose/ β-Schardinger dextrin, cyclodextrin B.

**Chemical formula:** \((C_6H_{10}O_5)_7\)

**EINECS number:** 231-493-2

**CAS Number:** 7585-39-9

**Functional Class:** Encapsulating agent for food additives, flavourings and vitamins.

**Specification:**

**Definition:** β-Cyclodextrin is a non-reducing cyclic saccharide consisting of seven α-linked D-glucopyranosyl units.

**Manufacture:** β-Cyclodextrin is obtained by the action of cyclodextrin transglycolase on hydrolysed starch followed by purification of the β-cyclodextrin. Purification is carried out by preparation of a β-cyclodextrin /solvent inclusion compound followed by steam-stripping of the solvent before final purification.

**EC specifications:** E 459 β-Cyclodextrin [6].

Assay: Not less than 98.0% of \((C_6H_{10}O_5)_7\) on the anhydrous basis. The specification includes purity criteria on Water, Other cyclodextrins, Residual solvents, Reducing substances (as glucose), Sulphated ash, Arsenic and Lead.

**JECFA specifications:** β-Cyclodextrin [4].

Assay: Not less than 98.0% of \((C_6H_{10}O_5)_7\) on the anhydrous basis. The specification includes purity criteria on Water, Other cyclodextrins, Residual solvents, Reducing substances (as glucose), Sulphated ash, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted as carrier for food additives. Maximum level 1g/kg, which means that it will take 300 g of a food with the maximum level to reach the ADI. Not included in the EU monitoring system, as it is a new substance (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** An ADI of 5 mg/kg bw was allocated in 1996 to beta-cyclodextrin manufactured using a CGTase preparation from Bacillus circulans [5]. The basis was the NOEL of 1.25% in the diet (equal to 470 mg/kg bw/day) found in a 1-year study in dogs and a safety factor on 100 [5]. The higher dose, 5% in diet, had minimal effects on kidney function. No other effects were presented from that study.
On 22 June 2000 the ADI was extended to cover also beta-cyclodextrin produced using cycloglycosyltransferase obtained from Paenibacillus macerans (http://europa.eu.int/comm/food/fs/sc/scf/out59_en.pdf) and from a recombinant Bacillus licheniformis (http://europa.eu.int/comm/food/fs/sc/scf/out58_en.pdf).

**JECFA status:** An ADI 0-5 mg/kg bw was allocated in 1995 [1]. The new data available in 1995 confirmed the low systemic toxicity of β-cyclodextrin. The basis was the NOEL of 1.25% in the diet (equal to 470 mg/kg bw/day) found in the 1-year study in dogs and a safety factor on 100 [1]. The higher dose, 5% in diet, had minimal effects on kidney function.

**Background data:**
**Subacute/subchronic toxicity:** No obvious toxic effects.

A 13-week study is available in rats. No adverse effects were noticed [5].

A number of short-term studies are available in mice, rats, and dogs. They show low if any oral toxicity [2].

**Genotoxicity:** No evidence of genotoxicity.

A number of *in vitro* and *in vivo* mutagenicity studies are available. No mutagenic potential was noticed [5].

Several *in vitro* and *in vivo* studies are available. No mutagenic potential was noticed [2].

**Chronic toxicity/Carcinogenicity:** No evidence of carcinogenicity.

SCF notes that one-year studies in rats and dogs are available [5]. The NOAEL was 466 mg/kg bw/day (1.25% in diet, highest dose 5% had minimal effects on kidney function). No effects were noted [5].

A multi-generation study is available in rats [5] indicating a NOEL for reproductive effects around 550-3000 mg/kg bw/day over different phases of the study. No evidence of carcinogenicity was reported in that [5]. Chronic toxicity/carcinogenicity studies are available in rat and mouse [5]. No adverse effects were noticed [5].

The results of a 1-year oral toxicity study in dogs and a 1-year study in rats are available. The NOEL was 1.25% in diet for both species, equivalent to 650 and 470 mg/kg bw/day, respectively. At higher doses there were minor clinical biochemical, kidney, and liver changes [3]. The results of carcinogenicity studies in mice and rats are available. The NOEL was 25 mg/kg bw/day in the study in mice. At higher doses species-specific effects on the lower gastrointestinal tract were noticed usual for a bulking agent. No effects were noted in the study in rats. No carcinogenicity was observed mice or rats [3].

Carcinogenicity studies of β-cyclodextrin in rats and mice showed no adverse effects [8;9].

**Reproduction toxicity:** No indication of effects on reproduction or teratogenic parameters.

A teratology study in rats was available to SCF. No adverse effects were noticed [5].
See the multi-generation study mentioned above. SCF concluded that a teratology study in a second species was not required [5].

The results of a 3-generation reproductive toxicity study in rats were available to JECFA. The NOEL was 1.25% in diet, equivalent to 560-2900 mg/kg bw/day, depending on the stage of the study. The only effect on higher doses was impaired pub growth during lactation [3]. Teratogenicity studies are available in rats and rabbits. No adverse effects including foetotoxicity were demonstrated [2].

**Allergy/Intolerance:** Studies on irritancy, sensitisation, and eye irritancy showed no abnormal reactions [2].

**Effect in humans:** In human volunteers, a dose of 24 g β-cyclodextrin/day was well tolerated on a short-term basis. At higher doses (48 g/day) or when dosed for prolonged time, “traditional complains” for intake of bulky substances were noticed [2].

**Other:** *Biochemical aspects:* The submitted metabolism data are limited, but indicate in both animals and man, that β-cyclodextrin is not absorbed but degraded in colon by the microflora and endogenous enzymes [5]

Studies on absorption, distribution, and excretion are available. They showed that a small fractional was excreted via urine. No significant tissue disposition was noticed [2].

Metabolic studies in animals and humans consistently indicate that β-cyclodextrin is poorly hydrolysed or absorbed in the upper gastrointestinal tract but is largely utilised by the gut micro flora in the lower gut. A small proportion may be absorbed intact [2].

The results of *in vitro* and *in vivo* studies on the effect of β-cyclodextrin on the bioavailablity of lipophilic nutrients indicate no effect [3].

Absorption, distribution, excretion and metabolism of orally administered $^{14}$C-β-cyclodextrin have been investigated in rats [7].

**Conclusion:** The available studies include what would normally be required for an additive to be evaluated. These studies showed no adverse effects. This additive is close to novel food.

No need for a re-evaluation of the ADI.

β-Cyclodextrin as defined by the specifications is covered by the toxicological evaluation.

**References:**

2. [1993, FAS 32-JECFA 41]  

3. [1995, FAS 35-JECFA 44]  


MICROCRYSTALLINE CELLULOSE AND POWDERED CELLULOSE

**E number:**
Microcrystalline cellulose: E 460 (i)
Powdered cellulose: E 460 (ii)

**Recommendation:** A re-evaluation of MC is not necessary. The potential for intestinal persorption should be kept in mind particularly in infants and individuals with affected intestinal function/integrity.

**Chemical name/synonyms:**
Microcrystalline cellulose: Cellulose gel.
Powdered cellulose: Cellulose, Linear polymer of 1:4 linked glucose residues.

**Chemical formula:** \((C_6H_{10}O_5)_n\)

**EINECS number:** 232-674-9

**CAS number:** 9004-34-6

**Functional Class:** Emulsifier, stabiliser, anticaking agent.

**Specification:**
**Manufacture:** Microcrystalline cellulose is obtained by treating alpha-cellulose, derived as a pulp from fibrous plant material, with mineral acids.
Powdered cellulose is obtained by purification and mechanical disintegration of alpha-cellulose.

**Microcrystalline cellulose**
**Definition:** Microcrystalline cellulose is a purified, partially depolymerised cellulose. The degree of polymerisation is typically less than 400. It is insoluble in water, ethanol, ether and dilute mineral acids. It is slightly soluble in sodium hydroxide solution.

**EC specifications:** E 460 (i) Microcrystalline cellulose [1].
Assay: Not less than 97% calculated as cellulose on the anhydrous basis.
Particle size: Not less than 5 µm (not more than 5% of particles of less than 5 µm)
In addition the specification includes purity criteria on Loss on drying, Water-soluble matter, Sulphated ash, pH of a 10% suspension in water, Starch, Carboxyl groups, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Microcrystalline cellulose [2].
Assay: Not less than 97% calculated as cellulose on the dried basis.
Particle size: Not more than 10% of the particles have a diameter below 5 µm.
The specification includes purity criteria on Loss on drying, Water-soluble matter, Sulphated ash, pH of a 10% suspension in water, Starch and Lead.
**Powdered cellulose**

**Definition:** Powdered cellulose is mechanically disintegrated cellulose. It is slightly soluble in sodium hydroxide solution.

**EC specifications:** E 460 (ii) Powdered cellulose [1].

Assay: Not less than 92%.

Particle size: Not less than 5 µm (not more than 5% of particles of less than 5 µm)

In addition the specification includes purity criteria on Loss on drying, Water-soluble matter, Sulphated ash, pH of a 10% suspension in water, Starch, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Powdered cellulose [3].

Assay: Not less than 92%.

The specification includes purity criteria on Loss on drying, Water-soluble matter, Total ash, pH of a 10% suspension in water, Starch, Arsenic, Lead and Heavy metals.

**Exposure:** The celluloses are permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substances were for that reason not included in the EU monitoring system (tier 0).

Not permitted in foods particularly intended for children.

Cellulose has been a natural component of food throughout the evolution of man.

**SCF/JECFA evaluation:**

**SCF status:** An ADI “not specified” was allocated for both celluloses in 1978 [4]. Here, SCF endorsed the ADI established by JECFA, but did not give any details of the data considered. In 1993 the Committee advised that particle size for microcrystalline cellulose should not exceed 5µm and that microcrystalline cellulose, whatever particle size, should not be used in infant and weaning foods [5]. In 1997 the Committee evaluated additional toxicological information submitted and confirmed the validity of the ADI “not specified”, but, as a matter of precaution, repeated its advise that particle size should not exceed 5 µm (with a tolerance of 10%) and that it should not be used in foods specially prepared for infants and young children including foods for special medical purposes [6].

**JECFA status:** An ADI “not specified” was allocated for both celluloses in 1976 [7]. The basis was lack of adverse toxicity in the available toxicity studies from humans and animals. These studies include what would be normally required for an ADI to be set for a food additive. In 1997 JECFA considered the data on persorption of microcrystalline cellulose and set a limit for the particle size of 5 µm and a content of not more than 10% smaller [8].

SCF and JECFA consider microcrystalline cellulose and powdered cellulose to be similar with respect to toxicity. Consequently, they do not specify the identity of the compound used for studies. Both are named “MC”.

**Background data:**

**Subacute/subchronic toxicity:** A 28-day toxicity study in rats is available: No adverse
toxicological effects, and no persorbed particles in gut or in the Peyers’patches at highest dose level were noticed [6] [8].

Three 90-day studies in rats are available: In the first study, NOAEL was approximately 4000 mg/kg bw/day, in the second study NOAEL was approximately 6000 mg/kg bw/day, and in the third study NOAEL was approximately 5000 mg/kg bw/day. No MC particles were found in any organ or tissue. No adverse histopathological effects, in particular no kidney lesions were found [6].

Several short-term studies are available to JECFA in rats. No adverse effects were demonstrated [8;9].

In earlier studies, persorption of MC was reported in various species including rats. A recent study in which a fine particle size preparation of MC (median diameter of particles 6µm) was administered to rats (5 g/kg bw/day) for 90-days failed to confirm the earlier observations. In this study precautions were taken to ensure that at autopsy, there was no cross-contamination of the tissue with fine particulate matter [8;9].

In 90-days toxicity tests, the NOEL exceeded 50 g/kg diet equivalent to 3800 and 4400 mg/kg bw/day in male and female rats, respectively [8;9].

**Genotoxicity:** There is no evidence that MC is genotoxic as indicated in a series of adequately performed mutagenicity test using different genetic endpoints.

**In vitro** studies:
Several studies are available [6;8]:
- Three bacterial microsomal reversion tests are available: No increase in number of revertants.
- Forward gene mutation tests in cultured mouse lymphoma cells are available: No increase in mutants.
- Cultured primary hepatocytes tests are available: No unscheduled DNA synthesis.

**In vivo** studies:
Several micronucleus tests in mice are available: No increase in number of micronuclei.

**Chronic toxicity/Carcinogenicity:** No evidence of carcinogenicity.

In a 6-months study in rats dosed with 0 or 330 ppm no adverse effects were reported [6]. A 2-years study is available [6]. See “Reproductive toxicity studies”.

Long-term toxicity/carcinogenicity studies are available in rats. No adverse effects were demonstrated. A two-year feeding study is available and is referred to. Despite the lack of evidence of toxic effects, the Committee considered that the execution and reporting of this study were not adequate to identify a NOEL (No reference was specified) [8;9]. It was concluded that MC has no effect on chemical induced tumour growth in rats [8;9].

**Reproduction toxicity:** Reproductive functions were not affected and no teratogenic potential has been reported.

A combined 2-years reproduction/chronic study in rats where F1 was fed 90% particles of <20 µm in diet (highest dose 20% in diet) showed no adverse effects on litter parameters. Food consumption
was increased. After 12 months MC particles could be detected in some organs and no microemboli were identified [6]. In a teratogenicity study in rats fed 25000 or 50000 mg/kg in diet from G6-G15 the NOAEL was 4410 mg/kg bw/day [6]. In another teratogenicity study in rats fed 25000 or 50000 mg/kg in diet from G6-G15 the NOAEL 4589 mg/kg bw/day [6].

A three-generation reproduction study (published 1964) in rats using 30% MC in the diet showed some effects that were considered to be a consequence of the quality of material reducing the energy density of the diet [8;9]. In recent embryotoxicity and teratogenicity studies in rats at dietary levels up to 50 g/kg diet (equivalent to 4.6 g/kg bw/day) there were no effects [8;9].

**Allergy/Intolerance:** No sensitisation potential was shown in guinea-pigs. No eye irritating effect in rabbits [8;9].

**Effect in humans:** Human clinical studies are available: Up to 30 g MC/day in diet had no adverse effect on the function of the gastrointestinal tract, on haematological or clinical biochemical parameters, but produced increased faecal output [6]. The available human data on particles other than MC and animal studies on MC and the GALT suggest that in normal adults, exposed over a comparatively short period, the intestinal persorption of MC particle size even down to at least 5 µm would be unlikely to cause any adverse pathological effects in the gut and GALT. The Committee stressed that there are no data available on the existence and the extent of persorption in very young animals or in human infants [6].

Studies in humans show no adverse systemic toxicity [8;9].

**Other:** *Biochemical aspects:* MC was the least digestible of 3 types of investigated cellulose tested in rats at 5% in diet [6]. A study on the determination of available energy from MC is submitted but no data are given [6]. Several other studies are available in rats and some in pigs, dog, and man [8]. These studies demonstrate minimal absorption, distribution and degradation.

Special studies on persorption:
Research has been carried out confirming that MC particles ranging in size from 5-150 µm could be persorbed and detected in venous blood taken 1-2 h after ingestion by rats, dogs, minipigs and in 1 human volunteer [6]. I.v. administration of MC particles to rats showed some effects on haematology and renal function. Particles could be identified in various tissues [6]. From numerous older studies reported in literature it appears that persorption is a universal physiological process similar in mammals, the rat being a good model for man in this respect. Man and animals do not show accumulated MC-particles in intestines, or in the GALT. In recent studies persorption has been shown to be an inefficient process. Persorption does not result in microembolic phenomena, nor does it appear to interfere with immune function or the GALT.
A new study in which fine particles size preparation of microcrystalline cellulose (median diameter of particles 6 µm) was administered orally to rats (5 g/kg bw/day) for 90 days failed to confirm earlier observations of persorption [8].

In conclusion, in the older studies contamination seems to be an explanation for (in part some) of the persorption and tissue distribution reported [6].
**Conclusion:** Cellulose has been a natural component of food throughout the evolution of man. Nowadays commercially available preparations of microcrystalline cellulose vary in particle size.

The toxicological studies available for SCF are also of newer date and include what normally would be required for an ADI to be set for a food additive. These studies show no effects. During the 1990-ies there has been a still ongoing debate about the intestinal persorption of MC of varying particle size, in particular if the particle size is less than 5 \( \mu \text{m} \). The Committee in 1997 stressed that there is no data available on the existence or extent of persorption in very young animals or in human infants. As a consequence a lower limit of particle size and content has been set as a matter of precaution.

Microcrystalline cellulose and powdered cellulose as defined by the specifications is covered by the toxicological evaluation, including restriction on particle size.

**References:**


7. **[1976, FNS 1/TRS 599-JECFA 20]**

8. **[1997, TRS 884-JECFA 49]**

9. **[1997, FAS 40-JECFA 49]**
MODIFIED CELLULOSES

E Number:
- Methyl cellulose: E 461
- Hydroxypropyl cellulose: E 463
- Hydroxypropyl methyl cellulose: E 464
- Ethyl methyl cellulose: E 465
- Carboxy methyl cellulose: E 466
- Sodium carboxy methyl cellulose: E 466
- Enzymatically hydrolysed carboxymethyl cellulose: E 469

Recommendation: A re-evaluation of these cellulose derivatives is not necessary.

Chemical name/synonyms:
- Methyl cellulose: Cellulose methyl ether.
- Hydroxypropyl cellulose: Cellulose hydroxypropyl ether.
- Hydroxypropyl methyl cellulose: 2-hydroxypropyl ether of methyl cellulose.
- Ethyl methyl cellulose: Ethyl methyl ether of cellulose.
- Carboxy methyl cellulose: -
- Sodium carboxy methyl cellulose: Carboxy methyl cellulose, CMC, NaCMC, sodium CMC, cellulose gum.
- Enzymatically hydrolysed carboxymethyl cellulose: Sodium carboxymethyl cellulose, partially hydrolysed.

Chemical formula: -

EINECS number: -

CAS number:
- Methyl cellulose: 9004-67-5
- Hydroxypropyl cellulose: 9004-64-2
- Hydroxypropyl methyl cellulose: 9004-65-3
- Ethyl methyl cellulose: 9004-69-7
- Carboxy methyl cellulose: -
- Sodium carboxy methyl cellulose: 9004-32-4
- Enzymatically hydrolysed carboxymethyl cellulose: -

Functional Class: Thickener, stabiliser, emulsifier.

Specification:
Methyl cellulose

Manufacture: Methyl cellulose is obtained by treatment of fibrous plant material with alkali and methyl chloride.
**Definition:** Methyl cellulose is a partial methyl ether of cellulose. It is insoluble in ethanol and ether and soluble in glacial acetic acid.

**EC specifications:** E 461 Methyl cellulose [1].
Assay: Content not less than 25% and not more than 33% of methoxyl groups (-OCH₃) and not more than 5% of hydroxyethoxyl groups (-OCH₂CH₂OH).
The specification includes purity criteria on Loss on drying, Sulphated ash, pH, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Methyl cellulose [2].
Assay: Content not less than 25% and not more than 33% of methoxyl groups (-OCH₃).
The specification includes purity criteria on Loss on drying, Sulfated ash, pH, Arsenic, Lead, and Heavy metals.

**Hydroxypropyl cellulose**

**Manufacture:** Hydroxypropyl cellulose is obtained by treatment of fibrous plant material with alkali and propylene oxide.

**Definition:** Hydroxypropyl cellulose is a partial hydroxypropyl ether of cellulose. It is soluble in ethanol and insoluble in ether.

**EC specifications:** E 463 Hydroxypropyl cellulose [1].
Assay: Content not less than 80.5% hydroxypropyl groups (-O CH₂CHOHCH₃) equivalent to not more than 4.6 hydroxypropyl groups per anhydroglucose unit on the anhydrous basis.
Propylene chlorohydrins: Not more than 0.1 mg/kg.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, pH, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Hydroxypropyl cellulose [3].
Assay: Content not less than 80.5% hydroxypropyl groups (-O CH₂CHOHCH₃) equivalent to not more than 4.6 hydroxypropyl groups per anhydroglucose unit on the anhydrous basis.
Propylene chlorohydrins: Not more than 0.1 mg/kg.
The specification includes purity criteria on Loss on drying, Sulfated ash, pH, Arsenic, Lead, and Heavy metals.

**Hydroxypropyl methyl cellulose**

**Manufacture:** Hydroxypropyl methyl cellulose is obtained by treatment of fibrous plant material with alkali, methyl chloride and propylene oxide.

**Definition:** Hydroxypropyl methyl cellulose is a methyl cellulose modified with a small amount of 2-hydroxypropyl groups attached through ether links to anhydroglucose units of the cellulose. It is soluble in ethanol and insoluble in ether.

**EC specifications:** E 464 Hydroxypropyl methyl cellulose [1].
Assay: Content not less than 19% and not more than 30% methoxyl groups (-OCH₃) and not less than 3% and not more than 12% of hydroxypropyl groups (-O CH₂CHOHCH₃), on the anhydrous basis.
Propylene chlorohydrins: Not more than 0.1 mg/kg.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, pH, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Hydroxypropyl methyl cellulose [3].
Assay: Content not less than 19% and not more than 30% methoxyl groups (-OCH₃) and not less than 3% and not more than 12% of hydroxypropyl groups (-O CH₂CHOHCH₃), on the anhydrous basis.
Propylene chlorohydrins: Not more than 0.1 mg/kg.
The specification includes purity criteria on Loss on drying, Sulfated ash, pH, Arsenic, Lead, and Heavy metals.

*Ethyl methyl cellulose*
**Manufacture:** Ethyl methyl cellulose is obtained by treatment of fibrous plant material with alkali, dimethyl sulphate and ethyl chloride.

**Definition:** Ethyl methyl cellulose is a mixed ether of cellulose in which both the methyl and ethyl groups are attached to the anhydroglucose units by ether linkages. It is insoluble in ethanol.

**EC specifications:** E 465 Ethyl methyl cellulose [1].
Assay: Content on the anhydrous basis not less than 3.5% and not more than 6.5% of methoxyl groups (-OCH₃) and not less than 14.5% and not more than 19% of ethoxyl groups (-O CH₂CH₃), and not less than 13.2% and not more than 19.6% of total alkoxyl groups, calculated as methoxyl.
The specification includes purity criteria on Loss on drying, Sulphated ash, pH, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Methyl ethyl cellulose [4].
Assay: Content on the anhydrous basis not less than 3.5% and not more than 6.5% of methoxyl groups (-OCH₃) and not less than 14.5% and not more than 19% of ethoxyl groups (-O CH₂CH₃), and not less than 13.2% and not more than 19.6% of total alkoxyl groups, calculated as methoxyl.
The specification includes purity criteria on Loss on drying, Sulfated ash, Arsenic, Lead, and Heavy metals.

*Carboxy methyl cellulose*
No information on manufacture, definition and specification for Carboxy methyl cellulose. It is doubtful whether this substance exists as a food additive.

*Sodium carboxy methyl cellulose*
**Manufacture:** Sodium carboxy methyl cellulose is obtained from cellulose by treatment with alkali and monochloro acetic acid or its sodium salt.

**Definition:** Sodium carboxy methyl cellulose is the partial sodium salt of a carboxy methyl ether of cellulose, the cellulose being obtained from fibrous plant material. It is insoluble in ethanol.

**EC specifications:** E 466 Sodium carboxy methyl cellulose [1].
Assay: Content not less than 99.5%.
The specification includes purity criteria on Degree of substitution, Loss on drying, pH, Total
glycolate, Sodium, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Sodium carboxymethyl cellulose [2].
Assay: Content not less than 99.5% on the anhydrous basis.
The specification includes purity criteria on Degree of substitution, Loss on drying, pH, Free
glycolate, Sodium, Sodium chloride, Arsenic, Lead and Heavy metals.

Enzymatically hydrolysed carboxy methyl cellulose
Manufacture: Enzymatically hydrolysed carboxy methyl cellulose is obtained from sodium
carboxy methyl cellulose by enzymatic treatment with Trichoderma reesei.

Definition: Enzymatically hydrolysed carboxy methyl cellulose is the sodium salt of carboxy
methyl cellulose which have been partially hydrolysed. The total content of mono- and
disaccharides does not exceed about 7.5%. It is soluble in water and insoluble in ethanol.

EC specifications: E 469 Enzymatically hydrolysed carboxymethyl cellulose [5].
Assay: Content not less than 99.5%, including mono- and disaccharides, on the dried basis.
The specification includes purity criteria on Degree of substitution, Loss on drying, pH, Total
glycolate, Residual enzyme activity and Lead.

JECFA specifications: Sodium carboxymethyl cellulose, enzymatically hydrolysed [6].
Assay: Content not less than 99.5%, including mono- and disaccharides, on the dried basis.
The specification includes purity criteria on Degree of substitution, Loss on drying, pH, Sodium
chloride and sodium glycolate, Residual enzyme activity and Lead.

Exposure: The modified celluloses are permitted generally in foodstuffs except those where
additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not
possible. The parent compound, cellulose, has been a natural component of food throughout the
evolution of man. ADI is “not specified” and the substances were for that reason not included in the
EU monitoring system (tier 0).

SCF/JECFA evaluation:
SCF status: A group ADI “not specified” was allocated for 5 of the celluloses in 1992 and later that
year enzymatically hydrolysed CMC was included in the group ADI [7]. The Committee, which
largely based its evaluation on JECFA, noted that all studies, normally required for setting an ADI,
were not available for all the substances. However, considering the very close structural and
functional similarities between the different celluloses, the Committee was of the opinion that safety
data on various substances can be used for the safety evaluation of the group

In 1997, when reviewing some additives for use in foods for infants and young children, the
Committee found the inclusion of up to 10 g per kg or litre of sodium carboxy methyl cellulose
acceptable in foods for special medical purposes [8].

JECFA status: In 1989, when new studies were submitted including studies in rats on cecal
enlargement and changes in cecal flora, teratology and development as well as in vitro mutagenicity
studies, the previous numerical ADI was changed to an ADI “not specified” for seven celluloses
[9]. The overall basis was lack of adverse toxicity in the available toxicity studies that include what
would be normally required for an ADI to be set for a food additive. The ability to produce lactation should be taken into account when using these substances as food additives [9].

Enzymatically hydrolysed-CMC was included in the ADI in 1998 [10]. The Committee concluded that there is no toxicological difference between carboxymethyl cellulose and enzymatically hydrolysed carboxymethyl cellulose.

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies are available for E461 (rats, dogs), E463 (rat, chicken), E464 (rats, rabbits, dogs), E465 (chicken), E466 (rats, guinea-pigs, rabbits, dogs, chicken), and E469 (rats). No adverse effects were noticed [11].

**Genotoxicity:** Studies *in vitro* and *in vivo* are available for E461 and E466. No mutagenic activity [11].

**Chronic toxicity/Carcinogenicity:** Long-term/carcinogenicity studies on E461 (rats), E464 (rats), E465 (mice, rats), and E466 (mice, rats) are available. They show no evidence of carcinogenicity [11].

**Reproduction toxicity:** Reproduction and teratology studies with E463 (rats, rabbits), E461 (mice, rats, hamsters, rabbits), and E466 (mice, rats) have been performed. No effect on the reproductive process, and no embryotoxic or developmental effects were observed [11].

**Allergy/Intolerance:** Irritation-sensitisation studies are available for E461, E463, E464, and E466 [7].

**Effect in humans:** E461, E464, and E466 have been investigated in humans and the usual effects of indigestible fibre on the bulk, the physical consistency, and the frequency of faeces are seen. Effects of as low doses as 5 g/person/day have been noticed. At higher doses diarrhoea has been reported in some subjects, but in others constipation developed. The highest doses were at 30 g/person/day [11].

**Other:** *Biochemical aspects:* Studies on absorption, distribution and excretion are available for E461, E463, E464, E465, E466, and E469. No absorption seems to occur and the substances are excreted quantitatively in the faeces [11].

**Conclusion:** Cellulose has been a natural component of food throughout the evolution of man. Considering the very close structural and functional similarities between the different cellulose derivatives, the safety data on various substances can be used for the safety evaluation of the group. The toxicological data on the cellulose derivatives collectively include what would normally be required for a food additive to be evaluated. In these studies no adverse effects were reported. A re-evaluation is therefore not warranted.

The modified celluloses as defined by the specifications are covered by the toxicological evaluation. However, the JECFA specifications have been prepared at several different meetings ranging from the seventeenth meeting (1973) to the fifty-first meeting (1998). It could therefore be desirable to revise the specifications for this group of substances at a future JECFA meeting.
References:


CROSS-LINKED SODIUM CARBOXYMETHYL CELLULOSE

E number: E 468

Recommendation: A re-evaluation of cross-linked CMC is not necessary.

Chemical name/synonyms: Cross-linked carboxymethyl cellulose, Cross-linked CMC, Cross-linked sodium CMC, Cross-linked cellulose gum.

Chemical formula: -

EINECS number: -

CAS number: -

Functional Class: Disintegration agent.

Specification:
Manufacture: Cross-linked sodium carboxymethyl cellulose is obtained from sodium carboxymethyl cellulose by treatment at elevated temperature.

Definition: Cross-linked sodium carboxymethyl cellulose is the sodium salt of thermally cross-linked partly O-carboxymethylated cellulose.

EC specifications: E 468 Cross-linked sodium carboxymethyl cellulose [1].
Assay: -
The specification includes purity criteria on Loss on drying, Water soluble matter, Degree of substitution, pH, Sodium, Arsenic, Lead, Mercury and Cadmium.

JECFA specifications: No JECFA specification has been prepared.

Exposure: Cross-linked sodium carboxymethyl cellulose is permitted only as carrier for sweeteners.

SCF/JECFA evaluation:
SCF status: Cross-linked sodium carboxymethyl cellulose was evaluated in 1994. No ADI could be established because the extent of available data was not sufficient, but the committee accepted the limited use as a tablet disintegrant in sweeteners [2]. In 1998 the acceptable use was extended to include also dietary supplements [3]. The acceptances was based on the lack of toxicity in the available studies and the long history of safe use of the parent compound i.e. sodium carboxymethyl cellulose.

JECFA status: Has not been evaluated by JECFA, but is on the agenda for 2002.
Background data:

Subacute/subchronic toxicity: A 90-day study in rats is available. The rats were fed diet containing 0, 10000 or 50000 ppm. No effects except reduced bodyweight in males and increased food consumption and mineralisation of kidneys in females given 50000 ppm were observed. The NOEL was 10000 ppm, equivalent to 757 and 893 mg/kg bw/day for males and females, respectively [3].

Genotoxicity: A gene mutation study in bacteria is available: No significant toxic effect [2].

Chronic toxicity/Carcinogenicity:

Reproduction toxicity:

Effect in humans: There is a long history of safe use of the parent compound (sodium carboxymethyl cellulose) [2].

Other: Biochemical aspects: The parent compound, sodium carboxymethyl cellulose (CMC), is poorly absorbed if at all in animals and man and shows little degradation in the gastrointestinal tract. It is likely that cross-linking reduces absorption even further [2].

Conclusion: The parent compound is carboxymethyl cellulose (CMC), which is allocated an ADI “not specified” (see previous monograph). There is a long history of safe use of this compound, which is poorly absorbed, if at all in animals and man and only shows little degradation in the gastrointestinal tract. It is likely that cross-linking reduces absorption even further. The limited toxicological data is not sufficient for allocating an ADI, but the available data gives no reason for concern for the very limited use as a tablet disintegrant and there seems to be no reason for a re-evaluation.

Cross-linked sodium carboxymethyl cellulose as defined by the specifications is covered by the toxicological evaluation.

References:


ENZYMATICALLY HYDROLYSED CARBOXYMETHYL CELLULOSE

E Number: E 469

See: E 461 Modified cellulos.
**SODIUM, POTASSIUM AND CALCIUM SALTS OF FATTY ACIDS, MAGNESIUM SALTS OF FATTY ACIDS AND FATTY ACIDS**

**E number:**
- Sodium, potassium and calcium salts of fatty acids: E 470a
- Magnesium salts of fatty acids: E 470b
- Fatty acids: E 570

**Recommendation:** A re-evaluation of these additives is not necessary. However, as the EU specification for fatty acids (E 570) includes acids not included in the SCF evaluation it should be investigated whether they are actually used or not. If not they should be excluded from the specification and if they are used, SCF should evaluate the acceptability of their inclusion.

**Chemical name/synonyms:** -

**Chemical formula:** -

**EINECS number:** -

**CAS number:** -

**Functional Class:** Anticaking agent, emulsifier.

**Specification:**
**Manufacture:** Sodium, potassium, calcium and magnesium salts of fatty acids are obtained by neutralisation of fatty acids either from edible fats and oils or from distilled fatty acids.

**Sodium, potassium and calcium salts of fatty acids**
**Definition:** Sodium, potassium, calcium of fatty acids occurring in food oils and fats. Sodium and potassium salts are soluble in water and ethanol. Calcium salts are insoluble in water and ethanol.

**EC specifications:** E 470a Sodium, potassium and calcium salts of fatty acids [1].
Assay: Not less than 95% on the anhydrous basis.
The specification includes purity criteria on Sodium, Potassium, Calcium, Unsaponifiable matter, Free fatty acids, Free alkali, Matter insoluble in alcohol, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Salts of fatty acids [2].
Assay: Not less than 95% on the anhydrous basis.
The specification includes purity criteria on Unsaponifiable matter, Free fatty acids, Arsenic and Heavy metals.

**Magnesium salts of fatty acids**
**Definition:** Magnesium of fatty acids occurring in food oils and fats. Magnesium salts are insoluble in water and partially soluble in ethanol.
**EC specifications:** E 470b Magnesium salts of fatty acids [1]. Assay: Not less than 95% on the anhydrous basis. The specification includes purity criteria on Magnesium, Unsaponifiable matter, Free fatty acids, Free alkali, Matter insoluble in alcohol, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

**Fatty acids**

**Definition:** Linear fatty acids, caprylic acid (C8), capric acid (C10), lauric acid (C12), myristic acid (C14), palmitic acid (C16), stearic acid (C18), oleic acid (C18:1).

**EC specifications:** E 570 Fatty acids [3]. Assay: Not less than 98% by chromatography. The specification includes purity criteria on Residue on ignition, Unsaponifiable matter, Water, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** The fatty acids and their sodium, potassium, calcium and magnesium salts are permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substances were for that reason not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** The fatty acids myristic, stearic, palmitic and oleic acid were allocated a group ADI “not specified” in 1990 [4]. The basis was, that they are all constituents of biological fat and are therefore present in food generally. They are also produced during the endogenous metabolism. The ADI was extended also to cover their sodium, potassium, calcium, magnesium and ammonium salts [4].

**JECFA status:** The “ADI not specified” was allocated in 1985 [5]. Fatty acids are natural constituents of food. The use of these additives does not represent a toxicological problem. The salts are also covered although they have not been evaluated individually [5].

**Conclusion:** No exhaustive systematic toxicological studies seem to have been carried out with these additives (myristic, stearic, palmitic, oleic acid). They are all constituents of biological fat and are therefore present in food generally. They are also produced during the endogenous metabolism of fat [4]. The permitted salts have likewise not been subject to systematic testing, but there is no reason to expect any health problems when used according to good manufacturing practise.

Sodium, potassium, calcium salts of fatty acids and magnesium salt of fatty acids as defined by the specifications are covered by the toxicological evaluation. However the specification for fatty acids include caprylic acid, capric acid and lauric acid, which were not included in the SCF evaluation of fatty acids.
References:


MONO- AND DIGLYCERIDES OF FATTY ACIDS

E Number: E 471

Recommendation: A re-evaluation is not needed.

Chemical name/synonyms: Glycerol monostearate, glyceryl monopalmitate, glyceryl monooleate etc., monostearin, monopalmitin, monoolein etc., GMS (for glyceryl monostearate).

Chemical formula: -

EINECS number: -

CAS number: -

Functional Class: Emulsifier.

Specification: The EU specifications for this group of substances apply to the additive free of sodium, potassium and calcium salts of fatty acids, however these substances may be present up to a maximum level of 6% (expressed as sodium oleate).

Manufacture: Mono- and diglycerides of fatty acids is usually manufactured by the glycerolysis of edible fats and oils, but may also be prepared by esterification of fatty acids with glycerol, with or without molecular distillation of the product.

Definition: Mono- and diglycerides of fatty acids is a mixture of mono- and diglyceryl esters of long chain, saturated and unsaturated fatty acids that occur in food fats.

EC specifications: E 471 Mono- and diglycerides of fatty acids [1].
Assay: Content of mono- and diesters not less than 70%.
The specification includes purity criteria on Water, Acid value, Free glycerol, Polyglycerols, Total glycerol, Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Mono- and diglycerides [2].
Assay: -
The specification includes purity criteria on Water, Acid value, Free glycerol, Soap, Arsenic and Heavy metals.

Exposure: Mono- and diglycerides of fatty acids are permitted generally in foodstuffs, including some of those where additives are normally not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. They are also naturally present in a normal diet and are natural constituents of the body. ADI is “not specified” and the substances were for that reason not included in the EU monitoring system (tier 0).
SCF/JECFA evaluation:
SCF status: Mono- and diglycerides of fatty acids have not been individually considered by SCF. However, in 1997 the Committee was asked to consider the safety-in-use of, among other substances, mono- and diglycerides, in infant formulae, follow-on formulae and weaning foods for infants and young children in good health and in foods for special medical purposes for infants and young children. At that occasion the Committee found that the ADI “not specified” established by JECFA [3] could be endorsed and that the requested uses were acceptable [4].

JECFA status: An ADI “not limited” was allocated in 1973 [3]. The basis was available toxicological studies and the wide experience with glycerides that are a normal constituent of the human diet.

Background data:
Subacute/subchronic toxicity: An old (published 1957) short-term study is available in hamsters. No adverse effects were reported [5].

Genotoxicity: -

Chronic toxicity/Carcinogenicity: Long-term studies are available in rats. No consistent adverse effects were observed [5].

Reproduction toxicity: Some data are available from a long-term study in rats. No adverse effects on reproductive performance were observed [5].

Effect in humans: Mono- and diglycerides are normal constituents of the diet and are formed endogenously. No harmful effects have been specifically associated with mono- and diglycerides [5].

Other: Biochemical aspects: Mono- and diglycerides are absorbed into the intestinal cells, and are endogenously largely converted to triglycerides. These additives join natural metabolism as other fats.

Conclusion: Mono- and diglycerides have only been subject to sporadic testing, but they are normal constituents of the diet and are formed endogenously. There is no reason to expect any adverse effect of the substances when used as food additives.

Mono- and diglycerides of fatty acids as defined by the specifications is covered by the toxicological evaluation.

References:


3. [1973, NMRS 53/TRS 539-JECFA 17]


5. [1973, FAS 5/NMRS 53A-JECFA 17]
**Esters of mono- and diglycerides of fatty acids**

**E number:**
- Acetic acid esters of mono- and diglycerides of fatty acids: E 472a
- Lactic acid esters of mono- and diglycerides of fatty acids: E 472b
- Citric acid esters of mono- and diglycerides of fatty acids: E 472c
- Tartaric acid esters of mono- and diglycerides of fatty acids: E 472d
- Mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids: E 472e
- Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids: E 472f

**Recommendation:** A reevaluation of E 472a, E 472b, E 472c and E 472d is not needed. The temporary ADI of E 472e is on the SCF agenda. As JECFA has included E 472f in the specification of E 472e this aspect should also be addressed by SCF. It is recommended that while reviewing these substances an update of the evaluation of also the other esters is performed. An exposure survey for E 472e (and f) is desirable.

**Chemical name/synonyms:**
- Acetic acid esters of mono- and diglycerides of fatty acids: ACEM.
- Lactic acid esters of mono- and diglycerides of fatty acids: LACTEM.
- Citric acid esters of mono- and diglycerides of fatty acids: CITREM.
- Tartaric acid esters of mono- and diglycerides of fatty acids: TARTREM.
- Mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids: DATEM.
- Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids: ?

**Chemical formula:** -

**EINECS number:** -

**CAS number:** -

**Functional Class:** Emulsifiers.

**Specification:** The EU specifications for this group of substances apply to the additive free of sodium, potassium and calcium salts of fatty acids, however these substances may be present up to a maximum level of 6% (expressed as sodium oleate).

**Acetic acid esters of mono- and diglycerides of fatty acids**

**Manufacture:** Acetic acid esters of mono- and diglycerides of fatty acids is obtained by esterification of glycerol with acetic acid and edible fatty acids or by reaction of a mixture of mono- and diglycerides of edible fatty acids with acetic acid.

**Definition:** Acetic acid esters of mono- and diglycerides of fatty acids consists of mixed glycerol esters of acetic acid and fatty acids of food fats. It contains mono- and diesters of fatty acids with glycerol. It may also contain free glycerol, free fatty acids and free acetic acid. It may be wholly or partially hydrolysed by the use of sodium hydroxide or potassium hydroxide. It is insoluble in water and soluble in ethanol.
**EC specifications:** E 472a Acetic acid esters of mono- and diglycerides of fatty acids [1].
Assay: -
The specification includes purity criteria on Acids other than acetic acid and fatty acids, Total acetic acids, Total glycerol, Free glycerol, Free fatty acids (and acetic acids), Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Acetic and fatty acid esters of glycerol [2].
Assay: -
The specification includes purity criteria on Acids, Arsenic and Heavy metals.

**Lactic acid esters of mono- and diglycerides of fatty acids**
**Manufacture:** Lactic acid esters of mono- and diglycerides of fatty acids is obtained by esterification of glycerol with lactic acid and edible fatty acids or by reaction of a mixture of mono- and diglycerides of edible fatty acids with lactic acid.

**Definition:** Lactic acid esters of mono- and diglycerides of fatty acids consists of mixed glycerol esters of lactic acid and fatty acids occurring in food fats and oils. It may contain minor amounts of free glycerol, free fatty acids, free lactic acid and free glycerides. It is insoluble in water and soluble in ethanol.

**EC specifications:** E 472b Lactic acid esters of mono- and diglycerides of fatty acids [1].
Assay: -
The specification includes purity criteria on Acids other than lactic acid and fatty acids, Total lactic acids, Total glycerol, Free glycerol, Free fatty acids (and lactic acids), Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Lactic acid and fatty acid esters of glycerol [2].
Assay: -
The specification includes purity criteria on Acids, Arsenic and Heavy metals.

**Citric acid esters of mono- and diglycerides of fatty acids**
**Manufacture:** Citric acid esters of mono- and diglycerides of fatty acids is obtained by esterification of glycerol with citric acid and edible fatty acids or by reaction of a mixture of mono- and diglycerides of edible fatty acids with citric acid.

**Definition:** Citric acid esters of mono- and diglycerides of fatty acids consists of mixed glycerol esters of lactic acid and fatty acids occurring in food oils and fats. It may also contain minor parts of free glycerol, free fatty acids, free citric acid and mono- and diglycerides. It may be wholly or partially neutralised with sodium hydroxide or potassium hydroxide. It is dispersible in hot water and soluble in oils and fats.

**EC specifications:** E 472c Citric acid esters of mono- and diglycerides of fatty acids [1].
Assay: -
The specification includes purity criteria on Acids other than citric acid and fatty acids, Total citric acids, Total glycerol, Free glycerol, Free fatty acids (and citric acids), Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.
**JECFA specifications:** Citric acid and fatty acid esters of glycerol [3].
Assay: -
The specification includes purity criteria on Sulfated ash, Free glycerol, Total glycerol, Total citric acid, Total fatty acids, Arsenic and Heavy metals.

**Tartaric acid esters of mono- and diglycerides of fatty acids**

**Manufacture:** Tartaric acid esters of mono- and diglycerides of fatty acids is obtained by esterification of glycerol with tartaric acid and edible fatty acids or by reaction of a mixture of mono- and diglycerides of edible fatty acids with tartaric acid.

**Definition:** Tartaric acid esters of mono- and diglycerides of fatty acids consists of mixed glycerol esters of tartaric acid and fatty acids occurring in food fats and oils. It may also contain minor parts of free glycerol, free fatty acids, free tartaric acid and mono- and diglycerides. It may be wholly or partially neutralised with sodium hydroxide or potassium hydroxide.

**EC specifications:** E 472d Tartaric acid esters of mono- and diglycerides of fatty acids [1].
Assay: -
The specification includes purity criteria on Acids other than tartaric acid and fatty acids, Total tartaric acids, Total glycerol, Free glycerol, Free fatty acids (and tartaric acids), Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared albeit the substance was included in the evaluation in the report from 1973 [7] (but not in the monograph).

**Mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids**

**Manufacture:** Mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids is obtained by interaction of diacetyl tartaric acid anhydride and mono- and diglycerides of fatty acids in presence of acetic acid.
Due to inter- and intra-molecular exchange, the method of production used for E 472e and for E 472f respectively lead to the same essential compounds, the distribution of which depends on the relative proportions of the basic raw materials, on temperature and on reaction time.

**Definition:** Mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids consists of mixed glycerol esters of mono- and diacetyl tartaric acid and fatty acids of food fats. It may contain small amounts of free glycerol, free fatty acids, free glycerides and free tartaric and acetic acids and their combinations. It is dispersible in cold and hot water and soluble in methanol and ethanol.

**EC specifications:** E 472e Mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids [1].
Assay: -
The specification includes purity criteria on Acids other than acetic, tartaric and fatty acids, Total tartaric acids, Total acetic acid, Total glycerol, Free glycerol, Free fatty acids, Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Diacetyltartaric and fatty acid esters of glycerol [4].
The specification covers both E 472e and E 472f since no information has been made available on how the two substances could be analytically distinguished.

**Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids**

**Manufacture:** Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids is obtained by esterification of mono- and diglycerides with tartaric acid and acetic acid in presence of acetic acid anhydride.

Due to inter- and intra-molecular exchange, the method of production used for E 472e and for E 472f respectively lead to the same essential compounds, the distribution of which depends on the relative proportions of the basic raw materials, on temperature and on reaction time.

**Definition:** Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids consists of mixed glycerol esters of mono- and diacetyl tartaric acid and fatty acids of food fats. It may contain small amounts of free glycerol, free fatty acids, free glycerides and free tartaric and acetic acids and their combinations. It is dispersible in cold and hot water and soluble in methanol and ethanol.

**EC specifications:** E 472f Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids [1].

**Assay:** -

The specification includes purity criteria on Acids other than acetic, tartaric and fatty acids, Total tartaric acids, Total acetic acid, Total glycerol, Free glycerol, Free fatty acids, Sulphated ash, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** The previous tentative specification for tartaric, acetic and fatty acid esters of glycerol, mixed (E 472f) has been withdrawn [5]. The existing specification for diacetyltartaric and fatty acid esters of glycerol (E 472e) covers both substances [4].

**Exposure:** All the esters listed (E 472 a, b, c, d, e, f) are permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. For a, b, c, d and f the ADI is “not specified” and the substances were for that reason not included in the EU monitoring system (tier 0). As E 472e has a numerical ADI it has been transferred to tier 3. If SCF agrees with JECFA that E 472e and f are identical, it should be considered whether the latter should also be examined at tier 3.

**SCF/JECFA evaluation:**

**SCF status:** The JECFA ADI “not specified” for E 472 a, b, c, d, f: was endorsed in 1977/1978 [6]. For E472e (DATEM) the JECFA ADI of 50 mg/kg bw, as endorsed in 1978 [6], was changed to 25 mg/kg bw and made temporary at the 107th meeting on 13 June 1997 [http://europa.eu.int/comm/food/fs/sc/oldcomm7/out11_en.html]. At that meeting E472e was temporarily accepted in certain kinds of food for special medical purposes. The Committee recalled that it wished to see the full presentation of the recently completed long-term study within 3 months from 106th Meeting. Furthermore, within 2 years from the 107the meeting studies on reproduction and teratology conducted to modern standards, and a test for chromosomal aberrations in mammalian cells *in vitro* should be available.

**JECFA status:** The ADI “not limited was established in 1973 for 472 a, b, c, d, and f. The basis was biochemical and metabolic studies showing that the breakdown products are normal dietary
E 472a-f Esters of mono- and diglycerides of fatty acids

constituent and toxicological data [7]. For E 472e (DATEM) an ADI of 0-50 mg/kg bw was established. The basis was the level causing no toxicological effects in rats on 10% in diet corresponding to 5000 mg/kg bw. The safety factor was 100. No details about NOEL or potential effects at higher doses were specified [7]. No studies specifically on E472d are reported, but it is included in the evaluation while stressing of tartaric acid should not exceed the ADI of 30 mg/kg as established for this acid and its salts (see E 334). JECFA prepared no specification for E 472d.

At its 51st meeting in 1998 JECFA revised the specifications for E 472e (DATEM) and included in this specification also the previous E 472f. As 472e and f previously were assigned different ADIs the Committee expressed its wish to evaluate the material, defined in the specification, toxicologically. At its meeting in 2001 JECFA confirmed it ADI for 272e and withdrew the ADI for 242f.

Background data:
Subacute/subchronic toxicity: Short-term studies are available for E472a (rat), E472b (rat), E472c (species not specified), E472e (dog). No adverse effects [8].

Genotoxicity:-

Chronic toxicity/Carcinogenicity:
Long-term studies were available to JECFA for E472a (rat), E472b (rat), E472e (rat), and E472f (rat). No carcinogenic effects were noticed. In the study on E472e, rats were fed 0, 5, 10, or 20% in diet. No details were specified on effects.

A recent long-term/carcinogenicity study has been performed on 472e but not yet reviewed. SCF requested a full presentation at its 107th Meeting.

Reproduction toxicity: In the long-term study on E 472f no adverse effects have been found on reproduction [8].

Other: Biochemical aspects: These additives (E472a, b, and c) are readily hydrolysed in the gastrointestinal tract and dealt with in the body similar to other glycerides [8]. Diacetyl tartaric acid, E472e is not a natural constituent of the diet, and its low rate of hydrolysis possibly allows the absorption of the unhydrolysed compound.

Conclusion: The additives E 472a, E 472b and E 472c are degraded in the gastrointestinal tracts to their basic components. The JECFA evaluation (ADI not specified) was based on evaluation of the single components, which are all present in food and can be synthesised endogenously.

E 472e is on the SCF agenda. E 472e and E 472f have been evaluated as two different substances for the reason that it was presumed that mono- and diacetyl tartaric acid was only present in E 472e, while it was presumed that this moiety was not present in E 472f. However exhaustive investigations on the composition of these two substances have shown, that 1) mono- and diacetyl tartaric acid is present in both substances and 2) the specifications for E 472e also includes E 472f. It is therefore recommended that SCF also include considerations of E 472f when the requested information on E 472e is being reviewed. JECFA has expressed a wish to re-evaluate the toxicology of E 472e and f.
The JECFA specifications for this group of additives have been prepared at three different JECFA meetings ranging from the seventeenth meeting (1973) to the fifty-first meeting (1998). It would be desirable to revise the specifications for these additives as a group at a future JECFA meeting.

References:


**SUCROSE ESTERS OF FATTY ACIDS AND SUCROGLYCERIDES**

**E number:**
Sucrose esters of fatty acids: E 473
Sucroglycerides: E 474

**Recommendation:** These substances are on the agenda of SCF.

The specifications for the substances appear not to cover the restrictions mentioned by SCF at its 83rd meeting.

If monitoring at tier 3 level confirms the potential for exceeding the ADI, a restriction of permitted uses should be considered.

**Chemical name/synonyms:**
Sucrose esters of fatty acids: Sucroesters, sugar esters.
Sucroglycerides: Sugar glycerides.

**Chemical formula:** -

**EINECS number:** -

**CAS number:** -

**Functional Class:** Emulsifier.

**Specification:** The EU specification for these substances apply to the additive free of sodium, potassium and calcium salts of fatty acids, however these substances may be present up to a maximum level of 6% (expressed as sodium oleate).

**Sucrose esters of fatty acids**

**Manufacture:** Sucrose esters of fatty acids is obtained by reaction between sucrose and methyl and ethyl esters of food fatty acids or by extraction from sucroglycerides. Only the following solvents may be used for the production: dimethyl formamide, dimethyl sulfoxide, ethyl acetate, isopropanol, propylene glycol, isobutanol and methyl ethyl ketone.

**Definition:** Sucrose esters of fatty acids consists of essentially the mono-, di- and triesters of sucrose with fatty acids occurring in food fats and oils. It is sparingly soluble in water and soluble in ethanol.

**EC specifications:** E 473 Sucrose esters of fatty acids [1].
Assay: Not less than 80%.
The specification includes purity criteria on Sulphated ash, Free sugar, Free fatty acids, Methanol, Dimethyl sulfoxide, Dimethyl formamide, 2-methyl-1-propanol, Ethylacetate, propane-2-ol and propylene glycol, Methyl ethyl ketone, Arsenic, Lead, Mercury, Cadmium and Heavy metals.
JECFA specifications: Sucrose esters of fatty acids [2].
Assay: Not less than 80%.
The specification includes purity criteria on Sulphated ash, Free sucrose, Acids value, Methanol, Dimethyl sulfoxide, Dimethyl formamide, 2-methyl-1-propanol, Ethylacetate, propane-2-ol and propylene glycol, Methyl ethyl ketone and Lead.

Sucroglycerides

Manufacture: Sucroglycerides is obtained by reaction between sucrose and methyl and edible fat or oil (including palm oil) in or without presence of a solvent. Only the following solvents may be used for the production: cyclohexane, dimethyl formamide, ethyl acetate, isopropanol and isobutanol.

Definition: Sucroglycerides consists of essentially the mono-, di- and triesters of sucrose and fatty acids together with residual mono-, di- and triglycerides from fat or oil. It is insoluble in cold water and soluble in ethanol.

EC specifications: E 474 Sucroglycerides [1].
Assay: Not less than 40% and not more than 60% of sucrose fatty acid esters.
The specification includes purity criteria on Sulphated ash, Free sugar, Free fatty acids, Methanol, Dimethyl formamide, 2-methyl-1-propanol, Cyclohexane, Ethyl acetate, propane-2-ol, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Sucroglycerides [3].
Assay: Not less than 40% and not more than 60% of sucrose fatty acid esters.
The specification includes purity criteria on Sulphated ash, Free sucrose, Acids value, Dimethyl formamide, 2-methyl-1-propanol, Arsenic, Lead and Heavy metals.

Exposure: Sucrose esters of fatty acids and sucroglycerides are permitted in a variety of foods of which can be mentioned beverage whiteners 10 g/kg and powders for the preparation of hot beverages 10 g/l, fine bakery wares, sauces 5g/kg and dairy-based drinks, non-alcoholic drinks based on aniseed, coconut or almond 5 g/l and on the surface of fresh fruits and in dietary food supplements q.s. To reach ADI for an adult it would take 120 g of a product with 10 g/kg and 240 g with 5 g/kg while the corresponding intake figures for a child of 20 kg is 40 and 80 grams respectively.

In the EU monitoring system sucrose esters of fatty acids and sucroglycerides were examined at tier 2 and he calculated intake by adults and the whole population is reported in the range of 4 - 138% of ADI. The calculated intake by young children is reported in the range of 226 - 374%. The investigators concluded that examination at tier 3 is needed.

SCF/JECFA evaluation:
SCF status: A group ADI of 20 mg/kg bw was allocated for these two substances at the 83rd meeting in April 1992 (Minutes of 83rd meeting, Document III/3280/92, CEC DG III, Brussels). No basis or any toxicological data for the numerical value were specified and no report issued. The basis might be the NOEL of 2000 mg/kg bw/day in a long-term study in rats as referred to by JECFA. This evaluation was also based on information that the lower fatty acid esters are
hydrolysed in the gut to the constituent fatty acids and sucrose which are well-known components of food [4].

E 473 was accepted in certain baby food up to 120 mg/l at the 107th meeting in 1997 [4].

In the evaluation at the 83rd meeting the Committee noted that the evaluation covers sucroglycerides and sucrose esters derived from palm oil, lard and tallow fatty acids. The Committee was not satisfied that the toxicity data could be used to provide assurance of safety for products derived from other feedstocks or based on other fatty acids. To establish the safety of these products, satisfactory biochemical data would be required to indicate the degree to which the esters were broken down and absorbed in the gut and, in the case of any product derived from rapeseed oil, that the feedstocks were low in erucic acid. The satisfactory results of mutagenicity tests would be required if hydrolysis in the gut is proved to be incomplete. It was also stressed that the specification should limit the content of tetra- and higher esters to not more than 7%.

**JECFA status:** In 1997 the previous established ADI of 0-20 mg/kg bw was changed to a full ADI of 0-30 mg/kg bw 1997. The basis was a new tolerance study in man showing the potential of these two additives to cause laxative effects at doses exceeding 30 mg/kg bw/day. The safety factor was 1 [5].

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies are available in rats and dogs. No adverse effects were demonstrated [6;7].

Rats have been administered via diet for 13-weeks or 3 months. No adverse effects were demonstrated [8;9].

**Genotoxicity:**

**Chronic toxicity/Carcinogenicity:** Long-term studies are available in mice and rats. The NOEL in recent the long-term study in rats was 5% in diet (highest dose) equivalent to 2000 mg/kg bw/day [7]. No evidence of carcinogenicity was demonstrated[6;7].

**Reproduction toxicity:**

**Effect in humans:** Human volunteers participated in a oral tolerance study. This study showed a potential for gastro-intestinal disturbance (soft stools, diarrhoea, flatulence, bloating) at intakes of 70 mg/kg bw/day, and not of 30 mg/kg bw/day (Unpublished report submitted to JECFA; [10] and quoted in [4]).

The fermentation has been studied in humans including VFA formation. No adverse effects were reported [11].
Other: *Biochemical aspects:* In the rat, the sucrose esters are hydrolysed in the mucosal epithelium cells before intestinal absorption. The lower fatty acid esters are hydrolysed in the gut to the constituent fatty acids and sucrose which are well-known components of food [4].

Absorption, distribution, and excretion studies are available in rats, dogs, and humans. A small amount of the monoesters were observed in all three species, whereas it appears unlikely that the diesters were absorbed. The absorbed monoesters were completely metabolised and either excreted as CO$_2$ or integrated into body components [7].

Hydrolysis is supported by *in vitro* data. Absorption is also indicated in studies in humans. There seems not to be any tissue accumulation of esters or metabolites in animals or man [12].

The metabolism has been studied in rats [13;14] and *in vitro* [15].

**Conclusion:** The toxicological data available for SCF about these two additives do not include what normally is required for an ADI to be set for a food additive. Hydrolysis in the gut to the constituent fatty acids and sucrose that are well-known food components and the results of the long-term studies, however justifies the ADI. JECFA has allocated an ADI, which is based on human data and higher than that from SCF, which apparently is based on the long term study in rats.

If the potential for exceeding the ADI is confirmed an adjustment of the permitted levels should be considered.

The EU specifications for sucrose esters of fatty acids and sucroglycerides are not covering the comments on fat source and degree of esterification as specified by SCF at its 83rd meeting.

**References:**


**POLYGlycEROL ESTERS OF FATTY ACIDS**

**E number:** E 475

**Recommendation:** A re-evaluation of polyglycerol esters of fatty acids is not necessary. A further estimate of potential exposure is desirable.

**Chemical name/synonyms:** Polyglycerol fatty acid esters, Polyglycerin esters of fatty acids.

**Chemical formula:** -

**EINECS number:** -

**CAS number:** -

**Functional Class:** Emulsifier.

**Specification:** The EU specification for these substances apply to the additive free of sodium, potassium and calcium salts of fatty acids, however these substances may be present up to a maximum level of 6% (expressed as sodium oleate).

**Manufacture:** Polyglycerol esters of fatty acids is obtained by reacting polymerised glycerols with edible fats, oils or fatty acids.

**Definition:** Polyglycerol esters of fatty acids consists of mixed partial esters of polyglycerol and fatty acids of which the polyglycerol moiety is predominantly di- tri- and tetrarglycerol and contains no more than 10% of polyglycerols equal to or higher than heptaglycerol. It contains minor amounts of mono-, di- and triglycerides, free glycerol and polyglycerols and free fatty acids. The esters range from very hydrophilic to very lipophilic, but as a class tend to be dispersible in water and soluble in organic solvents and oils.

**EC specifications:** E 476 Polyglycerol esters of fatty acids [1].

Assay: Content of total fatty acid esters not less than 90%.

The specification includes purity criteria on Sulphated ash, Acids other than fatty acids, Total glycerol and polyglycerol, Free glycerol and polyglycerol, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Polyglycerol esters of fatty acids [2].

Assay: -

The specification includes purity criteria on Acids, Composition of polyglycerols, Arsenic and Heavy metals.

**Exposure:** Polyglycerol esters of fatty acids are permitted in a limited number of food categories among which fine bakers wares and Granola-type breakfast cereals may contain up to 10 g/kg, emulsified liqueurs, fat emulsions, milk and cream analogues and some dietetic foods 5 g/kg, and desserts and sugar confectionary 2 g/kg. For an adult the ADI of 25 mg/kg bw can be reached by
consuming 150 g with 10 g/kg and 300 g with 5 g/kg. For a child of 20 kg the figures are 50 and 100 g.

In the EU monitoring system polyglycerol esters of fatty acids were examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 3 - 53% of ADI, while the calculated intake by young children is reported by one member state as 114 - 160%. It was concluded that examination at tier 3 of intakes by young children is needed.

**SCF/JECFA evaluation:**

**SCF status:** The latest evaluation is from 1978, when SCF endorsed the JECFA ADI of 25 mg/kg bw from 1973. The Committee noted a discrepancy between JECFA and EEC specifications: EEC specifications permit the presence of not more than 10% polyglycerols equal to or higher than heptaglycerol, whereas JECFA specifies that “no polyglycerols higher than hexaglycerols should be present”. The Committee was informed that the difference was not a sign of a change in composition, but of better analytical technology, and it concluded that the toxicity data on which JECFA based its evaluation in 1973 was obtained on material described by the EEC specification [3].

**JECFA status:** An ADI of 0-25 mg/kg bw was established in 1973 to a product having an average chain length of up to three glycerol units [4]. The basis was the level causing no toxicological effect in a rat study i.e. 50000 ppm, 5% (highest dose), equivalent to 2500 mg/kg bw and a safety factor of 100 combined with metabolic studies showing that the esters are hydrolysed in the gastro-intestinal tract. The Committee requested proper biochemical studies on other members of this group, particularly those containing short-chain fatty acids [5].

In 1989 the Committee was requested to increase the range of average polyglycerol chain lengths permitted from three to ten glycerol units without a review of the toxicological data on these substances. The Committee did not receive any data to support the request and concluded that the ADI of 0-25 mg/kg bw only applies to polyglycerol esters of fatty acids having an average chain length of up to three glycerol units [6].

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies are available in rats. No adverse effects were shown [5].

**Genotoxicity:** -

**Chronic toxicity/Carcinogenicity:** Long-term studies are available in mouse and rats. No adverse effects were shown[5]. The level causing no toxicological effect in a rat study was 50000 ppm, 5%, equivalent to 2500 mg/kg bw. This was the highest dose[5].

**Reproduction toxicity:** -

**Effect in humans:** Studies are available in human volunteers. These studies showed no adverse effects[5].

**Other:** *Biochemical aspects:* *In vitro* and *in vivo* studies in rats are available. The metabolic studies point to hydrolysis of these polyglycerol esters in the gastrointestinal tract. The utilisation and
digestibility studies justify the assumption that the fatty acid moiety is metabolised in a normal manner. There is no evidence of accumulation of the polyglycerol moiety in body tissues [5].

**Conclusion:**
The polyglycerol esters have not been fully tested according to modern standard. However, is has been shown that this additive after ingestion is broken down to its constituents and the existing toxicity data support the safety of this additive. There is therefore no need for a re-evaluation as long as the chain-length does not increase above what has been accepted by the Committees.

Polyglycerol esters of fatty acids as defined by the specifications is covered by the toxicological evaluation.

**References:**


POLYGLYCEROL POLYRICINOLEATE

E number: E 476

Recommendation: A re-evaluation of polyglycerol polyricinoleate is not necessary.

Chemical name/synonyms: Glycerol esters of condensed castor oil fatty acids, polyglycerol esters of polycondensed fatty acids from castor oil, polyglycerol esters of interesterified ricinoleic acid, PGPR.

Chemical formula: -

EINECS number: -

CAS number: -

Functional Class: Emulsifier.

Specification: The EU specification for these substances apply to the additive free of sodium, potassium and calcium salts of fatty acids, however these substances may be present up to a maximum level of 6% (expressed as sodium oleate).

Manufacture: Polyglycerol polyricinoleate is obtained by esterification of polyglycerol with condensed castor oil fatty acids.

Definition: Polyglycerol polyricinoleate consists of polyglycerol esters of interesterified fatty acids present in castor oil. It is insoluble in water and ethanol and soluble in ether.

EC specifications: E 476 Polyglycerol polyricinoleate [5].
Assay: -
Polyglycerols: The polyglycerol moiety shall be composed of not less than 75% of di-, tri- and tetruglycerol and shall contain not more than 10% of polyglycerols equal to or higher than heptaglycerol.
In addition the specification includes purity criteria on Hydroxyl value, Acid value, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Polyglycerol esters of interesterified ricinoleic acid [4].
Assay: -
Polyglycerols: The polyglycerol moiety shall be composed of not less than 75% of di-, tri- and tetruglycerol and shall contain not more than 10% of polyglycerols equal to or higher than heptaglycerol.
In addition the specification includes purity criteria on Arsenic and Heavy metals.

Exposure: Polyglycerol polyricinoleate is permitted only in cocoa-based confectionary, including chocolate up to 5 g/kg and in some fat-products up to 4 g/kg. It takes 90 chocolate with 5 g and 112.5 g fat product with 4 g additive to reach the ADI of 7.5 mg/kg bw.
In the EU monitoring system polyglycerol polyricinoleate was examined at tier 2 level and the calculated intake by adults and the whole population is reported in the range of 4 - 33% of ADI, while the calculated intake by young children is reported by one member state as 49 - 53%. It was concluded that no further examination was needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** An ADI 0-7.5 mg/kg bw was established in 1978 [3]. The basis was not specified but it may be that the 1973 JECFA ADI was endorsed. The Committee noted that rats fed the substance at dietary levels of 18% developed a hepatomegaly, which was reversible and not associated with any significant abnormalities in the enlarged livers. Otherwise no toxicological data were specified.

**JECFA status:** An ADI 0-7.5 mg/kg bw was established in 1973 [1]. The basis was a study in rats with a level causing no toxicological effects on 15000 ppm (1.5%, highest dose) equivalent to 750 mg/kg bw in a long-term study in rats. The safety factor was 100. In other long-term studies liver and kidney enlargement was noticed at higher doses, 5 and 10%.

**Background data:**

**Subacute/subchronic toxicity:** No obvious adverse effects. The liver hypertrophy can be regarded as a normal functional response to an increased hepatic work load.

Short-term studies are available in rat and chicken. Liver enlargement was noticed in two (same author) of eight studies in rats. Enlarged kidney and liver was reported in the only study conducted in chicken. These effects were not accompanied by effects as revealed by histopathology. In some special studies on the liver enlargement the effects were reversible in mice and not proportional to the feeding level. The hypertrophy was regarded as a normal functional response to an increased hepatic workload. No hyperplasia was observed. No other effects were demonstrated [2].

**Genotoxicity:** -

**Chronic toxicity/Carcinogenicity:** No evidence of carcinogenicity. The liver hypertrophy can be regarded as a normal functional response to an increased hepatic work load.

Long-term studies are available in mice and rats. The long-term studies in rats and mice did not show carcinogenic potential. The enlargement of liver and kidneys observed in long-term tests was not accompanied by any lesions detectable by histopathology. Only the rat study showed a no-effects level for liver enlargement, which was 1.5%, in the diet. The kidney lesions were not followed by histopathological findings [2]. The significance of the findings in kidneys is not possible to predict.

Carcinogenicity studies in rats and mice showed no carcinogenicity at 5% in the diet (highest dose). No kidney or liver effects were reported [8].

**Reproduction toxicity:** A three-generation study was carried out in rats. No adverse effect were noted even at the highest dose i.e. 1.5% [2].

One recent communication deals with teratology by suggesting that this additive may increase the sex ratio (proportion male). This may be caused by glycerol that may be involved in the process of sex selection [7]. However, this hypothesis is not supported by recent metabolism studies [6].
three-generation reproduction study in rats showed no effects on breeding performance at 1.5% in diet (highest dose) [9].

**Effect in humans:** A study is available in human volunteers eating up to 10 g/day for 2 weeks. This study showed no adverse effects [2].

A recent study in human volunteers showed no adverse effects at intake of 10g/day for 2 weeks (highest dose) [10].

**Other:** A study where rats were fed diet containing 18% of the substance (no dosing period specified) is available. It revealed the development of reversible hepatomegaly. No histopathological abnormalities of the enlarged livers were found. The hepatomegaly was not associated with hyperplasia [3].

**Biochemical aspects:** *In vitro* and *in vivo* studies are available. Radiolabel from orally administered substance was found in faeces, urine, and CO₂. It was suggested that the label in faeces was present as free polyglycerols, indicating hydrolysis in the gastrointestinal tract [2].

A thorough study on the metabolism in rats is published recently. Ingested polyglycerol polyricinoleate is extensively digested in the intestinal tract to its two major polymeric components: the polyglycerols, which are quantitatively excreted unchanged, and polyricinoleic acid that is degraded to ricinoleic acid that is absorbed and readily metabolised. Data show no evidence of tissue storage of its two major components [6].

**Conclusion:** The toxicological data available to JECFA in 1973 or to SCF in 1977 did not include all the data, which are normally required for an ADI to be set for a food additive. However, later data confirm the safety of the substance within the ADI, and taken together with the limited exposure, there seems to be no need for an re-evaluation.

Polyglycerol polyricinoleate as defined by the specifications seems to be covered by the toxicological evaluation.

**References:**


PROPANE-1,2-DIOL ESTERS OF FATTY ACIDS

**E number:** E 477

**Recommendation:** A re-evaluation of propane-1,2-diol esters of fatty acids is not necessary. SCF is proposed to express the status of the requested information as expressed in 1977.

**Chemical name/synonyms:** Propylene glycol esters of fatty acids.

**Chemical formula:** -

**EINECS number:** -

**CAS number:** -

**Functional Class:** Emulsifier.

**Specification:** The EU specification for these substances apply to the additive free of sodium, potassium and calcium salts of fatty acids, however these substances may be present up to a maximum level of 6% (expressed as sodium oleate).

**Manufacture:** Propane-1,2-diol esters of fatty acids is obtained either by direct esterification of propylene glycol with fatty acids or by transesterification of propylene glycol with oils and fats. The process may be followed by molecular distillation to separate the monoesters.

**Definition:** Propane-1,2-diol esters of fatty acids is mixtures of propylene glycol mono- and diesters of saturated and unsaturated fatty acids derived from edible oils and fats. When prepared by transesterification, the product may contain residual mono- and diglycerides and glycerol. It is insoluble in water and soluble in ethanol.

**EC specifications:** E 477 Propane-1,2-diol esters of fatty acids [7].
Assay: Not less than 85% of total fatty acid esters.
The specification includes purity criteria on Sulphated ash, Acids other than fatty acids, Free fatty acids, Total propane-1,2-diol, Free propane-1,2-diol, Dimer and trimer of propylene glycol, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Propylene glycol esters of fatty acids [5].
Assay: Not less than 85% of total fatty acid esters.
The specification includes purity criteria on Sulphated ash, Acids, Total propane-1,2-diol, Free propane-1,2-diol, Dimer and trimer of propylene glycol and Heavy metals.

**Exposure:** The permitted uses of propane-1,2-diol esters of fatty acids are restricted to few commodities among which fine bakery wares, sugar confectionery, desserts and milk and cream analogues may contain 5 g/kg, edible ices 3 g/ kg and dietetic foods intended for special medical purposes 1 g/kg. Whipped dessert toppings may contain up to 30 g/ kg.
In the EU monitoring system propane-1,2-diol esters of fatty acids was examined at tier 1. As the calculated intake did not exceed the ADI, the investigators concluded that no further examination is needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation in 1977, when the Committee endorsed the ADI of 25 mg/kg (expressed as propane-1,2-diol) as established by JECFA in 1973. The basis for the evaluation and the reviewed toxicological data were not specified [3].

The Committee stressed that the ADI was only covering a substances with less than 0.5% dimer and trimer. and accepted the temporarily use in food, without establishing an ADI for compounds containing 0.5% to 4% dimer and trimer, but specified a series of tests, which should be submitted if such substances were to be used for longer time [3]. In 1983 the Committee was informed that the use of substances with a content of dimer and trimer of more that 0.5% was being phased out and that as a consequence the information requested by the Committee would not be forthcoming [4]. The present specification reflects this by excluding the use of a product with higher than 0.5% dimer and trimer [5].

Propane-1,2-diol was last evaluated by SCF in 1996 [6]. The Committee concluded that a full ADI of 25 mg/kg bw could be reassigned (see E 1520).

**JECFA status:** The ADI 0-25 mg/kg bw expressed as propylene glycol was established in 1973 [1].

The JECFA evaluation was based primarily on the biochemical evidence that the compound is hydrolysed into fatty acids and propylene glycol. The product did not contain appreciable quantities of dimer and trimer [1].

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies are available in rats and dogs. No signs of toxicity were noticed [2].

**Genotoxicity:** -

**Chronic toxicity/Carcinogenicity:**
No long-term study were available to SCF or JECFA.

**Reproduction toxicity:** -

**Other:** Biochemical aspects: *In vitro* and *in vivo* studies in rats are available. They report excretion via faeces, urine, and CO₂. There is evidence that the propylene glycol esters of fatty acids are hydrolysed to propylene glycol and fatty acids [2].

**Conclusion:** The toxicological data available do not include what normally is required for an ADI to be set for a food additive. The JECFA evaluation was based primarily on the biochemical evidence that the compound is hydrolysed into fatty acids and propylene glycol and as the biological fate of these constituents are fully known there is no need for requesting further data. Propane-1,2-diol esters of fatty acids as defined by the specifications is covered by the toxicological evaluation.
References:

1. [1973, NMRS 53/TRS 539-JECFA 17]
   Toxicological evaluation of certain food additives with a review of general principles and of
   specifications (Seventeenth report of the Joint FAO/WHO Expert Committee on Food
   539, 1974, and corrigendum.

2. [1973, FAS 5/NMRS 53A-JECFA 17]
   Toxicological evaluation of some food additives including anticaking agents, antimicrobials,
   antioxidants, emulsifiers, and thickening agents. FAO Nutrition Meetings Report Series, No.

3. Reports from the scientific committee for food (7th series). Opinion expressed 1977. Food-
   science and techniques, 1978.

4. Reports from the scientific committee for food (15th series). Opinion expressed 1983. Food-
   science and techniques, 1984.


6. Reports from the scientific committee for food (40th series). Opinion expressed 1996. Food-
   science and techniques, 1997.

   criteria on food additives other than colours and sweeteners, 1998.
**THERMALLY OXIDISED SOYA BEAN OIL INTERACTED WITH MONO- AND DIGLYCERIDES OF FATTY ACIDS (TOSOM)**

**E number:** E 479b

**Recommendation:** A re-evaluation of TOSOM is not necessary.

**Chemical name/synonyms:** TOSOM.

**Chemical formula:** -

**EINECS number:** -

**CAS number:** -

**Functional Class:** Emulsifier, antispattering agent.

**Specification:**

**Manufacture:** Thermally oxidised soya bean oil interacted with mono- and diglycerides of fatty acids is obtained by interaction and desodorisation under vacuum at 130°C of 10% of thermally oxidised soya bean oil and 90% of mono- and diglycerides of food fatty acids.

**Definition:** Thermally oxidised soya bean oil interacted with mono- and diglycerides of fatty acids is a complex mixture of esters of glycerol and fatty acids found in edible fat and fatty acids from thermally oxidised soya bean oil. It is insoluble in water and soluble in hot oil and fat.

**EC specifications:** E 479b Thermally oxidised soya bean oil interacted with mono- and diglycerides of fatty acids [6].

- Assay: -
- Peroxide value: Not more than 3.
- Epoxides: Not more than 0.03% oxiran oxygen.

In addition the specification includes purity criteria on Melting range, Free fatty acids, Free glycerol, Total fatty acids, Total glycerol, Fatty acid methyl esters, not forming adduct with urea, Fatty acids insoluble in petroleum ether, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Thermally oxidised soya bean oil interacted with mono- and diglycerides of fatty acids (INS 479) [4].

- Assay: -
- Peroxide value: Not more than 3.
- Epoxides: Not more than 0.03% oxiran oxygen.

In addition the specification includes purity criteria on Melting range, Free fatty acids, Free glycerol, Total fatty acids, Total glycerol, Fatty acid methyl esters, not forming adduct with urea, Fatty acids insoluble in petroleum ether, Arsenic, Lead and Heavy metals.
**Exposure:** TOSOM is only permitted in fat emulsions for frying purposes up to 5 g/kg. This means that even theoretically the ADI cannot be reached from this source.

**SCF/JECFA evaluation:**

**SCF status:** TOSOM was first evaluated in 1978 when an ADI could not be established and further studies were requested [2]. These were received and in 1988 an ADI of 25 mg/kg bw was established [3]. The basis for evaluation was a variety of studies and the Committee established an overall no-effect dose of 2.5 g/kg bw/day i.e. not derived from a single study [3]. The safety factor was 100.

**JECFA status:** An ADI of 0-30 mg/kg bw was established in 1992 [1]. The basis was the observation that the highest dose in the 2.5-year rat study (approx. 6000 mg kg bw/day) produced no adverse effects. The safety factor was 200. The reason applying this factor was not specified.

**Background data:**

**Subacute/subchronic toxicity:** The Committees reviewed subchronic studies in rats and pigs. No obvious toxic effects have been reported [3] [5].

**Genotoxicity:** -

**Chronic toxicity/Carcinogenicity:** Several long-term studies are available in rats. In a newer 2.5-year long-term study in rats, the only effects noted were transient minor variations in blood count (leucocytes, lymphocytes), which were not considered to be of toxicological significance. JECFA concluded, that TOSOM is not carcinogenic in the rats [5][3].

Other chronic toxicity studies in rats are available but are carried out before 1970 [3].

**Reproduction toxicity:** Reproduction toxicity studies, carried out in rats before 1970, were available to SCF, but not to JECFA. No adverse effects were reported [3].

**Other:** *Biochemical aspects:* Studies *in vitro* and *in vivo* in mice, rats, and guinea-pigs applying oral dosing are available. Radiolabel is excreted in faeces, urine, and CO₂. The pattern of excretion of radiolabel from TOSOM was comparable to that of soya bean oil. The absorption was slower than that of refined soybean oil [5] [2;3].

**Conclusion:** The toxicological data available for SCF include what generally would be required for an ADI to be set for a food additive. Exposure is low. There has been found no information that could necessitate a re-evaluation of TOSOM.

Thermally oxidised soya bean oil interacted with mono- and diglycerides of fatty acids as defined by the specifications is covered by the toxicological evaluation.

**References:**


5. [1992, FAS 30-JECFA 39]

SODIUM STEAROYL-2-LACTYLATE AND CALCIUM STEAROYL-2-LACTYLATE

E number:
Sodium stearoyl-2-lactylate: E 481
Calcium stearoyl-2-lactylate: E 482

Recommendation: A re-evaluation of sodium- or calcium stearoyl-2-lactylate is not necessary. However, exposure data are desirable.

Chemical name/synonyms:
Sodium stearoyl-2-lactylate: Sodium stearoyl lactylate, sodium stearoyl lactate.
Calcium stearoyl-2-lactylate: Calcium stearoyl lactylate, calcium stearoyl lactate.

Chemical formula: (major components):
Sodium stearoyl-2-lactylate: C_{21}H_{39}O_{4}Na
C_{19}H_{35}O_{4}Na
Calcium stearoyl-2-lactylate: C_{42}H_{78}O_{8}Ca
C_{38}H_{70}O_{8}Ca

EINECS number:
Sodium stearoyl-2-lactylate: 246-929-7
Calcium stearoyl-2-lactylate: 227-335-7

CAS number:
Sodium stearoyl-2-lactylate: 25383-99-7
Calcium stearoyl-2-lactylate: 5793-94-2

Functional Class: Emulsifier, stabiliser.

Specification:
Manufacture: Sodium stearoyl-2-lactylate and calcium stearoyl-2-lactylate are obtained by the esterification of commercial stearic acid with lactic acid followed by neutralisation to the sodium or calcium salts respectively.

Sodium stearoyl-2-lactylate
Calcium stearoyl-2-lactylate:
Definition: Sodium stearoyl-2-lactylate is a mixture of the sodium salts of stearoyl lactic acid and its polymers and minor amounts of sodium salts of other related acids, manufactured by the reaction of stearic acid and lactic acid. Other food fatty acids may also be present, free or esterified, due to their presence in the stearic acid used. It is insoluble in water and soluble in ethanol.

EC specifications: E 481 Sodium stearoyl-2-lactylate [1].
Assay: -
The specification includes purity criteria on Sodium, Ester value, Acid value, Total lactic acid, Arsenic, Lead, Mercury, Cadmium and Heavy metals.
**JECFA specifications:** Sodium stearoyl-2-lactylate [2].
Assay: -
The specification includes purity criteria on Sodium, Ester value, Acid value, Total lactic acid and Heavy metals.

**Calcium stearoyl-2-lactylate**
**Definition:** Calcium stearoyl-2-lactylate is a mixture of the calcium salts of stearoyl lactylic acid and its polymers and minor amounts of calcium salts of other related acids, manufactured by the reaction of stearic acid and lactic acid. Other food fatty acids may also be present, free or esterified, due to their presence in the stearic acid used. It is insoluble in water and soluble in ethanol.

**EC specifications:** E 481 Calcium stearoyl-2-lactylate [1].
Assay: -
The specification includes purity criteria on Calcium, Ester value, Acid value, Total lactic acid, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Calcium stearoyl-2-lactylate [2].
Assay: -
The specification includes purity criteria on Calcium, Ester value, Acid value, Total lactic acid and Heavy metals.

**Exposure:** The permitted uses are restricted to few commodities of which can be mentioned fat emulsions 10 g/kg, emulsified liqueur and spirits less than 15% 8 g/l, fine bakery wares, breakfast cereals, desserts, sugar confectionary and cereal and potato-based snacks 5 g/kg, bread and beverage whiteners 3 g/kg and powders for the preparation of hot beverages 2 g/l.

An adult can reach the ADI of 20 mg/kg bw by consuming 240 g of a product with 5 g/kg and a child of 20 kg by consuming 80 g.

In the EU monitoring system stearoyl-2-lactylates were examined at tier 2. The calculated intake by adults and the whole population is reported in the range of 2 - 114% of ADI. The calculated intake by young children is reported in the range of 136 - 268%. The investigators concluded that examination at tier 3 is needed.

**SCF/JECFA evaluation:**
**SCF status:** An ADI of 20 mg/kg bw (single or in combination) was established in 1978 [3]. The Committee endorsed the ADI established by JECFA. No toxicological data were presented by SCF. The basis was not given.

**JECFA status:** An ADI of 0-20 mg/kg bw was established in 1973 [4]. The basis was the overall level causing no toxicological effect in rats on 20000 ppm (2%) in the diet equivalent to 1000 mg/kg bw/day in the available subchronic studies in rats (see below). The safety factor was 50. The basis for that safety factor was not given.

**Background data:**
**Subacute/subchronic toxicity:** Extensive short-term/subchronic studies in rats have given variable and inconsistent results as regards levels producing no-effect on growth or relative liver weight. The 2% level has been taken as the overall NEL in rats for these effects (no specific study but the available relevant studies in general). The dog seems to be less sensitive [5].
Genotoxicity: -

Chronic toxicity/Carcinogenicity: No long-term study is available to JECFA. The substances seem to be totally hydrolysed to lactic acid and stearic acid. This justifies to consider conventional long-term studies as unnecessary [5].

Reproduction toxicity: -

Other: Biochemical aspects: Adequate biochemical studies have revealed no differences between the metabolisms of $^{14}$C-labelled lactic acid when present as stearoyl ester and when mixed with an equivalent amount of stearic acid. The additives seem to be totally hydrolysed to lactic acid and stearic acid [5]. These basal components are normal constituents of food and a part of general endogenous metabolism.

A study is published on the metabolism of calcium stearoyl-2-lactylate in mouse, guinea pig, and man suggesting that the biological fate of this additive is similar in these species and that the additive is unlikely to present a hazard to man in terms of its metabolic fate [6].

Conclusion: It is evidenced that these additives following ingestion are converted to their basic components, stearic acid and lactic acid, both of which are components of natural food and part of endogenous metabolism. Both acids can be synthesised endogenously. There seems, therefore, to be no need for a re-evaluation even if the existing studies are old and several studies, normally considered crucial when allocating an ADI, are missing.

References:


STEARYL TARTRATE

E number: E 483

Recommendation: Stearyl tartrate should be re-evaluated. Data on hydrolysis are required to show whether the supposed hydrolysis to constituents, normally occurring naturally in food, takes place.

Chemical name/synonyms: Stearyl palmityl tartrate.

Chemical formula: Distearyl tartrate: \( \text{C}_{40}\text{H}_{78}\text{O}_{6} \)
Dipalmityl tartrate: \( \text{C}_{36}\text{H}_{70}\text{O}_{6} \)
Stearylpalmityl tartrate: \( \text{C}_{38}\text{H}_{74}\text{O}_{6} \)

EINECS number: -

CAS number: -

Functional Class: Dough strengthening agent.

Specification:
Manufacture: Stearyl tartrate is obtained by esterification of tartaric acid with commercial stearyl alcohol, which consists essentially of stearyl and palmityl alcohols.

Definition: Stearyl tartrate consists mainly of diesters with minor amounts of monoesters and of unchanged starting materials. It is insoluble in water and soluble in hot ethanol.

EC specifications: E 483 Stearyl tartrate [1].
Assay: Not less than 90% of total ester content corresponding to an ester value within the range of 163 to 180.
The specification includes purity criteria on Hydroxyl value, Acid value, Total tartaric acid content, Sulphated ash, Unsaponifiable matter, Iodine value, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Stearyl tartrate [2].
Assay: Not less than 90% of total ester content corresponding to an ester value within the range of 163 to 180.
The specification includes purity criteria on Acid value, Total tartaric acid content, Sulfated ash, Unsaponifiable matter and Heavy metals.

Exposure: The permitted use of stearyl tartrate is restricted to bakery wares (except bread) 4 g/kg and desserts 5 g/kg. For an adult the ADI can be reached by consuming 300 or 240 g of product with 4 or 5 g substance, respectively, per kg product.

In the EU monitoring stearyl tartrate was examined at tier 2. The calculated intake by adults and the whole population is reported in the range of 1 - 98% of ADI. The calculated intake by young
children is reported in the range of 49 - 112%. The investigators concluded that examination at tier 3 of intakes by young children is needed.

SCF/JECFA evaluation:
SCF status: An ADI of 20 mg/kg bw was allocated in 1978 [3] in the Fifth Series of Reports. No details, basis, toxicological data or references were given for the conclusion, but the evaluation was restricted to the use in fine bakers’ wares to a maximum of 3 g/kg e. i. below the present permitted level.

JECFA status: No ADI allocated. The Committee in 1965 accepted the use of 500 mg/kg in flour as dough strengthening agent [4;5]. In the report from the 55th JECFA Meeting held 6-15 June 2000, it was mentioned that the basis for the 1965 decision was data on the hydrolysis, metabolism, and toxicity experiments in animals. No new data were submitted or found in an extensive search of the literature in relation to the 2000 meeting. The references from the 1965 meeting are no longer accessible to JECFA. The Committee noted that the use levels brought to its attention are much higher than envisaged in 1967 and concluded that new studies are required demonstrating hydrolysis in vivo before an evaluation can be completed [6].

Background data:
Subacute/subchronic toxicity: -

Genotoxicity: -

Chronic toxicity/Carcinogenicity: -

Reproduction toxicity: -

Conclusion: No toxicological data were presented by SCF in 1978 and what was/is available is not known. From the old data mentioned by JECFA in 1965, it may be assumed that stearyl tartrate following ingestion is converted to its basic components, stearic acid and tartaric acid, both of which are components of natural food. They can both be synthesised endogenously. However, data for hydrolysis are missing and should be provided.

References:


4. [1965, NMRS 40/TRS 339-JECFA 9]
Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids, and

5. [1965, FAS 67.29/NMRS 40A,B,C-JECFA 9]

6. [2000, TRS 901-JECFA 55]
SORBITAN MONOSTEARATE, SORBITAN TRISTEARATE AND SORBITAN MONOPALMITATE

**E number:**
- Sorbitan monostearate: E 491
- Sorbitan tristearate: E 492
- Sorbitan monopalmitate: E 495

**Recommendation:** As the data on these substances are incomplete a re-evaluation is recommended. The potential for exceeding the ADI should be addressed. See also E 493-4.

**Chemical name/synonyms:**
- Sorbitan monostearate: -
- Sorbitan tristearate: -
- Sorbitan monopalmitate: Sorbitan palmitate.

**Chemical formula:** -

**EINECS number:**
- Sorbitan monostearate: 215-664-9
- Sorbitan tristearate: 247-891-4
- Sorbitan monopalmitate: 247-568-8

**CAS number:**
- Sorbitan monostearate: 1338-41-6
- Sorbitan tristearate: 26658-19-5
- Sorbitan monopalmitate: 26266-57-9

**Functional Class:** Emulsifier.

**Specification:**
**Manufacture:** The sorbitan esters, sorbitan monostearate, sorbitan tristearate and sorbitan monopalmitate are obtained by esterification of commercial stearic or palmitic acid respectively with polyols derived from sorbitol.

*SORBITAN MONOSTEARATE*

**Definition:** Sorbitan monostearate is a mixture of partial esters of sorbitol and its anhydrides with edible, commercial stearic acid. It is insoluble in cold water but dispersible in hot water.

**EC specifications:** E 491 Sorbitan monostearate [1].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters.
The specification includes purity criteria on Water, Sulphated ash, Acid value, Saponification value, Hydroxyl value, Arsenic, Lead, Mercury, Cadmium and Heavy metals.
**JECFA specifications:** Sorbitan monostearate [2].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters. The specification includes purity criteria on Water, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

**Sorbitan tristearate**
Sorbitan monopalmitate

**Definition:** Sorbitan tristearate is a mixture of partial esters of sorbitol and its anhydrides with edible, commercial stearic acid. It is insoluble in water, methanol and ethanol and dispersible in vegetable oils.

**EC specifications:** E 492 Sorbitan tristearate [1].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters. The specification includes purity criteria on Water, Sulphated ash, Acid value, Saponification value, Hydroxyl value, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Sorbitan tristearate [3].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters. The specification includes purity criteria on Water, Sulfated ash, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

**Sorbitan monopalmitate**

**Definition:** Sorbitan monopalmitate is a mixture of partial esters of sorbitol and its anhydrides with edible, commercial palmitic acid. It is insoluble in cold water but dispersible in hot water.

**EC specifications:** E 495 Sorbitan monopalmitate [1].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters. The specification includes purity criteria on Water, Sulphated ash, Acid value, Saponification value, Hydroxyl value, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Sorbitan monopalmitate [2].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters. The specification includes purity criteria on Water, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

**Exposure:** Permitted uses comprise milk and cream analogues, beverage whitener, deserts, sugar confectionary, emulsified sauces and dietetic foods, 5 g/kg, fine bakery wares, fat emulsions and cocoa-based confectionery including chocolate 10 g/kg. It will take 150 g product with 10 g/kg and 300 g with 5 g/kg to reach the ADI.

In the EU monitoring system the substances were examined at tier 2 level. The calculated intake by adults and the whole population is reported in the range of 3 - 75% of ADI. The calculated intake by young children is reported in the range of 150 – 190%. Examination at tier 3 of intakes by young children is needed.
SCF/JECFA evaluation:
SCF status: An ADI of 25 mg/kg bw (the three substances single or in combination) was established in 1978 when the Committee endorsed the JECFA ADI [4]. No basis or any toxicological data were specified.

JECFA status: The ADI of 0-25 mg/kg bw (group ADI) was established in 1973 [5]. The basis was the level causing no toxicological effect in rats receiving 50000 ppm (5%) in the diet equivalent to 2500 mg/kg bw/day. No study was specified. Several exist. The safety factor was 100. In 1982 two other esters (E 493 and E 494) were included in the group ADI as JECFA concluded that, from a toxicological point of view, the evidence provides a basis for evaluating the sorbitan esters as a whole [6].

Background data:
Subacute/subchronic toxicity: Short-term studies are available in rats (E 491). No consistent compound-related toxicological effects were demonstrated. Short-term studies in dogs (fed E 491) and monkeys (fed E 491) showed no adverse effects [7].

Genotoxicity: No relevant data are available.

Chronic toxicity/Carcinogenicity: Long-term studies in rats are available for E491, E492, and E495. No compound-related effects were observed when the esters were fed at 5% of the diet [7]. Several long-term studies exist in rats, most are old. The general level causing no toxicological effect in rats was 5% in the diet equivalent to 2500 mg/kg bw/day. Higher levels (10, 20%) have been shown to cause a.o. growth retardation and diarrhoea [7].

A study has been published on long-term toxicity of sorbitan monostearate in mice demonstrating no evidence of carcinogenic activity at any of the applied dose levels (0, 0.5, 2, or 4% in diet) [8].

Reproduction toxicity: A study has been published on the effect of oral administration of sorbitan monostearate on pre- and postnatal development of rats, but no abstract was presented and the paper was published in Japanese [9].

Effect in humans: Studies in human volunteers given doses up to 6/day for 28 days of E491 showed no harmful effects [7].

Other: Biochemical aspects: Metabolic studies indicate that a significant portion of the sorbitan esters are hydrolysed to the fatty acid moiety and andydrides of sorbitol [7].

Conclusion: The data on these substances are old and incomplete and there is a potential for exceeding the ADI. A re-evaluation including also E 493-4 is therefore recommended.
References:


5. [1973, NMRS 53/TRS 539-JECFA 17]

6. [1982, TRS 683-JECFA 26]

7. [1982, FAS 17-JECFA 26]


SORBITAN MONOLAURATE AND SORBITAN MONOOLEATE

E number:
Sorbitan monolaurate: E 493
Sorbitan monooleate: E 494

Recommendation: In the light of the discrepancy between the SCF and the JECFA ADI’s and the high potential intake compared with the SCF ADI a re-evaluation of the ADI seems appropriate if a reduction in permitted use levels is not introduced. See also E 491-2+5.

Chemical name/synonyms: -

Chemical formula: -

EINECS number:
Sorbitan monolaurate: 215-663-3
Sorbitan monooleate: 215-665-4

CAS number:
Sorbitan monolaurate: 1338-39-2
Sorbitan monooleate: 1338-43-8

Functional Class: Emulsifier.

Specification:
Manufacture: Sorbitan monolaurate and sorbitan monooleate are obtained by esterification of commercial lauric or oleic acid respectively with polyols derived from sorbitol.

Sorbitan monolaurate
Definition: Sorbitan monolaurate is a mixture of partial esters of sorbitol and its anhydrides with edible, commercial lauric acid. It is dispersible in hot and cold water.

EC specifications: E 493 Sorbitan monolaurate [5].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters.
The specification includes purity criteria on Water, Sulphated ash, Acid value, Saponification value, Hydroxyl value, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

JECFA specifications: Sorbitan monolaurate [6].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters.
The specification includes purity criteria on Water, Sulfated ash, Acid value, Saponification value, Hydroxyl value and Lead.

Sorbitan monooleate
Definition: Sorbitan monooleate is a mixture of partial esters of sorbitol and its anhydrides with edible, commercial oleic acid. It is insoluble in cold water but dispersible in hot water.
**EC specifications:** E 494 Sorbitan monooleate [5].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters.
The specification includes purity criteria on Water, Sulphated ash, Acid value, Saponification value, Hydroxyl value, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Sorbitan monooleate [4].
Assay: Not less than 95% of a mixture of sorbitol, sorbitan and isosorbide esters.
The specification includes purity criteria on Water, Sulfated ash, Acid value, Saponification value, Hydroxyl value, Arsenic and Heavy metals.

**Exposure:** Permitted uses comprise milk and cream analogues, beverage whitener, deserts, sugar confectionary, emulsified sauces and dietetic foods, 5 g/kg, fine bakery ware, fat emulsions and cocoa-based confectionery including chocolate 10 g/kg. It will take 30 g product with 10 g/kg and 60 g with 5 g/kg to reach the ADI of 5 mg/kg.

In the EU monitoring system the substances were examined at tier 2 level. The calculated intake by adults and the whole population is reported in the range of 16 - 354% of ADI. The calculated intake by young children is reported in the range of 657 – 802%. Examination at tier 3 is needed.

**SCF/JECFA evaluation:**
**SCF status:** An ADI of 5 mg/kg bw, (single or in combination) was established in 1977 [2].
The committee reviewed and based the ADI evaluation on unpublished studies from 1947 and two newer short-term studies. No toxicological data were presented for any of these studies. This ADI is differing from that of JECFA’s.

**JECFA status:** An ADI of 0-25 mg/kg bw was established in 1982 [1]. The basis was the level causing no toxicological effect in rats on 50000 ppm (5%) in the diet equivalent to 2500 mg/kg bw/day and a safety factor of 100. The Committee concluded that from a toxicological point of view, the evidence provides a basis for evaluating all the sorbitan esters as a group and therefore included also the stearic and palmitic esters (E 491, E 492, and E 495) in the group ADI [1].

**Background data:**
**Subacute/subchronic toxicity:** Some changes in liver and kidney have been reported in short-term studies with mono-laurate (E 493) and mono-oleate (E 494) at dietary levels of 10%. The changes appeared to be related to the fatty acid moiety of the ester [3].
Short-term studies are available in hamsters (E 393). Traditional effects were seen in the gastrointestinal tract. Kidney alterations were regarded reversible [3].
Short-term studies are available in rats (E 493, or E 494). No consistent compound-related toxicological effects were demonstrated. Short-term studies in monkeys (fed E 493) showed no adverse effects [3].

**Genotoxicity:** No relevant data are available.

**Chronic toxicity/Carcinogenicity:** Long-term studies in rats are available for E 493, and E 494. No compound-related effects were observed when the esters were fed at 5% of the diet [3].

**Reproduction toxicity:** No relevant data are available.
Allergy/Intolerance: No relevant data are available.

Effect in humans: No relevant data are available.

Other: Biochemical aspects: Metabolic studies indicate that a significant portion of the sorbitan esters are hydrolysed to the fatty acid moiety and andydrides of sorbitol [3].

Conclusion: SCF has allocated an ADI, which is one fifth of that of JECFA, but no toxicological data were presented by SCF. The data presented to JECFA were limited compared to what would be requested to day. As also the potential intake is likely to exceed the SCF ADI a re-evaluation of the ADI is recommended (together with E 491-2 + E 495).

References:

1. [1982, TRS 683-JECFA 26]


3. [1982, FAS 17-JECFA 26]


CALCICUM CARBONATE, SODIUM CARBONATES, POTASSIUM CARBONATES, AMMONIUM CARBONATES AND MAGNESIUM CARBONATES

E number:
Calcium carbonate: E 170 (i)
Calcium hydrogen carbonate: E 170 (ii)
Sodium carbonate: E 500 (i)
Sodium hydrogen carbonate: E 500 (ii)
Sodium sesquicarbonate: E 500 (iii)
Potassium carbonate: E 501 (i)
Potassium hydrogen carbonate: E 501 (ii)
Ammonium carbonate: E 503 (i)
Ammonium hydrogen carbonate: E 503 (ii)
Magnesium carbonate: E 504 (i)
Magnesium hydroxide carbonate: E 504 (ii)

Recommendation: No need for a re-evaluation. The actual existence as food additives of calcium hydrogen carbonate and magnesium carbonate has been questioned.

Chemical name/synonyms:
Calcium carbonate: Calcium carbonate.
Calcium hydrogen carbonate: -
Sodium carbonate: Sodium carbonate/ soda ash.
Sodium hydrogen carbonate: Sodium hydrogen carbonate/ sodium bicarbonate, bicarbonate of soda, baking soda.
Sodium sesquicarbonate: Sodium monohydrogen dicarbonate.
Potassium carbonate: Potassium carbonate.
Potassium hydrogen carbonate: Potassium hydrogen carbonate/ potassium bicarbonate, acid potassium carbonate.
Ammonium carbonate: Ammonium carbonate.
Ammonium hydrogen carbonate: Ammonium hydrogen carbonate/ ammonium bicarbonate.
Magnesium carbonate: -
Magnesium hydroxide carbonate: Magnesium carbonate hydroxide hydrated/ magnesium hydrogen carbonate, magnesium subcarbonate (light or heavy), hydrated basic magnesium carbonate, magnesium carbonate hydroxide.

Chemical formula:
Calcium carbonate: CaCO₃
Calcium hydrogen carbonate: -
Sodium carbonate: Na₂CO₃
Sodium hydrogen carbonate: NaHCO₃
Sodium sesquicarbonate: Na₂CO₃·NaHCO₃·2H₂O
Potassium carbonate: K₂CO₃
Potassium hydrogen carbonate: KHCO₃
Ammonium carbonate: CH₅N₂O₂, CH₈N₂O₃ and CH₅NO₃
Ammonium hydrogen carbonate: CH₅NO₃
Magnesium carbonate: -
Magnesium hydroxide carbonate: $4\text{MgCO}_3\cdot\text{Mg(OH)}_2\cdot5\text{H}_2\text{O}$

**EINECS number:**
- Calcium carbonate: 215-279-6
- Calcium hydrogen carbonate: -
- Sodium carbonate: 207-838-8
- Sodium hydrogen carbonate: 205-633-8
- Sodium sesquicarbonate: 208-580-9
- Potassium carbonate: 209-529-3
- Potassium hydrogen carbonate: 206-059-0
- Ammonium carbonate: 233-786-0
- Ammonium hydrogen carbonate: 213-911-5
- Magnesium carbonate: -
- Magnesium hydroxide carbonate: 235-192-7

**CAS number:**
- Calcium carbonate: 471-34-1
- Calcium hydrogen carbonate: -
- Sodium carbonate: 497-19-8
- Sodium hydrogen carbonate: 144-55-8
- Sodium sesquicarbonate: 533-96-0
- Potassium carbonate: 584-08-7
- Potassium hydrogen carbonate: 10361-29-2
- Ammonium carbonate: 7722-76-1
- Magnesium carbonate: 546-93-0
- Magnesium hydroxide carbonate: -

**Functional Class:** Alkali, buffering agent. Calcium carbonate: colour, nutrient, anticaking agent.

**Specification:**
*Calcium carbonate*

**Manufacture:** Calcium carbonate is obtained from ground limestone or by precipitation of calcium ions with carbonate ions.

**Definition:** Calcium carbonate is practically insoluble in water, dissolves with effervescence in diluted acetic acid, diluted hydrochloric acid and diluted nitric acid.

**EC specifications:** E 170 Calcium carbonate [1].
Assay: Not less than 98% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Acid-insoluble matter, Magnesium and alkali salts, Fluoride, Antimony, copper, chromium, zinc and barium, Arsenic, Lead and Cadmium.

**JECFA specifications:** Calcium Carbonate [2].
Assay: Not less than 98.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Acid-insoluble matter, Magnesium and alkali salts, Free alkali, Fluoride, Barium, Arsenic, Lead and Heavy metals.
**Calcium hydrogen carbonate**

**Manufacture:** No information on manufacturing processes for calcium hydrogen carbonate as a food additive.

**Definition:** Calcium hydrogen carbonate only exists as a solution. No information has been received on calcium hydrogen used as a food additive.

**EC specifications:** No EC specification has been prepared.

**JECFA specifications:** No JECFA specification has been prepared.

**Sodium carbonate**

**Manufacture:** No information on manufacturing processes of sodium carbonate as a food additive.

**Definition:** Sodium carbonate is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 500 (i) Sodium carbonate [3].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Arsenic, Lead and Mercury.

**JECFA specifications:** Sodium carbonate [4].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Arsenic and Heavy metals.

**Sodium hydrogen carbonate**

**Manufacture:** No information on manufacturing processes of sodium hydrogen carbonate as a food additive.

**Definition:** Sodium hydrogen carbonate is soluble in water and insoluble in ethanol.

**EC specifications:** E 500 (ii) Sodium hydrogen carbonate [3].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Ammonium salts, Arsenic, Lead and Mercury.

**JECFA specifications:** Sodium hydrogen carbonate [4].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Water-insoluble matter, Ammonium salts, Arsenic and Heavy metals.

**Sodium sesquicarbonate**

**Manufacture:** No information on manufacturing processes of sodium sesquicarbonate as a food additive.

**Definition:** Sodium sesquicarbonate is freely soluble in water.

**EC specifications:** E 500 (iii) Sodium sesquicarbonate [3].
Assay: Between 35.0% and 38.6% of NaHCO₃ and between 46.4% and 50.0% of Na₂CO₃.
The specification includes purity criteria on Sodium chloride, Iron, Arsenic, Lead and Mercury.

**JECFA specifications:** Sodium sesquicarbonate [5].
Assay: Between 35.0% and 38.6% of NaHCO₃ and between 46.4% and 50.0% of Na₂CO₃.
The specification includes purity criteria on Water, Sodium chloride, Iron, Arsenic and Heavy metals.

**Potassium carbonate**
**Manufacture:** No information on manufacturing processes of potassium carbonate as a food additive.

**Definition:** Potassium carbonate is very soluble in water and insoluble in ethanol.

**EC specifications:** E 501 (i) Potassium carbonate [3].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Arsenic, Lead and Mercury.

**JECFA specifications:** Potassium carbonate [4].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Arsenic, Lead and Heavy metals.

**Potassium hydrogen carbonate**
**Manufacture:** No information on manufacturing processes of potassium hydrogen carbonate as a food additive.

**Definition:** Potassium hydrogen carbonate is very soluble in water and insoluble in ethanol.

**EC specifications:** E 501 (ii) Potassium hydrogen carbonate [3].
Assay: Not less than 99.0% and not more than 101.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Arsenic, Lead and Mercury.

**JECFA specifications:** Potassium hydrogen carbonate [4].
Assay: Not less than 99.0% and not more than 101.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Normal carbonate, Arsenic and Heavy metals.

**Ammonium carbonate**
**Manufacture:** No information on manufacturing processes of ammonium carbonate as a food additive.

**Definition:** Ammonium carbonate is soluble in water.

**EC specifications:** E 503 (i) Ammonium carbonate [3].
Assay: Not less than 30.0% and not more than 34.0% of NH₃.
The specification includes purity criteria on Non-volatile matter, Chloride, Sulphate, Arsenic, Lead and Mercury.
JECFA specifications: Ammonium carbonate [6].
Assay: Not less than 30.0% and not more than 34.0% on of NH₃.
The specification includes purity criteria on Non-volatile matter, Chloride, Sulphate, Arsenic and Heavy metals.

Ammonium hydrogen carbonate
Manufacture: No information on manufacturing processes of ammonium hydrogen carbonate as a food additive.

Definition: Ammonium hydrogen carbonate is freely soluble in water.

EC specifications: E 503 (ii) Ammonium hydrogen carbonate [3].
Assay: Not less than 99.0%.
The specification includes purity criteria on Non-volatile matter, Chloride, Sulphate, Arsenic, Lead and Mercury.

JECFA specifications: Ammonium hydrogen carbonate [6].
Assay: Not less than 96% and not more than 102%.
The specification includes purity criteria on Fluoride, Arsenic and Heavy metals.

Magnesium carbonate
 Manufacture: No information on manufacturing processes of magnesium carbonate as a food additive.

Definition: Magnesium carbonate does not exist commercially as a well-defined chemical substance. JECFA has specified a substance under the title Magnesium carbonate. In the specification the substance is defined as a basic hydrated or a normal hydrated magnesium carbonate or a mixture of the two. However, on the basis of the specified composition the substance in question is identical with the substance specified under the title Magnesium hydroxide carbonate at a different JECFA meeting. No information on Magnesium carbonate used as a food additive to facilitate the preparation of an EC specification has been submitted.

EC specifications: No EC specification has been prepared.

JECFA specifications: Magnesium carbonate [2].
Assay: Not less than 24.0% and not more than 26.4% of Mg.
The specification includes purity criteria on Acid-insoluble substances, Water-soluble substances, Calcium, Arsenic, Lead and Heavy metals.

Magnesium hydroxide carbonate
Manufacture: No information on manufacturing processes of magnesium hydroxide carbonate as a food additive.

Definition: Magnesium hydroxide carbonate is practically insoluble in water and insoluble in ethanol.
**EC specifications:** An EC specification for magnesium hydroxide carbonate is currently in preparation.

**JECFA specifications:** Magnesium hydroxide carbonate [7].
Assay: Not less than 40.0% and not more than 45.0% of MgO.
The specification includes purity criteria on Acid-insoluble substances, Soluble salts, Calcium, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible, but is also not considered necessary.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1990, ADI not specified based on the fact that these substances are normal constituents of the diet and their metabolism is well described. However, SCF stated that large doses of magnesium ions cause diarrhoea and should be avoided [8].

**JECFA status:** Latest evaluation 1965. ADI not specified when used in accordance with good manufacturing practice [9]. In 1985 JECFA mentioned that magnesium salt given in a large single dose has laxative effect and should be avoided [10]. Ammonium carbonate and Ammonium bicarbonate was evaluated in 1982 and included in the ADI not specified based on the evidence from human exposure to relative high doses ammonium chloride that the only toxic effect is alteration in acid-base balance. It would appear that this would be less of a problem with ammonium carbonate [11].

**Conclusion:** Carbonates are safe food additives. The basis for the EC specifications has in most cases been the respective JECFA specification. However in general the JECFA specifications are old. In addition the JECFA specifications have been prepared at several different meetings.

**References:**


9. [1965, NMRS 40/TRS 339-JECFA 9]

10. [1985, TRS 733-JECFA 29]

11. [1982, TRS 683-JECFA 26]
HYDROCHLORIC ACID, POTASSIUM CHLORIDE, CALCIUM CHLORIDE AND MAGNESIUM CHLORIDE

**E Number:**
- Hydrochloric acid: E 507
- Potassium chloride: E 508
- Calcium chloride: E 509
- Magnesium chloride: E 511

**Recommendation:** No need for a re-evaluation.

**Chemical name/synonyms:**
- Hydrochloric acid: Hydrochloric acid/ hydrogen chloride, muriatic acid.
- Potassium chloride: Potassium chloride/ Sylvine, Sylvite.
- Calcium chloride: Calcium chloride.
- Magnesium chloride: Magnesium chloride.

**Chemical formula:**
- Hydrochloric acid: HCl
- Potassium chloride: KCl
- Calcium chloride: CaCl₂·nH₂O (n = 0,2 or 6)
- Magnesium chloride: MgCl₂·6H₂O

**EINECS number:**
- Hydrochloric acid: 231-595-7
- Potassium chloride: 231-211-8
- Calcium chloride: 233-140-8
- Magnesium chloride: 232-094-6

**CAS Number:**
- Hydrochloric acid: 7647-01-0
- Potassium chloride: 7447-40-7
- Calcium chloride: 10043-52-4
- Magnesium chloride: 7786-30-3

**Functional Class:** Firming agent, stabiliser, acidity regulator.

**Specification:**
- **Manufacture:** No information on manufacturing processes of food grade hydrochloric acid and the salts.

*Hydrochloric acid*

**Definition:** Hydrochloric acid is a naturally occurring inorganic acid. It is soluble in water and in ethanol.

**EC specifications:** E 507 Hydrochloric acid [1].
- **Assay:** Hydrochloric acid is commercially available in varying concentrations. Concentrated hydrochloric acid contains not less than 35.0% HCl.
The specification includes purity criteria on Total organic compounds, Non-volatile matter, Reducing substances, Oxidising substances, Sulphate, Iron, Arsenic, Lead and Mercury.

**JECFA specifications:** Hydrochloric acid [2].
Assay: Not less than 97.0% and not more than 103.0% of the labelled amount.
The specification includes purity criteria on Total organic compounds, Non-volatile matter, Reducing substances, Oxidising substances, Sulphate, Iron and Lead.

**Potassium chloride**
**Definition:** Potassium chloride is the potassium salt of hydrochloric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 508 Potassium chloride [1].
Assay: Not less than 99% on the dried basis.
The specification includes purity criteria on Loss on drying, Sodium, Arsenic, Lead, Mercury, Cadmium and Heavy metals.

**JECFA specifications:** Potassium chloride [3].
Assay: Not less than 99.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Acidity or alkalinity, Iodide or bromide, Sodium, Arsenic and Heavy metals.

**Calcium chloride**
**Definition:** Calcium chloride is the calcium salt of hydrochloric acid. Calcium chloride, anhydrous is freely soluble in water and in ethanol, calcium chloride dihydrate is freely soluble in water and soluble in ethanol, calcium chloride is very soluble in water and ethanol.

**EC specifications:** E 509 Calcium chloride [1].
Assay: Not less than 93.0% on the anhydrous basis.
The specification includes purity criteria on Magnesium and alkali salts, Fluoride, Arsenic, Lead and Mercury.

Assay: Anhydrous: not less than 93% of CaCl$_2$, dihydrate: not less than 99.0% and not more than 107.0% of CaCl$_2$−2H$_2$O, hexahydrate: not less than 98.0% and not more than 110% of CaCl$_2$−6H$_2$O.
The specification includes purity criteria on Free alkali, Magnesium and alkali salts, Fluoride, Arsenic, Lead and Heavy metals.

**Magnesium chloride**
**Definition:** Magnesium chloride is the magnesium salt of hydrochloric acid. It is very soluble in water and freely soluble in ethanol.

**EC specifications:** E 511 Magnesium chloride [1].
Assay: Not less than 99.0%.
The specification includes purity criteria on Ammonium, Arsenic, Lead and Mercury.

**JECFA specifications:** Magnesium chloride [4].
Assay: Not less than 99.0% and not more than 105.0% of MgCl$_2$−6H$_2$O.
The specification includes purity criteria on Ammonium, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible, but is also not considered necessary.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990, ADI not specified based on the fact that these substances are normal constituents of the diet and their metabolism is well described. However, SCF stated that large doses of magnesium ions cause diarrhoea and should be avoided [5].

**JECFA status:** Latest evaluations 1979, 1985. Group ADI “not limited” for hydrochloric acid and its magnesium, potassium salts [6]. In 1985 JECFA mentioned that magnesium salt given in a large single dose is has laxative effect [7].

Due to the fact that these substances are natural constituents of the diet and the intake from food additives is likely to be insignificant compared to the intake from natural sources there is no need for specific toxicity data.

**Conclusion:** Chlorides are safe food additives. Hydrochloric acid and its salts as described by the specifications are covered by the toxicological evaluation. The JECFA specifications are old and have in addition been prepared at different meetings. It is therefore suggested to revise these specifications at a future JECFA meeting.

**References:**


6. [1979, TRS 648-JECFA 23]

7. [1985, TRS 733-JECFA 29]
STANNOUS CHLORIDE

E number: E 512

Recommendation: No need for an immediate re-evaluation but at some occasion the new data concerning genotoxicity should be taken into consideration.

Chemical name/synonyms: Stannous chloride dihydrate/ tin chloride, tin dichloride.

Chemical formula: SnCl$_2$·2H$_2$O

EINECS number: 231-868-0

CAS number: 7772-99-8

Functional Class: Antioxidant synergist.

Specification:
Manufacture: No information on manufacturing processes for food grade stannous chloride.

Definition: Stannous chloride is the dihydrated tin (II) salt of hydrochloric acid. It is freely soluble in water and soluble in ethanol.

EC specifications: E 512 Stannous chloride [1].
Assay: Not less than 98.0%.
The specification includes purity criteria on Sulphate, Arsenic, Lead and Mercury.

JECFA specifications: Stannous chloride [2].
Assay: Not less than 98.0%.
The specification includes purity criteria on Hydrochloric acid insoluble matter, Sulfate, Arsenic and Heavy metals.

Exposure: Stannous chloride may only be used in canned and bottled white asparagus in quantities up to 25mg/kg as Sn. It is impossible to reach the PMTDI with this concentration and it is also well below the concentration, which can elicit acute symptoms and also lower than concentrations which have been found acceptable by SCF and JECFA when migrating from cans.

SCF/JECFA evaluation:
SCF status: Latest evaluation 1990, where the Committee accepts the use of stannous chloride for stabilizing the white colour of certain vegetable product because the contribution to the intake of tin from this source lies well below the PMTDI as established by JECFA in 1982 [3]. In 2002 concurs with the JECFA conclusion that levels of 150 mg/kg in canned beverages or 250 mg/kg in other canned foods may cause gastric irritation in some individuals
http://europa.eu.int/comm/food/fs/sc/scf/out110_en.pdf

JECFA status: In 2000 JECFA evaluated tin [4] and confirm the PTWI of 14 mg/kg bw established in 1988 [5]. The evaluation is based on human data caused by either intoxication...
incidence caused by ingestion of canned foodstuff or by volunteers intake of food containing high levels of tin [6].

**Background data:**

**Subacute/subchronic toxicity:** Several studies report a decrease in haemoglobin, haemotocrit and calcium levels when rats are given more than 0.05% in the diet [7].

**Genotoxicity:** In two studies indicate that stannous chloride form single strand breaks and other damage to DNA *in vitro* through a mechanism involving the formation of reactive oxygen species [8;9]. Another study suggests that stannous chloride causes damage to the DNA repair system [10].

**Chronic toxicity/carcinogenicity:** In a 105 weeks study, where groups of male and female b6c3f1 mice (numbers not given) were given a diet containing 0, 0.1 % or 0.2 % stannous chloride, a significant dose-related trend towards either hepatocellular adenomas or carcinomas was observed in the females. However, the highest incidence was within the historical range for female b6c3f1 mice so the conclusion was that stannous chloride was not carcinogenic for b6c3f1 mice [7]. In a similar experiment in rats with 50/animals/sex/treatment group there was seen a trend towards increased C-cell adenomas and carcinomas of the thyroid in males with increased tin exposure. Also in this study the highest incidence was within the historical control data, whic led to the conclusion that stannous chloride was not carcinogenic for F-344 rats [7].

**Reproduction studies:** In a three generation rat study with doses up to 0.08% in the diet there was seen an increased mortality during the first 10 days of lactation, and the haemoglobin contents in the pups decrease. Teratogenicity studies in mice, rats and hamsters indicate no adverse effects when given 50 mg/kg bw. [7].

**Effects in human:** Human data exist partly from industrial workers chronically exposed to stannous dust and partly from some cases of intoxication caused by ingestion of contaminated food. Most of the intoxication incidents were caused by canned fruit juice. The symptoms are vomiting diarrhoea and abdominal bloating. Nausea, vomiting and diarrhoea were observed in a large unspecified number of persons in Kuwait who consumed formulated orange juice and apple juice containing 250-385 ppm tin [11]. In 97 well documented cases, severe abdominal bloating, vomiting and diarrhoea were noted after the consumption of canned tomato juice with tin levels ranging from 141 to 405 ppm [11]. Several other similar incidences have been reported. Studies with few volunteers given food containing similar amount of tin did not show the same problems [11]. From these studies JECFA concluded that exact doses for these episodes have not been established but the threshold concentration is estimated to be 200 mg/kg food [7]. The JECFA evaluation is based on these data.

**Other:** There has been some concern for a possible bioalkylation of inorganic stannous compounds. No such reaction has been reported in humans although trace levels of monomethyl- and dimethyl stannous compounds were found in urine in humans with no known exposure to these compounds [7]. A literature search for more recent reports revealed no new information.

Studies on the metabolism of stannous have shown that inorganic stannous compounds induce P450 [12].

**Conclusion:** Although the toxicological data are less than normally required, the very limited use of stannous chloride as a food additive is considered to pose no risk to food safety. The JECFA specification is old. It is therefore suggested to revise this specification at a future JECFA meeting.
References:


4. [2000, TRS 901-JECFA 55]

5. [1988, TRS 776-JECFA 33]

6. [1982, TRS 683-JECFA 26]

7. [1982, FAS 17-JECFA 26]


11. [1988, FAS 24-JECFA 33]

**SULPHURIC ACID, SODIUM SULPHATE, POTASSIUM SULPHATE, CALCIUM SULPHATE AND AMMONIUM SULPHATE**

**E Number:**
- Sulphuric acid: E 513
- Sodium sulphate: E 514
- Potassium sulphate: E 515
- Calcium sulphate: E 516
- Ammonium sulphate: E 517

**Recommendation:** No need for a re-evaluation.

**Chemical name/synonyms:**
- Sulphuric acid: Sulphuric acid/oil of vitriol, dihydrogen sulphate.
- Sodium sulphate: Sodium sulphate.
- Sodium hydrogen sulphate/ acid sodium sulphate, sodium bisulphate, nitre cake.
- Potassium sulphate: Potassium sulphate.
- Potassium hydrogen sulphate/ Potassium bisulphate, acid potassium sulphate.
- Calcium sulphate: Calcium sulphate/ gypsum, selenite, anhydrite.
- Ammonium sulphate: Ammonium sulphate.

**Chemical formula:**
- Sulphuric acid: H₂SO₄
- Sodium sulphate: Na₂SO₄·nH₂O (n = + or 10)
- Sodium hydrogen sulphate: NaHSO₄
- Potassium sulphate: K₂SO₄
- Potassium hydrogen sulphate: KHSO₄
- Calcium sulphate: CaSO₄
- Ammonium sulphate: (NH₄)₂SO₄

**EINECS number:**
- Sulphuric acid: 231-639-5
- Sodium sulphate: -
- Sodium hydrogen sulphate: -
- Potassium sulphate: -
- Potassium hydrogen sulphate: -
- Calcium sulphate: 231-900-3
- Ammonium sulphate: 231-984-1

**CAS Number:**
- Sulphuric acid: 7664-93-9
- Sodium sulphate: 7757-82-6 (anhydrous), 7727-73-3 (decahydrate)
- Sodium hydrogen sulphate: 7681-38-1
- Potassium sulphate: 7778-80-5
- Potassium hydrogen sulphate: -
- Calcium sulphate: 7778-18-9
- Ammonium sulphate: 7783-20-2
**Functional Class:** Acidity regulator, sequestrant.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade sulphuric acid and the salts.

**Sulphuric acid**

**Definition:** Sulphuric acid is a naturally occurring inorganic acid. It is miscible with water and with ethanol.

**EC specifications:** E 513 Sulphuric acid [1].

Assay: Sulphuric acid is commercially available in varying concentrations. The concentrated form contains not less than 96.0%.

The specification includes purity criteria on Ash, Reducing matter, Nitrate, Chloride, Iron, Selenium, Arsenic, Lead and Mercury.

**JECFA specifications:** Sulfuric acid [2].

Assay: Sulphuric acid contains not less than the minimum amount specified by the vendor.

The specification includes purity criteria on Total ash, Reducing matter, Nitrate, Chloride, Iron, Selenium, Arsenic, Lead and Heavy metals.

**Sodium sulphate**

**Definition:** Sodium sulphate is the disodium salt of sulphuric acid. It is freely soluble in water and practically insoluble in ethanol.

**EC specifications:** E 514 (i) Sodium sulphate [1].

Assay: Not less than 99.0% on the anhydrous basis.

The specification includes purity criteria on Loss on drying, Selenium, Arsenic, Lead and Mercury.

**JECFA specifications:** Sodium sulfate [2].

Assay: Not less than 99.0% on the anhydrous basis.

The specification includes purity criteria on Loss on drying, Selenium and Lead.

**Sodium hydrogen sulphate**

**Definition:** Sodium hydrogen sulphate is the monosodium salt of sulphuric acid.

**EC specifications:** E 514 (ii) Sodium hydrogen sulphate [1].

Assay: Not less than 95.2% on the anhydrous basis.

The specification includes purity criteria on Loss on drying, Water-insoluble matter, Selenium, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

**Potassium sulphate**

**Definition:** Potassium sulphate is the dipotassium salt of sulphuric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 515 (i) Potassium sulphate [1].

Assay: Not less than 99.0%.
The specification includes purity criteria on Selenium, Arsenic, Lead and Mercury.

**JECFA specifications:** Potassium sulfate [3].
Assay: Not less than 99.0%.
The specification includes purity criteria on Selenium, Arsenic and Heavy metals.

*Potassium hydrogen sulphate*

**Definition:** Potassium hydrogen sulphate is the monopotassium salt of sulphuric acid.

**EC specifications:** E 515 (ii) Potassium hydrogen sulphate [1].
Assay: Not less than 99%.
The specification includes purity criteria on Selenium, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

*Calcium sulphate*

**Definition:** Calcium sulphate is the calcium salt of sulphuric acid. It is slightly soluble in water and insoluble in ethanol.

**EC specifications:** E 516 Calcium sulphate [1].
Assay: Not less than 99% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Fluoride, Selenium, Arsenic, Lead and Mercury.

**JECFA specifications:** Calcium sulfate [4].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Fluoride, Selenium, Arsenic, Lead and Heavy metals.

*Ammonium sulphate*

**Definition:** Ammonium sulphate is the calcium salt of sulphuric acid. It is slightly soluble in water and insoluble in ethanol.

**EC specifications:** E 517 Ammonium sulphate [1].
Assay: Not less than 99.0% and not more than 100.5%.
The specification includes purity criteria on Residue on ignition, Selenium and Lead.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** With the exception of ammonium sulphate these substances are permitted generally in foodstuffs except those where additives are not permitted. Ammonium sulphate is only permitted as a carrier for food additives. No upper levels are specified and an exposure estimate is, therefore, not possible, but is also not considered necessary.

**SCF/JECFA evaluation:**

**SCF status:** ADI not specified based on the fact these substances are normal constituents of the diet and their metabolism is well described with no undesired effect [5].
JECFA status: Due to the fact that these substances are natural constituents of the diet and the intake from food additives is likely to be insignificant compared to the intake from natural sources there is no need for specific toxicity data [6].

Conclusion: There is no reason for a re-evaluation of sulphates as food additives. The JECFA specifications have been prepared at different meetings and in addition some are old. It is therefore suggested to revise the specifications for this group of substances at a future JECFA meeting.

References:


6. [1985, TRS 733-JECFA 29]
**ALUMINIUM SULPHATE, ALUMINIUM SODIUM SULPHATE, ALUMINIUM POTASSIUM SULPHATE AND ALUMINIUM AMMONIUM SULPHATE**

**E number:**
- Aluminium sulphate: E 520
- Aluminium sodium sulphate: E 521
- Aluminium potassium sulphate: E 522
- Aluminium ammonium sulphate: E 523

**Recommendation:** The limited permitted uses of these substances will ensure that exposure from this source is minimal. However, a re-evaluation of aluminium from all sources, including food additive uses is recommended. For the evaluation of aluminium in general see E 541 aluminium.

**Chemical name/synonyms:**
- Aluminium sulphate: Aluminium sulphate/ alum.
- Aluminium sodium sulphate: Aluminium sodium sulphate/ soda alum, sodium alum.
- Aluminium potassium sulphate: Aluminium potassium sulphate/ potassium alum, potash alum.
- Aluminium ammonium sulphate: Aluminium ammonium sulphate/ ammonium alum.

**Chemical formula:**
- Aluminium sulphate: \( \text{Al}_2(\text{SO}_4)_3 \)
- Aluminium sodium sulphate: \( \text{AlNa}(\text{SO}_4)_{2-n}\cdot n\text{H}_2\text{O} \) (\( n = 0 \) or 12)
- Aluminium potassium sulphate: \( \text{AlK}(\text{SO}_4)_2\cdot 12\text{H}_2\text{O} \)
- Aluminium ammonium sulphate: \( \text{AlNH}_4(\text{SO}_4)_2\cdot 12\text{H}_2\text{O} \)

**EINECS number:**
- Aluminium sulphate: 233-135-0
- Aluminium sodium sulphate: 233-277-3
- Aluminium potassium sulphate: 233-141-3
- Aluminium ammonium sulphate: 232-055-3

**CAS number:**
- Aluminium sulphate: 10043-01-3
- Aluminium sodium sulphate: 10102-71-3
- Aluminium potassium sulphate: 10043-67-1
- Aluminium ammonium sulphate: 7784-25-0

**Functional Class:**
- Aluminium sulphate: Firming Agent.
- Aluminium sodium sulphate: Buffering Agent, Neutralising Agent, Firming Agent.
- Aluminium potassium sulphate: Acidity Regulator, Stabiliser.
- Aluminium ammonium sulphate: Stabiliser, Firming Agent.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade aluminium sulphates.

*Aluminium sulphate*
**Definition:** Aluminium sulphate is the aluminium salt of sulphuric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 520 Aluminium sulphate [7].
Assay: Not less than 99.5% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Alkalies and alkali earths, Selenium, Fluoride, Arsenic, Lead and Mercury.

**JECFA specifications:** Aluminium sulfate (anhydrous) [3] Assay: Not less than 99.5% on the ignited basis.
The specification includes purity criteria on Loss on ignition, Alkalis and alkali earths, Fluoride, Lead, and Selenium.

*Aluminium sodium sulphate*

**Definition:** Aluminium sodium sulphate is the aluminium and sodium salt of sulphuric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 521 Aluminium sodium sulphate [7].
Assay: Not less than 96.5% (anhydrous) and 99.5% (dodecahydrate).
The specification includes purity criteria on Loss on ignition, Ammonium salts, Selenium, Fluoride, Arsenic, Lead and Mercury.

**JECFA specifications:** Aluminium potassium sulfate [5].
Assay: Not less than 96.5% (anhydrous) after drying and 99.5% (dodecahydrate) after drying.
The specification includes purity criteria on Loss on drying, Ammonium salts, Selenium, Fluoride, Arsenic, Lead and Heavy metals.
This specification was tentative and was withdrawn in 2000 as JECFA was not provided with relevant information [3].

*Aluminium potassium sulphate*

**Definition:** Aluminium potassium sulphate is the aluminium and potassium salt of sulphuric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 522 Aluminium potassium sulphate [7].
Assay: Not less than 99.5%.
The specification includes purity criteria on Ammonium salts, Selenium, Fluoride, Arsenic, Lead and Mercury.

**JECFA specifications:** Aluminium potassium sulfate [3].
Assay: Not less than 99.5%.
The specification includes purity criteria on Ammonium salts, Selenium, Fluoride, and Lead.

*Aluminium ammonium sulphate*

**Definition:** Aluminium ammonium sulphate is the aluminium and ammonium salt of sulphuric acid. It is freely soluble in water and insoluble in ethanol.

**EC specifications:** E 522 Aluminium ammonium sulphate [7].
Assay: Not less than 99.5%.
The specification includes purity criteria on Alkali metals and alkaline earths, Selenium, Fluoride, Arsenic, Lead and Mercury.
**JECFA specifications:** Aluminium ammonium sulfate [6].
Assay: Not less than 99.5%.
The specification includes purity criteria on Loss on drying, Ammonium salts, Selenium, Fluoride, Arsenic, Lead and Heavy metals.

**Exposure:** The aluminium sulphates are only permitted in egg white (30 mg/kg as Al) and in candied, crystallized and glace fruit and vegetables (200 mg/kg as Al).

In the EU monitoring system these and other aluminium salts were subject to a tier 2 testing which suggested that intake may be as high as 624 % of PTWI. This figure is likely to be highly overestimated, especially for these substances.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation in 1990 when the JECFA PTWI of 7 mg Al/kg bw from all sources was endorsed [4]. The toxicological data and conclusion are covered by the evaluation of E 173 aluminium.

**JECFA status:** Latest evaluation of aluminium ammonium sulphate 1988, PTWI 7 mg/kg bw based on the evaluation of aluminium [2]. Latest evaluation of aluminium sulphate, aluminium sodium sulphate and aluminium potassium sulphate, 1978, No ADI allocated [1].

**Background data:** Aluminium is allocated a group PTWI for all aluminium containing food additives based on the evaluation of aluminium phosphate (E 541). The background data the aluminium containing food additives covered by PTWI are presented in this monograph.

**Conclusion:** These substances should be included when re-evaluating the overall toxicity of aluminium from all sources.

**References:**

1. [1978, TRS 631-JECFA 22]

2. [1988, TRS 776-JECFA 33]

3. [2000, TRS 901-JECFA 55]


SODIUM HYDROXIDE, POTASSIUM HYDROXIDE, CALCIUM HYDROXIDE, AMMONIUM HYDROXIDE, MAGNESIUM HYDROXIDE, CALCIUM OXIDE AND MAGNESIUM OXIDE

**E Number:**
- Sodium hydroxide: E 524
- Potassium hydroxide: E 525
- Calcium hydroxide: E 526
- Ammonium hydroxide: E 527
- Magnesium hydroxide: E 528
- Calcium oxide: E 529
- Magnesium oxide: E 530

**Recommendation:** No need for a re-evaluation.

**Chemical name/synonyms:**
- Sodium hydroxide: Sodium hydroxide/ caustic soda, lye.
- Potassium hydroxide: Potassium hydroxide/ caustic potash.
- Calcium hydroxide: Calcium hydroxide/ slaked lime, hydrated lime.
- Ammonium hydroxide: Ammonium hydroxide/ strong ammonia solution.
- Magnesium hydroxide: Magnesium hydroxide.
- Calcium oxide: Calcium oxide/ burnt lime.
- Magnesium oxide: Magnesium oxide.

**Chemical formula:**
- Sodium hydroxide: NaOH
- Potassium hydroxide: KOH
- Calcium hydroxide: Ca(OH)₂
- Ammonium hydroxide: NH₄OH
- Magnesium hydroxide: Mg(OH)₂
- Calcium oxide: CaO
- Magnesium oxide: MgO

**EINECS number:**
- Sodium hydroxide: 215-185-5
- Potassium hydroxide: 215-181-3
- Calcium hydroxide: 215-137-3
- Ammonium hydroxide: -
- Magnesium hydroxide: 215-170-3
- Calcium oxide: 215-138-9
- Magnesium oxide: 215-171-9

**CAS Number:**
- Sodium hydroxide: 1310-73-2
- Potassium hydroxide: 1310-58-3
- Calcium hydroxide: 1305-62-0
- Ammonium hydroxide: 1336-21-6
- Magnesium hydroxide: 1309-42-8
- Calcium oxide: 1305-78-8
- Magnesium oxide: 1309-48-4
**Functional Class:** Alkali, anticaking agent (the oxides).

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade hydroxides.

**Sodium hydroxide**

**Definition:** Sodium hydroxide is a strong base. It is very soluble in water and freely soluble in ethanol.

**EC specifications:** E 524 Sodium hydroxide [4]. Assay: Content of solid form not less than 98.0% of total alkali (as NaOH). Content of solutions accordingly, based on the stated or labelled percentage of NaOH. The specification includes purity criteria on Water insoluble and organic matter, Carbonate, Arsenic, Lead and Mercury.

**JECFA specifications:** Sodium hydroxide [3]. Assay: Content of solid form not less than 95.0% of total alkali (as NaOH). The specification includes purity criteria on Water-insoluble substances, Carbonate, Arsenic, Lead, Mercury and Heavy metals.

**Potassium hydroxide**

**Definition:** Potassium hydroxide is a strong base. It is very soluble in water and freely soluble in ethanol.

**EC specifications:** E 525 Potassium hydroxide [4]. Assay: Content of solid form not less than 85.0% of alkali (as KOH). The specification includes purity criteria on Water insoluble, Carbonate, Arsenic, Lead and Mercury.

**JECFA specifications:** Potassium hydroxide [3]. Assay: Content of solid form not less than 85.0% of total alkali (as KOH). The specification includes purity criteria on Water-insoluble substances, Carbonate, Arsenic, Lead, Mercury and Heavy metals.

**Calcium hydroxide**

**Definition:** Calcium hydroxide is a strong base. It is very soluble in water and freely soluble in ethanol.

**EC specifications:** E 526 Calcium hydroxide [4]. Assay: Content of solid form not less than 92.0% of alkali (as KOH). The specification includes purity criteria on Acid-insoluble ash, Magnesium and alkali salts, Barium, Fluoride, Arsenic and Lead.

**JECFA specifications:** Calcium hydroxide [3]. Assay: Content of solid form not less than 92.0% of total alkali (as KOH). The specification includes purity criteria on Acid-insoluble ash, Magnesium and alkali salts, Barium, Fluoride, Arsenic, Lead and Heavy metals.

**Ammonium hydroxide**
**Definition:** Ammonium hydroxide is a strong base.

**EC specifications:** E 527 Ammonium hydroxide [4].
Assay: Not less than 27% of NH$_3$.
The specification includes purity criteria on Non-volatile matter, Arsenic and Lead.

**JECFA specifications:** Ammonium hydroxide [3].
Assay: Not less than 27% and not more than 30% of NH$_3$.
The specification includes purity criteria on Non-volatile matter, Readily oxidisable matter, Arsenic and Heavy metals.

**Magnesium hydroxide**
**Definition:** Magnesium hydroxide is a strong base. It is practically insoluble in water and in ethanol.

**EC specifications:** E 528 Magnesium hydroxide [4].
Assay: Not less than 95.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Loss on ignition, Calcium oxide, Arsenic and Lead.

**JECFA specifications:** Magnesium hydroxide [3].
Assay: Not less than 27% and not more than 30% of NH$_3$.
The specification includes purity criteria on Loss on drying, Loss on ignition, Alkalies (free) and soluble salts, Calcium oxide, Arsenic, Lead and Heavy metals.

**Calcium oxide**
**Definition:** Calcium oxide is a naturally occurring oxide of calcium. It is slightly soluble in water and insoluble in ethanol.

**EC specifications:** E 529 Calcium oxide [4].
Assay: Not less than 95.0% on the ignited basis.
In addition the specification includes purity criteria on Loss on ignition, Acid-insoluble matter, Barium, Magnesium and alkali salts, Fluoride, Arsenic and Lead.

**JECFA specifications:** Calcium oxide [3].
Assay: Not less than 95.0% on the ignited basis.
In addition the specification includes purity criteria on Loss on ignition, Acid-insoluble matter, Barium, Magnesium and alkali salts, Fluoride, Arsenic, Lead and Heavy metals.

**Magnesium oxide**
**Definition:** Magnesium oxide is a naturally occurring oxide of magnesium. It is practically insoluble in water and insoluble in ethanol.

**EC specifications:** E 530 Magnesium oxide [4].
Assay: Not less than 98.0% on the ignited basis.
In addition the specification includes purity criteria on Loss on ignition, Calcium oxide, Arsenic and Lead.

**JECFA specifications:** Magnesium oxide [3].
Assay: Not less than 96.0% on the ignited basis.
In addition the specification includes purity criteria on Loss on ignition, Alkali (free) and soluble salts, Calcium oxide, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible, but is also not considered necessary.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1990, ADI not specified based the fact that these substances are normal constituents of the diet and can not be distinguished from the same ions already present in food from other sources when used according to good manufacturing practice. However, SCF stated that large doses of magnesium ions cause diarrhoea and should be avoided [2].

**JECFA status:** Latest evaluation 1967: ADI “not limited”. The Committee stated that there is no toxicological reason to limit their use if they are used according to good manufacturing practice [1].

Due to the fact that these substances are natural constituents of the diet and the intake from food additives is likely to be insignificant compared to the intake from natural sources there is no need for specific toxicity data.

**Conclusion:** There is no reason for a re-evaluation. The JECFA specifications are old. It is therefore suggested to revise the specifications for this group of substances at a future JECFA meeting.

**References:**


**SODIUM FERROCYANIDE, POTASSIUM FERROCYANIDE AND CALCIUM FERROCYANIDE**

**E number:**
- Sodium ferrocyanide: E 535
- Potassium ferrocyanide: E 536
- Calcium ferrocyanide: E 538

**Recommendation:** No need for a re-evaluation.

**Chemical name/synonyms:**
- Sodium ferrocyanide: Sodium ferrocyanide/ Yellow prussiate of soda, sodium hexacyanoferrate.
- Potassium ferrocyanide: Potassium ferrocyanide/ Yellow prussiate of potash, potassium hexacyanoferrate.
- Calcium ferrocyanide: Calcium ferrocyanide/ Yellow prussiate of lime, calcium hexacyanoferrate.

**Chemical formula:**
- Sodium ferrocyanide: $\text{Na}_4\text{Fe(CN)}_6\cdot 10\text{H}_2\text{O}$
- Potassium ferrocyanide: $\text{K}_4\text{Fe(CN)}_6\cdot 3\text{H}_2\text{O}$
- Calcium ferrocyanide: $\text{Ca}_2\text{Fe(CN)}_6\cdot 12\text{H}_2\text{O}$

**EINECS number:**
- Sodium ferrocyanide: 237-081-9
- Potassium ferrocyanide: 237-722-2
- Calcium ferrocyanide: 215-476-7

**CAS number:**
- Sodium ferrocyanide: 13601-19-9
- Potassium ferrocyanide: 13943-58-3
- Calcium ferrocyanide: 1327-39-5

**Functional Class:** Anticaking agents.

**Specification:**
**Manufacture:** No information on manufacturing processes for food grade ferrocyanides.

**Sodium ferrocyanide**

**Definition:** Sodium ferrocyanide is the sodium salt of iron (II) cyanide. It is soluble in water and insoluble in ethanol.

**EC specifications:** E 535 Sodium ferrocyanide [2].
- Assay: Not less than 99.0%.
- Free cyanide: Not detectable.
- Ferricyanide: Not detectable.
- In addition the specification includes purity criteria on Free moisture, Water-insoluble matter, Chloride, Sulphate and Lead.
**JECFA specifications:** see calcium ferrocyanide.

*Potassium ferrocyanide*

**Definition:** Potassium ferrocyanide is the potassium salt of iron (II) cyanide. It is soluble in water and insoluble in ethanol.

**EC specifications:** E 536 Potassium ferrocyanide [2].
- Assay: Not less than 99.0%.
- Free cyanide: Not detectable.
- Ferricyanide: Not detectable.
- In addition the specification includes purity criteria on Free moisture, Water-insoluble matter, Chloride, Sulphate and Lead.

**JECFA specifications:** see calcium ferrocyanide.

*Calcium ferrocyanide*

**Definition:** Calcium ferrocyanide is the calcium salt of iron (II) cyanide. It is soluble in water.

**EC specifications:** E 538 Calcium ferrocyanide [2].
- Assay: Not less than 99.0%.
- Free cyanide: Not detectable.
- Ferricyanide: Not detectable.
- In addition the specification includes purity criteria on Free moisture, Water-insoluble matter, Chloride, Sulphate and Lead.

**JECFA specifications:** Ferrocyanides of calcium, potassium and sodium [1].
- Assay: Not less than 99.0%.
- Free cyanide: Not detectable.
- Ferricyanide: Not detectable.

**Exposure:** The ferrocyanides may only be used as anticaking agents in salt and salt substitutes up to 20 mg/kg salt. ADI can only be reached by consuming 75 g salt (adult) or 19 g salt (15 kg child). This is not possible with a normal diet, and ADI, therefore, cannot be reached from this source. In the EU monitoring system the intake by young children was transferred to tier 3 as no information on calculated intake by young children had been received. This exercise is, however, not necessary, as explained above.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1991. ADI = 0.025 mg/kg bw. Based on JECFA [5].

**JECFA status:** Latest evaluation 1974. ADI = 0.025 mg/kg bw based on a short-term study in rat where the NOEL was 25 mg/kg bw. and using a safety factor of 1000 [4].

**Background data:**

**Subacute/subchronic toxicity:** The kidneys are the target organs for ferrocyanides. Short-term studies with few animals have been performed on rat and dog with a NOEL = 25 mg/kg bw in rat [4].
Genotoxicity: No data available.

Chronic toxicity/carcinogenicity: No data available.

Reproduction toxicity: No data available.

Other: Recently it has been suggested that the renal toxicity of the ferrocyanide could be increased by interaction with other food additives like diphenyl and o-phenylphenol but further investigations are needed [3].

Conclusion: A full toxicological evaluation is not possible without long-term and reproduction studies. However, these substances are ingested in very small quantities, therefore it is unlikely that their use will cause any safety problem. The JECFA specification for ferrocyanides is old. It is therefore suggested to revise this specification at a future JECFA meeting.

References:


**SODIUM ALUMINIUM PHOSPHATE, ACIDIC**

**E number:** E 541

**Recommendation:** Aluminium from all sources including food additive uses should be re-evaluated. The permitted use of this particular salt could easily lead to exceeding the PTWI for aluminium from this source alone.

**Chemical name/synonyms:**
I: Sodium trialuminium tetradecahydrogen octaphosphate tetrahydrate.
II: Trisodium dialuminium pentadecahydrogen octaphosphate.

**Chemical formula:**
I: \( \text{NaAl}_3\text{H}_{14}(\text{PO}_4)_8\cdot 4\text{H}_2\text{O} \)
II: \( \text{Na}_3\text{Al}_3\text{H}_{15}(\text{PO}_4)_8 \)

**EINECS number:** 232-090-4

**CAS number:** -

**Functional Class:** Raising agent.

**Specification:**

**Manufacture:** No information on manufacturing processes of food grade sodium aluminium phosphate, acidic.

**Definition:** Sodium aluminium phosphate, acidic is either the monosodium trialuminium tetratecahydrate salt of phosphoric acid or the trisodium dialuminium pentadecahydrate salt of phosphoric acid. It is insoluble in water.

**EC specifications:** E 541 Sodium aluminium phosphate, acidic [4].
Assay: Not less than 95.0%.
The specification includes purity criteria on Loss on ignition, Fluoride, Arsenic, Lead, Cadmium and Mercury.

**JECFA specifications:** Sodium aluminium phosphate, acidic [3].
Assay: Not less than 95%.
The specification includes purity criteria on Loss on ignition, Fluoride, Arsenic, Lead and Heavy metals.

**Exposure:** Only permitted in fine bakery wares (scones and sponge wares only) 1 g/kg expressed as aluminium. It will take 60 g product with that amount to reach PTWI (60 kg person) from this source alone.

In the EU monitoring system this and other aluminium salts were subject to a tier 2 testing which suggested that intake may be as high as 624 % of PTWI. Although this figure is likely to be highly overestimated it should be considered to reduce permitted levels.
SCF/JECFA evaluation:
SCF status: Latest evaluation in 1990 when the PTWI of 7 mg/kg bw, as expressed by JECFA, was endorsed. The PTWI is expressed as aluminium from all sources [2].

JECFA status: Latest evaluation 1988 when the previous ADI for this substance of 0.6 mg/kg bw was changed to a group PTWI 7 of mg/kg bw expressed as aluminium from all sources [1].

The toxicological data and conclusion are presented in the monograph for aluminium (E 173).

Conclusion: The intake of food where this additive is used to the maximum level could lead to exceeding the PTWI. However, this salt is not soluble, so it should be investigated whether the aluminium is available to the same extent as from soluble aluminium salts.

References:

1. [1988, TRS 776-JECFA 33]


**SILICON DIOXIDE, CALCIUM SILICATE, MAGNESIUM SILICATE, MAGNESIUM TRISILICATE AND TALC**

**E number:**
- Silicon dioxide: E 551
- Calcium silicate: E 552
- Magnesium silicate: E 553a (i)
- Magnesium trisilicate: E 553a (ii)
- Talc: E 553b

**Recommendation:** An immediate re-evaluation is not needed but the next evaluation should include a proper carcinogenicity test.

**Chemical name/synonyms:**
- Silicon dioxide: Silicon dioxide/ silica, silicium dioxide.
- Calcium silicate: Calcium silicate.
- Magnesium silicate: -
- Magnesium trisilicate: Magnesium trisilicate.
- Talc: Magnesium hydrogen metasilicate/ talcum.

**Chemical formula:**
- Silicon dioxide: \((\text{SiO}_2)_n\)
- Calcium silicate: -
- Magnesium silicate: -
- Magnesium trisilicate: \(\text{Mg}_2\text{Si}_3\text{O}_8\cdot n\text{H}_2\text{O}\) (Approximate composition)
- Talc: \(\text{Mg}_3(\text{Si}_4\text{O}_{10})(\text{OH})_2\)

**EINECS number:**
- Silicon dioxide: 231-545-4
- Calcium silicate: 215-710-8
- Magnesium silicate: -
- Magnesium trisilicate: 239-076-7
- Talc: 238-877-9

**CAS number:**
- Silicon dioxide: 7631-86-9
- Calcium silicate: 1344-95-2
- Magnesium silicate: -
- Magnesium trisilicate: -
- Talc: 14807-96-6

**Functional Class:** Anticaking agent, talc: anticaking agent, filtering aid, surface-finishing agent.

**Specification:**
- Silicon dioxide

**Manufacture:** Silicon dioxide is produced by either a vapour phase hydrolysis process, yielding fumed silica, or by a wet process, yielding precipitated silica, silica gel or hydrous silica.
Definition: Silicon dioxide is an amorphous substance. Fumed silica is produced in essentially an anhydrous state, whereas the wet process products are obtained as hydrates or contain surface absorbed water. It is insoluble in water and in ethanol.

EC specifications: E 551 Silicon dioxide [8].
Assay: Content after ignition not less than 99.0% (fumed silica) or 94.0% (hydrated forms). The specification includes purity criteria on Loss on drying, Loss on ignition, Soluble ionisable salts, Arsenic, Lead and Mercury.

JECFA specifications: Silicon dioxide, amorphous [5].
Assay: Content after ignition not less than 99.0% (fumed silica) or 94.0% (hydrated forms). The specification includes purity criteria on Loss on ignition, Arsenic, Lead and Heavy metals.

Calcium silicate
Manufacture: Calcium silicate is produced by various reactions between siliceous material (e.g. diatomaceous earth) and natural calcium compounds (e.g. lime with varying proportions of other elements, such as magnesium etc.).

Definition: Calcium silicate is a synthetic calcium silicate or polysilicate with varying proportions of CaO and SiO₂. It is insoluble in water and in ethanol.

EC specifications: E 552 Calcium silicate [8].
Assay: Content on the anhydrous basis not less than 50% and not more than 95% as SiO₂ and not less than 3% and not more than 35% as CaO. The specification includes purity criteria on Loss on drying, Loss on ignition, Sodium, Fluoride, Arsenic, Lead and Mercury.

JECFA specifications: Calcium silicate [5].
Assay: -
The specification includes purity criteria on Fluoride, Asbestos, Arsenic, Lead and Heavy metals.

Magnesium silicate
Manufacture: No information on manufacturing processes of food grade magnesium silicate.

Definition: Magnesium silicate is a synthetic compound of which the molar ratio of magnesium oxide to silicon dioxide is approximately 2:5. It is insoluble in water and in ethanol.

EC specifications: E 553a (i) Magnesium silicate [8].
Assay: Content on not less than 15% of MgO and not less than 67% of SiO₂ on the ignited basis. The specification includes purity criteria on Loss on drying, Loss on ignition, Free alkali, Fluoride, Arsenic, Lead and Mercury.

JECFA specifications: Magnesium silicate (synthetic) [6;7].
Assay: Content on not less than 15% of MgO and not less than 67% of SiO₂ on the ignited basis. The specification includes purity criteria on Loss on drying, Loss on ignition, Free alkali, Soluble salts, Fluoride, Silicon dioxide, Arsenic, Lead and Heavy metals.

Magnesium trisilicate
Manufacture: No information on manufacturing processes of food grade magnesium trisilicate.
**Definition:** -

**EC specifications:** E 553a (ii) Magnesium trisilicate [8].
Assay: Content on not less than 29.0% of MgO and not less than 65.0% of SiO₂ on the ignited basis.
The specification includes purity criteria on Loss on drying, Loss on ignition, Free alkali, Fluoride, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

**Talc**

**Manufacture:** Food grade talc is derived from deposits that are known not to contain associated asbestos.

**Definition:** Talc is a naturally occurring form of hydrous magnesium silicate containing varying proportions of such associated minerals as alpha-quartz, calcite, chlorite, dolomite, magnesite and phlogopite.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Talc [7].
Assay: -
The specification includes purity criteria on Loss on ignition, Loss on drying, Water-soluble substances, Water-soluble iron, Acid-soluble substances and Lead.

**Exposure:** Permitted as anticaking agents in dried powdered foodstuffs, salt and salt substitutes, sliced hard cheese and sliced processed cheese, 10 g/kg. Dietary supplements q.s. E 551 and E 552 also permitted as carrier for emulsifiers and colours, max. 5%.

As the silicates have ADI “not specified” they were not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990. Group ADI not specified based on the available data on orally administrated silica and silicates which appear to substantiate the biological inertness of those compounds [4].

**JECFA status:** Latest evaluation 1985 and 1986. Group ADI not specified [1;2].

**Background data:**

**Subacute/subchronic toxicity:** No adverse effects were seen in rats and rabbits [3]. Dogs given 0.8 g/kg bw for 4 weeks revealed renal lesions [3]. Chicken fed a silicate free diet for 25-35 days were smaller and had badly developed bone structure compared with chicken given normal food [3].

**Genotoxicity:** A study on peripheral human blood lymphocytes indicates that calcium silicate in doses of 10 micrograms/ml significantly increases frequencies of chromosomal aberrations and sister-chromatide exchanges [9].
**Chronic toxicity/Carcinogenicity:** In a rat study where 20 male and 20 female rats were given pellets containing 100 mg/kg bw/day of amorphous silica for 104 week there was no indication of carcinogenic effect [3].

A database search gives many hits on this subject because silicates are suspected to be carcinogenic when inhaled (e.g. [10]). These studies are not relevant from a food additive point of view.

**Reproduction toxicity:** A small two generation study on rat did not indicate any reproduction toxicity [3].

**Effect in humans:** Silicates are poorly absorbed. A single dose of 2.5 g amorphous polymeric silicon dioxide given to volunteers did not significantly raise the SiO₂ excretion in the urine [3]. No adverse effects were seen when humans given 60-100 g 12% amorphous silicic acid for three to four weeks. Only 0.1 % of the dose was excreted in the urine [3]. Some human conditions especially growth retardation is associated with silicon deficiency [3].

**Conclusion:** The toxicological data are less than would normally be required. Silicates are poorly absorbed and although there are no indications of oral toxicity a proper carcinogenicity test is needed because it can not be excluded that this additive contain asbestos or asbestos like substances. The JECFA specifications for silicon dioxide and calcium silicate are old. It is therefore suggested to revise the specifications for silicates at a future JECFA meeting.

**References:**


SODIUM ALUMINIUM SILICATE, POTASSIUM ALUMINIUM SILICATE, CALCIUM ALUMINIUM SILICATE AND ALUMINIUM SILICATE

E number:
Sodium aluminium silicate: E 554
Potassium aluminium silicate: E 555
Calcium aluminium silicate: E 556
Aluminium silicate: E 559

Recommendation: As the potential for exceeding the PTWI of aluminium from the use of these additives is high, it is important that it is examined whether it is still justified, as done by SCF, to include these, insoluble, aluminium salts in the PTWI of aluminium, which was based on the soluble aluminium salts. If still considered within the PTWI a considerable reduction in permitted uses should be introduced. It should be kept in mind that a re-evaluation of aluminium from all sources, including food additives is recommended (see E 541).

Chemical name/synonyms:
Sodium aluminium silicate: Sodium aluminium silicate/ sodium silico aluminate, sodium aluminosilicate, aluminium sodium silicate, zeolite.
Potassium aluminium silicate: Potassium aluminium silicate/ mica.
Calcium aluminium silicate: Calcium aluminium silicate/ calcium silico aluminate, calcium aluminosilicate, aluminium calcium silicate.
Aluminium silicate: Kaolin.

Chemical formula:
Sodium aluminium silicate: -
Potassium aluminium silicate: KAl₂[AlSi₃O₁₀](OH)₂
Calcium aluminium silicate: -
Aluminium silicate: Al₂Si₂O₅(OH)₄ (kaolinite)

EINECS number:
Sodium aluminium silicate: -
Potassium aluminium silicate: 310-127-6
Calcium aluminium silicate: -
Aluminium silicate: 215-286-4

CAS number:
Sodium aluminium silicate: 73987-94-7
Potassium aluminium silicate: -
Calcium aluminium silicate: -
Aluminium silicate: 1335-30-4

Functional Class: Anticaking agent.

Specification:
Manufacture: No information on manufacturing processes for food grade aluminium silicates.

Sodium aluminium silicate
**Definition:** Sodium aluminium silicate is insoluble in water and in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Sodium aluminosilicate [4].

Assay: -
The specification includes purity criteria on Arsenic and Heavy metals.

**Potassium aluminium silicate**

**Definition:** Natural potassium aluminium silicate consists mainly of the mineral muscovite. It is insoluble in water and in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** No JECFA specification has been prepared.

**Calcium aluminium silicate**

**Definition:** Calcium aluminium silicate is insoluble in water and in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Calcium aluminium silicate [5].

Assay: Not less than 44% and not more than 50% of SiO₂, not less than 3% and not more than 5% of Al₂O₃, not less than 32% and not more than 38% of CaO and not less than 0.5% and not more than 4% of Na₂O.
The specification includes purity criteria on Loss on ignition, Loss on drying, Fluoride, Arsenic, Lead and Heavy metals.

**Aluminium silicate**

**Definition:** Aluminium silicate hydrous (kaolin) is a purified white plastic clay composed of kaolinite, potassium aluminium silicate, feldspar and quartz. Processing should not include calcination. It is insoluble in water and in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Aluminium silicate [4].

Assay: -
The specification includes purity criteria on Water-insoluble substances, Acid-insoluble substances, Asbestos, Arsenic and Heavy metals.

**Exposure:** These additives are permitted in dried powdered foodstuffs, salt and salt substitutes, sliced hard cheese and sliced processed cheese 10 g/kg. E 559 also permitted as carrier for colours, max. 5%.

Intake of only 24 g of the foodstuffs with permitted use is sufficient to reach the PTWI (calculating with \( \frac{1}{4} \) Al in the salts). In the EU monitoring system these and other aluminium salts were subject to a tier 2 testing which suggested that intake may be as high as 624 % of PTWI. It should therefore be clarified whether these non-soluble substances need being included in the PTWI for aluminium.

**SCF/JECFA evaluation:**
SCF status: Evaluated in 1990 when the group PTWI 7 mg/kg bw, as established by JECFA in 1988 for aluminium from all sources, was endorsed to cover these and other listed aluminium containing food additives. Although it is likely that only minute amounts of Al are absorbed from aluminium silicates SCF considered that this contribution should be included in the group PTWI for Aluminium, but stated that if evidence of minute availability is presented the Committee would reconsider its position. The Committee stressed that when setting conditions of use for aluminium salts, the intake from other food and drink sources should also be taken into account [3].

JECFA status: Latest evaluation in 1985 when the group ADI “not limited”, as established at 17th meeting 1973 was changed to ADI “not specified” for aluminium silicate and calcium and sodium aluminosilicate because of the insolubility of these [1].

Background data:
Subacute/subchronic toxicity: When given 10,000 ppm zeolithe (a sodium aluminium silicate) in the food for 90 days silicon accumulate in the kidney. No effects were seen with lower doses [6]. JECFA quotes various studies where some effects were seen at 10% of sodium aluminosilicate in the diet, but not in lower doses [2].

Genotoxicity: Sodium silicoaluminate did not induce mutations in host mediated assays with S. typhimurium and Saccharomyces cerevisiae (non-activated or activated) or in a dominant lethal assay [2].

Chronic toxicity/Carcinogenicity: Long-term study in rat given 0.6 g zeolithe/kg/day in the feed did not give any indication of carcinogenicity [6].

Reproduction toxicity: Sodium silicoaluminate showed no evidence of teratogenicity after oral administration at levels up to 1600 mg/kg bw/day to pregnant mice (day 6 through gestation); to pregnant rats (day 6 through 15 of gestation, or to pregnant rabbits (day 6 through 18 of gestation) [2].

Other: Metabolic studies on zeolithe (sodium aluminium silicate indicate a very low uptake of silicate and no uptake of aluminium [6].

Conclusion: The low toxicity of aluminium silicates is probably caused by the tight bounding of aluminium in this compound. The toxicological data indicate that the substances are less toxic than the more soluble aluminium salts. Still SCF included also these substances in the PTWI because no studies showing less bioavailability had been submitted.

The JECFA specifications are old. It is therefore suggested to revise the specifications for this group of substances at a future JECFA.

References:

1. [1985, TRS 733-JECFA 29]
2. [1988, FAS 24-JECFA 33]


**BENTONITE**

**E number:** E 558

**Recommendation:** It should be clarified whether this aluminium containing additive still need be considered together with the soluble aluminium salts. It could be considered to include a threshold for impurity of dioxine in the specification.

**Chemical name/synonyms:** -

**Chemical formula:** \((\text{Al, Mg})_8\text{(Si}_4\text{O}_{10})_4\text{(OH)}_8\cdot12\text{H}_2\text{O}\)

**EINECS number:** 215-108-5

**CAS number:** 1302-78-9

**Functional Class:** Anticaking agent.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade bentonite.

**Definition:** Bentonite is a natural clay containing a high proportion of montmorillonite, a native hydrated aluminium silicate in which some aluminium and silicon atoms were naturally replaced by other atoms, such as magnesium and iron. Calcium and sodium ions are trapped between the mineral layers. There are four common types of bentonite: natural sodium bentonite, natural calcium bentonite, sodium-activated bentonite and acid-activated bentonite.

**EC specifications:** E 558 Bentonite [1].

**Assay:** Montmorillonite content not less than 80 %

The specification includes purity criteria on loss on drying, Arsenic and Lead

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** Permitted only as a carrier for colours with max. 5%. The potential exposure of aluminium from this source is thus minimal with the exposure from other sources. In the EU monitoring system bentonite was grouped together with the other aluminium salts and it has been decided to examine also this additive at tier 3 level.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990. Included in the group PTWI 7 mg/kg bw (expressed as aluminium) for aluminium from all sources including aluminium containing food additives [2].

**JECFA status:** Latest evaluation 1976, No ADI allocated because JECFA was unaware of any significant use of bentonite in food industry and because no data were available on impurities in commercially available products [3].

**Background data:** There has never been performed a toxicological evaluation of bentonite. Aluminium silicates have been used as anticaking agent in animal feed and some of these
substances have been contaminated with dioxine. This could be a problem to human health because dioxine will accumulate in the adipose tissue in the animals and this could lead to a high level of human exposure when the animals are consumed. Therefore, the specification for aluminium silicates used in animal feed includes a threshold for dioxine impurity. This threshold has been exceeded by a factor 200 for some aluminium silicates and it can not be excluded that the level of dioxine in bentonite is at the same magnitude. However, the human exposure to bentonite is very limited and the bioaccumulation in animals used as food shall not be taken into account.

**Conclusion:** No toxicological data available, but exposure is very small to this naturally occurring aluminium silicate and there is no reason to expect any untoward effects from the permitted use as a carrier even if there is a minor impurity of dioxine in the product. As the bioavailability of aluminium is likely to be much lower than that from soluble aluminium salts the need for including this additive in the PTWI covering other aluminium salts could be examined. SCF could consider to include a threshold for dioxine impurity in the specification to ensure the lowest possible exposure to dioxine. See also aluminium silicates (E 554, E 555, E556 and E559) and sodium aluminium phosphate (E 541).

**References:**


FATTY ACIDS

E Number: E 570

See: E 470 Salts of fatty acids.
GLUCONIC ACID, GLUCONO-DELTA-LACTONE, SODIUM GLUCONATE, POTASSIUM GLUCONATE AND CALCIUM GLUCONATE

E number:
Gluconic acid: E 574
Glucono-delta-lactone: E 575
Sodium gluconate: E 576
Potassium gluconate: E 577
Calcium gluconate: E 578

Recommendation: A re-evaluation is not needed.

Chemical name/synonyms:
Gluconic acid: Gluconic acid/ D-gluconic acid, dextronic acid.
Glucono-delta-lactone: D-Glucono-1,5-lactone/gluconolactone, GDL, D-gluconic acid delta-lactone, delta-gluconolactone, glucono-δ-lactone.
Sodium gluconate: Sodium D-gluconate/ sodium salt of D-gluconic acid.
Potassium gluconate: Potassium D-gluconate/ potassium salt of D-gluconic acid.
Calcium gluconate: Calcium di-D-gluconate/ calcium salt of D-gluconic acid.

Chemical formula:
Gluconic acid: \( \text{C}_6\text{H}_{12}\text{O}_7 \) (gluconic acid)
Glucono-delta-lactone: \( \text{C}_6\text{H}_{10}\text{O}_6 \)
Sodium gluconate: \( \text{C}_6\text{H}_{11}\text{NaO}_7 \)
Potassium gluconate: \( \text{C}_6\text{H}_{11}\text{KO}_7\cdot\text{nH}_2\text{O} \) (n = 0 or 1)
Calcium gluconate: \( \text{C}_{12}\text{H}_{22}\text{CaO}_{14}\cdot\text{nH}_2\text{O} \) (n = 0 or 1)

EINECS number:
Gluconic acid: -
Glucono-delta-lactone: 202-016-5
Sodium gluconate: 208-407-7
Potassium gluconate: 206-074-2
Calcium gluconate: 206-075-8

CAS number:
Gluconic acid: -
Glucono-delta-lactone: 90-80-2
Sodium gluconate: 527-07-1
Potassium gluconate: 299-27-4 (anhydrous), 35398-15-3 (monohydrate)
Calcium gluconate: 299-28-5

Functional Class: Acidity regulator, raising agent, sequestrant.

Specification:
Manufacture: No information on manufacturing processes for food grade gluconic acid and the gluconates.
**Gluconic acid**

**Definition:** Gluconic acid is an aqueous solution of gluconic acid and glucono-delta-lactone.

**EC specifications:** E 574 Gluonic acid [5].
Assay: Not less than 50% as gluconic acid.
The specification includes purity criteria on Residue on ignition, Reducing matter, Chloride, Sulphate, Sulphite, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

**Glucono-delta-lactone**

**Definition:** Gluco-delta-lactone is the cyclic 1,5-intramolecular ester of D-gluconic acid. In aqueous media it is hydrolysed to an equilibrium mixture of D-gluconic acid (55-60%) and the delta- and gamma-lactones.

**EC specifications:** E 575 Glucono-delta-lactone [5].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Water, Reducing substances and Lead.

**JECFA specifications:** Gluco-delta-lactone [3].
Assay: Not less than 99.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Sulfated ash, Reducing substances and Lead.

**Sodium gluconate**

**Definition:** Sodium gluconate is the sodium salt of D-gluconic acid.

**EC specifications:** E 576 Sodium gluconate [5].
Assay: Not less than 98.0%.
The specification includes purity criteria on Reducing substances and Lead.

**JECFA specifications:** Sodium gluconate [3].
Assay: Not less than 98.0%.
The specification includes purity criteria on Reducing substances and Lead.

**Potassium gluconate**

**Definition:** Potassium gluconate is the potassium salt of D-gluconic acid.

**EC specifications:** E 577 Potassium gluconate [5].
Assay: Not less than 97.0 and not more than 103.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Reducing substances and Lead.

**JECFA specifications:** Potassium gluconate [3].
Assay: Not less than 97.0 and not more than 103.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Reducing substances and Lead.

**Calcium gluconate**

**Definition:** Calcium gluconate is the calcium salt of D-gluconic acid.

**EC specifications:** E 578 Calcium gluconate [5].
Assay: Not less than 98.0 and not more than 102.0% on the anhydrous and monohydrate basis. The specification includes purity criteria on Loss on drying, Reducing substances and Lead.

**JECFA specifications:** Calcium gluconate [3].
Assay: Not less than 98.0 and not more than 102.0% on the dried basis. The specification includes purity criteria on Loss on drying, Reducing substances and Lead.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible, but is also not considered necessary.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1990, group ADI not specified for gluconic acid and its salts because gluconates and glucono-delta-lactone are intermediates in the glucose metabolism [2].

**JECFA status:** Latest evaluation 1998, group ADI not specified based on data previously considered and new data on short-term toxicity [1].

**Subacute/subchronic toxicity:** No relevant adverse effects were seen when rats were given up to 2000 mg/kg bw for four weeks [4].

**Genotoxicity:** All tests with and without metabolic activation were negative [4].

**Chronic toxicity/carcinogenicity:** No adverse effects were seen in a study were groups of 20 rats of each sex were given food containing 0.4% glucono-δ-lactone for 29 months [4].

**Reproduction toxicity:** No adverse effects were seen when pregnant mice, rats, hamsters and rabbits received 0-700 mg/kg bw by oral intubation on days 6-15 of gestation.

**Effect in humans:** Single doses of more than 20g glucono-δ-lactone have laxative effect in humans [4].

**Conclusion:** There is no reason to believe that these intermediates in the glucose metabolism should possess any risk to humans. The substances, as defined by the specifications, are covered by the toxicological evaluation.

**References:**


4. [1998, FAS 42-JECFA 51]

FERROUS GLUCONATE AND FERROUS LACTATE

E number:
Ferrous gluconate: E 579
Ferrous lactate: E 585

Recommendation: No need for a re-evaluation.

Chemical name/synonyms:
Ferrous lactate: Iron (II) lactate, Iron (II) 2-hydroxy propanoate, propanoic acid, 2-hydroxy-iron (2+) salt (2:1).

Chemical formula:
Ferrous gluconate: C_{12}H_{22}FeO_{14} \cdot 2H_{2}O
Ferrous lactate: C_{6}H_{10}FeO_{6} \cdot nH_{2}O (n = 2 or 3)

EINECS number:
Ferrous gluconate: 206-076-3
Ferrous lactate: 227-608-0

CAS number:
Ferrous gluconate: 299-29-6
Ferrous lactate: 5905-52-2

Functional Class: Stabilizer.

Specification:
Manufacture: No information on manufacturing processes for food grade quality of these ferrous salts.

Ferrous gluconate
Definition: Ferrous gluconate is the iron (II) salt of gluconic acid. It is soluble with slight heating in water and practically insoluble in ethanol.

EC specifications: E 579 Ferrous gluconate [1].
Assay: Not less than 95% on the dried basis.
The specification includes purity criteria on Loss on drying, Oxalic acid, Reducing substances, Iron (III), Arsenic, Lead, Cadmium and Mercury.

JECFA specifications: Ferrous gluconate [2].
Assay: Not less than 95% on the dried basis.
The specification includes purity criteria on Loss on drying, Reducing sugars, Iron (III), Lead and Mercury.
**Ferrous lactate**

**Definition:** Ferrous lactate is the iron (II) salt of lactic acid. It is soluble in water and practically insoluble in ethanol.

**EC specifications:** E 585 Ferrous lactate [1].
Assay: Not less than 96% on the dried basis.
The specification includes purity criteria on Loss on drying, Iron (III), Arsenic, Lead, Cadmium and Mercury.

**JECFA specifications:** Ferrous lactate [3].
Assay: Not less than 96% on the dried basis.
The specification includes purity criteria on Loss on drying, Sulfate, Chloride, Iron (III), Lead and Arsenic.

**Exposure:** Only permitted in olives darkened by oxidation 150 mg/kg expressed as iron. The potential exposure from this source of iron is insignificant compared with other dietary sources.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990. SCF found the use of ferrous gluconate and lactate acceptable for the use as a colour stabilising agent in olives based on the JECFA PMTDI of 0.8 g/kg bw for iron [4].

**JECFA status:** Latest evaluation 1987 (ferrous gluconate [5]) and 1989 (ferrous lactate [6]): Because both salts are soluble bioavailable ferrous salts it was decided to include them in the PMTDI of 0.8 mg/kg bw for iron established in 1983 [7]. For the evaluation of the gluconate and lactate moieties see monographs on E 475, gluconic acid and E 270 lactic acid.

**Conclusion:** As these substances have a long history of use as iron sources in dietary supplements and the use as food additives is very limited, the contribution of iron from these sources can be considered insignificant, and although there are few toxicological data on these salts, there is no reason for further examination.

**References:**


5. *[1987, TRS 759-JECFA 31]*
   Evaluation of certain food additives and contaminants (Thirty-first report of the Joint
6. [1989, TRS 789-JECFA 35]
Evaluation of certain food additives and contaminants (Thirty-fifth report of the Joint
1990, and corrigenda.

7. [1983, TRS 696-JECFA 27]
Evaluation of certain food additives and contaminants (Twenty-seventh report of the Joint
1983, and corrigenda.
GLUTAMIC ACID, MONOSODIUM GLUTAMATE, MONOPOTASSIUM GLUTAMATE, CALCIUM DIGlutamate, MonoAmMIONIum glutamate AND MAGNEsIUM DIGlutamate

E number:
Glutamic acid: E 620
Monosodium glutamate: E 621
Monopotassium glutamate: E 622
Calcium diglutamate: E 623
Monoammonium glutamate: E 624
Magnesium diglutamate: E 625

Recommendation: There is no need for immediate action. However, in the light of the continuous debate concerning these substances, a more comprehensive report, addressing the controversial issues including the effects of monosodium glutamate on special sensitive subjects, is desirable.

Chemical name/synonyms:
Glutamic acid: L-Glutamic acid, L-2-amino-pentadioic acid/ L-α-aminoglutaric acid
Monosodium glutamate: Monosodium L-glutamate monohydrate/ sodium glutamate, MSG.
Monopotassium glutamate: Potassium L-glutamate monohydrate/ potassium glutamate, MPG.
Calcium diglutamate: Mono calcium di-L-glutamate.
Monoammonium glutamate: Monoammonium L-glutamate monohydrate/ ammonium glutamate.
Magnesium diglutamate: Monomagnesium di-L-glutamate tetrahydrate/ magnesium glutamate

Chemical formula:
Glutamic acid: C$_5$H$_9$NO$_4$
Monosodium glutamate: C$_5$H$_8$NaNO$_4$H$_2$O
Monopotassium glutamate: C$_5$H$_8$KNO$_4$H$_2$O
Calcium diglutamate: C$_{10}$H$_{16}$CaN$_2$O$_8$nH$_2$O (n = 0, 1, 2 or 4)
Monoammonium glutamate: C$_5$H$_{12}$N$_2$O$_4$H$_2$O
Magnesium diglutamate: C$_{10}$H$_{16}$MgN$_2$O$_8$4H$_2$O

EINECS number:
Glutamic acid: 200-293-7
Monosodium glutamate: 205-538-1
Monopotassium glutamate: 243-094-0
Calcium diglutamate: 242-905-5
Monoammonium glutamate: 231-447-1
Magnesium diglutamate: 242-413-0

CAS number:
Glutamic acid: 56-86-0
Monosodium glutamate: 142-47-2
Monopotassium glutamate: 19473-49-5
Calcium diglutamate: 19238-49-4
Monoammonium glutamate: 7558-63-6
Magnesium diglutamate: 18543-68-5
**Functional Class:** Flavour enhancer, salt substitute.

**Specification:**
**Manufacture:** No information on manufacturing processes for food grade glutamic acid and glutamates.

**Glutamic acid**
**Definition:** Glutamic acid is a naturally occurring \(\alpha\)-amino acid. It is sparingly soluble in water and practically insoluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECA specifications:** Glutamic acid [1].
Assay: Not less than 99.0% on the dried basis.
Pyrrolidone carboxylic acid: Passes test.
In addition the specification includes purity criteria on Loss on drying, pH, Specific rotation, Sulfated ash, Chlorides, Arsenic, Lead and Heavy metals.

**Monosodium glutamate**
**Definition:** Monosodium glutamate is the monosodium salt of glutamic acid. It is freely soluble in water and sparingly soluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECA specifications:** Monosodium glutamate [1].
Assay: Not less than 99.0%.
Pyrrolidone carboxylic acid: Passes test.
In addition the specification includes purity criteria on Loss on drying, pH, Specific rotation, Chlorides, Arsenic, Lead and Heavy metals.

**Monopotassium glutamate**
**Definition:** Monopotassium glutamate is the monopotassium salt of glutamic acid. It is freely soluble in water and slightly soluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECA specifications:** Monopotassium glutamate [1].
Assay: Not less than 99.0%.
Pyrrolidone carboxylic acid: Passes test.
In addition the specification includes purity criteria on Loss on drying, pH, Specific rotation, Chlorides, Arsenic, Lead and Heavy metals.

**Calcium diglutamate**
**Definition:** Calcium diglutamate is the monocalcium salt of glutamic acid. It is freely soluble in water.

**EC specifications:** An EC specification is currently in preparation.

**JECA specifications:** Calcium diglutamate [1].
Assay: Not less than 98.0% on the anhydrous basis.
Pyrrolidone carboxylic acid: Passes test.
In addition the specification includes purity criteria on Water, Specific rotation, Chlorides, Arsenic, Lead and Heavy metals.

**Monoammonium glutamate**
**Definition:** Monoammonium glutamate is the monoammonium salt of glutamic acid. It is freely soluble in water.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Monoammonium glutamate [1].
Assay: Not less than 99.0%.
Pyrrolidone carboxylic acid: Passes test.
In addition the specification includes purity criteria on Loss on drying, pH, Specific rotation, Sulphated ash, Arsenic, Lead and Heavy metals.

**Magnesium diglutamate**
**Definition:** Magnesium diglutamate is the monomagnesium salt of glutamic acid. It is very soluble in water and insoluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Magnesium diglutamate [1].
Assay: Not less than 95.0% and not more than 105.0% on the anhydrous basis.
Pyrrolidone carboxylic acid: Passes test.
In addition the specification includes purity criteria on Water, pH, Specific rotation, Chlorides, Sulphates, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted.
10 g/kg. Condiments and seasonings q.s. As the ADI is “not specified” the substances were not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1990: ADI not specified based on the data provided and in view of the large normal dietary intake of glutamates [2].

**JECFA status:** Latest evaluation 1987: Group ADI not specified for L-Glutamic acid and its ammonium, calcium, magnesium, monosodium and potassium salts based on arguments similar to SCF [3].

**Background data:**
**Subacute/subchronic toxicity:** No adverse effects were seen when doses up to 2000 mg/kg bw. were given orally to rats for 90 days [4].

**Genotoxicity:** *In vitro*: L-glutamic acid and potassium glutamate were not mutagenic with or without activation in numerous strains [4].

**Chronic toxicity/carcinogenicity:** In several studies in mic, rats and dogs have been performed no adverse effects were seen [4].
**Reproduction toxicity:** There exist many multigeneration studies on monosodium glutamate in mice, rats, hamsters and rabbits. None of them report adverse effects when the substance were given orally [4].

**Allergy/Intolerance:** Glutamates are not true allergens but some allergy like reactions have been observed. It has been associated with the so-called “Chinese restaurant syndrome” with symptoms like headache, sweating, disorientation and others. This complex of symptoms was investigated in a double-blinded, placebo-controlled, randomised study where 61 subjects, who were self-identified as monosodium glutamate sensitive, were given doses of 0 g, 1.25 g, 2.5 g and 5 g monosodium glutamate. The conclusion was that monosodium glutamate sensitivity exists but there was no statistically significant dose response and therefore there could not be established a NOEL. The doses given is in the same magnitude as the average daily intake in the industrialised countries, which normally is from 0.3 g to 1 g but up to 5 g in some special dishes[5].

Early and late asthmatics were investigated in a double-blind, placebo-controlled, randomised study with 12 subjects who were self-identified as monosodium glutamate sensitive. This study did not indicate asthma induced by monosodium glutamate [6]. This conclusion is supported by a placebo-controlled study with 40 mild to severe asthmatics [7].

It has been suggested that the mechanism behind the so-called “Chinese restaurant syndrome” is related to deficiency of vitamin B6 [8]. The symptoms can be prevented by prior supplementation with vitamin B6 [9]. The presence and degree of deficiency of vitamin B6 in 155 students on no supplemental B6 was determined. Twenty-seven of these were vitamin B6 deficient and 12 of these revealed the Chinese restaurant syndrome when challenged with glutamate. The 12 "responders" were treated with pyridoxine or a placebo for 12 weeks, and then re-challenged with glutamate and a placebo. Three received placebo to pyridoxine and all revealed the symptoms of the syndrome when given glutamate. Nine received pyridoxine and eight of these failed to respond to glutamate [8].

**Other:** Glutamate is absorbed from the gut by an active and saturable transport system specific to amino acids. It is metabolised rapidly in the liver. This means that the plasma level only raises moderately after even very high doses of glutamate.

Several studies indicate that monosodium glutamate is neurotoxic in mice when administrated systemically [10]. One study has confirmed a neurotoxic effect when mice were dosed orally, in this study the mice where deprived fluids overnights and then administrated 2.5-10% in the drinking water [4]. In other studies there were no adverse effects when the substance was given orally [4].

The threshold blood levels associated with neuronal damage in mouse (the most sensitive species) are 100-130 µmol/dl in neonates rising to 380 µmol/dl in weanlings and >630 µmol/dl in adult animal. Plasma levels of this magnitude have never been recorded even after intake of 150 mg/kg bw. [11]. Human babies metabolise glutamate as effectively as adults and comparison of maternal and foetal levels after high doses indicate that foetus is not at increased risk [11].

**Conclusion:** Three different effects of glutamate have been subject to concern: Neurotoxic, allergy-like reactions and intolerance in asthmatic patients. Due to the active uptake and rapid turnover it is unlikely that plasma concentration can reach a neurotoxic level under normal condition. It is difficult to draw conclusions about the other effects due to the lack of a NOEL and the subjective, immeasurable symptoms. Both Committees have shortly mentioned the possibility for hypersensitivity, but not discussed the issue in any detail.
Glutamic acid and its salts as defined by the specifications are covered by the toxicological evaluation.

References:


3. [1987, TRS 759-JECFA 31]

4. [1987, FAS 22-JECFA 31]


E 626-35 Guanylates and inosinates

GUANYLIC ACID, DISODIUM GUANYLATE, DIPOTASSIUM GUANYLATE, CALCIUM GUANYLATE, INOSINIC ACID, DISODIUM INOSINATE, DIPOTASSIUM INOSINATE, CALCIUM INOSINATE, CALCIUM-5′-RIBONUCLEOTIDES, AND DISODIUM-5′-RIBONUCLEOTIDES

E number:
Guanylic acid: E 626
Disodium guanylate: E 627
Dipotassium guanylate: E 628
Calcium guanylate: E 629
Inosinic acid: E 630
Disodium inosinate: E 631
Dipotassium inosinate: E 632
Calcium inosinate: E 633
Calcium-5′-ribonucleotides: E 634
Disodium-5′-ribonucleotides: E 635

Recommendation: A re-evaluation is not needed. An exposure survey should be considered as the evaluation was linked to exposure estimates.

Chemical name/synonyms:
Guanylic acid: Guanosine-5′-monophosphoric acid/ 5′-guanylic acid.
Disodium guanylate: Disodium guanosine-5′-monophosphate/ sodium guanylate, sodium 5′-guanylate.
Dipotassium guanylate: Dipotassium guanosine-5′-monophosphate/ potassium guanylate, potassium 5′-guanylate.
Calcium guanylate: Calcium guanosine-5′-monophosphate/ calcium 5′-guanylate.
Inosinic acid: Inosine-5′-monophosphoric acid/ 5′-inosinic acid.
Disodium inosinate: Disodium inosine-5′-phosphate/ sodium inosinate, sodium 5′-inosinate.
Dipotassium inosinate: Dipotassium inosine-5′-phosphate/ potassium inosinate, potassium 5′-inosinate.
Calcium inosinate: Calcium inosine 5′-monophosphate.
Calcium-5′-ribonucleotides: Calcium inosine 5′-monophosphate and calcium guanosine 5′-monophosphate.
Disodium-5′-ribonucleotides: Disodium inosine 5′-monophosphate and disodium guanosine 5′-monophosphate.

Chemical formula:
Guanylic acid: \( \text{C}_{10}\text{H}_{14}\text{N}_{5}\text{O}_{8}\text{P} \)
Disodium guanylate: \( \text{C}_{10}\text{H}_{12}\text{N}_{5}\text{Na}_{2}\text{O}_{8}\text{P}\cdot\text{nH}_{2}\text{O} \) (n = approximately 7)
Dipotassium guanylate: \( \text{C}_{10}\text{H}_{12}\text{N}_{5}\text{K}_{2}\text{O}_{8}\text{P} \)
Calcium guanylate: \( \text{C}_{10}\text{H}_{12}\text{CaN}_{5}\text{O}_{8}\text{P}\cdot\text{nH}_{2}\text{O} \)
Inosinic acid: \( \text{C}_{10}\text{H}_{13}\text{N}_{4}\text{O}_{8}\text{P} \)
Disodium inosinate: \( \text{C}_{10}\text{H}_{11}\text{N}_{4}\text{Na}_{2}\text{O}_{8}\text{P}\cdot\text{H}_{2}\text{O} \)
Dipotassium inosinate: \( \text{C}_{10}\text{H}_{11}\text{N}_{4}\text{K}_{2}\text{O}_{8}\text{P} \)
Calcium inosinate: \( \text{C}_{10}\text{H}_{11}\text{N}_{4}\text{CaO}_{8}\text{P}\cdot\text{nH}_{2}\text{O} \)
Calcium-5′-ribonucleotides: \( \text{C}_{10}\text{H}_{11}\text{N}_{4}\text{CaO}_{8}\text{P}\cdot\text{nH}_{2}\text{O} \) (calcium inosine 5′-monophosphate)
Guanylic acid: $\text{C}_{10}\text{H}_{12}\text{CaN}_{5}\text{O}_{8}\text{P} \cdot \text{nH}_{2}\text{O}$ (calcium guanosine 5’-monophosphate)

Disodium-5’-ribonucleotides: $\text{C}_{10}\text{H}_{11}\text{N}_{4}\text{Na}_{2}\text{O}_{8}\text{P} \cdot \text{nH}_{2}\text{O}$ (disodium inosine 5’-monophosphate)

C 10H12 Na2N5O8P ⋅ nH2O (disodium guanosine 5’-monophosphate)

**EINECS number:**

- Guanylic acid: 201-598-8
- Disodium guanylate: 221-849-5
- Dipotassium guanylate: 226-914-1
- Calcium guanylate: -
- Inosinic acid: 205-045-1
- Disodium inosinate: 225-146-4
- Dipotassium inosinate: 243-652-3
- Calcium inosinate: -
- Calcium-5’-ribonucleotides: -
- Disodium-5’-ribonucleotides: -

**CAS number:**

- Guanylic acid: 85-32-5
- Disodium guanylate: 5550-12-9
- Dipotassium guanylate: 3254-39-5
- Calcium guanylate: 38966-30-2
- Inosinic acid: 131-99-7
- Disodium inosinate: 4691-65-0
- Dipotassium inosinate: 20262-26-4
- Calcium inosinate: 76079-57-7
- Calcium-5’-ribonucleotides: -
- Disodium-5’-ribonucleotides: -

**Functional Class:** Flavour enhancer.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade guanylic acid and guanylates, for inosinic acid and inosinates and for 5’-ribonucleotides.

**Guanylic acid**

**Definition:** Guanylic acid is a naturally occurring ribonucleic acid. It is slightly soluble in water and practically insoluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Guanylic acid [1].

Assay: Not less than 97.0% on the dried basis.

The specification includes purity criteria on Loss on drying, pH, Related foreign substances, Arsenic, Lead and Heavy metals.
Disodium guanylate

**Definition:** Disodium guanylate is the disodium salt of guanylic acid. It is soluble in water and sparingly soluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Disodium guanylate acid [2].
Assay: Not less than 97.0% and not more than 102.0% on the dried basis.
The specification includes purity criteria on Loss on drying, pH, Related foreign substances, Arsenic, Lead and Heavy metals.

Dipotassium guanylate

**Definition:** Dipotassium guanylate is the dipotassium salt of guanylic acid. It is freely soluble in water and practically insoluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Dipotassium guanylate [1].
Assay: Not less than 97.0% and not more than 102.0% on the dried basis.
The specification includes purity criteria on Loss on drying, pH, Related foreign substances, Arsenic, Lead and Heavy metals.

Calcium guanylate

**Definition:** Calcium guanylate is the dicalcium salt of guanylic acid. It is sparingly soluble in water.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Calcium guanylate [3].
Assay: Not less than 97.0% and not more than 102.0% on the dried basis.
The specification includes purity criteria on Loss on drying, pH, Water-soluble matter, Amino acids, Related foreign substances, Arsenic, Lead and Heavy metals.

Inosinic acid

**Definition:** Inosinic acid is a naturally occurring ribonucleic acid. It is freely soluble in water and slightly soluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Inosinic acid [1].
Assay: Not less than 97.0% and not more than 102.0% on the dried basis.
The specification includes purity criteria on Loss on drying, pH, Related foreign substances, Arsenic, Lead and Heavy metals.
Disodium inosinate  
**Definition:** Disodium inosinate is the disodium salt of inosinic acid. It is soluble in water and sparingly soluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Disodium inosinate [2].  
Assay: Not less than 97.0% and not more than 102.0% on the dried basis.  
The specification includes purity criteria on Water, pH, Related foreign substances, Amino acids, Arsenic, Lead and Heavy metals.

Dipotassium inosinate  
**Definition:** Dipotassium inosinate is the dipotassium salt of inosinic acid. It is freely soluble in water and practically insoluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Dipotassium inosinate [1].  
Assay: Not less than 97.0% and not more than 102.0% on the dried basis.  
The specification includes purity criteria on Water, pH, Related foreign substances, Arsenic, Lead and Heavy metals.

Calcium inosinate  
**Definition:** Calcium inosinate is the dicalcium salt of inosinic acid. It is sparingly soluble in water.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Calcium inosinate [3].  
Assay: Not less than 97.0% and not more than 102.0% on the dried basis.  
The specification includes purity criteria on Water, pH, Related foreign substances, Water-soluble matter, Amino acids, Arsenic, Lead and Heavy metals.

Calcium-5'-ribonucleotides  
**Definition:** Calcium-5'-ribonucleotides consist essentially of a mixture of calcium inosine 5'-monophosphate and calcium guanosine 5'-monophosphate. It is sparingly soluble in water.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Calcium-5'-ribonucleotides [3].  
Assay: Not less than 97.0% and not more than 102.0% of C_{10}H_{11}N_{4}CaO_{8}P and C_{10}H_{12}N_{5}CaO_{8}P on the dried basis. The proportion of C_{10}H_{11}N_{4}CaO_{8}P or C_{10}H_{12}N_{5}CaO_{8}P to the sum of them is between 47% and 53%.  
The specification includes purity criteria on Loss on drying, pH, Related foreign substances, Water-soluble matter, Amino acids, Arsenic, Lead and Heavy metals.
Disodium-5'-'-ribonucleotides

**Definition:** Disodium-5'-ribonucleotides consist essentially of a mixture of disodium inosine 5'-monophosphate and disodium guanosine 5'-monophosphate. It is soluble in water and sparingly soluble in ethanol.

**EC specifications:** An EC specification is currently in preparation.

**JECFA specifications:** Disodium-5'-ribonucleotides [3].

Assay: Not less than 97.0% and not more than 102.0% of C₁₀H₁₁N₄Na₂O₈P and C₁₀H₁₂N₅Na₂O₈P on the dried basis. The proportion of C₁₀H₁₁N₄Na₂O₈P or C₁₀H₁₂N₅Na₂O₈P to the sum of them is between 47% and 53%

The specification includes purity criteria on Loss on drying, pH, Related foreign substances, Water-soluble matter, Amino acids, Arsenic, Lead and Heavy metals.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. 500 mg/kg. Condiments and seasonings q.s. As the ADI is “not specified” the substances were not included in the EU monitoring system (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990: Group ADI “not specified”. These substances are widely distributed in all tissues of animals and plants. The intake from natural sources is 400-600 mg/day and the likely intake from food additives uses is 10-30 mg/day. Therefore, the intake from food additives can be considered as insignificant compared to the intake from natural sources. The ADI is based partly on this and partly on data from short- and long-term studies, reproduction studies, teratology studies and mutagenicity studies [4].

**JECFA status:** Latest evaluation of disodium guanylate and disodium inosinate 1993 [5], of guanylic acid, dipotassium guanylate, calcium guanylate, inosinic acid, dipotassium inosinate and calcium inosinate 1985 [6] and of calcium-5’-ribonucleotides, and disodium-5’-ribonucleotides 1974 [7]. The substances were allocated a group ADI not specified based partly on toxicity data and partly on the fact that the intake of nucleotides from flavour enhancers is low compared with daily intake of naturally occurring nucleotides [5].

**Background data:**

**Subacute/subchronic toxicity:** No adverse effects were seen in rats in several studies on rats and dogs when the oral doses were lower than 3 % of the food. At higher intake an increased kidney weight in the rats was reported [8].

**Genotoxicity:** In vitro: No mutagenic effects were seen in the salmonella/microsome test with and without metabolic activation. Studies on chromosomal aberration were positive [8].

**Chronic toxicity/carcinogenicity:** No adverse effects were seen when groups of 14 male and 14 female rats were given up to 8% disodium 5’–inosinate for 95 weeks [8].

**Reproduction toxicity:** No adverse effects were seen in mice, rats, rabbits, chickens or monkeys [8].
Other: These substances are widely distributed in all animal and plant tissues. They are intermediates in the purin metabolism.

Conclusion: Due to the fact that the existing data show no untoward effects and that the intake of these substances from food additives normally contributes less than 10% to the total intake there is no need for a re-evaluation. However it may be desirable to examine whether the exposure estimates still hold. Guanylic acid and its salts, inosinic acid and its salts, calcium ribonucleotides and sodium ribonucleotides as defined by the specifications are covered by the toxicological evaluation.

References:


**GLYCINE AND ITS SODIUM SALT**

**E number:** E 640

**Recommendation:** A re-evaluation is not needed as long as uses does not include use as a sweetener.

**Chemical name/synonyms:**
Glycine: Aminoacetic acid/ glycocoll.
Sodium salt: Sodium glycinate.

**Chemical formula:**
Glycine: C₂H₅NO₂
Sodium salt: C₂H₄NNaO₂

**EINECS number:**
Glycine: 200-272-2
Sodium salt: 227-842-3

**CAS number:**
Glycine: 56-40-6
Sodium salt: 6000-44-8

**Functional Class:** Acidity regulator, flavour modifier, humectant.

**Specification:**
**Manufacture:** No information on manufacturing processes for food grade glycine and the sodium salt.

**Definition:** Glycine is a naturally occurring amino acid.

**EC specifications:** E 640 Glycine and its sodium salt [1].
Assay: Not less than 98.5% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Residue on ignition, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1990: Acceptable when used according to good manufacturing practice. The evaluation is based on nutritional, biochemical and toxicological information as well as on the fact that glycine is a natural constituent of the diet (amino acid) and the intake from food additives is likely to be insignificant compared to the intake from natural sources. Therefore, there is no need for specific toxicity data. The Committee stressed, however, that this was the case when used only as an acidity regulator, flavour modifier and humectant and the use as a sweetener is thus
not included in the evaluation as it could result in intakes much higher than can be achieved from the normal diet [2].

**JECFA status:** Not evaluated.

**Conclusion:** As long as the uses of these substances are restricted to those envisaged by SCF there is no need for a re-evaluation. Glycine and its sodium salt as defined by the specifications is covered by the toxicological evaluation.

**References:**


**DIMETHYL POLYSILOXANE**

**E number:** E 900

**Recommendation:** It should be verified that the specification reflects the toxicological evaluation.

**Chemical name/synonyms:** Siloxanes and silicones, dimethyl/ polydimethyl siloxane, silicone fluid, silicone oil, dimethyl silicone.

**Chemical formula:** \((\text{CH}_3)_2\text{Si}-[\text{O-Si(\text{CH}_3)_2}]_n\text{O-Si-(CH}_3)_3\)

**EINECS number:** -

**CAS number:** 8050-81-5

**Functional Class:** Antifoaming agent, anticaking agent.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade dimethyl polysiloxane.

**Definition:** Dimethyl polysiloxane is a mixture of fully methylated linear siloxane polymers containing repeating units of the formula \((\text{CH}_3)_2\text{SiO}\) and stabilised with trimethylsiloxy end-blocking units of the formula \((\text{CH}_3)_3\text{SiO}\). It is insoluble in water and in ethanol.

**EC specifications:** E 900 Dimethyl polysiloxane [1].
Assay: Content of total silicon not less than 37.3% and not more than 38.5%.
The specification includes purity criteria on Loss on drying, Viscosity, Arsenic, Lead and Mercury.

**JECFA specifications:** Polydimethylsiloxane [2].
Assay: Content of total silicon not less than 37.3% and not more than 38.5%.
The specification includes purity criteria on Loss on drying, Viscosity, Arsenic and Heavy metals.

**Exposure:** Only permitted in few food commodities. Maximum limit is 10 mg/kg or litre except for chewing gum, 100 mg/kg. Even worst case calculations will only result in potential intake well below the ADI.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990: The JECFA-ADI of 1.5 mg/kg bw was endorsed. The ADI is based on studies on metabolism, acute, short-term and long-term toxicity and observations in man [3].

**JECFA status:** Latest evaluation in 1974 ADI of 1.5 mg/kg bw based on a NOEL of 150 mg/kg bw in a long-term study in rat [4]. In 1979 JECFA specified that the ADI only covers a molecular mass in the range 200 to 300 [5].
Background data:

**Subacute/subchronic toxicity:** Small study groups of five male and five female rats were given feed containing 0.0%, 0.5% and 2% silicone emulsion for 260 days without adverse effects [6]. Similar results were obtained in a number of other small studies in rat [6]. Small studies in rabbit, dog and monkey confirm these results [6].

**Genotoxicity:** *In vitro* studies with and without metabolic activation did not indicate any mutagenic effect [7].

**Chronic toxicity/carcinogenicity:** Groups of 30 female and 10 male rats were given a diet containing 0, 0.01 and 0.1% silicone fluid for 2 years without adverse effects [6]. Other studies give similar results [6]. A long-term feeding study in mice showed no evidence of absorption or carcinogenic potential [3].

**Reproduction toxicity:** No adverse effects were seen in a small two-generation study in rats [6].

**Effect in human:** Dimethyl polysiloxane has been used therapeutically in doses up to 200 mg/day [6]. Twenty-seven patients received 48 ml dimethyl polysiloxane in divided doses for 3-13 month without significant toxic effects except occasional nausea [6]. The uptake of polymers with different molecular weight has been studied. Two groups of humans (number not given) were orally given either a dimethyl polysiloxane, which contain low molecular weight polymers, or a dimethyl polysiloxane, which did not contain low molecular weight polymers. After 72 hours the urinary excretion of silicon were measured. The urinary excretion of total or organosoluble compound was significantly increased in the group given a compound containing low molecular weight polymers. In the other group the urinary excretion was not increased [6].

**Other:** After oral administration to mouse and monkey almost all dimethyl polysiloxane is excreted in the faeces[6].

Two studies indicate that implants of dimethyl polysiloxane are carcinogenic in rats [8;9]. Studies on metabolism in mice, rats and monkeys do not indicate any uptake when dimethyl polysiloxane is given orally [3;6].

**Conclusion:** The evaluations of these substances are based on a data set, which does not fulfil modern standard. However the existing studies do not indicate any undesirable side effects and the present restrictions in use ensures that potential intake through use as food additive lies well below the ADI. The studies indicating that dimethyl polysiloxane may be carcinogenic when used as implants are considered irrelevant for the use as a food additive as the substance is not absorbed.

It is unclear whether the specification covers the toxicological evaluation.

**References:**


**BEESWAX**

**E number:** E 901

**Recommendation:** The present uses appear to be of no toxicological concern. Possibly SCF should re-evaluate beeswax in order to remove the temporary status.

**Chemical name/synonyms:** White wax, yellow wax.

**Chemical formula:** -

**EINECS number:** 232-383-7 (beeswax)

**CAS number:** 8012-89-3 (white beeswax)  
8006-40-4 (yellow beeswax)

**Functional Class:** Glazing agent.

**Specification:**

**Manufacture:** Yellow beeswax is obtained by melting the walls of the honeycomb made by the homey bee, *Apis mellifera* L., with hot water and removing foreign matter. White beeswax is obtained by bleaching yellow beeswax.

**Definition:** Beeswax consists of a mixture of esters of fatty acids and fatty alcohols, hydrocarbons and free fatty acids, minor amounts of free fatty alcohols are also present. It is insoluble in water and sparingly soluble in ethanol.

**EC specifications:** E 901 Beeswax [5].

**Assay:** -

The specification includes purity criteria on Acid value, Saponification value, Peroxide value, Glycerol and other polyols, Ceresin, paraffins and certain other waxes, Fats, Japan wax and soaps, Arsenic, Lead and Mercury.

**JECFA specifications:** Beeswax [2].

**Assay:** -

The specification includes purity criteria on Melting range, Acid value, Saponification value, Peroxide value, Glycerol and other polyols, Ceresin, paraffins and certain other waxes, Fats, Japan wax and soaps, Arsenic, Lead and Heavy metals.

**Exposure:** Bees wax is permitted as glazing agent only for confectionery including chocolate, small products of fine bakery wares coated with chocolate, snacks, nuts, coffee beans, dietary food supplements, fresh citrus fruits, melons, apples and pears; quantum satis. Exposure likely to be very small. Not included in the EU monitoring system as it has been found acceptable by the SCF for the present uses (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** SCF has in 1990 evaluated beeswax to be temporarily acceptable as glazing agent [3].
**JECFA status:** JECFA has in 1992 evaluated the use of beeswax as a food constituent as acceptable, and the present uses to be of no toxicological concern [1;4].

**Background data:**
**Subacute/subchronic toxicity:** No information available.

**Genotoxicity:** Only *in vitro* data have been reported. Beeswax has not been found mutagenic to *S. typhimurium* or *Saccharomyces cerevisiae* with or without metabolic activation [4].

**Chronic toxicity/Carcinogenicity:** No information available.

**Reproduction studies:** No information available.

**Allergy/Intolerance:** Beeswax may contain pollen, which is a well-known allergen.

**Conclusion:** Only an oral LD₅₀ value and reports on the absence of mutagenic effects *in vitro* in microbial assays are available on beeswax. However, beeswax can be regarded as a food constituent, and the long history of use of the wax in the human diet without apparent adverse effects provides assurance that the present uses are of no toxicological concern.

SCF has only evaluated beeswax used as glazing agent. However, beeswax is used in food for a wider range of purposes than evaluated by SCF. The JECFA evaluation covers beeswax used as glazing agent, release agent, component of chewing gum base, and carrier for flavour.

**References:**

1. [1992, TRS 828-JECFA 39]


4. [1992, FAS 30-JECFA 39]

**CANDELILLA WAX**

**E number:** E 902

**Recommendation:** The present uses appear to be of no toxicological concern. Possibly SCF should re-evaluate candelilla wax in order to remove the temporary status.

**Chemical name/synonyms:** -

**Chemical formula:** -

**EINECS number:** 232-347-0

**CAS number:** 8006-44-8

**Functional Class:** Glazing agent.

**Specification:**

**Manufacture:** Candelilla wax is obtained from the candelilla plant, *Euphorbia antisyphilitica* by water extraction and subsequent refining with sulphuric acid [2].

**Definition:** Candelilla wax is a complex mixture of several chemical compounds, consisting primarily of hydrocarbons with odd-numbered straight carbon chains from $\text{C}_{29}$ to $\text{C}_{33}$ together with esters of acids and alcohols with even numbered carbon chains from $\text{C}_{28}$ to $\text{C}_{34}$. Free acids, free alcohols, sterols, neutral resins and mineral matter are also present. It is insoluble in water [2].

**EC specifications:** E 902 Candelilla wax [5].

**Assay:** -

The specification includes purity criteria on Acid value, Saponification value, Glycerol and other polyols, Ceresin, paraffins and certain other waxes, Fats, Japan wax and soaps, Arsenic, Lead and Mercury.

**JECFA specifications:** Candelilla wax [2].

**Assay:** -

The specification includes purity criteria on Melting range, Acid value, Saponification value, Arsenic, Lead and Heavy metals.

**Exposure:** Candelilla wax is permitted as glazing agent only for confectionery including chocolate, small products of fine bakery wares coated with chocolate, snacks, nuts, coffee beans, dietary food supplements, fresh citrus fruits, melons, apples and pears, quantum satis. Exposure is likely to be small. Not included in the EU monitoring system as it has been found acceptable by the SCF for the present uses (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990. Temporarily acceptable as glazing agent [3].

**JECFA status:** Latest evaluation 1992. Acceptable and commented that the present uses to be of no toxicological concern [1].
Background data:

Subacute/subchronic toxicity: No treatment related changes were observed in two studies performed in the 1940’s, where 12-17 Wistar rats/sex/group were fed up to 2.5% Candelilla wax in the diet for 8 and 27 weeks, respectively. In addition, no treatment related changes were reported in a subacute study, where 12 rats (strain not specified)/sex/group were fed up to 2400 mg/kg bw/day Candelilla wax in the diet for 180 days. In 1953, it was moreover published that no treatment related changes were observed in a subacute oral study, where dogs (strain not specified), 1-2 males and 2-3 females per group, were fed up to 600 mg/kg bw/day Candelilla wax in the diet for 6 months [4].

Genotoxicity: Only data from in vitro studies have been reported. Candelilla wax has not been found mutagenic to *S. typhimurium*, *Escherichia coli* or *Saccharomyces cerevisiae* with or without metabolic activation [4].

Chronic toxicity/Carcinogenicity: No treatment related effects were reported in a study with 30 Sprague-Dawley rats/sex/group receiving up to 750 mg/kg bw Candelilla wax in the diet for 2 years. In a poorly performed study, 15 C57 mice/sex/group received up to 7500 mg/kg bw Candelilla wax in the diet for 12-13 months. The number of deaths in the group receiving the highest dose exceeded those in the lower and control groups, but it was reported that the gum base-Candelilla wax mixture was not carcinogenic [4].

Reproduction studies: No standard reproduction studies have been performed. In a study from 1949, 3 male and 3 female rats per group were, however, fed up to 3420 mg/kg bw/day Candelilla wax in the diet for 5 months prior to mating. Two of three females per group from each dose level conceived, and produced normal litters [4].

Conclusion: No treatment related effects were observed in several old subacute oral studies with rats and dogs, and in a well-performed 2-year study with rats. Several microbial tests for mutagenicity were also negative, but no data are available from eukaryotic genotoxicity tests. The present uses appear to be of no toxicological concern.

SCF has only evaluated candelilla wax used as glazing agent. However, candelilla wax is used for a wider range of purposes than evaluated by SCF. The JECFA evaluation covers candelilla wax used as glazing agent, component of chewing gum base, surface-finishing agent, carrier for flavour.

References:

1. [1992, TRS 828-JECFA 39]


4. [1992, FAS 30-JECFA 39]

**CARNAUBA WAX**

**E number:** E 903

**Recommendation:** Recently re-evaluated by SCF. No further need for action.

**Chemical name/synonyms:** -

**Chemical formula:** -

**EINECS number:** 232-399-4

**CAS number:** 8015-86-9

**Functional Class:** Glazing agent.

**Specification:**

**Manufacture:** Carnauba wax is the refined wax obtained from the leaves of the Brazilian tropical palm tree *Copernica cerifera*.

**Definition:** Carnauba wax is a complex mixture of several chemical compounds, predominantly esters, eg.
- aliphatic esters (straight-chain acids with even-numbered carbon chains from C_{24} to C_{28} and straight-chain alcohols with even-numbered carbon chains from C_{30} to C_{34}),
- hydroxy esters (straight-chain hydroxy acids with even-numbered carbon chains from C_{22} to C_{28}, straight-chain acids with even-numbered carbon chains from C_{24} to C_{28}, straight-chain monohydric alcohols with even numbered carbon chains from C_{24} to C_{34} and dihydric alcohols with even-numbered carbon chains from C_{24} to C_{34}),
- cinnamic aliphatic diesters (p-methoxycinnamic acid and dihydric alcohols with even-numbered carbon chains from C_{24} to C_{34}).

It also contains free acids (straight-chain acids with even-numbered carbon chains from C_{24} to C_{28}), free alcohols (straight-chain alcohols with even-numbered carbon chains from C_{30} to C_{34}), hydrocarbons (straight-chain odd-numbered carbon chains from C_{27} to C_{31}) and resins. It is insoluble in water and partly soluble in boiling ethanol.

**EC specifications:** E 903 Carnauba wax [5].

**Assay:** -

The specification includes purity criteria on Sulphated ash, Acid value, Ester value, Unsaponifiable matter, Arsenic, Lead and Mercury.

**JECFA specifications:** Carnauba wax [4].

**Assay:** -

The specification includes purity criteria on Sulphated ash, Acid value, Ester value, Unsaponifiable matter and Lead.

**Exposure:** Carnauba wax is permitted as glazing agent only for confectionery including chocolate, small products of fine bakery wares coated with chocolate, snacks, nuts, coffee beans, dietary food supplements, fresh citrus fruits, melons, apples and pears, quantum satis. Exposure is
likely to be small. Not included in the EU monitoring system as it has been found acceptable by the SCF for the present uses (tier 0).

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1990. Temporarily acceptable as glazing agent [2]. In 1994 the wax was re-evaluated and supplementary data on chromosome aberrations in mammalian cells *in vitro* and on the readiness of carnauba wax ester to hydrolyse was requested.

Since the edition was closed the SCF has evaluated the requested data and accepted the continued use of carnauba wax as glazing agent. ([http://europa.eu.int/comm/food/fs/sc/scf/out94_en.pdf](http://europa.eu.int/comm/food/fs/sc/scf/out94_en.pdf))

**JECFA status:** Latest evaluation 1992. ADI of 7 mg/kg bw to Carnauba wax [1;3]. Carnauba is evaluated by JECFA as glazing agent, bulking agent, acidity regulator and carrier.

**Background data:**

**Subacute/subchronic toxicity:** In a 90-day study, a diet containing 10% Carnauba wax was fed to groups of 15 male and 15 female Wistar rats, and no treatment related effects were observed. A diet containing 0.1%, 0.3%, and 1.0% (w/w) Carnauba wax was fed to groups of six male and female pure-bred Beagle dogs. The dogs were fed the test diet for 6 months, and no treatment related effects were observed. A new 90-day study with a 90-day reversal phase in F-344 rats is under evaluation by SCF.

**Genotoxicity:** Carnauba wax has not been found mutagenic in three studies with *S. typhimurium* test strains and in one study with *Saccharomyces cerevisiae* D4 with or without metabolic activation. However, in one study with *S. typhimurium*, inconsistent increases in the colony counts were observed with two test strains in the presence of metabolic activation systems. A new study on chromosomal aberrations in human lymphocytes is under evaluation by SCF.

**Chronic toxicity/Carcinogenicity:** No information is available.

**Reproduction studies:** A diet containing 0.1%, 0.3%, and 1.0% (w/w) Carnauba wax was fed to groups of 24 male and female Wistar rats. The rats were fed the wax through one full generation, and through a full gestation period. The pups were also fed the wax through the time of weaning to their maturity, and their litters were examined for teratogenicity. No treatment related effects were observed in the first group of rats, and there were no effects on the reproductive indices in the first or second generation.

**Conclusion:** Carnauba wax is safe in use as a glazing agent.

**References:**


3. [1992, FAS 30-JECFA 39]


SHELLAC

E number: E 904

Recommendation: The present uses appear to be of no toxicological concern. Possibly SCF should re-evaluate shellac in order to remove the temporary status.

Chemical name/synonyms: Bleached shellac, white shellac.

Chemical formula: -

EINECS number: 232-549-9

CAS number: 9000-59-3

Functional Class: Glazing agent.

Specification:
Manufacture: Shellac is obtained from lac, the resinous secretion of the insect Laccifer (Lachardia) lacca Kerr (Fam. Coccidae). Bleached shellac is obtained by dissolving the lac in aqueous sodium carbonate, followed by bleaching with sodium hypochlorite, precipitation of the bleached lac with dilute sulphuric acid and drying; wax free bleached shellac is prepared by further treatment whereby the wax is removed by filtration.

Definition: Shellac is a polyester resin.

EC specifications: E 904 Shellac [5].
Assay: -
The specification includes purity criteria on Sulphated ash, Acid value, Ester value, Unsaponifiable matter, Arsenic, Lead and Mercury.

JECFA specifications: Shellac, bleached [4].
Assay: -
The specification includes purity criteria on Loss on drying, Rosin, Wax and Lead.

Exposure: Shellac is permitted as glazing agent only for confectionery including chocolate, small products of fine bakery wares coated with chocolate, snacks, nuts, coffee beans, dietary food supplements, fresh citrus fruits, melons, apples and pears, quantum satis. Exposure is likely to be small. Not included in the EU monitoring system as it has been found acceptable by the SCF for the present uses (tier 0).

SCF/JECFA evaluation:
SCF status: SCF has evaluated Shellac in 1990 to be temporarily acceptable as glazing agent [2].

JECFA status: JECFA has in 1992 evaluated the use of Shellac as a food constituent as acceptable, and the present uses to be of no toxicological concern [1].
Background data:

**Subacute/subchronic toxicity:** A preliminary report of a 90-day rat feeding study is available, but it was confounded by failure of the air condition equipment. Groups of 14 female rats were daily fed 2% of two types of Shellac. The rats fed the Shellac products tended to have enlarged ceceae and swelling in the proximal region of colon. However, no pathological treatment related effects were observed [3].

**Genotoxicity:** Shellac has not been found mutagenic to *S. typhimurium* and *Saccharomyces cerevisiae* D4 with or without metabolic activation. Data from eukaryotic systems lack [3].

**Chronic toxicity/Carcinogenicity:** No information available.

**Reproduction studies:** A reproduction and subchronic feeding study has been performed in Sprague-Dawley rats. Concentrations of 1,000, 3,000, and 10,000 ppm were mixed in the feed, and groups of male and female rats were fed the test diet for 28 days. A single litter (F1) was delivered, and 24 F1 weaned F1 rats from each group were fed the test diet for additional 90 days. No treatment related toxic effects were observed in any of the groups, and fertility, reproductive performance, and pup development were not subject to any adverse effects [3].

**Conclusion:** No treatment related effects were observed in a subacute oral study with female rats, and in a reproduction study with rats. Several microbial tests for mutagenicity were also negative. The present uses appear to be of no toxicological concern.

**References:**


MICROCRYSTALLINE WAX

E number: E 905

Recommendation: Recently evaluated by SCF. No need for further action.

Chemical name/synonyms: Petroleum wax.

Chemical formula: -

EINECS number: -

CAS number: -

Functional Class:
Component of chewing gum base, protective coating, antifoaming agent, glazing agent.

Specification:
Manufacture: Microcrystalline wax is obtained from petroleum by various refining processes, such as distillation, desulphonation (catalytic hydrogenation or conventional treatment), extraction.

Definition: Microcrystalline wax is a refined mixture of solid, saturated hydrocarbons, mainly branched paraffins.

EC specifications: Preparation of an EC specification is in progress.

JECFA specifications: Microcrystalline wax [3].
Assay: -
Viscosity (100°C): Not less than 11 cSt.
Carbon number at 5% distillation point: Not more than 5% of molecules with carbon number less than 25.
Average molecular weight: Not less than 500.
In addition the specification includes purity criteria on Residue on ignition, Colour, Sulfur, Polycyclic aromatic hydrocarbons, Arsenic and Lead.

Exposure: Microcrystalline wax is permitted as glazing agent only for confectionery excluding chocolate, chewing gum, melons, papaya, mango and avocado, quantum satis. Exposure is likely to be very small. Not included in the EU monitoring system as it is a new additive (tier 0).

SCF/JECFA evaluation:
SCF status: Latest evaluation 1995. A full group ADI of 0-20 mg/kg bw was allocated to highly refined mineral hydrocarbon waxes with a viscosity not less than 11 cSt at 100°C, a carbon number not less than 25 at the 5% boiling point, and a average molecular weight not less than 500 [4].

JECFA status: Latest evaluation 1995. The previous ADI "not specified" allocated to low and intermediate melting point waxes was withdrawn. A group ADI of 0-20 mg/kg bw was allocated to high melting point (HMP) mineral hydrocarbon waxes and waxes with a high sulphur content (HSW) [1:2].
Background data:

Subacute/subchronic toxicity: In 1995, four new 90-days rat studies with food-grade mineral hydrocarbons were evaluated by the SCF. The studies were carried out with doses ranging from 0.002% to 2% in the feed. The most toxic materials were a low melting point and an intermediate wax, synthetic waxes, and the oils with low viscosity. The data indicated that the toxicity was correlated to accumulation of the mineral hydrocarbons, especially in the liver and lymph nodes. The main histopathological findings were granulatoma in the liver and focal collections of vacuolated macrophages in the lymph nodes. The high sulphur wax and the high melting point wax did not cause toxicity or accumulate in the tissues. F344 rats were used in all the studies referred to above, and the findings are in marked contrast to the negative observations reported in several subchronic and chronic toxicity studies in several animal species, including Beagle dogs, and Sprague-Dawley and Long-Evans rats [5].

Genotoxicity: No adequate data available. Genotoxicity appears to be associated with PAH contamination, which should be absent according to specification.

Chronic toxicity/Carcinogenicity: Groups of fifty 6-8 week old male and female Sprague Dawley rats were fed diets with 10% wax for 2 years (five different petrolatum waxes). No wax associated toxic effects were observed [6]. No accumulation of the waxes in the reticuloendothelial system or granulomas in the liver was observed.

Reproduction studies: No adequate information available.

Conclusion: Microcrystalline wax as defined by the JECFA specifications is covered by the toxicological evaluation carried out by JECFA and the SCF. Present uses will be well below the present ADI of 20 mg/kg bw.

References:


MONTAN ACID ESTERS

E number: E 912

Recommendation: Presently being reviewed by SCF.

Chemical name/synonyms: -

Chemical formula: -

EINECS number: -

CAS number: -

Functional Class: Glazing agent.

Specification:
Manufacture: Montan acid esters are produced by oxidative bleaching of natural montan wax – a fossil palm wax – followed by esterification of the montan acids with ethylene glycol and/or 1,3-butylene glycol and/or partial saponification with calcium hydroxide [1].

Definition: Montan acid ester consists of montan acid and/or esters with ethylene glycol and/or 1,3-butandiol and/or glycerol.

EC specifications: An EC specification is currently in preparation.

JECFA specifications: No JECFA specification has been prepared.

Exposure: Permitted only for surface treatment of fresh citrus fruits, melon, mango, papaya, avocado and pineapple.

SCF/JECFA evaluation:
SCF status: Latest evaluation 1990. Temporarily acceptable as glazing agents up to 140 mg/kg [1]. SCF has, on its request, received supplementary data, which is presently being reviewed.

JECFA status: Not evaluated.

Background data:
Subacute/subchronic toxicity: Two Montan waxes have been tested in subchronic toxicity tests in Beagle dogs (4 males and 4 females per dose level). The experiments lasted 140 days using dosages of 5,000, 20,000 and 50,000 ppm in the food. No significant treatment related effects were produced by either of the waxes in the study. A Montan wax has been tested in a 90-days subchronic toxicity test in

Genotoxicity: Two Montan waxes have been tested for bacterial mutagenicity in S. typhimurium strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 and in Escherichia coli strain WP uvr A. Doses of 4, 20, 100, 500, 2,500 and 10,000 µg per plate were tested, and the tests were performed with and without metabolic activation derived from rat liver homogenate. No bacterial mutagenicity was observed in any of the tests. The absence of bacterial mutagenicity of Montan wax appears to be

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sufficiently documented. No documentation on the mutagenicity or clastogenicity of Montan wax in mammalian cells is available.
SPF Wistar rats lasting 90 days using dosages of 2,000, 10,000 and 50,000 ppm in the food. 15 males and 15 females were used in each group. No treatment related intoxication or organ damage was found after administration of up to 50,000 ppm of the wax in the feed to rats for 90 days.

**Chronic toxicity/Carcinogenicity:** Two Montan waxes have been tested in chronic toxicity tests in male and female crossbred albino rats (25 males and 25 females per dose). The studies lasted 2 years using dosages of 5,000, 20,000 and 50,000 ppm in the food. The results indicate that administration of the waxes in the feed up to concentrations of 50,000 ppm for two years did not lead to treatment related toxic effects.

**Reproduction studies:** No studies on reproductive effects or the teratogenicity of montan wax or its esters are available.

**Conclusion:** Montan acid esters is under re-evaluation by SCF following submission of new data. Exposure is likely to be very low, if any at all (only to be used on the surface of fruits, where the peel is normally not consumed).

No specification has yet been prepared for montan acid esters.

**References:**

OXIDISED POLYETHYLENE WAXES

E-number: E 914

Recommendation: Data requested by SCF should be submitted for a re-evaluation.

Chemical name/synonyms: -

Chemical formula: -

EINECS number: -

CAS number: -

Functional Class: Glazing agent.

Specification:
Manufacturer: Oxidised polyethylene waxes are produced by partial oxidation of polyethylene wax or linear polyethylene with air [1].

Definition: Oxidised polyethylene wax consists of polar reaction products created by mild oxidation of polyethylene.

EC specifications: An EC specification is currently in preparation.

JECFA specifications: No JECFA specification has been prepared.

Exposure: Permitted for surface treatment of only fresh citrus fruits, melon mango, papaya, avocado and pineapple. Thus exposure must be expected to be very low if any at all.

SCF/JECFA evaluation:
SCF status: SCF has in 1990 evaluated oxidised polyethylene wax to be temporarily acceptable as glazing agents up to 140 mg/kg [1].

JECFA status: JECFA has not evaluated oxidised polyethylene wax.

Genotoxicity: No information available.

Background data:
Subacute/subchronic toxicity:
Data on the subchronic toxicity in the rats for two polyethylene waxes have been considered by SCF. No compound related effects were observed in the studies at dietary level of the waxes up to 5% [1].

Chronic toxicity/Carcinogenicity: No information available.

Reproduction studies: No information available.
**Conclusion:** Sufficient data appear only to be present concerning the subacute toxicity of two oxidised polyethylene waxes. Although exposure is likely to be very low the data requested by SCF should be submitted or the authorisation withdrawn.

No specification has been prepared for oxidised polyethylene wax.

**References:**

**L-CYSTEINE**

**E number:** E 920

**Recommendation:** A re-evaluation is not needed.

**Chemical name/synonyms:** L-Cystein.

**Chemical formula:** C$_3$H$_7$NO$_2$S·HCl·nH$_2$O (n = 0 or 1)

**EINECS number:** 200-157-7 (anhydrous)

**CAS number:** -

**Functional Class:** Flour treatment agent.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade L-cystein.

**Definition:** L-cysteine hydrochloride or hydrochloride monohydrate. Human hair may not be used as a source for this substance.

**EC specifications:** E 920 L-Cysteine [1].

Assay: Not less than 98.0% and not more than 101.5% on the anhydrous basis.

The specification includes purity criteria on Loss on drying, Residue on ignition, Ammonium-ion, Arsenic and Lead.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** Only permitted as a flour treatment agent, q.s. The exposure from this source is insignificant compared with that from the natural occurrence in food.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation in 1990. This non-essential amino acid occurs in a variety of foods. It is used in bakery processes as dough improver. The contribution to the daily intake from this source is insignificant compared to the intake from natural sources. Therefore SCF considered the use of L-cysteine as flour treatment toxicological acceptable although toxicological data are lacking [2].

**JECFA status:** Not evaluated by JECFA.

**Conclusion:** Cysteine occurs naturally in a variety of foods. The contribution to the intake from food additive is insignificant compared to the total intake. No further evaluation is necessary.

**References:**

CARBAMIDE

**E number:** E 927b

**Recommendation:** Re-evaluation not needed.

**Chemical name/synonyms:** / urea.

**Chemical formula:** CH₄N₂O

**EINECS number:** 200-315-5

**CAS number:** 57-13-6

**Functional Class:** Texturiser in chewing gum.

**Specification:**
**Manufacture:** No information on manufacturing processes for food grade carbamide.

**Definition:** Carbamide is the naturally occurring diamide of carbonic acid.

**EC specifications:** E 927b Carbamide [1].
Assay: Not less than 99.0% on the anhydrous basis.
The specification includes purity criteria on Loss on drying, Sulphated ash, Ethanol-insoluble matter, Alkalinity, Ammonium-ion, Biuret, Arsenic and Lead.

**JECFA specifications:** Urea [2].
Assay: Not less than 99.0% and not more than 101.0% on the dried basis.
The specification includes purity criteria on Loss on drying, Sulphated ash, Ethanol-insoluble matter, Alkalinity, Ammonium-ion, Biuret, Arsenic and Heavy metals.

**Exposure:** Carbamide is only permitted in sugar-free chewing gum, up to 3%, which is in line with the toxicological evaluations.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1991: Acceptable in sugar-free chewing gum at a level up to 3% (the requested level) [3]

**JECFA status:** Latest evaluation in 1993. Due to the fact that carbamide is a naturally constituent of the body, and is excreted in an amount of 20g/day JECFA concluded that the use of carbamide in the requested level of up to 3% in chewing gum is of no toxicological concern [4].

**Background data:**
**Subacute/subchronic toxicity:** There were no toxic effects when 12 dogs were injected subcutaneously with 3000-4000 mg/kg bw every 8 hours for 45 days [5].
**Genotoxicity:** Some data indicate mutagenicity but the concentration used were unrealistic high, up to several times the lethal dose [5]. Therefore, these data are of little relevance. Better data are warranted.

**Chronic toxicity/Carcinogenicity:** In studies in mice and rats both with 50 animal of each sex carbamide was non-carcinogenic although the results were not completely unambiguous [5]

**Reproduction toxicity:** No data available.

**Effect in humans:** Several studies, and some accidents, on healthy subjects indicate that very high doses of carbamide can result in symptoms like nausea and vomiting. The substance is cleared in less than 3 hours [5].

**Conclusion:** The toxicological data are limited for a through toxicological evaluation. However since the substance is a naturally occurring component in humans and the contribution from the use, as additive to chewing gum is insignificant compared to this, there is no need for requesting further data. Carbamide as defined by the specifications is covered by the toxicological evaluation.

**References:**


ARGON, HELIUM, NITROGEN, NITROUS OXIDE AND OXYGEN

E number:
Argon: E 938
Helium: E 939
Nitrogen: E 941
Nitrous oxide: E 942
Oxygen: E 948

Recommendation: A (re)-evaluation is not needed.

Chemical name/synonyms:
Argon: Argon.
Helium: Helium.
Nitrogen: Nitrogen.
Nitrous oxide: Nitrous oxide.
Oxygen: Oxygen.

Chemical formula:
Argon: Ar
Helium: He
Nitrogen: N₂
Nitrous oxide: N₂O
Oxygen: O₂

EINECS number:
Argon: 231-147-0
Helium: 231-168-5
Nitrogen: 231-783-9
Nitrous oxide: 233-032-0
Oxygen: 231-956-9

CAS number:
Argon: 7440-37-1
Helium: 7440-59-7
Nitrogen: 7727-37-9
Nitrous oxide: 10024-97-2
Oxygen: 7782-44-7

Functional Class: Packaging gas, propellant.

Specification:
Argon

Manufacture: Argon is obtained from atmospheric air, by fractionated distillation.

Definition: Argon is a naturally occurring inert gas.

EC specifications: E 938 Argon [1].
Assay: Not less than 99%.
The specification includes purity criteria on Water, Methane and other hydrocarbons calculated as methane.

**JECFA specifications:** Argon [2].
Assay: Not less than 99%.
The specification includes purity criteria on Water, Oxygen, Nitrogen and Hydrogen.

**Helium**
**Manufacture:** Helium is obtained from atmospheric air, by fractionated distillation.

**Definition:** Helium is a naturally occurring inert gas.

**EC specifications:** E 939 Helium [1].
Assay: Not less than 99%.
The specification includes purity criteria on Water, Methane and other hydrocarbons calculated as methane.

**JECFA specifications:** Helium [2].
Assay: Not less than 99%.
The specification includes purity criteria on Air and Carbon monoxide.

**Nitrogen**
**Manufacture:** Nitrogen is obtained from atmospheric air, by fractionated distillation.

**Definition:** Nitrogen is a naturally occurring atmospheric gas.

**EC specifications:** E 941 Nitrogen [1].
Assay: Not less than 99%.
The specification includes purity criteria on Water, Carbon monoxide, Methane and other hydrocarbons calculated as methane, Nitrogen dioxide and nitrogen oxide and Oxygen.

**JECFA specifications:** Nitrogen [2].
Assay: Not less than 99.0% v/v.
The specification includes purity criteria on Carbon monoxide and Oxygen.

**Nitrous oxide**
**Manufacture:** No information on manufacturing processes for food grade nitrous oxide.

**Definition:** Nitrous oxide is a gas, naturally occurring in very small concentration.

**EC specifications:** E 942 Nitrous oxide [1].
Assay: Not less than 99%.
The specification includes purity criteria on Water, Carbon monoxide and Nitrogen dioxide and nitrogen oxide and Oxygen.

**JECFA specifications:** Nitrous oxide [3].
Assay: Not less than 97% v/v.
The specification includes purity criteria on Carbon monoxide, Nitric oxide and nitrogen dioxide, Halogens and hydrogen sulfide and Arsine and phosphine.
Oxygen

**Manufacture:** No information on manufacturing processes for food grade oxygen.

**Definition:** Oxygen is a naturally occurring atmospheric gas.

**EC specifications:** E 948 Oxygen [1].
Assay: Not less than 99%.
The specification includes purity criteria on Water and Methane and other hydrocarbons calculated as methane.

**JECFA specifications:** Oxygen [2].
Assay: Not less than 99%.
The specification includes purity criteria on Carbon monoxide and Carbon dioxide.

**Exposure:** Permitted q.s to all foods as packaging gases and propellants. Exposure from these uses is likely to be very small.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation 1990 [4]: Argon is an completely inert gas. The exposure to nitrogen and oxygen from these sources is insignificant compared to the exposure from the atmosphere. SCF therefore finds the use of these gasses acceptable provided a food grade specification is available. The pharmacological and pharmacokinetic properties of nitrous oxide are known from its wide and established use as an anaesthetic and the residues in food likely to be low. The Committee therefore accepted also this gas provided the specification excludes the presence of other oxides of nitrogen. Helium has not formally been evaluated by SCF.

**JECFA status:** Latest evaluation 1985: For nitrous oxide “acceptable as a propellant” [5].
Nitrogen was evaluated in 1980: “No ADI necessary” [6]. The other gases have not formally been evaluated by JECFA, albeit specifications have been made.

**Conclusion:** Due to the insignificant contribution to the intake from these substances used as food additives there is no need for further evaluation. Helium has not formally been evaluated by SCF, but like argon it is completely inert.

**References:**


5. *[1985, TRS 733-JECFA 29]*
   Evaluation of certain food additives and contaminants (Twenty-ninth report of the Joint

6. [1980, TRS 653-JECFA 24]
ACESULFAME POTASSIUM

E Number: E 950

Recommendation: No need for a re-evaluation.

Chemical name/synonyms: 6-methyl-1,2,3-oxathiazin-4(3H)-on-2,2-dioxide, potassium salt/acesulfame K, acesulfam kalium, potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxthiazin-4-on-2,2-dioxide.

Chemical formula: C₄H₄KNO₄S

EINECS number: 259-715-3

CAS number: 55589-62-3

Functional Class: Sweetener, flavour enhancer.

Specification:
Definition: Acesulfame potassium is an artificial intensive sweetener, about 200 times as sweet as sucrose. It is freely soluble in water and very slightly soluble in ethanol.

Manufacture: Acesulfame potassium is obtained by chemical synthesis and purified through re-crystallisation.

EC specifications: E 950 Acesulfame potassium [1].
Assay: Not less than 99% of C₄H₄KNO₄S on the dried basis.
Purity criteria on Loss on drying, Arsenic, Selenium, Fluoride, Lead and Organic impurities.

JECFA specifications: Acesulfame potassium [2].
Assay: Not less than 99.0% and not more than 101.0% on the dried basis.
Purity criteria on Loss on drying, Organic impurities, Fluoride and Heavy metals.

Exposure: Acesulfame potassium is permitted in beverages up to 350 mg/l and in a variety of solid foods in amounts between 350-1000 mg/kg.

In the EU monitoring system Acesulfame potassium was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 2 - 37% of ADI. The calculated intake by young children is reported in the range of 3 - 107%. It was concluded by the investigators that an examination at tier 3 of intakes by young children is needed.

Additional information: A Swedish study conducted in January 1999 on 1120 Swedish diabetics adults (16 – 90 years) and children (0 – 15 years) was reported. Maximum allowed level was used for the calculation. An estimated worst case calculation was performed assuming that all the foods consumed were sweetened by the same sweetener. The study showed that the estimated intake of Acesulfame K could be close to or exceed the ADI for the population of diabetics if they consume only one type of sweetener.
SCF/JECFA evaluation:

SCF status: In 1984 an ADI of 9 mg/kg bw was allocated. The Committee considered the highest level of acesulfame potassium, tested in rats and dogs of 3% as the no-adverse-effect level (NOAEL), equivalent to 1500 mg/kg bw per day in the rat and 900 mg/kg bw per day in the dog, and established an ADI of 9 mg/kg bw, based on the data from the dog being the most sensitive species [3].

In 1991 SCF was asked to consider whether the rat study could be considered as basis for the ADI resulting in an ADI of 15 mg/kg bw as had been decided by JECFA. The committee, however, found no reason to deviate from its previous decision [4]. In March 2000 when considering a similar request to increase the ADI to 15 mg/kg bw the committee took into account previously available and new toxicokinetic data in a variety of species including man, based on limited evidence of toxicokinetic similarity between humans and dogs and the observation that, for the same total daily dose, the plasma peak concentration for the dog is several fold higher than that for rat, the committee considers, that dog remains the appropriate species on which to base the ADI and reaffirms its previous ADI of 9 mg/kg bw. At the same time the Committee considered new mutagenicity studies and claims that the old long-term studies indicate that acesulfame should have a carcinogenic potential. The Committee found that such claims could not be substantiated on basis of the available data [5].

JECFA status:

1981: No ADI allocated because of some shortcomings in the long-term/carcinogenicity studies in mouse and rat [6]. A monograph was prepared [7].

1983: An ADI of 0-9 mg/kg bw was allocated based on the long-term dog study, mentioned above under SCF, with a NOEL at the highest tested dose, 900 mg/kg bw, and a safety factor of 100 [8]. A monograph was prepared [9].

In 1990 the ADI was changed to 0-15 mg/kg bw. Since acesulfame potassium was not metabolised in any species tested, including man, and further studies in rat in which repeated doses were given did not reveal any induction of metabolism or change in pharmacokinetic behaviour, the committee concluded that the rat appeared to be an appropriate model for humans. Consequently, the committee decided that, since the 2-year study in rats represented a greater proportion of the lifespan of the species than did the 2-year study in dogs and included exposure in utero, the ADI should be based on the NOEL in rat, which was 1500 mg/kg bw/day [10]. A monograph was prepared [11].

Background data:

Subacute/subchronic toxicity: In a 90-days feeding study in rats (dietary levels of 0, 1.0, 3.0 or 10% acesulfame K; 10 males and 10 females per group) no compound related differences between the control and test groups in terms of urinanalysis, serum enzyme and albumin levels, gross pathology and histopathology were detected. The no-toxic level was placed at 3%, equivalent to 1.5 g/kg bw, because the depressed feed consumption, body weight gain, slight diarrhoea and increased faecal water content, caecal enlargement, slight changes in haematological parameters were recorded at 10% level [11].

Genotoxicity: Acesulfame potassium was not mutagenic in several in vitro and in vivo assays (mouse micronucleus assay, unscheduled DNA synthesis, In vitro mammalian gene mutation, in vitro chromosome aberration test, Ames test [11]. In 1997 a study indicating a strong clastogenic
effect of acesulfame was published but the re-evaluation of the slides from this study did not confirm the reported clastogenicity and a new *in vivo* cytogenic study was negative [12].

**Chronic toxicity/Carcinogenicity:** In the 2-year feeding study in Beagle dogs (dietary levels of 0, 0.3, 1.0 or 3.0% acesulfame K; 4 males and 4 females per group) no compound related differences between the control and test groups in terms of general appearance, condition, behaviour, survival, and gross and microscopical pathology were recorded. Therefore, the no-toxic effect level was found to be higher than 3% in the diet, equivalent to 900 mg/kg bw [11].

A first 2-year combined chronic toxicity and carcinogenicity study in rats (dietary levels of 0, 0.3, 1.0 or 3.0% acesulfame K; 60 males and 60 females per group) was found not adequate for evaluation of safety of acesulfame K. This was due to the poor survival of the animals and the occurrence of chronic respiratory disease during the study, which was regarded as a confounding factor in interpretation of the results. It was not possible to exclude a carcinogenic effect of the test compound from this study [11].

In a second combined chronic toxicity and carcinogenicity study in a different rat strain (dietary levels of 0, 0.3, 1.0 or 3.0% acesulfame potassium; 60 males and 60 females per group obtained from parents which had been maintained on the same test diets since weanling) no adverse effects other than decreased body weight in the high-dose group were observed. NOAEL was than assigned to 3% in the diet [11].

In a 80-week carcinogenicity study in mice (dietary levels of 0, 0.3, 1.0 or 3.0%; 100 males and 100 females per group) a slight growth depressing effect of acesulfame potassium at the high dose was recorded for both sexes. The incidence, location and type of tumours did not reveal any significant differences between the test and the control groups. It was concluded that feeding of mice with acesulfame potassium at levels up to 3% through the major part of their lifetime did not reveal any carcinogenic effect [11].

**Reproduction toxicity:** In a multigeneration study in rats (dietary levels of 0, 0.3, 1.0 or 3.0% for 3 successive generations, each comprising 2 consecutive litters) growth rate was slightly decreased in the top dose group of F₀ and F₁ generations, and in the mid-dose group of the F₀ generation. All other parameters were within the normal limits [11].

In a teratogenicity study with 15 females per group of the F₂b and F₃a generations from the multigeneration study (see above) no adverse effects were seen in appearance, feed consumption, autopsy of the dams, organ weights, or litter data; no visceral or skeletal abnormalities attributable to the treatment were recorded [11].

In a teratogenicity study in rats (dietary levels of 0, 0.3, 1.0 or 3.0% acesulfame K from day six to day 15 of gestation) no teratogenic effects attributable to the feeding of the test compound were recorded [11].

In a reproduction study (dietary levels of 0, 0.3, 1.0 or 3.0%; males and females exposed to acesulfame potassium for 12 weeks prior to mating, the dams kept on the same diet during pregnancy and lactation) no adverse effects attributable to the test compound were recorded on female fertility, litter size, sex rates, gross abnormalities, mortality body weight and resorption quotient. No dose-related effects were seen in any of the observations made on the offspring [11].
In an embryotoxicity study in female rabbits (doses of 0, 100, 300 or 900 mg/kg bw by gavage; mated females treated from the seventh to the nineteenth day after mating) no evidence of compound related malformations was found [11].

**Allergy/Intolerance:** Acesulfame potassium showed no antigenic effect when tested for potential antigenicity in an active systemic anaphylaxis test in guinea pigs [11].

**Effect in humans:** Studies on metabolism of acesulfame potassium in serum and urine from human volunteers receiving a single dose of 30 mg/person demonstrated lack of metabolism as only the original substance was detected in the samples [11].

**Other:** The metabolism of acesulfame potassium was studied in rats, dogs and pigs [11]. The compound is not metabolised in any of the tested species.

The potential breakdown products of acesulfame potassium are: acetoacetamide and acetoacetamide-N-sulfonic acid. Acetoacetamide may be formed during long-term incubation of acesulfame potassium in fluids with low pH. N-sulfonic acid of acetoacetamide is formed to a small extent when acesulfame K is incubated at low pH and is thus a potential minor contaminant. A review on toxicological studies on both compound is available [11].

**Conclusion:** The safety of acesulfame K is well documented by the studies reviewed by SCF, JECFA and national authorities: A re-evaluation is not recommended as the compound was recently re-evaluated by SCF [5].

**References:**


E 950 Acesulfame potassium


ASPARTAME

E Number: E 951

Recommendation: Aspartame is presently being reviewed by SCF in the light of all the papers published since the last evaluation.

Chemical name/synonyms: N-L-α-aspartyl-L-phenylalanine-1-methylester, 3-amino-N-(α-carbomethoxy-phenethyl-succinamicacid/ Aspartyl phenylalanine methyl ester, APM.

Chemical formula: C₁₄H₁₈N₂O₅

EINECS number: 245-261-3

CAS number: 22389-47-0

Functional Class: Sweetener.

Specification:
Definition: Aspartame is an intensive sweetener, about 200 times as sweet as sucrose. It is slightly soluble in water and in ethanol.

Manufacture: No information at present.

EC specifications: E 951 Aspartame [1].
Assay: Not less than 98% of C₁₄H₁₈N₂O₅ on the dried basis.
5-benzyl-3,6-dioxo-2-pipazineacetic acid: Not more than 1,5% on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, pH, Transmittance, Specific rotation, Arsenic, Lead and Heavy metals.

JECFA specifications: Aspartame [2].
Assay: Not less than 98% and not more than 102 of C₁₄H₁₈N₂O₅ on the dried basis.
5-benzyl-3,6-dioxo-2-pipazineacetic acid: Not more than 1,5% on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Sulphated ash, pH, Transmittance, Specific rotation, Other optical isomers, Arsenic, Lead and Heavy metals.

Exposure: Aspartame may be used in a variety of products up to 600 mg/kg in beverages and between 300 and 2000 mg/kg i solid foods.

In the EU monitoring system the calculated intake for young children indicate the possibility for exceeding the ADI. In the examination at tier 2 intake is reported in the range of 1 - 40% by young children. The investigators concluded that no further examination is needed at this stage. Additional information: A Swedish study conducted in January 1999 on 1120 Swedish diabetics adults (16 – 90 years) and children (0 – 15 years) was reported. Maximum allowed level was used for the calculation. An estimated worst case calculation was performed assuming that all the foods consumed were sweetened by the same sweetener. The study showed that the estimated intake of aspartame can be close to or exceed the ADI for the population of diabetics if they consume only one type of sweetener.
SCF/JECFA evaluation:

SCF status:
1984: An ADI of 40 mg/kg bw was allocated based on the NOAEL established from long-term studies in mice, rat and dogs [3].

1988: Evaluation of new data concerning the effect of aspartame on blood and tissue levels of phenylalanine and the possibility of behavioural and other neurotoxic effects due to consumption of aspartame. ADI unchanged [4].

1996: At the 107th meeting held 12-13 June 1997 (document XXIV/1270/97-EN) SCF responded to reports alleging a connection between aspartame and increases in the incidence of brain tumours in USA [5]. The committee examined the report and concluded that there is no new evidence to justify a re-examination of aspartame [6]. The data presented by Olney and co-workers have also been evaluated by the UK Department of Health’s Committee on Carcinogenicity, which reached a similar conclusion. FDA has stated that analysis of the National Cancer Institute public database on cancer incidence in the United States does not support an association between the use of aspartame and an increased incidence of brain tumours [6].

JECFA status:
1980: An ADI of 0-40 mg/kg bw was established based on the NOAEL from long-term animal studies [7]. A monograph was prepared [8].

1981: The ADI of 0-40 mg/kg bw was confirmed. An additional long-term study in rats of aspartame and the diketopiperazine (DKP) impurity and further biochemical studies of aspartame in humans were examined [9]. An addendum to the monograph was prepared [10].

Background data:
Subacute/subchronic toxicity: In a 4-week feeding study in mice (dietary levels of 0, 3, 5 and 13 mg/kg/day aspartame; 5 males and 5 females per group) no compound related differences between control and test groups in terms of body weight, feed consumption, motor or behavioural effects were seen [8].

In a 4-week feeding study in rats (dietary levels of 0, 2, 4 and 10 mg/kg/day aspartame; 5 males and 5 females per group) no compound related differences between control and test groups in terms of body weight, feed consumption or behavioural effects were seen [8].

In a 2-month feeding study in rats (dietary levels of 0, 5 and 1250 mg/kg/day aspartame; 10 males and 10 females per group) no compound related effects were noted on appearance, behaviour, eye appearance, body weight, feed consumption, urinanalysis, haematology or gross and macroscopic pathology [8].

In a 9-week feeding study in rats (basal diet or basal diet with aspartame (100:9 w/w), or basal diet with phenylalanine (100:5 w/w) both aspartame and phenylalanine groups had decreased growth (11%) and feed consumption (20%). Furthermore, aspartame treated males had significantly lower SGPT, plasma Ca\(^{++}\) and Cl\(^{-}\) levels. No compound related effects were noted on haematology, urinanalysis, organ weights and gross and microscopic pathology [8].

In a 8-week study in Beagle dogs (doses of 5 or 125 mg/kg aspartame in capsules; 2 males and 3 females per each dose group, and 2 males and 2 females in the untreated control group) no
compound related differences between the control and test groups were seen in body weights, feed consumption, haematology, biochemistry, urinanalysis, ophtalmoscopy, organ weights, or by gross and microscopic pathology [8].

**Genotoxicity:** Mutagenicity studies (host-mediated assay, dominant lethal and cytogenetic studies with aspartame or with its conversion product diketopiperazine (DKP) did not indicate that either aspartame nor DKP are mutagenic [8].

**Chronic toxicity/Carcinogenicity:** In a 104-week study in Beagle dogs (doses of 0, 1000, 2000 and 4000 mg/kg/day aspartame incorporated into 200g of powdered basal diet; 5 males and 5 females per group) the growth was depressed at all dose levels. In the high-dose a consistent and statistically significant lowering of haemoglobin, haematocrit and red blood cell count was recorded. No compound related findings were recorded by gross and microscopic pathology [8].

Seven newborn rhesus monkey were divided into three dosage groups (1, 3 or 4-6 g/kg/day of aspartame) and treated *ad minimum* for 204 and *ad maximum* for 363 days with aspartame administrated in a commercial milk formula. For the high-dose level the mean calculated dose of aspartame was 3600 mg/kg/day (range 1210 – 5330 mg/kg/day). All animals in the intermediate and high-dose exhibited convulsions observed for the first time following 218 days of treatment. The convulsions were similar to those induced by feeding L-phenylalanine to infant monkeys and were ascribed to the L-phenylalanine moiety of aspartame. No pathological examination was performed at termination [8].

In a 110-week feeding study in mice (doses of 0, 1000, 2000, 4000 mg/kg/day; 72 males and 72 females in the untreated control group, 36 males and 36 females per dose group) no compound related effects were recorded on appearance, behaviour and survival. Body weights of treated groups were not markedly different from those in the controls but feed intake was decreased in a dose–dependent manner. No other observations indicative for any carcinogenic effect or any other effects of obvious toxicological significance were recorded [8].

In a 104-week feeding study in rats (doses of 0, 1000, 2000, 4000 or 8000 mg/kg/day; 60 males and 60 females in the untreated control group, 40 males and 40 females per dose group) no effects were seen on the appearance. The growth and feed consumption were decreased in 4000 and 8000 mg/kg/day groups. The survival was significantly decreased in females from 4000 and 8000 mg/kg/day groups. Gross and microscopic pathology findings were evaluated not treatment or dose related. However, the following incidences of brain tumour were recorded: astrocytoma – 0, 4, 1, 4, 1 and oligodendrogloma – 0, 0, 1, 0 in the control, 1000, 2000, 4000 and 8000 mg/kg/day groups, respectively [8].

In a 104-week feeding study in rats (doses of 0, 2000 or 4000 mg/kg/day; 60 males and 60 females in the untreated control group, 40 males and 40 females per dose group; all animals selected from the F1A litter of a multigeneration study in which the parents had been exposed to corresponding dietary levels of aspartame for 60 days prior to mating) no compound related effects were noted on physical appearance, behaviour and survival. The growth and feed consumption were decreased in the high-dose group. Brain tumours were recorded with the following incidences: astrocytoma – 4, 3, 1 and meningoma – 0, 0, 1 in the control, low- and high-dose groups respectively [8].

In a 46-week feeding study in hamsters (doses of 0, 1000, 2000, 4000 or 12000 mg/kg/day, 10 males and 10 females in the control group, 5 males and 5 females per dose group; each group replicated 7 times) neoplastic changes were not recorded. Other microscopic lesions reported were with no apparent treatment relationship. The high mortality in all groups was ascribed to
unidentified infection “wet tail”, which was also given as a reason for termination of the study at 46 weeks. [8].

In a 104-week feeding study in rats (doses of 0, 1, 2, 4 g/kg/day aspartame or 4 g/kg/day aspartame and DKP (3:1); (86 males and 86 females per group; interim sacrifices after 26 weeks: 10 males and 10 females per group and after 52 weeks, 16 males and 16 females per group) no brain tumours were recorded at 26 or 52 weeks. The brain tumours were recorded in animals exposed to the test compounds for more than 1 year with the following incidence: 1 (astrocytoma), 1 (oligodendroglioma) 2 (astrocytoma and ependymoma), 1 (astrocytoma), 1 (oligodendroglioma) in the control, 1, 2, 4 g/kg/day aspartame and 4 g/kg/day of aspartame and DKP respectively [9].

**Reproduction toxicity:** In a two –generation reproduction study in rats (doses of 0, 2 or 4 g/kg/day aspartame, P1 generation of 12 males and 24 females per dose level, P2 generation of 10 males and 20 females per dose group) body weights of F1A and F2A weanlings were significantly reduced. All other parameters were within the normal limits [8].

In a teratogenicity study in rats (doses of 0, 2 or 4 g/kg/day, 24 mated females per dose exposed to aspartame from 6 to 15 day of gestation) no embryotoxic or teratogenic effects on developing foetus or on pregnant rats were recorded [8].

In a teratogenicity study in rats (doses of 0, 2.5 or 4.4 g/kg/day aspartame in the diet, 24 mated females per dose exposed to aspartame from 6 to 15 day of gestation) no embryotoxic or teratogenic effects on developing foetus or on pregnant rats were recorded [8].

Results from special studies on the effect of aspartame, cyclamate or sucrose in chicken embryo did not indicate any adverse effect of the test compound [8].

**Allergy/Intolerance:** No clearly reproducible allergy effects were found for aspartame [10].

**Effect in humans:** Aspartame was tested in normal adults, obese adults, normal children and adolescents, subjects heterozygous for phenylketonuria (PKU) (natural parents and PKU children), PKU and normal adolescents, and insulin and non-insulin dependent diabetics using various doses of aspartame and various treatment periods. Under condition of these studies aspartame did not cause any effects of toxicological significance [4;7]. Numerous reports on various effects of aspartame in humans have been published since aspartame was last evaluated by SCF and JECFA. These studies are presently being reviewed by SCF.

**Other:** The metabolism of aspartame has been studied in several animal species [4]. The metabolites of importance are phenylalanine, methanol and aspartate. Grossly elevated plasma phenylalanine concentrations such as found in children with phenylketonuria (PKU), are associated with mental retardation. Therefore, sufferers from clinical PKU, who stay on phenylalanine-low diet, should be informed that this sweetener is a source of phenylalanine when ingested. [10;11]. The methanol load resulting from the consumption of aspartame-sweetened beverages is comparable to that from consumption of fruit juice, thus with no toxicological importance [10]. High doses of aspartate are known to cause hypothalamic neuronal necrosis in neonatal rodents. Based on the results from animal studies and studies in humans on aspartate concentrations after ingestion of aspartame there is no indication of aspartate-induced neuronal damage [10].

When aspartame is present in prepared foods, it may be converted to diketopiperazine (DKP; 5-benzyl-3,6-dioxo-2-piperazine-acetic acid), the amount being dependent on the moisture content,
pH, storage temperature, and time of storage of the food. Furthermore, aspartame usually contains about 1% of DKP as an impurity (see specifications). Extensive toxicological studies were performed with DKP. No toxicological effect in a two year study in the rat was 750 mg/kg bw and the ADI was established at 0-7.5 mg/kg bw. Review on toxicological studies is available [8].

In addition special studies with aspartame and diketopiperazine (see below) to elucidate the possible effect of the compounds on enzyme induction, gastrointestinal, cardiovascular and central nervous systems, their hormonal properties and anti-inflammatory activity have been performed [8].

**Conclusion:** The safety of aspartame is well documented by the studies reviewed by SCF, JECFA and national authorities. Since the evaluation numerous studies have been published which question the safety of the compound and express a specific concern about its carcinogenicity, though the general lack of carcinogenic response was demonstrated in several bioassays. SCF is presently reviewing these studies. There is presently being performed an NTP study in transgenic mice.

**References:**

CYCLAMATES: CYCLAMIC ACID, SODIUM CYCLAMATE AND CALCIUM CYCLAMATE

E Number:
Cyclamic acid: E 952 (i)
Sodium cyclamate: E 952 (ii)
Calcium cyclamate: E 952 (iii)

Recommendation: No need for further evaluation. However, the permitted use levels may need a reduction to secure intake below ADI, unless reliable exposure data can show that exceeding of the ADI is unlikely.

Chemical name/synonyms:
Cyclamic acid: Cyclohexylsulfamic acid, cyclohexanesulfamic acid/ cyclamate.
Sodium cyclamate: Sodium cyclohexylsulfamic acid, sodium cyclohexanesulfamic acid.
Calcium cyclamate: Calcium cyclohexylsulfamic acid, calcium cyclohexanesulfamic acid.

Chemical formula:
Cyclamic acid: C₆H₁₃NO₃S
Sodium cyclamate: C₆H₁₂NNaO₃S
Calcium cyclamate: Anhydrous: C₁₂H₂₄N₂O₆S₂, dihydrate: C₁₂H₂₄N₂O₆S₂·2H₂O

EINECS number:
Cyclamic acid: 202-898-1
Sodium cyclamate: 205-348-9
Calcium cyclamate: 205-349-4

CAS Number:
Cyclamic acid: 100-88-9
Sodium cyclamate: 139-05-9
Calcium cyclamate: 139-06-0

Functional Class: Sweetener.

Specification:
Cyclamic acid:
Definition: Cyclamic acid is an artificial intensive sweetener, about 40 times as sweet as sucrose. It is soluble in water and in ethanol.

Manufacture: Cyclamic acid is obtained by isolation from the sodium salt.

EC specifications: E 952 (i) Cyclamic acid [1].
Assay: Not less than 98% and not more than 102% of C₆H₁₃NO₃S on the dried basis.
Cyclohexylamine: Not more than 10 mg/kg on the dried basis.
Dicyclohexylamine: Not more than 1 mg on the dried basis.
Purity criteria on Loss on drying, Aniline, Selenium, Arsenic, Lead and Heavy metals.

JECFA specifications: Cyclohexylsulfamic acid [2].
Assay: Not less than 98.0% and not more than 102.0% of C₆H₁₃NO₃S on the dried basis.
Cyclohexylamine: Not more than 10 mg/kg on the dried basis.
Dicyclohexylamine: Not more than 1 mg on the dried basis.
Purity criteria on Loss on drying and Heavy metals.

**Sodium cyclamate:**

**Definition:** Sodium cyclamate is the sodium salt of cyclamic acid. It is an artificial intensive sweetener, about 30 times as sweet as sucrose. It is soluble in water and practically insoluble in ethanol.

**Manufacture:** Sodium cyclamate is obtained by chemical synthesis.

**EC specifications:** E 952 (ii) Sodium cyclamate [1].
Assay: Not less than 98% and not more than 102% of C₆H₁₂NNaO₃S on the dried basis.
Dicyclohexylamine: Not more than 1 mg on the dried basis.
Purity criteria on Loss on drying, Aniline, Selenium, Arsenic, Lead and Heavy metals.

**JECFA specifications:** Sodium cyclamate [2].
Assay: Not less than 98.0% and not more than 101.0% of C₆H₁₂NNaO₃S on the dried basis.
Dicyclohexylamine: Not more than 10 mg/kg on the dried basis.
Purity criteria on Loss on drying and Heavy metals.

**Calcium cyclamate:**

**Definition:** Calcium cyclamate is the calcium salt of cyclamic acid. It is an artificial intensive sweetener, about 30 times as sweet as sucrose. It is soluble in water and sparingly soluble in ethanol.

**Manufacture:** Calcium cyclamate is obtained by chemical synthesis.

**EC specifications:** E 952 (iii) Calcium cyclamate [1].
Assay: Not less than 98% and not more than 101% of C₁₂H₂₄N₂O₆S₂ on the dried basis.
Dicyclohexylamine: Not more than 10 mg/kg on the dried basis.
Purity criteria on Loss on drying, Aniline, Selenium, Arsenic, Lead and Heavy metals.

**JECFA specifications:** Calcium cyclamate [2].
Assay: Not less than 98.0% and not more than 101.0% of C₁₂H₂₄N₂O₆S₂ on the dried basis.
Dicyclohexylamine: Not more than 1 mg on the dried basis.
Purity criteria on Loss on drying and Heavy metals.

**Exposure:** Cyclamate is permitted in beverages up to 400 mg/l and in a variety of solid foods in amounts between 250-1000 mg/kg.

In the EU monitoring system cyclamate was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI, an examination at tier 2 level was performed. The calculated intake by adults and the whole population is reported in the range of 0 - 10% of the previous ADI of 11 mg/kg bw. The calculated intake by young children is reported in the range of 1 - 74%. It was concluded by the investigators that no further testing is needed.
**Additional information:** A Spanish study on intake of cyclamates conducted in 1992 in a region of Spain (Catalonia) provided clear indications of the major contribution soft drinks make to cyclamate exposure and confirms that even if it was unlikely to have caused any safety concerns at the time of the study, the margin of safety between the exposure and the ADI is small for high consumers of cyclamates. A Swedish study conducted in January 1999 on 1120 Swedish diabetics adults (16 – 90 years) and children (0 – 15 years) was reported. Maximum allowed level was used for the calculation. An estimated worst-case calculation was performed assuming that all the foods consumed were sweetened by the same sweetener. The study showed that the estimated intake of cyclamate can be close to or exceed the ADI for the population of diabetics if they consume only one type of sweetener.

As the ADI has been reduced by SCF since these studies were performed a more detailed investigation of the intake of cyclamate is desirable.

**SCF/JECFA evaluation:**

**SCF status:**

1984: A temporary ADI of 11 mg/kg bw was allocated based on a NOAEL of 100 mg/kg bw for cyclohexylamine (CHA) with respect to testicular toxicity in a 90-day feeding study in the rat. Safety factor was 100 for CHA and a conversion factor was applied to account for the amount of CHA likely to be formed from cyclamate. The ADI received a temporary status because of the existing areas of uncertainty relating to relevance for man of the testicular damage found in rats fed cyclohexylamine [3].

1988: The temporary ADI of 11 mg/kg bw confirmed [4].

1991: The temporary ADI of 11 mg/kg bw. confirmed [5].

1995: The temporary ADI of 11 mg/kg bw maintained [6]

March 2000: Revised opinion on cyclamate was adopted by SCF. A new ADI of 0-7 mg/kg bw was allocated [7]. In light of a large inter-individual variations in conversion rates of cyclamate to CHA and a lack of knowledge about the minimal time span of exposure to CHA that might result in testicular damage, it was concluded that the maximum observed individual overall conversion of cyclamate to CHA and absorption of the latter should be 85% and should be used for calculating the ADI along with the reduced safety factor for inter-individual differences.

**JECFA status:**

1977: A temporary ADI of 0-4 mg/kg bw was allocated based on no effect level of cyclohexylamine (CHA) (free base) in rat (testicular atrophy). Following calculations were taken into consideration: NOEL for CHA in rat = 74 mg/kg bw/day. Temporary ADI (200 safety factor) for man for CHA =0.37 mg/kg bw. To convert an ADI for CHA to an ADI for cyclic acid and its salts it is necessary to multiply by the ratio of the molecular weight of cyclic acid to the molecular weight of CHA, which is equal to 2. Thus, if all cyclamate was converted to CHA the ADI for cyclamate would be 0.74 mg/kg bw. Since only 60% of the ingested cyclamate is available for conversion and only 30% of cyclamate is converted to CHA, the temporary ADI for cyclamate is 0.74/(0.6 x 0.3) ~ 4 mg/kg bw expressed as cyclic acid. [8].

1980: The temporary ADI 0-4 mg/kg bw maintained [9].
1982: An ADI of 0-11 mg/kg bw was allocated based on new data [10]. Calculation of the ADI: NOEL for CHA in the rat is 100 mg/kg bw. Approximately 37% of cyclamate is absorbed in man. Thus 63% is available for conversion to CHA by intestinal flora. Absorbed cyclamate is not metabolised. Human conversion rate of cyclamate to CHA is 30%. The ratio mol wt. cyclamate/mol wt.CHA = 2. NOEL for cyclamate: 100 x 2/0.63 x 0.3 = 1058. ADI: NOEL/safety factor of 100 = 10.6 mg/kg bw ~ 11 mg/kg bw. A new monograph was prepared [11].

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies in rats and dogs have been performed to test effects on CHA on male reproduction organs. Effects were observed but no NOEL was given [11].

**Genotoxicity:** Cyclamate was negative in Ames’ test [11]. Sodium cyclamate slightly increased number of dominant lethals [11]. Chromosome analysis of blood samples collected from human converters and non-converters demonstrated no changes [11].

**Chronic toxicity/Carcinogenicity:** In a 80-week study in mice (dietary levels of 0, 0.7, 1.75, 3.5 or 7.0% sodium cyclamate) no apparent differences in mortality, organ weights, incidences of histopathological changes or tumours were recorded. Haemoglobin concentrations of both sexes at 7% level were significantly decreased in both sexes. The NOEL was 3% in the diet calculated to approximately 5 mg/kg bw [11].

In a 2-year study in rats (dietary levels of 0 or 2% during first 10 weeks and 4% of sodium cyclamate thereafter; 50 males and 50 females per group, whose bladders were instilled with a solution containing 2 mg of N-methyl-N-nitrosourea (MNU); in addition an untreated control of 100 rats) several pathological changes in urinary tract were recorded in all MNU treated animals. No differences were recorded in the incidence or the latency periods of the tumours between the MNU treated animals kept on diet with or without sodium cyclamate [11].

In a lifetime study in rats untreated or pretreated with MNU (a single dose of 2 mg intravesicular) fed diet with 0 or 2 g/kg bw of sodium cyclamate, the sweetener was found to promote MNU-induced bladder tumors [11].

In a feeding study with cyclamate (daily doses of 100 or 500 mg/kg bw, 5 days a week for an average of 94 and 95 months) to monkeys no evidence of toxicity was recorded [11].

In a long term study in mice (dietary levels of 0, 2 or 5% sodium cyclamate, 0.2 or 0.5% saccharin, 2% of sodium cyclamate and 0.2% of saccharin, 5% sodium cyclamate and 0.5% saccharin, or 0.5% CHA; 50 males and 50 females per group of parental, F\textsubscript{3b} and F\textsubscript{6a} generations obtained in six-generation study) no evidence of carcinogenic effect of sodium cyclamate was obtained [11]. This study was a part of a six-generation study (see below).

**Reproduction toxicity:** In a six-generation study (dietary treatments: 0, 2 or 5% sodium cyclamate, 0.2 or 0.5% saccharin, 2% of sodium cyclamate and 0.2% of saccharin, 5% sodium cyclamate and 0.5% saccharin, or 0.5% CHA; generations of 10 males and 20 females) both cyclamate and saccharin alone or in combinations did not have any toxic, embryotoxic or teratogenic effects. The 5% of CHA caused growth retardation and embryonal death [11].

**Effect in humans:** Several studies, including epidemiological studies, have been conducted to elucidate the magnitude, intra- and inter-individual variation of conversion of cyclamate to CHA, the effect of cyclamate and CHA on human reproductive parameters [11;12].
Other: Several studies concerning the pathophysiological effects of cyclamate on liver, kidneys, gastrointestinal tract, heart, blood, endocrine glands and reproductive system have been conducted [12].

Cyclamate can be converted to CHA by gut flora. Several studies have been performed on CHA, as it is the principal metabolite of cyclamate. The results from the following studies with CHA are summarised in the monograph [11]: special studies on mutagenicity (mouse, hamster), special studies on reproduction (rat), short-term studies (rat, dog), long-term studies (mouse and rat).

Conclusion: No need for re-evaluation as the compound has been recently re-evaluated by SCF.

References:


**ISOMALT**

**E Number:** E 953

**Recommendation:** No need for a toxicological re-evaluation. However a monitoring of actual uses and exposure is recommended.

**Chemical name/synonyms:** 6-O-α-D-Glucopyranosyl-D-sorbitol (1,6-GPS) and 1-O-α-D-Glucopyranosyl-D-mannitol dihydrate (1,1-GPM)/ hydrogenated isomaltulose, palatinit.

**Chemical formula:**
- 6-O-α-D-Glucopyranosyl-D-sorbitol: $\text{C}_{12}\text{H}_{24}\text{O}_{11}$
- 1-O-α-D-Glucopyranosyl-D-mannitol dihydrate: $\text{C}_{12}\text{H}_{24}\text{O}_{11}\cdot 2\text{H}_{2}\text{O}$

**EINECS number:** -

**CAS Number:** 6419-82-0

**Functional Class:** Sweetener, bulking agent.

**Specification:**

**Definition:** Isomalt is an equimolar mixture of 1,6-GPS and 1,1-GPM. It is a bulk sweetener about half as sweet as sucrose. The product contains also minor amounts of D-mannitol and D-sorbitol. It is soluble in water and very slightly soluble in ethanol.

**Manufacture:** Isomalt is obtained by catalytic (nickel) hydrogenation of isomaltulose prepared by enzymatic isomerisation of sucrose.

**EC specifications:** E 953 Isomalt [1].

Assay: Not less than 98% of hydrogenated mono and disaccharides and not less than 86% of the mixture of 6-O-α-D-Glucopyranosyl-D-sorbitol and 1-O-α-D-Glucopyranosyl-D-mannitol dihydrate on the anhydrous basis.
- D-sorbitol: Not more than 6%.
- D-mannitol: Not more than 3%.
- Nickel: Not more than 2 mg/kg.

Purity criteria on Water, Sulphated ash, Reducing sugars, Arsenic, Lead and Heavy metals.

**JECFA specifications:** Isomalt [2].

Assay: Not less than 98% of hydrogenated mono and disaccharides and not less than 86% of the mixture of 6-O-α-D-Glucopyranosyl-D-sorbitol and 1-O-α-D-Glucopyranosyl-D-mannitol dihydrate on the anhydrous basis.
- D-sorbitol: Not more than 6%.
- D-mannitol: Not more than 3%.
- Nickel: Not more than 2 mg/kg.

Purity criteria on Water, Sulphated ash, Reducing sugars, Arsenic, Lead and Heavy metals.
Exposure: Isomalt is permitted as a sweetener in a variety of foods not including beverages. No upper limit is specified. For other purposes than sweetening isomalt is permitted *quantum satis* in all foods where additives may be used except beverages other than liqueurs. As no upper limits of use has been specified an exposure estimate is not possible and isomalt was not included in the EU monitoring system (tier 0). As isomalt, as other bulk sweeteners, has the sweetening effect less than that of sugar it could, in principle, replace all sugar in solid foods (it is not permitted in beverages). Assuming an average intake of sugar of 60 g/day and a high intake of 180 g/day and that half of this could be from solid foods a potential intake of 30 g/day (average) and 90 g/day (high) can be calculated. As this theoretically calculated exposure exceeds the laxative threshold as defined by SCF a monitoring of actual exposure is desirable. Also non-sweetener use of this and the other sugar alcohols should be taken into account.

**SCF/JECFA evaluation:**

**SCF status:**
1984: The Committee considered the continued use of isomalt acceptable provided limitations due to its laxative action were kept in mind. The committee noted that consumption in the order of 20 g/person/day of this and other polyols alone or in combination is unlikely to cause undesirable laxative symptoms [3].

1987 and 1988: The Committee were supplied with data on laxative effect of isomalt suggesting a change in the evaluation, but the Committee maintained the original evaluation from 1984 [4].

**JECFA status:**
1981: A temporary ADI of 0-25 mg/kg bw was allocated based on a NOEL with respect to laxation [5]. A toxicological monograph was prepared [6].

1985: ADI was changed to “not specified” [7]. A toxicological monograph was prepared [8].

**Background data:**

**Subacute/subchronic toxicity:** In a three months rat feeding study (dietary levels of 0, 3.3, 10 and 30% isomalt or 30% sucrose, 15 males and 15 females per group) dietary concentrations of up to 10% isomalt were tolerated without obvious organic damage. Taken the transient diarrhoea into account, 3.3% dietary isomalt was well tolerated. However, it was not possible to establish a no-effect level, due to the elevated plasma bilirubin concentrations recorded in females at all treatment levels [3;8].

In a 13-week study in beagle dogs (dietary levels of 0, 5, 10, and 20% isomalt, 4 males and 4 females per group) the concentrations of up to 20% isomalt did not produce any toxic injury. Allowing for the occasional ill-formed faeces in the 10% -dose group, the no-effect level was placed at 5% of the diet, equal to 1.67 g/kg bw/day [8].

**Genotoxicity:** Isomalt was not mutagenic in the Ames’ test [8].

**Chronic toxicity/Carcinogenicity:** In a 2-year feeding study in mice (dietary levels of 0, 2.5, 5.0, or 10% isomalt, 50 males and 50 females per group) the feeding of isomalt at dietary levels up to 10% did not show any carcinogenic effect or any other effects of obvious toxicological significance [8].

In a long-term toxicity/carcinogenicity study in rats (dietary levels of 0, 2.5, 5.0 and 10% isomalt or 10% sucrose, 50 males and 50 females per group derived from parents that had been fed the same
diets before mating and during the gestation and lactation periods, duration of 128 weeks for males and 130 weeks for females) no indications were found of carcinogenic properties of isomalt or any effects of obvious toxicological importance [8].

In a 1-year feeding study in rats (dietary levels of 0, 2.5, 5.0 and 10% isomalt or 10% sucrose, 10 males and 10 females per group derived from parents that had been fed the same diets before mating and during the gestation and lactation periods) no effects of obvious toxicological importance were recorded [8].

In a 1-year feeding study in beagle dogs (dietary levels of 0, 2.5, 5.0 and 10% isomalt or 10% sucrose or 10% maize starch, 4 males and 4 females per group) concentrations of isomalt up to 10% were tolerated without harm, apart from the occurrence of pappy to liquid faeces at all dose levels [8].

**Reproduction toxicity:** In a multigeneration study in rats (dietary levels of 0, 2.5, 5.0, or 10% isomalt, 20 males and 20 females per group, 3 successive generations) the levels up to 10% isomalt in the diet did not affect fertility or reproduction nor did it affect the health or survival of the progeny [8].

Isomalt was not embryotoxic nor teratogenic in Wistar rats (dietary levels of 0, 2.5, 5.0 and 10% isomalt, exposure from day 0 to day 29 of gestation) [8].

In New Zealand White rabbits (dietary levels of 0, 2.5, 5.0 and 10% isomalt, exposure from day 0 to day 21 of gestation) isomalt was non-toxic to pregnant rabbits and did not induce any teratogenic or embryo/foetotoxic effects [8].

Embryotoxic effects were observed in FB30 rats (dietary levels of 0, 2.5, 5.0 and 10% isomalt, or 10% sucrose and an additional control group on basic feed at level of 80% of the amount consumed by the control; 25 females per group; exposure from day 0 to day 21 of gestation). The embryotoxicity was probably the results of maternal intolerance caused by the elevated acute doses of isomalt at the beginning of gestation, and therefore considered a secondary embryotoxic effect. The latter interpretation was supported by the fact that these effects were avoided by adaptation of the mothers to isomalt before gestation [8].

**Effect in humans:** Several tolerance studies were conducted. Laxative effects due to ingestion of isomalt were noted at 20-30g/day [8].

**Other:** Several studies to elucidate the biochemical aspects such as absorption, distribution and excretion of isomalt in rats and fistulated and normal pigs are summarised in [8].

**Conclusion:** The safety of isomalt is well documented. However, a laxative effect in man after ingestion of high amounts of this compound should be taken into account when considering its appropriate levels of use alone and in combination with other sugar alcohols.

**References:**


**Saccharin, Sodium Saccharin, Calcium Saccharin and Potassium Saccharin**

**E Number:** E 954

**Recommendation:** No need for re-evaluation.

**Chemical name/synonyms:**
- Saccharin: 3-oxo-2,3-dihydrobenzo[d]isothiazol-1,1-dioxid.
- Sodium saccharin: Sodium salt of 3-oxo-2,3-dihydrobenzo[d]isothiazol-1,1-dioxid/ sodium o-benzosulfimide.
- Calcium saccharin: Calcium salt of 3-oxo-2,3-dihydrobenzo[d]isothiazol-1,1-dioxid/ calcium o-benzosulfimide.
- Potassium saccharin: Potassium salt of 3-oxo-2,3-dihydrobenzo[d]isothiazol-1,1-dioxid/ potassium o-benzosulfimide.

**Chemical formula:**
- Saccharin: \( \text{C}_7\text{H}_5\text{NO}_3\text{S} \)
- Sodium saccharin: \( \text{C}_7\text{H}_4\text{NNaO}_3\text{S} \cdot 2\text{H}_2\text{O} \)
- Calcium saccharin: \( \text{C}_{14}\text{H}_8\text{CaN}_2\text{O}_6\text{S}_2 \cdot \text{H}_2\text{O} \)
- Potassium saccharin: \( \text{C}_7\text{H}_4\text{KNO}_3\text{S} \cdot \text{H}_2\text{O} \)

**EINECS number:**
- Saccharin: 201-321-0
- Sodium saccharin: 204-886-1
- Calcium saccharin: 229-349-9
- Potassium saccharin: -

**CAS Number:**
- Saccharin: 81-07-2
- Sodium saccharin: 128-44-9
- Calcium saccharin: -
- Potassium saccharin: 10332-51-1

**Functional Class:** Sweetener.

**Specification:**

**Saccharin**

**Definition:** Saccharin is an artificial intense sweetener about 300-500 times as sweet as sucrose. It is slightly soluble in water, soluble in alkaline solutions and sparingly soluble in ethanol.

**Manufacture:** Saccharin is obtained by chemical synthesis.

**EC specifications:** E 954(i) Saccharin [1].
- Assay: Not less than 99% of \( \text{C}_7\text{H}_5\text{NO}_3\text{S} \) on the dried basis.
- o-Toluenesulfonamide: Not more than 10 mg /kg on the dried basis.
- p-Toluenesulfonamide: Not more than 10 mg /kg on the dried basis.
- Benzoic acid p-toluenesulfonamide: Not more than 25 mg /kg on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Melting range, Sulphated ash, Benzoic acid and salicylic acid, Readily carbonizable substances, Arsenic, Selenium, Lead and Heavy metals.

**JECFA specifications:** Saccharin [2].
Assay: Not less than 99% of C_7H_5NO_3S on the dried basis.
Toluenesulfonamides: Not more than 25 mg /kg on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Melting range, Sulfated ash, Benzoic acid and salicylic acid, Readily carbonizable substances, Arsenic, Selenium and Heavy metals.

**Sodium saccharin**
**Definition:** Sodium saccharin is the sodium salt of saccharin. It is an artificial intense sweetener about 300-500 times as sweet as sucrose. It is freely soluble in water and sparingly soluble in ethanol.

**Manufacture:** Sodium saccharin is obtained by chemical synthesis.

**EC specifications:** E 954 (ii) Sodium saccharin [1].
Assay: Not less than 99% of C_7H_4NNaO_3S on the dried basis.
o-Toluenesulfonamide: Not more than 10 mg /kg on the dried basis.
p-Toluenesulfonamide: Not more than 10 mg /kg on the dried basis.
Benzoic acid p-toluenesulfonamide: Not more than 25 mg /kg on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Benzoic acid and salicylic acid, Readily carbonizable substances, Arsenic, Selenium, Lead and Heavy metals.

**JECFA specifications:** Sodium saccharin [3].
Assay: Not less than 99% and not more than 101% of C_7H_5NO_3S on the dried basis.
Toluenesulfonamides: Not more than 25 mg /kg on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Acidity and alkalinity, Benzoic acid and salicylic acid, Readily carbonizable substances, Arsenic, Selenium and Heavy metals.

**Calcium saccharin**
**Definition:** Calcium saccharin is the calcium salt of saccharin. It is an artificial intense sweetener about 300-500 times as sweet as sucrose. It is freely soluble in water and sparingly soluble in ethanol.

**Manufacture:** Calcium saccharin is obtained by chemical synthesis.

**EC specifications:** E 954(iii) Calcium Saccharin [1].
Assay: Not less than 99% of C_{14}H_8CaN_2O_6S_2 on the dried basis.
o-Toluenesulfonamide: Not more than 10 mg /kg on the dried basis.
p-Toluenesulfonamide: Not more than 10 mg /kg on the dried basis.
Benzoic acid p-toluenesulfonamide: Not more than 25 mg /kg on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Benzoic acid and salicylic acid, Readily carbonizable substances, Arsenic, Selenium, Lead and Heavy metals.

**JECFA specifications:** Calcium saccharin [3].
Assay: Not less than 99% of C_{14}H_8CaN_2O_6S_2 on the dried basis.
Toluensulfonamides: Not more than 25 mg/kg on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Benzoic acid and salicylic acid, Readily carbonizable substances, Arsenic, Selenium and Heavy metals.

**Potassium saccharin**

**Definition:** Potassium saccharin is the potassium salt of saccharin. It is an artificial intense sweetener about 300-500 times as sweet as sucrose. It is freely soluble in water and sparingly soluble in ethanol.

**Manufacture:** Potassium saccharin is obtained by chemical synthesis.

**EC specifications:** E 954 (iv) Potassium saccharin [1].
Assay: Not less than 99% of C$_7$H$_4$KNO$_3$S on the dried basis.
o-Toluensulfonamide: Not more than 10 mg/kg on the dried basis.
p-Toluensulfonamide: Not more than 10 mg/kg on the dried basis.
Benzoic acid p-toluensulfonamide: Not more than 25 mg/kg on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Benzoic acid and salicylic acid, Readily carbonizable substances, Arsenic, Selenium, Lead and Heavy metals.

**JECFA specifications:** Potassium saccharin [4].
Assay: Not less than 99% of C$_7$H$_4$KNO$_3$S on the dried basis.
Toluensulfonamides: Not more than 25 mg/kg on the dried basis.
In addition the specification includes purity criteria on Loss on drying, Acidity and alkalinity, Benzoic acid and salicylic acid, Readily carbonizable substances, Arsenic, Selenium and Heavy metals.

**Exposure:** Saccharin is permitted in a variety of products, primarily sugar-free, of which can be mentioned beverages 80 mg/l, various desserts 100 mg/kg, ices 80 mg/kg, confectionary 500 mg/kg and in various food supplements.

In the EU monitoring system saccharin was examined at tier 1 level. As the calculation suggested a possibility for children exceeding the ADI, the intake was examined at tier 2 level. The calculated intake by young children was reported as 2-51% of the ADI and it was concluded that no further examination is needed at this stage.

**Additional information:** A Swedish study conducted in January 1999 on 1120 Swedish diabetics adults (16 – 90 years) and children (0 – 15 years) was reported. Maximum allowed level was used for the calculation. An estimated worst case calculation was performed assuming that all the foods consumed were sweetened by the same sweetener. The study showed that the estimated intake of saccharin can be close to or exceed the ADI for the population of diabetics if they consume only one type of sweetener.

**SCF/JECFA evaluation:**

**SCF status:**
1977: A temporary ADI of 2.5 mg/kg bw allocated [5].

1984: The temporary ADI of 2.5 mg/kg bw unchanged [6].

1988: The temporary ADI of 2.5 mg/kg bw unchanged [7].
Latest evaluation in 1995: A full ADI of 5 mg/kg bw expressed as sodium saccharin was allocated. Saccharin is not genotoxic but it is a bladder carcinogen in male rats when given in very large doses. Although it is unlikely that this carcinogenic effect is relevant in humans the ADI is based on the NOEL of 500 mg/kg bw for male rats and a safety factor of 100 [8].

**JECFA status:**
1967 and 1974: An unconditional ADI of 0-5 mg/kg bw and a conditional ADI of 0-15 mg/kg bw allocated for dietetic purposes only [9;10].

1977: Change of the existing ADI to a temporary ADI of 0-2.5mg/kg bw and abolition of the conditional ADI of 0-15 mg/kg bw [11].

1980: The temporary ADI of 0-2.5 mg/kg bw extended [12].

1982: The temporary ADI of 0-2.5 mg/kg bw extended [13]. A monograph was prepared [14].

1984: The temporary ADI of 0-2.5 mg/kg bw was confirmed based on a no-effect level of 1% in the diet (equivalent to 500 mg/kg bw.) in rat and a safety factor of 200 [15].

1993: A full ADI of 0-5mg/kg bw is allocated for saccharin and its calcium, potassium and sodium salts based on the NOEL of 500 mg/kg bw/day in a 2-generation long-term feeding study in rats and a safety factor of 100 [16]. An addendum to the toxicological monograph was prepared [17].

**Background data:**
**Subacute/subchronic toxicity:** Quoted from [14]: In a 13-week feeding study in rats feeding of 20000 ppm (2%) sodium saccharin alone and in doses of up to 2000 ppm(0.2%) together with o-sulfamoylbenzoic acid and o-carboxybenzenesulfonate no consistent or significant effects in hematology, clinical chemistry, organ weights, macroscopy or histology were found.

In a 38-day study in rats (dietary level o or 0.55 so$ium saccharin ; 14 males and 14 females per group) diarrhoea, depression of body weight gain, gross and microscopic inflammatory and hydropic changes in the liver and kidneys were recorded for saccharin-treated animals.

In a 36-week feeding study (dietary levels of 0, 1.0 or 10% saccharin; 5 males and 20 females per group) the only adverse effect recorded was decreased body weight in the 10% group.

In a 4-week study in rats (dietary levels of 0, 1, 3, 5 or 7.5% sodium saccharin) a transient diarrhoea was recorded in 5 and 7.5% groups as well as a dose dependent decrease in urinary amonia and decreased faecal odour.

Feeding of 0 or 7.5% saccharin to rats for 10 days resulted in increased caecal weight, inability to detect some specific anaerobic microbes without decreasing the total number of anaerobic microbes , increased the number of aerobic microbes, and reduced the amount of amonia produced from urea by proteus vulgaris.

In a 16-week feeding study in Beagle dogs (3 males and 3 females per dose group) feeding of 20000 ppm (2%) sodium saccharin alone and in doses of up to 2000 ppm(0.2%) together with o-sulfamoylbenzoic acid and o-carboxybenzenesulfonate caused no significant treatment-related effects.
In a 100 day-study dogs given daily doses of 175-350 mg saccharin developed hyperaemia of the lungs, liver, myocardium and kidney and other changes in kidneys.

In a 11-month study dogs (4 animals per group) received 6 daily doses of 0.065 g/kg of sodium saccharin in the water by gastric intubation. Except for a soft stool no other adverse effects attributable to the treatment were recorded.

Studies in monkeys (daily doses of 0 or 500 mg saccharin, 3 males and 3 females per dose; and 20 or 100 mg/day, 6 days per week, 2 males and 2 females per group) demonstrated no compound related effects on growth, haematology, clinical chemistry and pathology.

**Genotoxicity:** The following tests were negative: Ames test, mitotic recombination in yeast, unscheduled DNA synthesis, the Pol A test, Drosophila sex-linked recessive lethal test, *in vitro* transformation test and the induction of plasminogen activator. The following tests were positive: sister chromatid exchange studies conducted with human lymphocytes, the mouse lymphoma forward mutation test and the Chinese hamster ovary cell test for chromosomal aberration [14].

Saccharin did not produce oncogenic transformation of mouse embryo fibroblasts unless an initiating dose of 3-methylcholanthrene was used [14].

The following genotoxicity studies were positive: cell mutation/ouabain resistance in human Rsa cells, *in vitro* chromosomal aberration in Chinese hamster lung fibroblasts, *in vitro* chromosomal aberration in ICR/Swiss male mice, dominant lethal in ICR/Swiss male and female mice. The insect genotoxicity in Drosophila melanogaster, meiosis repair deficient was negative [17].

The fact that sodium saccharin exhibited clastogenic activity in a number of *in vitro* and *vivo* genotoxicity tests could be attributable to ionic imbalances at the chromosomal level at high concentrations [17].

**Chronic toxicity/Carcinogenicity:** In a 18-month feeding study in female mice (dietary levels of 10% sucrose or 5% saccharin given to mice intragastrically pretreated with single dose of either 0.2 ml propylene glycol or 0.2 ml propylene glycol which contained 50 µg benzo(a)pyrene (BP)). BP clearly increased the incidence of fore stomach neoplasms, while the dietary treatment with sucrose or saccharin had no effect on this type of neoplasm. No neoplasms of the urinary bladder were seen at macroscopy but no histological examination was performed [14].

In a long-term study in mice (dietary levels of 0, 0.2 or 0.5% saccharin; 50 males and 50 females per group of parental, F1b and F6a generations obtained in a six-generation study) no significant treatment related tumorigenic effects were recorded [14].

In a lifetime study in hamsters (levels saccharin in the drinking water of 0, 0.156, 0.312, 0.625, 1.25%; 30 males and 30 females per group) with an average survival of 50-60 weeks no differences in tumor type were recorded between the controls and saccharin treated animals. No urinary tract tumors were recorded in either of group [14].

In a 2-year feeding study in rats (dietary levels of 0, 1.0 or 5.0% saccharin; 7 male and 9 females in the control group and 9 males and 9 females in the test groups) 7 animals (sex unspecified) from 5% group had lymphatic sarcomas. The urinary bladder was not examined. The 5% level caused a slight growth depression [14].
In another 2-year feeding study in rats (dietary levels of 0, 0.005, 0.05, 0.5, or 5.0% saccharin; 20 males and 20 females per group; a positive control received 1ml of 1% aqueous solution of trypan blue s.c. every 2 weeks for one year) growth depression was observed at 5% level. In this group one female had a transitional cell carcinoma and another one hyperplasia and papillomatosis in urinary bladder. Thus no significant tumorigenic effects were observed [14].

In a 28-month feeding study in rats (dietary levels of 0, 0.2, 1.0 or 5.0% saccharin (54 males per group) no significant tumorigenic effects were observed [14].

In a 24-month feeding study in rats (dietary levels of 0, 10 000 or 50 000 saccharin (25 males per group, the study performed in duplicate) no significant tumorigenic effects were observed [14].

In a 28-month feeding study in rats (dietary levels of 0 or 2.5 g sodium saccharin/kg bw/day, 0.2, 1.0 or 5.0% saccharin (54-56 males per group, interim sacrifices at 12 months of 16 rats per group) no bladder abnormalities were reported for either control or treated animals. The 2.5g/kg bw sodium saccharin caused a significant growth depression [14].

In a 26-month feeding study in rats (dietary levels of 0, 90,270, 810 or 2340 mg of saccharin/kg/day; 60 males and 60 females per group) saccharin administration was not accompanied by increased tumor incidence, although the high doses were associated with reduction of body weight in both sexes [14].

In a 100-week feeding study in rats (dietary levels of 0, 0.05, 0.5 or 5% saccharin; all animals were F1 generation from parents kept on the respective diets for approximately 3 months before mating) transitional cell carcinomas of urinary bladder were found in 7 males in the 5% group. In females squamous cell carcinomas were found in 1 animal in the 0.05%, in 2 animals in the 0.5% group and in the 5% group [14].

In a 28-month feeding study in rats (dietary levels of 0, 0.01, 0.1, 1.0, 5.0 or 7.5% saccharin; all animals were the F1 generation from parents kept on the respective diets for 3 months before mating) apart from the depressing effect of the test compound on body weight, the following number of animals with urinary bladder transitional cell carcinomas was recorded: 1 in the controls, none in the 0.01, 0.1 and 1.0 groups, 1 in the 5% group and 8 (7 males and 1 female) in the 7.5% group. Additionally 1 female in the 7.5% group had a urinary bladder transitional cell papilloma [14].

To clarify if o-toluen-sulfonamide (o-TS) present in saccharin used in the two studies with F1 generations (see above) could be the chemical responsible for bladder tumors a special study was performed. F0 generation (50 males and 50 females per group) was kept for 142 weeks on following diets: control, 2.5 mg o-TS/kg/day, 25 mg o-TS/kg/day, 250 mg o-TS/kg/day with 1% NH4Cl in the drinking water or 5% sodium saccharin. F1 generation obtained from F0 kept on the respective diets for 3 months was kept on the respective diets for their lifetime (30-32 months). The treatment related effects in this study were a decreased growth rate in the two highest o-TS groups and the saccharin group and increased tumor incidence [14].

In the two generation carcinogenicity study the NOEL was 1% in the diet [18].

In studies on promotion of bladder carcinogenicity the used control groups received 5% sodium, calcium and acid saccharin in the diet. After 2 years or 72 weeks, the feeding with sodium saccharin resulted in higher incidence of simple hyperplasia when compared with the untreated controls but
the incidence of papillomas or carcinomas of the bladder was comparable to that in the untreated controls [17].

**Reproduction toxicity:** Quoted from [14]:
In mice the feeding of 40-168 mg/kg bw of saccharin through the production of 3 successive litters had no adverse effects on growth, litter number and litter size when compared to the controls fed sugar.

In a six-generation study in mice (dietary levels of 0, 0.2 or 0.5% sodium saccharin) the treatment with the test compound had no adverse effect on reproductive performance parameters. No teratogenic effects attributable to the test compound were reported.

In a reproduction study in rats (dietary levels of 0, 0.05, 0.5 or 5% saccharin; 20 males and females per dose; mating of rats from the same treatment group on 1:1 basis) the results showed no effect of saccharin on mating efficiency, survival of pups born alive, weight gain of pups, but all saccharin groups had smaller average litter size and reduced percent live births when compared with the controls. No evidence of teratogenicity was found.

In a 3-generation study in rats (dietary levels of 0, 0.01, 0.1, 1.0, 5.0 or 7.5% sodium saccharin) a decreased body weight was recorded in males from F₁ generation in 5 and 7.5% groups. The litter size was slightly decreased for dams in 5 and 7.5% groups in F₂a. Also survival index, weaning index and body weights of these pups were below controls. In the F₂b litters, only body weight at weaning was lower than controls for the same two groups.

In a 2-generation study in rats to clarify if the o-TS a major impurity in saccharin used in two 2 generation carcinogenicity study could be responsible for bladder tumors no treatment related effect on reproduction was recorded in the 5% saccharin group.

Several special studies on teratology in mice, rats and rabbits were negative. In one study in rats (dietary level of 0.3% saccharin administered throughout gestation increased incidence of lens abnormalities was recorded when compared with controls.

**Allergy/Intolerance:** Allergic responses, principally skin reactions of a phototoxic or photosensitivity type were reported but the etiology was not completely clear. On the other hand, contact dermatitis and photosensitivity or phototoxic reaction were not noted in persons occupationally exposed to saccharin [14].

**Effect in humans:** Single doses of 5-10 g have been tolerated. Digestive disturbances were noted in some volunteers ingesting doses of 1-1.5 g saccharin/day. Doses of 4.8 g saccharin/day during 5 months did not cause any adverse effects in diabetics. Doses of 0.4-0.5 g/day for 15-24 years were received by diabetics with no adverse effects [14]. Several epidemiological studies conducted to elucidate a possible carcinogenic effect of saccharin in humans do not suggest an association between the saccharin intake and bladder cancer [17]. The epidemiological studies are also reviewed in [15] and [18].

**Other:** Metabolism of saccharin was studied in several species. Special studies on promoting activity, on cell transformation, on the effect on urine composition and bladder epithelial proliferation, on urine volume, and on possible significance of exposure to saccharin through lactation were conducted [17].
Conclusion: In 1974 saccharin was reported to induce bladder cancer in male rats [14]. Others have later verified the results in rats, but no such effects have been found in other animals. Several epidemiological studies on the effect of saccharin in humans did not find increased risk of bladder cancer. The general opinion today is that the carcinogenicity of saccharin is species specific and with a no effect level, and will not induce bladder cancer in humans within the ADI.

References:


13. [1982, TRS 683-JECFA 26]
   Evaluation of certain food additives and contaminants (Twenty-sixth report of the Joint
   1982.

14. [1982, FAS 17-JECFA 26]
    Toxicological evaluation of certain food additives. *WHO Food Additives Series*, No. 17,
    1982.

15. [1984, TRS 710-JECFA 28]
    Evaluation of certain food additives and contaminants (Twenty-eighth report of the Joint
    1984, and corrigendum.

16. [1993, TRS 837-JECFA 41]
    Evaluation of certain food additives and contaminants (Forty-first report of the Joint
    1993.

17. [1993, FAS 32-JECFA 41]
    Toxicological evaluation of certain food additives and contaminants. *WHO Food Additives

18. [1984, FAS 19-JECFA 28]
    Toxicological evaluation of certain food additives and contaminants. *WHO Food Additives
E 957 Thaumatin

THAUMATIN

E Number: E 957

Recommendation: No need for re-evaluation.

Chemical name/synonyms: Thaumatin, Talin™.

Chemical formula: -

EINECS number: 258-822-2

CAS Number: 53850-34-3

Functional Class: Sweetener, flavour enhancer.

Specification:
Definition: Thaumatin consists essentially of the two proteins thaumatin I and thaumatin II together with minor amounts of other plant constituents derived from the source material. It is a naturally occurring intense sweetener about 2000-3000 times as sweet as sucrose. It is very soluble in water and insoluble in acetone.

Manufacture: Thaumatin is obtained by aqueous extraction of the arils of the fruit of Thaumatococcus danielli (Benth).

EC specifications: E 957 Thaumatin [1].
Assay: Not less than 16% of nitrogen on the dried basis equivalent to not less than 94% protein (N x 5.8).
In addition the specification includes purity criteria on Loss on drying, Carbohydrates, Sulphated ash, Aluminium, Arsenic, Lead and Microbiological impurities.

JECFA specifications: Thaumatin [2].
Assay: Not less than 15.1% of nitrogen on the dried basis equivalent to not less than 93% protein (N x 6.2).
In addition the specification includes purity criteria on Loss on drying, Spectrophotometry, Carbohydrates, Sulphated ash, Aluminium, Lead and Microbiological impurities.

Exposure: As sweetener thaumatin is only permitted in confectionery 50 mg/kg and in vitamin and dietary preparations 400 mg/kg. As a flavour enhancer thaumatin is permitted to only chewing gum 10 mg/kg, desserts 5 mg/kg and non-alcoholic beverages 0.5 mg/l. The potential exposure will thus be very low.

SCF/JECFA evaluation:
SCF status:
1984: Temporarily acceptable. The Committee requested the data be provided within 3 years on a number of questions raised concerning possible receptor binding and possible endocrine activity of the sweetener [3].
1988: The requested data were submitted and the sweetener was found “acceptable”. No formal ADI was allocated [4].

**JECFA status:**
1983: No ADI established [5].
1985: ADI not specified [6]. A monograph was prepared [7].

**Background data:**

**Subacute/subchronic toxicity:** 90-day study in CD rats [7]. Four groups of CD rats, each of 10 male and 10 female, were fed either a basal diet with 8% casein w/w (control) or a basal diet with 1.0, 4.0 or 8.0% w/w thaumatin for 13 weeks. The body weight gains of males fed 4.0 or 8.0% thaumatin were 6% and 9% lower than those of casein-fed controls. Body weight gain of females fed thaumatin was not affected by treatment. Feed consumption of both sexes fed 4.0 or 8.0% thaumatin was 5-11% lower than that in the controls. Haemoglobin content of females fed 8.0% thaumatin was statistically significantly decreased, although the values were within the range normally found for animals of comparable age and weight. The absolute and relative weights of liver of both sexes in high-dose group were statistically significantly increased compared with those in the control. No other abnormalities were reported.

90-day study in CD rats [7]. Four groups of CD rats, each of 20 male and 20 female, were fed either 0, 0.3, 1.0 or 3.0% w/w of thaumatin in the diet. Body weight and feed consumption were recorded weekly. Additionally, the liver, kidneys, heart, lungs, spleen, and brain from all animals from low- or mid-dose were examined microscopically. Body weight of males from the high-dose group was 6% higher than that in the control. Body weight of females form the mid-dose group was 6% lower than that in the control. Feed intake of females from the high dose group was 7% lower than that in the control. In week 12, the haematocrits of males fed 1.0 and 3.0% thaumatin were 8 and 13% increased while in females fed 0.3 and 1.0% thaumatin a significant reduction of 10 and 12% was recorded respectively. No treatment-related changes were seen by macroscopy in any group. For treated females an increase of 8% in absolute and of 13% in the relative kidney weights was recorded. Absolute and relative thyroid weights of all treated males were significantly increased and of all treated females were significantly decreased compared with the respective sex controls. No treatment-related changes were seen in the tissue sections taken from the control and 3.0% groups, which were examined microscopically. No treatment-related changes were seen by microscopy in the thyroid tissue sections from all treatment groups.

90-day study in dogs [7]. Four groups of beagle dogs, each of 4 male and 4 female, were fed either 0, 0.3, 1.0 or 3.0% w/w of thaumatin in the diet for a minimum 90 days. Body weight was recorded weekly and feed consumption daily. After termination following organs were weighed: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate, spleen, testes, thyroid and uterus. The survival was 100%. Males fed thaumatin had slightly increased body weight. Feed and water consumption of both sexes were unaffected by treatment. Males from 3% group had slightly decreased haemoglobin concentration, erythrocyte count and haematocrit. The absolute relative liver weight of males from 3% group was 20% increased, but no increase was recorded in the relative liver weight. Microscopic examination revealed no changes that authors considered to be related to thaumatin treatment.

**Genotoxicity:** *In vitro.* Ames test: no mutagenicity reported [7].

*In vivo.* Dominant-lethal assay in CD1 mice: thaumatin did not induce dominant-lethal mutations in the gametes of male mice under the conditions of the study [7].
Chronic toxicity/Carcinogenicity: No information available.

Reproduction toxicity: No multigeneration study available.
Special study on teratogenicity in CD rats [7]. Four groups of pregnant CD rats, each of 20 animals, received by gavage either 0, 0.2, 0.6 or 2.0 g/kg bw thaumatin from day 6 to day 15 of gestation. No adverse effects were observed in the pregnant females or on litter responses. No visceral or skeletal abnormalities in the foetuses attributable to the treatment were observed.

Allergy/Intolerance: The following studies are summarized in the JECFA monograph [7]:
1. Special studies on allergenicity (in vitro and in vivo animal studies).
   a) In vitro studies on the ability of thaumatin to initiate histamine release non-immunologically
   b) Studies on ileum preparations from guinea-pigs).
   c) Studies in rats.
   d) Studies in baboons and rhesus monkeys. Examination of sera for antibodies to thaumatin by the passive subcutaneous anaphylaxis technique in baboons and rhesus monkeys showed no reactions when challenged sc or orally with thaumatin.
2. Studies in humans.
   a) Assessment of oral allergenicity in humans. Thaumatin was assessed for oral allergenicity in human volunteers (4 women, 6 men) given 100 mg/day thaumatin or lactose in gelatine capsules for a period of 14 days using a double-blind cross-over design. All volunteers were prick-tested for common allergens and with a solution of thaumatin before the study. Seven volunteers were tested with thaumatin a second time before the study commenced to determine if sensitisation to thaumatin could result from prick-testing itself. No sensitisation was observed. No sensitisation was detected by the prick-test at the completion of the study.
   b) Assessment of oral sensitivity and irritation. Thaumatin was assessed for oral sensitivity and irritation in humans. Twenty-five volunteers received thaumatin in chewing gum containing 150 ppm of the sweetener. The volunteers chewed five 5.3 g gum stick per day, each stick for 15 minutes, during 28 days. Another group of 25 volunteers received in treated gum and served as a control. The prick-test of all volunteers before and after the completion of the study was negative, nor were any visible signs of irritant or allergic responses detected on the oral mucosa after chewing either treated or untreated gum.
   c) Prick-testing. Prick-testing of laboratory personnel who had inhaled thaumatin intermittently for periods up to 7 years showed that about one-half (67/140) responded to common inhalant allergens. A positive response to thaumatin was observed in 13 subjects, all except one of whom were atopic or allergic.

Effect in humans:
   a) Allergy: See above.
   b) Assessment of the effect on haematological and blood biochemistry parameters [7]. Eighteen male and 12 female volunteers were randomly assigned into two groups and received either 280 mg thaumatin or 210 mg albumin in capsules, 1 capsule per day, during 13 consecutive weeks. Blood samples were collected prior to and after 4, 8 and 12 weeks of treatment. No treatment-related changes in either chemical or cellular composition of the blood were observed. The cumulative intake of 25 mg per volunteer was considered by the authors of the study to be 140 times the estimated maximum consumer intake of thaumatin over this period.
**Other:** Study on hypo/hyperthyroid effects in CD rats [7]. Two groups (10 male & 10 female each) were fed 3% thaumatin or 3% e.g. albumin in the diet for 4 weeks. There was no statistically significant difference between the groups in thyroid hormone levels determined in blood samples taken at the end of experimental feeding. The authors concluded that thaumatin had no effect on thyroid function in rats at dietary levels of 3%.

**Conclusion:** The safety evaluation is based on the results of several studies, except for carcinogenicity and multigeneration studies, which were not conducted. On the other hand the available toxicological data and the history of use of the fruit, which is the natural source of the sweetener by African population, demonstrate the safety of the sweeteners. Taking into account the low estimated intake of the compound due to its strong sweetness the request of carcinogenicity and multigeneration studies seems not necessary.

**References:**


**NEOHESPERIDINE DIHYDROCHALCONE**

**E Number:** E 959

**Recommendation:** There is nothing in the existing data to suggest undesirable side effects from the limited use of this additive, but because of incomplete data and the publication of a new study since the SCF evaluation, it is proposed to update the evaluation.

**Chemical name/synonyms:** 2-O-α-L-rhamnopyranosyl-4’-β-d-glycopyranosyl-hesperetin dihydrochalcon/ NHDC, hesperetin, dihydrochalcon-4’-β-neohesperidosid, neohesperidin DC.

**Chemical formula:** C_{28}H_{36}O_{15}

**EINECS number:** 243-978-6

**CAS Number:** 20702-77-6

**Functional Class:** Sweetener, flavour enhancer.

**Specification:**

**Definition:** Neohesperidine dihydrochalcone is an intense sweetener about 1000 – 1800 times as sweet as sucrose. It is freely soluble in hot water, very slightly soluble in cold water and practically insoluble in ether and in benzene.

**Manufacture:** Neohesperidine dihydrochalcone is obtained by catalytic hydrogenation of neohesperidine.

**EC specifications:** E 959 Neohesperidine dihydrochalcone [1].

Assay: Not less than 96% of neohesperidine dihydrochalcone on the dried basis.

In addition the specification includes purity criteria on Loss on drying, Sulphated ash, Arsenic, Lead and Heavy metals.

**JECFA specifications:** No JECFA specification has been prepared.

**Exposure:** Neohesperidine dihydrochalcone is permitted as a sweetener in a variety of foods up to 30 mg/l in non-alcoholic beverages and between 50 and 150 mg/kg in most of the solid foods and somewhat higher in a few commodities less important from an exposure point of view. As a flavour enhancer it is permitted with 5 mg/kg in e.g. meat products and 150 mg/kg in chewing gum. For a person of 60 kg it will thus take 10 l soft drink with 30 mg/l and 2 kg of confectionary with 150 mg/kg to reach the ADI of 5 mg/kg bw. Exceeding the ADI with the permitted levels is therefore not possible.

In the EU monitoring the calculated intake for young children in tier 1 suggested the possibility of exceeding the ADI. Examination at tier 2 of the intake by young children was reported in the range of 1 – 18%. It was concluded that no further examination is needed.
**SCF/JECFA evaluation:**

**SCF status:**
1984: SCF concluded “not toxicologically acceptable” due to lack of data [2]. The SCF did not include the data from a long-term feeding study in rat carried by USDA up to 1978 while evaluating NHDC because the quality of the data was unsatisfactory. In the case of the USDA two year study in dog, which was by authors considered as preliminary, the SCF used its results to estimate the no-effect level for NDHC at 1000 mg/kg bw.

1988: An ADI of 5 mg/kg bw was allocated based on the lowest no-effect level of 500 mg/kg bw/day in all studies which were carried out in the rat [3].

**JECFA status:** Not evaluated.

**Background data:**

**Subacute/subchronic toxicity:** A 90 day study in rat indicates that high doses of NHDC result in slight depression accompanied by transient reduction in food intake, the NOEL was 750 mg/kg bw/day [4]. Other data were evaluated by SCF but no details were given [2].

**Genotoxicity:** Neohesperidine DC was not mutagenic in *in vitro* and *in vivo* tests [2].

**Chronic toxicity/Carcinogenicity:** Chronic toxicity was studied in rat and dog but according to SCF neither of the studies in the two species established a clear NOAEL, but SCF did not specify any details [2].

**Reproduction toxicity:** The data from a multigeneration study and teratogenicity study were evaluated by SCF [2]. No compound related adverse effects were reported, but SCF did not specify any details.

**Other:** Studies on metabolism were evaluated by SCF [2].

**Conclusion:** No report on carcinogenicity was available during the safety evaluation of the compound by SCF, but the result on metabolism, mutagenicity, acute toxicity, subchronic toxicity, reproduction and chronic toxicity were considered sufficient by SCF for acceptance of the compound as a food additive. Although the existing data do not suggest any undesirable side effects from the limited use of this substance it is suggested to update the evaluation to specify better the basis for the ADI and to include new data.

**References:**


MALTITOL AND MALTITOL SYRUP

E Number: E 965

Recommendation: No need for a toxicological re-evaluation. However a monitoring of actual uses and exposure is recommended.

Chemical name/synonyms:
Maltitol: D-maltitol/ hydrogenated maltose.
Maltitol syrup: Hydrogenated high-maltose-glucose syrup, hydrogenated glucose syrup, HGS, Lycasin.

Chemical formula: Maltitol: C\(_{12}\)H\(_{24}\)O\(_{11}\)

EINECS number:
Maltitol: 209-567-0
Maltitol syrup: 270-337-8

CAS Number: Maltitol: 585-88-6

Functional Class: Sweetener.

Specification:
Definition: Maltitol and maltitol syrup are polyols. They are bulk sweeteners having about the same sweetness as sucrose. Maltitol may contain very small amounts of other polyols, while maltitol syrup contains significant amounts of other polyols, ranging from sorbitol to hydrogenated polysaccharides containing more than three glucose or glucitol units. Maltitol and maltitol syrup are very soluble in water and slightly soluble in ethanol.

Manufacture: Maltitol and maltitol syrup are manufactured by catalytic hydrogenation of high-maltose-glucose syrup. Maltitol is isolated by crystallisation.

EC specifications:
Maltitol: E 965 (i) [1].
Assay: Not less than 98.0% of maltitol on the dried basis.
Nickel: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Water, Sulphated ash, Reducing sugars, Chlorides, Sulphates, Arsenic, Lead and Heavy metals.

Maltitol syrup: E 965 (ii) [2].
Assay: Not less than 99% of total hydrogenated saccharides on the anhydrous basis and not less than 50% of maltitol on the anhydrous basis.
Nickel: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Water, Sulphated ash, Reducing sugars, Chlorides, Sulphates and Lead.
**JECFA specifications:**

**Maltitol: Maltitol [3].**  
Assay: Not less than 98.0% of maltitol.  
Nickel: Not more than 2 mg/kg.  
In addition the specification includes purity criteria on Water, Specific rotation, Sulfated ash, Reducing sugars, Chlorides, Sulfates, Lead and Heavy metals.

**Maltitol syrup: Maltitol syrup [4].**  
Assay: Not less than 99.0% of total hydrogenated saccharides on the anhydrous basis and not less than 50.0% of maltitol on the anhydrous basis.  
Nickel: Not more than 2 mg/kg.  
In addition the specification includes purity criteria on Water, Sulfated ash, Reducing sugars, Chlorides, Sulfates and Lead.

**Exposure:** Maltitol and maltitol syrup are permitted as sweeteners in a variety of foods not including beverages. No upper limit is specified. For other purposes than sweetening maltitol and maltitol syrup are permitted *quantum satis* in all foods where additives may be used except beverages other than liqueurs.  
As no upper limits of use has been specified an exposure estimate is not possible and maltitol and maltitol syrup were not included in the EU monitoring system (tier 0). As maltitol and maltitol syrup, as other bulk sweeteners, have the sweetening effect close to that of sugar it could, in principle, replace all sugar in solid foods (it is not permitted in beverages). Assuming an average intake of sugar of 60 g/day and a high intake of 180 g/day and that half of this could be from solid foods a potential intake of 30 g/day (average) and 90 g/day (high) can be calculated. As this theoretically calculated exposure exceeds the laxative threshold as defined by SCF a monitoring of actual exposure is desirable. Also non-sweetener use of this and the other sugar alcohols should be taken into account.

**SCF/JECFA evaluation:**

**SCF status:**  
1984: The Committee considered the continued use of maltitol and maltitol-based products acceptable provided limitations due to its laxative action were kept in mind. The committee noted that consumption in the order of 20 g/person/day of this and other polyols alone or in combination is unlikely to cause undesirable laxative symptoms [5].

1999: Evaluation of maltitol with new specifications [6].

**JECFA status:**  
1980: The available information was found inadequate for an evaluation [7].

1983: A temporary ADI of 0-25 mg/kg bw was allocated for hydrogenated glucose syrup, with maltitol as a main component of 50-90% of the product. Furthermore JECFA requested that data of a lifetime feeding study should be made available [8].

1985: ADI changed to “not specified”. The previously requested lifetime feeding study was found unnecessary [9]. A toxicological monograph was prepared [10].

1988: The name hydrogenated glucose syrup was changed to maltitol syrup and the ADI “not specified” was confirmed and extended also to cover maltitol as such [11].
1993: Review of a long-term carcinogenicity study in rats. The ADI “not specified” was confirmed [12]. An addendum to the toxicological monograph was prepared [13].

1999: ADI not specified was confirmed and it was concluded that this ADI could be applied to maltitol syrup with the revised specification [14]. An addendum to the toxicological monograph was prepared [15].

**Background data:**

**Subacute/subchronic toxicity:** In a 3-month feeding study in rats (dietary levels of 1, 15, or 20% HGS or 20% sucrose; 10 male and 10 females per group) no effects of toxicological importance were recorded [10].

In a 90-day feeding study in rats (dietary levels of 20% HGS or 20% sorbitol; 20 males and 20 females per group) no effects of toxicological importance were recorded [10].

In a 90-day feeding study in rats (dietary levels of 0, 2, 5 or 15% Lycasin 65/63 [mixture of 10.5% D-sorbitol, 7.5% maltitol, 25% tri-to hexasaccharide alcohols and 57% higher-than-hexasaccharide alcohols]; 15 males and 15 females per group) no effects of toxicological importance were recorded. The NOEL was the highest dose tested, 15% of the diet equal to 15 g/kg/day in males and 18g/kg/day in females [15].

In a 13-week feeding study in rats (dietary levels of 0, 1.25, 2.5 or 5% hydrogenated dextrin; 15 males and 15 females per group) the data suggested that that hydrogenated dextrin was not toxic up to the highest dose tested 5% (equal to 4.0 g/kg bw/day in males and 5,2 g/kg bw/day in females) [15].

In a 13-week feeding study in Beagle dogs (daily doses of 4.95g/kg; 4 males and 4 females) no effects of toxicological importance were recorded but the animals had diarrhoea [10].

In a 90-day feeding study in Beagle dogs (dietary levels of 0, 2, 5 or 15% Lycasin 65/63 [mixture of 10.5% D-sorbitol, 7.5% maltitol, 25% tri-to hexasaccharide alcohols and 57% higher-than-hexasaccharide alcohols]; 4males and 4 females per group) the data suggested that the test compound was not toxic up to the highest dose tested 15% (equal to 43 g/kg bw/day) [12].

**Genotoxicity:** The results from in vitro assays, with and without metabolic activation indicate that maltitol has no mutagenic, clastogenic, genotoxic or neoplastic transformation effect. In vivo no clastogenic effect was observed [10]. Hydrogenated dextrin (a compound which is a source for hydrogenated polysaccharides present in maltitol syrup) was not mutagenic in either S. typhimurium or E.Coli in the absence or presence of rat S9 activation [15].

**Chronic toxicity/Carcinogenicity:** In a 31-week feeding study in wealing Wistar-derived male rats (dietary levels of 0, 5, 10, 20 or 30% of maltitol or sucrose, or 20% HGS; 4 males per dose group) the body weights and selected organ weights of groups fed 5 to 30% maltitol were similar to those from rats fed 5 to 30% sucrose [10].

In a feeding study up to 13 months in Wistar rats with HGS (dietary levels of 0, 1, 3 or 10%; 10 animals/sex/group) no effects of toxicological significance were recorded. At interim sacrifices after 3 and 6 months some of treated animals hag slight oedema of colonic mucosa. Furthermore, a dilatation of the stomach was observed in about half of the treated rats sacrificed after 6 months [10].
In a 78-week feeding study with HGS in Wistar rats (dietary levels of 0, 3, or 10%; 26 males and 26 females per group, interim sacrifice at week 52, 3 males and 4 females per group) an increased incidence of neoplasms of adrenal glands was recorded in the highest dose females and of the thyroid gland in the highest dose males. Tumours of the skin and mammary region were not compound-related [10].

In a 24-month study in Sprague-Dawley rats (50 males and 50 females per group) receiving 0 or 18% (v/v) HGS in drinking water (equal to 13.9 g/kg/day in males and 21.5 g/kg bw/day in females) no treatment related tumours were recorded [10].

**Reproduction toxicity:** In a multigeneration study in rats receiving 0 or 18% (dry weight/volume) HGS in drinking water (initial number of animals in each generation of 10 males and 10 females per group; 3 successive generations, each comprising 2 consecutive litters) the treatment with the test compound did not affect the general condition, fertility or reproduction. Sex ratios of treated litters exhibited an approximate 10% decrease in the number of female pups [10].

In a gavage study in rats (dietary levels of 0, 3000, 5000 or 7000 mg/kg/day; 30 pregnant females, treatment from day 6 to day 15 of gestation) HGS was non-toxic to pregnant females and did not induce any teratogenic or embryo/foetotoxic effects [10].

**Effect in humans:** Several studies in healthy and diabetic subjects were performed in order to investigate the effect of maltitol on blood glucose, excretion, haematological and biochemical parameters and tolerance to possible laxative effect of the compound. The results demonstrated no unfavourable side effects of the compound. The laxative effect was recorded at intake of 30-50 g/day [10].

**Other:** Absorption, distribution, biotransformation and excretion of the compound was investigated in several animal species [10].

**Conclusion:** The safety of maltitol is well documented. However, a laxative effect in man after ingestion of high amounts of this compound should be taken into account when considering its appropriate levels of use alone or in combination with other sugar alcohols.

**References:**


7. [1980, TRS 653-JECFA 24]

8. [1983, TRS 696-JECFA 27]

9. [1985, TRS 733-JECFA 29]

10. [1985, FAS 20-JECFA 29]

11. [1988, TRS 776-JECFA 33]

12. [1993, TRS 837-JECFA 41]

13. [1993, FAS 32-JECFA 41]

14. [1997, TRS 884-JECFA 49]

15. [1997, FAS 40-JECFA 49]
LACTITOL

**E Number:** E 966

**Recommendation:** No need for a toxicological re-evaluation. However a monitoring of actual uses and exposure is recommended.

**Chemical name/synonyms:** 4-O-β-D-galactopyranosyl-D-glucitol/ lactositol, lactit, lactobiosit.

**Chemical formula:** C_{12}H_{24}O_{11}

**EINECS number:** 209-566-5

**CAS Number:** 585-86-4

**Functional Class:** Sweetener (bulk sweetener).

**Specification:**
- **Definition:** Lactitol is a polyol. It is a bulk sweetener about half as sweet as sucrose. It may contain minor amounts of other polyols. It is very soluble in water.

- **Manufacture:** Lactitol is obtained by catalytic hydrogenation (nickel) of lactose.

**EC specifications:** E 966 Lactitol [1].
- Assay: Not less than 95% of lactitol on the anhydrous basis.
- Other polyols: Not more than 2.5% on the anhydrous basis.
- Nickel: Not more than 2 mg/kg on the anhydrous basis.
- In addition the specification includes purity criteria on Water, Reducing sugars, Chlorides, Sulphates, Sulphated ash, Arsenic, Lead and Heavy metals.

**JECFA specifications:** Lactitol [2].
- Assay: Not less than 95.0% of lactitol on the anhydrous basis.
- Other polyols: Not more than 2.5% on the anhydrous basis.
- Nickel: Not more than 2 mg/kg on the anhydrous basis.
- In addition the specification includes purity criteria on Water, Reducing sugars, Chlorides, Sulfates, Sulfated ash, Arsenic, Lead and Heavy metals.

**Exposure:** Lactitol is permitted as a sweetener in a variety of foods not including beverages. No upper limit is specified. For other purposes than sweetening lactitol is permitted *quantum satis* in all foods where additives may be used except beverages other than liqueurs. As no upper limits of use have been specified an exposure estimate is not possible and lactitol was not included in the EU monitoring system (tier 0). As lactitol, as other bulk sweeteners, has the sweetening effect less than that of sugar it could, in principle, replace all sugar in solid foods (it is not permitted in beverages). Assuming an average intake of sugar of 60 g/day and a high intake of 180 g/day and that half of this could be from solid foods a potential intake of 30 g/day (average) and 90 g/day (high) can be calculated. As this theoretically calculated exposure exceeds the laxative threshold as defined by SCF a monitoring of actual exposure is desirable. Also non-sweetener use of this and the other sugar alcohols should be taken into account.
**SCF/JECFA evaluation:**

**SCF status:**
1984: The Committee considered the continued use of lactitol acceptable provided limitations due to its laxative action were kept in mind. The committee noted that consumption in the order of 20 g/person/day of this and other polyols alone or in combination is unlikely to cause undesirable laxative symptoms [3].

In 1988 the Committee considered new data on metabolism and gastric effects, but maintained the original evaluation from 1984 concerning laxative effects [4].

**JECFA status:** Evaluated in 1983 when an ADI not specified was allocated [5]. A toxicological monograph was prepared [6].

**Background data:**

**Subacute/subchronic toxicity:** A 13-week feeding study in rats (dietary levels of 0, 5, 10 or 20% lactitol or 25% lactose, 10 males and 10 females per group) and a 26-week feeding study in dogs (dietary levels of 0, 5, 10 and 15% lactitol or 15% lactose, 6 males or 6 females per group) reviewed in [6] did not reveal any pathological changes that could be attributed to the feeding of lactitol. The no-effect level in the dog study was 5% lactitol as diarrhoea was observed at dietary levels of 10 and 15%.

**Genotoxicity:** Lactitol was not mutagenic in microbial systems with or without metabolic activation [6].

**Chronic toxicity/Carcinogenicity:** A 52-week feeding study in rats (dietary levels of 0, 2, 5 and 10% lactitol or 20% lactose, 10 males and 10 females per group selected from the first litter of parent rats which had already been treated with lactitol or lactose 12 weeks before mating) did not reveal compound-related pathological changes [6].

A 2-year feeding study in mice (dietary levels of 0, 2, 5, and 10% lactitol and 20% lactose, 50 males and 50 females per group) did not show any important toxicological effects [6].

A 2-year feeding study in rats (dietary levels of 0, 2, 5, and 10% lactitol, 50 males and 50 females per group) did not show any important compound-related toxicological effects. The incidence of adrenal medullary pheochromocytomas in treated males was increased in a non-dose related manner [6].

**Reproduction toxicity:** Lactitol was not teratogenic in a study with 25 pregnant rats originating from the corresponding test diet groups of F1a young of the multigeneration study and fed until day 21 of pregnancy of 0, 2, 5, and 10% in the diet [6]. The multigeneration study revealed some embryotoxicity or foetotoxicity at 5 and 10% levels. Therefore the 2% level was taken as a level causing no toxicological effect [6].

**Allergy/Intolerance:** Skin sensitisation was investigated by a maximization test in young male guinea pigs. It was concluded that lactitol exhibited slight sensitisation properties [6].

**Effect in humans:** Diarrhoea in man occurred following ingestion of 50 g but not 24 g of lactitol [6].
Other: Absorption, distribution and excretion were studied in rats. The laxative effect was studied in animals and humans. The effect on dental plaque formation was studied in vitro [6].

Conclusion: The safety of lactitol is well documented. However, a laxative effect in man after ingestion of high amounts of this compound should be taken into account when considering its appropriate levels of use alone or in combination with other sugar alcohols.

References:


5. [1983, TRS 696-JECFA 27]

6. [1983, FAS 18-JECFA 27]
   Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 18, 1983.
XYLITOL

E Number: E 967

Recommendation: No need for a toxicological re-evaluation. However a monitoring of actual uses and exposure is recommended.

Chemical name/synonyms: D-xylitol.

Chemical formula: C₅H₁₂O₅

EINECS number: 201-788-0

CAS Number: 87-99-0

Functional Class: Sweetener.

Specification:
Definition: Xylitol is a polyol. It is a bulk sweetener having about the same sweetness as sucrose. It may contain minor amounts of other polyols. It is very soluble in water and sparingly soluble in ethanol.

Manufacture: Xylitol is manufactured by catalytic hydrogenation of xylan obtained from xylan-rich plant material by acid hydrolysis.

EC specifications: E 967 Xylitol [1].
Assay: Not less than 98.5% of xylitol on the dried basis.
Other polyols: Not more than 1% on the dried basis.
Nickel: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Loss on drying, reducing sugars, Chlorides, Sulphates, Arsenic, Lead and Heavy metals.

JECFA specifications: Xylitol [2]
Assay: Not less than 98.5% and not more than 101.0% of xylitol on the dried basis.
Other polyols: Not more than 1% on the dried basis.
Nickel: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Loss on drying, reducing sugars, Chlorides, Sulphates, Lead and Heavy metals.

Exposure: Xylitol is permitted as a sweetener in a variety of foods not including beverages. No upper limit is specified. For other purposes than sweetening xylitol is permitted quantum satis in all foods where additives may be used except beverages other than liqueurs.
As no upper limits of use have been specified an exposure estimate is not possible and xylitol was not included in the EU monitoring system (tier 0). As xylitol, as other bulk sweeteners, has the sweetening effect close to that of sugar it could, in principle, replace all sugar in solid foods (it is not permitted in beverages). Assuming an average intake of sugar of 60 g/day and a high intake of 180 g/day and that half of this could be from solid foods a potential intake of 30 g/day (average) and 90 g/day (high) can be calculated. As this theoretically calculated exposure exceeds the laxative
threshold as defined by SCF a monitoring of actual exposure is desirable. Also non-sweetener use of this and the other sugar alcohols should be taken into account.

**SCF/JECFA evaluation:**

**SCF status:**
1984: The Committee considered the continued use of xylitol acceptable provided limitations due to its laxative action were kept in mind. The committee noted that consumption in the order of 20 g/person/day of this and other polyols alone or in combination is unlikely to cause undesirable laxative symptoms [3].

**JECFA status:**
1977 and 1978: No ADI was established [4;5]. A toxicological monograph was prepared in 1978 [6].

1983: An ADI “not specified established [7]. A toxicological monograph was prepared [8].

**Background data:**

**Subacute/subchronic toxicity:** A rat feeding study (dietary levels of 0 or 20% xylitol, 70 animals per group, 2 xylitol fed groups, one was gradually adopted beginning with 5% in the diet to prevent diarrhoea) of the duration up to 150 days with interim sacrifices did not show any important compound-related toxicological effects [8].

**Genotoxicity:** Xylitol caused no observable mutagenic effects in any of the systems studied: Ames test, host-mediated assay in mouse, micronucleus test, chromosome analysis of cultured PHA-stimulated human lymphocytes [6].

**Chronic toxicity/Carcinogenicity:** In a long-term feeding study in mice (dietary levels of 0, 2, 10, and 20% xylitol or 20% sucrose, 100 males and 100 females per group, termination of groups when 20% of survival was reached) an increased incidence of treatment related tumours, metaplasias and neoplasias in the urinary bladder, and an increased incidence of liver masses (histologically being mainly adenomas and a small proportion with structure suggestive of carcinomas) were recorded in 10% and 20% male groups only when compared with controls [6].

In a long-term (104 weeks) feeding study in rats (dietary levels of 0, 2, 10, and 20% xylitol, 50 males and 50 females per group, all animals derived from parents exposed to the respective diets for 60 days prior mating) histological examination indicated no treatment related effects on the major organ systems. However, the incidence of both unilateral and bilateral hyperplasia of the adrenal medulla was significantly increased in males from 10 and 20% xylitol groups and in females from 5, 10 and 20% xylitol groups. Additionally a significant increase in phaeochromocytoma was found in the 20% xylitol male group [6].

In a long-term (104 weeks) feeding study in beagle dogs (dietary levels of 0, 2, 10, and 20% xylitol, 8 males and 8 females per group) the major finding were increased liver weight, histological changes in periportal hepatocytes and increased levels of SPGT in 20% xylitol groups [4]. These changes, however, were considered of no statistical significance after the statistical re-evaluation of this study was carried out [8].

**Reproduction toxicity:** In a three-generation study in rats (dose levels 0, 2, 5, 10 and 20% xylitol, 20 males and 20 females per group) the lower values for total and viable litter size were recorded but no indication of teratogenic effect of the compound. Statistically significant lower absolute
thyroid weights were noted with 20% xylitol. Microscopic examination of tissues from 10 and 20% xylitol groups did not show any changes attributable to xylitol [6].

In a three-generation study in mice (dose levels 0 or 20% xylitol, initial size of the groups of three males and 12 females each) no abnormalities or differences attributable to xylitol were recorded. However, the body weights of xylitol-treated animals at birth were decreased as compared with controls, significantly lower weight gains were observed in the Fo litters of xylitol fed animals, and the caecum size was slightly increased in xylitol treated mice [8].

In a teratogenicity study in rats (dose levels of 2, 5, 10, 20% xylitol, or 20% rice starch, or 20% sucrose, 31-33 females per dose group, males kept on laboratory diets only) no clinical signs of toxicity were noted. The malformations or skeletal variations found in test groups receiving xylitol were not attributed to treatment [6].

**Effect in humans:** In a study on 9 subjects consuming xylitol for 4.8 and 5.3 years (dose levels ranging from 0.05 to 2.5 g/kg bw/day) no significant changes were recorded in any of the serum or urinary parameters measured [8].

A laxative effect of xylitol was recorded in children at 65 g/day [8].

**Other:** Oxalate formation in mice, rats and humans [8].

The special studies on the occurrence of adrenal medullary hyper- and neoplasia in rats were undertaken to elucidate the relevance of these findings (recorded at 5, 10 and 20% xylitol in the diet) to humans [8]. It was demonstrated that the normal diagnostic criteria used in human pathology are not applicable to the diagnosis of pheochromocytomas in the rat. According to JECFA [8] the toxicological significance of these findings could not be assessed.

**Conclusion:** The safety of xylitol is well documented. However, a laxative effect in man after ingestion of high amounts of this compound should be taken into account when considering its appropriate levels of use alone or in combination with other sugar alcohols.

**References:**


4. [1977, *TRS 617-JECFA 21*]

5. [1978, *TRS 631-JECFA 22*]
   Evaluation of certain food additives and contaminants (Twenty-second report of the Joint

6. [1978, FAS 13-JECFA 22]

7. [1983, TRS 696-JECFA 27]

8. [1983, FAS 18-JECFA 27]
Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 18, 1983.
**QUILLAIA EXTRACT**

**E number:** E 999

**Recommendation:** The evaluations are old and the data incomplete. It is recommended, in first instance, to perform an exposure estimate, and if the product is used to a significant extent, a re-evaluation is recommended to ascertain whether supplementary data should be requested.

**Chemical name/synonyms:** Soapbark extract, quillay bark extract, panama bark extract, quillai extract, Murillo bark extract, China bark extract.

**Chemical formula:** -

**EINECS number:** -

**CAS number:** -

**Functional Class:** Foaming agent.

**Specification:**

**Manufacture:** Quillaia extract is obtained by aqueous extract of the inner bark of *Quillaia saponaria* Molina or other *Quillaia* species, trees of the family Rosaceae.

**Definition:** Quillaia extract contains a number of triterpenoid saponins consisting of glycosides of quillaia acid. Some sugars including glucose, galactose, arabinose, xylose and rhamnose are also present, along with tannin, calcium oxalate and other minor components.

**EC specifications:** E 999 Quillaia extract [5].

Assay: -
The specification includes purity criteria on Water, Arsenic, Lead and Mercury.

**JECFA specifications:** Quillaia extract [4].

Assay: -
The specification includes purity criteria on Water, pH, Ash, and Lead.

**Exposure:** Quillaia extract is permitted in soft drinks up to 200 mg/l. This means that the ADI for an adult is contained in 1.5 litre drink.

In the EU monitoring system quillaia extract was examined at tier 1 level. As the calculation suggested a possibility for exceeding the ADI for children, an examination at tier 2 level was performed. The calculated intake by young children is reported as 1-71 %. It was concluded that no further examination was needed at this stage.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation 1978: ADI = 5 mg/kg bw as spray-dried extract. Based on long term studies on an extract conforming to the specification of the British Pharmacopoea, but no details were given [2].
**JECFA status:** Latest evaluation 1985: ADI = 5 mg/kg bw based on the long-term studies mentioned below [1].

**Background data:**

**Subacute/subchronic toxicity:** 15 male and 15 female rats were given feeds containing up to 4% quillaia extracts for 13 weeks. In high doses decreased relative liver weight for male rats were observed and increased relative stomach weight. The NOEL was 0.6% of the diet equivalent to 400 mg/kg bw. [3].

**Genotoxicity:** No data available.

**Chronic toxicity/carcinogenicity:** 48 male and 48 female mice were given up to 1.5% quillaia extract in the fed for 84 week. There was a slightly lower body weight gain in the higher doses but no carcinogenic effect was seen. The NOEL was 0.5% or 700 mg/kg bw [3]. Groups of 48 male and 48 female rats were given up to 0.3, 1 or 3% quillaia extract for 108 weeks. Male rats of the highest dose had significantly decreased weight compared to the control and females at the lowest dose had significantly higher weight than the control animals during the first six months of the study. The lower body weights in the 3% male group was considered to be due to decreased feed intake. The incidence of thyroid adenoma was significantly increased in the female 1% group but it was not considered treatment related because the incidence did not increase with increased doses and there was no significant change when both sexes were included and compared with the control [3].

**Reproduction toxicity:** No data available.

**Conclusion:** There are insufficient data available for a full evaluation. However, none of the studies performed indicate severe toxicity.

**References:**

1. [1985, TRS 733-JECFA 29]


3. [1982, FAS 17-JECFA 26]


INVERTASE

E number: E 1103

Recommendation: A re-evaluation is not needed.

Chemical name/synonyms: β-D-Fructofuranoside fructohydrolase, EC 3.2.1.26.

Chemical formula: -

EINECS number: 232-615-7

CAS number: -

Functional Class: Enzyme.

Specification:

Manufacture: Invertase is produced from Saccharomyces cerevisiae.

Definition: Invertase is an enzyme preparation having β-D-Fructofuranoside fructohydrolase as the main active principle.

EC specifications: E 1103 Invertase [1].

Assay: -
The specification includes purity criteria on Arsenic, Lead, Mercury and Microbiological criteria.

JECFA specifications: No JECFA specification has been prepared. This substance is on the agenda for the 57th JECFA June 2001.

Exposure: Permitted q.s. Only requested for use in certain sweets.

SCF/JECFA evaluation:

SCF status: Latest evaluation 1996. Acceptable when derived from Saccharomyces cerevisiae and based on the fact that the source organism has a long history for safe food use [2].


Background data: Not necessary as the enzyme is derived from a food source (bakers yeast).

Conclusion: As invertase is derived from a normal food ingredient (Saccharomyces cerevisiae = bakers yeast) there is no need for toxicological testing or further evaluation.
References:


**LYSOZYME**

**E number:** E 1105

**Recommendation:** No need for a re-evaluation.

**Chemical name/synonyms:** Enzyme Commission (EC) No.: 3.2.1.17/ lysozyme hydrochloride, muramidase.

**Chemical formula:** -

**EINECS number:** 232-620-4

**CAS number:** 9066-59-5

**Functional Class:** Preservative.

**Specification:**

**Manufacture:** Lysozyme is obtained from hens' egg whites. It is usually obtained as the hydrochloride.

**Definition:** Lysozyme is a linear polypeptide consisting of 120 amino acids. It possesses enzymatic activity in its ability to hydrolyse the β(1-4) linkages between N-acetylmuramic acid and N-acetylglucosamine in the outer membranes of bacterial species, in particular gram-positive organisms. It is soluble in water.

**EC specifications:** E 1105 Lysozyme [4].
Assay: Not less than 950 mg/g on the anhydrous basis.
The specification includes purity criteria on Water, Residue on ignition, Nitrogen, Arsenic, Lead, Mercury, Heavy metals and Microbiological criteria.

**JECFA specifications:** Lysozyme hydrochloride [2].
Assay: Not less than 950 mg/g on the anhydrous basis.
The specification includes purity criteria on Water, Residue on ignition, Nitrogen, Chloride, Sodium, Arsenic, Heavy metals and Microbiological criteria.

**Exposure:** Ripened cheese q.s. Exposure from food additive use is much less than can be expected from natural sources.

**SCF/JECFA evaluation:**

**SCF status:** SCF accepted the use of lysozyme derived from egg white for cheese making at its 80th meeting held on 10 December 1991. In accordance with its guidelines for evaluating food enzymes, the Committee did not ask for toxicity data, as the enzyme is derived from normal food. The opinion is not published in the series of SCF reports and is thus only available from the minutes of the meeting.

**JECFA status:** Latest evaluation in 1992: The use as an anti-blowing agent in milk for cheese production results in less than 400 mg enzyme pr. kg finished cheese while the concentration in
egg-white is about 5 g pr. kg. As the enzyme is derived from food JECFA considers it a food by itself and finds it acceptable for use in accordance with good manufacturing practice [1].

**Background data:** No data available. Not necessary according to the general practise of the Committees when evaluating enzymes derived from food sources.

**Allergy/Intolerance:** As a protein Lysozyme has allergenic potential but JECFA consider its potency to be of moderate degree and considerably lower than other proteins such as albumen and ovalbumin [3]. Infants have been given egg-white lysozyme in the milk for 7 weeks. No antibodies were detected [3]. One study indicates that thirty-five percent of egg-allergic patients had antilysozyme IgE [6] another that 5 out of 34 sera from individuals known to be egg allergic antilysozyme IgE were detected [5]. Inhalation of lysozyme can induce IgE-mediated bronchoconstrictions in exposed workers but only one case is known [7]. Even a latex allergen has been identified as a lysozyme [8].

**Effect in humans:** Cancer patients have been treated with a daily intravenous administration of lysozyme without adverse effects [3].

**Other:** Lysozyme is used in human therapy for treatment of viral and bacterial infections. It is also used in the prophylaxis and therapy of leukopenia induced by antiblastic and ionising radiation [3].

**Conclusion:** Lysozyme is a normal constituent in eggs and the intake from food additive use is much less than the intake from egg. Also the allergic reactions produced by egg-white lysozyme have been shown to be less severe than those seen with other egg proteins [3]. Nevertheless the allergic potential should be borne in mind. Lysozyme as defined by the specifications is covered by the toxicological evaluation.

**References:**

1. [1992, TRS 828-JECFA 39]


3. [1992, FAS 30-JECFA 39]


**POLYDEXTROSE**

**E number:** E 1200

**Recommendation:** No re-evaluation of polydextrose is necessary.

**Chemical name/synonyms:** Modified polydextroses.

**Chemical formula:** -

**EINECS number:** -

**CAS number:** 68424-04-4

**Functional Class:** Bulking agent, humectant, stabiliser, thickener.

**Specification:**

**Manufacture:** Polydextrose is obtained by melting and condensation of approximately 90 parts D-glucose, 10 parts sorbitol and 1 part citric acid or 0.1 part phosphoric acid.

**Definition:** Polydextrose consists of randomly bonded glucose polymers with some sorbitol end groups and with citric acid or phosphoric acid residues attached to the polymers by mono- or diesterbonds. The 1,6-glucoside linkage predominates in the polymers but other linkages are present. The product contains small quantities of free glucose, sorbitol, laevoglucosan (1,6-anhydro-D-glucose) and citric acid and may be neutralised with any food grade base and/or decolourised and deionised for further purification. The products may also be partially hydrogenised with Raney nickel catalyst to reduce residual glucose. Polydextrose N is neutralised polydextrose.

**EC specifications:** E 1200 Polydextrose [6].

Assay: Not less than 90% of polymer on the ash free and anhydrous basis.
The specification includes purity criteria on Water, Sulphated ash, Nickel, 1,6-Anhydro-D-glucose, Glucose and sorbitol, Molecular weight limit, 5-Hydroxymethylfurfural and Lead.

**JECFA specifications:** Polydextroses [5].

Assay: Not less than 90.0% of polymer on the ash free and anhydrous basis.
The specification includes purity criteria on Water, pH, Sulfated ash, Nickel, 1,6-Anhydro-D-glucose, Glucose and sorbitol, Molecular weight limit, 5-Hydroxymethylfurfural and Lead.

**Exposure:** Permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substances were for that reason not included in the EU monitoring system (*Tier 0*).

**SCF/JECFA evaluation:**

**SCF status:** An “ADI not specified” was established in 1990 [4]. The evaluation was based on the submitted data, but no details were specified [4]. The Committee notes that the laxative effect of polydextrose should be taken into account while considering appropriate levels for use. A mean laxative threshold dose of 90 g/day or 50 g as a single dose is quoted.
**JECFA status:** An ADI “not specified” was allocated in 1987 [1]. The basis was lack of adverse toxicity in the available toxicity studies that include what would be normally required for an ADI to be set for a food additive.

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies in rats, dogs, and monkeys did not reveal any significant effects [2; 3].

**Genotoxicity:** Several studies *in vitro* and *in vivo* are available. No indication of a mutagenic potential [2].

**Chronic toxicity/Carcinogenicity:** Long-term studies are available in 3 species at levels up to 10% in the diet: No toxic effects were found [4;7;9-11].

Long-term studies in mouse, rat, and dog fed polydextrose revealed no adverse effects at the highest doses studied i.e. 10% in diet [2].

**Reproduction toxicity:** Reproduction and teratology studies available in rats (3 and 2 studies, respectively) demonstrated that dietary levels up to 20% had no effect on reproductive indices, the extent of malformations, or postnatal growth and development [2].

**Effect in humans:** Several studies are available. Polydextrose at very high doses exerts a laxative effect with a mean laxative threshold of 90 g/day or 50 g as a single dose [3;4].

**Other:** Biochemical aspects:
This additive is poorly absorbed. A fraction is metabolised by the gut flora primarily to carbon dioxide and volatile fatty acids [4].

Several biochemical studies are available in man, rats, and dog. In conclusion, the metabolism of polydextroses is comparable in animals and man. Polydextroses are poorly absorbed and are metabolised by the gut flora to CO2 and volatile fatty acids [3].

**Energy value:**
The SCF concluded that the data available were indicative of an energy value in the range of 1-1.5 kcal/g but the data did not allow a precise value to be determined at the time of the evaluation [4]. At its 90th meeting in September 1993 the Committee preliminary endorsed a caloric value of 1.5 kcal/g.

Studies are available on the energy value of polydextrose in man and rat [7;9-11]. A review on the caloric value of polydextrose is published.

**Absorption of food constituents:**
One study indicates the retardant effect of polydextrose on the transport of triolein and cholesterol into the mesenteric lymph of rats [12]. Another study indicates that polydextrose selectively affected the metabolism of HDL and its major proteins, apo A-I and A-II [13].

**Conclusion:** The toxicological data available include what normally would be required for an ADI to be set for a food additive. Due to conflicting results, there has been a long debate about the energy value of polydextrose. In 1993 at its 90th meeting SCF concluded that the data available
were indicative of an energy value of 1-1.5 kcal/g but that the data did not allow a precise value to be determined.

Polydextrose as defined by the specifications is covered by the toxicological evaluation.

References:


POLYVINYLPYRROLIDONE AND POLYVINYLPOLYPYRROLIDONE

E number:
Polyvinylpyrrolidone: E 1201
Polyvinylpolypyrrolidone: E 1202

Recommendation: No need for a re-evaluation. However, the specification should reflect the opinion of SCF that residual monomer should not exceed 10 mg/kg additive.

Chemical name/synonyms:
Polyvinylpyrrolidone: Poly-[1-(oxo-1-pyrrolidinyl)-ethylene]/ povidone, PVP.
Polyvinylpolypyrrolidone: Poly-[1-(oxo-1-pyrrolidinyl)-ethylene]/ crosspovidone, cross linked polyvidone, insoluble polyvinylpyrrolidone, PVPP.

Chemical formula:
Polyvinylpyrrolidone: \((C_6H_9NO)_n\)
Polyvinylpolypyrrolidone: \((C_6H_9NO)_n\)

EINECS number:
Polyvinylpyrrolidone: 201-800-4
Polyvinylpolypyrrolidone: 201-800-4

CAS number:
Polyvinylpyrrolidone: 9003-39-8
Polyvinylpolypyrrolidone: -

Functional Class: Carrier for sweeteners, tableting adjunct. PVPP is also used as a clarifying agent in the production of wine and beer.

Specification:
Polyvinylpyrrolidone
Manufacture: No information on manufacturing processes for food grade polyvinylpyrrolidone.

Definition: Polyvinylpyrrolidone is a polymer of 1-(2-oxo-1-pyrrolidinyl)-ethylene (N-vinyl-2-pyrrolidone). It is soluble in water and in ethanol.

EC specifications: An EC specification is currently in preparation.

JECFA specifications: Polyvinylpyrrolidone [1].
Assay: Not less than 12.2% and not more than 13.0% of nitrogen on the anhydrous basis.
Monomer content: Not more than 1% (as vinylpyrrolidone).
Hydrazine: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Relative viscosity, Water, Total ash, Aldehyde, Arsenic and Heavy metals.

Polyvinylpolypyrrolidone
Manufacture: Polyvinylpolypyrrolidone is produced by the polymerization of N-vinyl-2-pyrrolidone in the presence of either caustic catalyst or N,N'-divinyl-imidazolidone.
Definition: Polyvinylpolypyrrolidone is a poly-1-(2-oxo-1-pyrrolidinyl)-ethylene, cross linked in a random fashion. It is soluble in water and in ethanol.

EC specifications: An EC specification is currently in preparation.

JECFA specifications: Insoluble polyvinylpyrrolidone [2].
Assay: Not less than 11.0% and not more than 12.8% of nitrogen on the anhydrous basis.
Free N-vinyl-pyrrolidone: Not more than 0.1%.
Free N,N'-divinyl imidazolidone: Not more than 2 mg/kg.
In addition the specification includes purity criteria on Water, pH, Sulfated ash, Water-soluble matter, Arsenic, Zinc and Heavy metals.

Exposure: Permitted only in dietary supplements in tablet and coated tablet form, q.s and as a carrier for sweeteners.

SCF/JECFA evaluation:
SCF status: The substances were evaluated in 1990 and found acceptable for the proposed uses as tableting adjuncts and processing aid, but no ADI was allocated [3]. The acceptance was based on the JECFA evaluation. In May 2001 SCF has issued an opinion on the residue levels of the monomer N-vinyl-2-pyrrolidone and recommended that it shall not exceed 10 mg/kg substance (http://europa.eu.int/comm/food/fs/sc/scf/out87_en.pdf).


Subacute/subchronic toxicity: No adverse effects were seen when rats were given doses of PVPP up to 10% of the fed for 4 weeks or dogs were given up to 5050 mg/kg bw/day [6]. Several short-term studies with PVP in rat, cat and dog show no toxic effects [7].

Genotoxicity: In vitro mutagenicity test performed on mice cells demonstrated that PVP is not mutagenic in concentrations of 0.5%, 1.0%, 5% and 10% in the media [7]. No information on PVPP.

Chronic toxicity/carcinogenicity: Groups of 50 male and 50 female rats were given PVP in doses of 0%, 1% and 10% of the food without adverse effects [8]. Other studies in mice, rabbits and dogs confirm this [7;8].

Reproduction toxicity: No adverse effects were seen on the pups when pregnant rats were given a suspension of PVPP in carboxy methyl cellulose up to 3000 mg/kg bw. [6]. Studies in rabbit where 500 µg PVP were injected show no teratogenic effects [8].

Other: The absorption of PVP from the intestine is very limited. In a single dose study in rat with radiolabelled PVP 98.4% of the administrated dose was recovered in the faeces after 48 hours. After 6 hours approximately 0.04% were detected in the urine [8]. Similar studies with PVPP show an almost complete lack of absorption of orally administrated PVPP [6].

Conclusion: The absorption of PVP is very limited and the toxicological data do not indicate adverse effects. PVPP is hardly absorbed at all and no effects are seen in toxicological testing. Besides exposure is very limited. However, there has been some concern about the residue level of the monomer N-vinyl-2-pyrrolidone in PVP and PVPP. SCF has in 2001 issued an opinion
recommending that the residue monomer level shall not exceed 10 mg/kg additive. If this is included in the specifications there is no reason for concern about these food additives.

References:


MODIFIED STARCHES

E number:
Oxidised starch: E 1404
Monostarch phosphate: E 1410
Distarch phosphate: E 1412
Phosphated distarch phosphate: E 1413
Acetylated distarch phosphate: E 1414
Acetylated starch: E 1420
Acetylated distarch apipate: E 1422
Hydroxypropyl starch: E 1440
Hydroxypropyl distarch phosphate: E 1442
Starch sodium octenyl succinate: E 1450
Acetylated oxidised starch: E 1451

Recommendation: A re-evaluation of the modified starches in general is not necessary. However the discrepancy between the advise of the SCF on residual propylene chlorohydrin and the specifications of E 1440 and E 1442 should be clarified. A monitoring of the present uses of these products in line with the request of SCF should also be considered.

Chemical name/synonyms:
Acetylated starch: Starch acetate.
Starch sodium octenyl succinate: SSOS.

Chemical formula: -

EINECS number: -

CAS number:
Acetylated starch: 9045-28-7
Acetylated distarch apipate: 68130-14-3
Hydroxy propyl starch: 9049-76-7
Hydroxy propyl distarch phosphate: 53124-00-8

Functional Class: Thickener, stabiliser, binder, emulsifier.

Specification:
Oxidised starch
Manufacture: Oxidised starch is obtained by treating food grade starches with sodium hypochlorite.

Definition: Oxidised starch consists of starches with a certain amount of carboxylic groups.

EC specifications: E 1404 Oxidised starch [1].
Assay: -
Carboxyl groups: Not more than 1.1%.
In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.
**JECFA specifications:** Modified starches - Oxidized starch [2].

**Assay:** -

**Carboxyl groups:** Not more than 1.1%.

In addition the specification includes purity criteria on Sulphur dioxide and Lead.

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**Monostarch phosphate**

**Manufacture:** Monostarch phosphate is obtained by esterification of food grade starches with ortho-phosphoric acid or sodium or potassium ortho-phosphate or sodium tripolyphosphate.

**Definition:** Monostarch phosphate consists of starches in which a partial substitution with phosphate groups in the 2-, 6- or 3-position of the anhydroglucose unit has taken place.

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**EC specifications:** E 1410 Monostarch phosphate [1].

**Assay:** -

**Residual phosphate:** Not more than 0.5% for wheat and potato starch.

Not more than 0.4% for other starches.

In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

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**JECFA specifications:** Modified starches – Monostarch phosphate [2].

**Assay:** -

**Residual phosphate:** Not more than 0.5% for wheat and potato starch.

Not more than 0.4% for other starches.

In addition the specification includes purity criteria on Sulphur dioxide and Lead.

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**Distarch phosphate**

**Manufacture:** Distarch phosphate is obtained by esterification of food grade starches with trimetaphosphate or phosphorous oxychloride.

**Definition:** Distarch phosphate consists of starches cross-linked with phosphate groups.

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**EC specifications:** E 1412 Distarch phosphate [1].

**Assay:** -

**Residual phosphate:** Not more than 0.5% for wheat and potato starch.

Not more than 0.4% for other starches.

In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

---

**JECFA specifications:** Modified starches - Distarch phosphate [2].

**Assay:** -

**Residual phosphate:** Not more than 0.5% for wheat and potato starch.

Not more than 0.4% for other starches.

In addition the specification includes purity criteria on Sulphur dioxide and Lead.

---

**Phosphated distarch phosphat**

**Manufacture:** Phosphated distarch phosphate is obtained from food grade starches by a combination of the processes described for E 1410 and E 1412.
**Definition:** Phosphated distarch phosphate consists of starches cross-linked with phosphate groups. In addition a partial substitution with phosphate groups in the 2-, 6- or 3-position of the anhydroglucose unit has taken place.

**EC specifications:** E 1413 Phosphated distarch phosphate [1].
- Assay: -
- Residual phosphate:  Not more than 0.5% for wheat and potato starch.
  - Not more than 0.4% for other starches.
In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

**JECFA specifications:** Modified starches - Phosphated distarch phosphate [2].
- Assay: -
- Residual phosphate:  Not more than 0.5% for wheat and potato starch.
  - Not more than 0.4% for other starches.
In addition the specification includes purity criteria on Sulphur dioxide and Lead.

**Acetylated distarch phosphate**

**Manufacture:** Acetylated distarch phosphate is obtained from food grade starches by cross-linking with trimethaphosphate or phosphorous oxychloride and esterification with acetic anhydride or vinyl acetate.

**Definition:** Acetylated distarch phosphate consists of starches cross-linked with phosphate groups. In addition a partial substitution with acetyl groups in the 2-, 6- or 3-position of the anhydroglucose unit has taken place.

**EC specifications:** E 1414 Acetylated distarch phosphate [1].
- Assay: -
- Acetyl groups:  Not more than 2.5%
- Residual phosphate:  Not more than 0.14% for wheat and potato starch.
  - Not more than 0.04% for other starches.
- Vinyl acetate:  Not more than 0.1 mg/kg
In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

**JECFA specifications:** Modified starches - Acetylated distarch phosphate [2].
- Assay: -
- Acetyl groups: Not more than 2.5%
- Residual phosphate:  Not more than 0.14% for wheat and potato starch.
  - Not more than 0.04% for other starches.
- Vinyl acetate:  Not more than 0.1 mg/kg
In addition the specification includes purity criteria on Sulphur dioxide and Lead.

**Acetylated starch**

**Manufacture:** Acetylated starch is obtained from food grade starches by esterification with acetic anhydride or vinyl acetate.

**Definition:** Acetylated starch consists of starches in which a partial substitution with acetyl groups in the 2-, 6- or 3-position of the anhydroglucose unit has taken place.
EC specifications: E 1420 Acetylated starch [1].
Assay: -
Acetyl groups: Not more than 2.5%.
Vinyl acetate: Not more than 0.1 mg/kg.
In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

JECFA specifications: Modified starches – Starch acetate [2].
Assay: -
Acetyl groups: Not more than 2.5%.
Vinyl acetate: Not more than 0.1 mg/kg.
In addition the specification includes purity criteria on Sulphur dioxide and Lead.

Acetylated distarch adipate
Manufacture: Acetylated distarch adipate is obtained from food grade starches by cross-linking with adipic anhydride and esterification with acetic anhydride.

Definition: Acetylated distarch adipate consists of starch cross-linked with adipate groups. In addition a partial substitution with acetyl groups in the 2-, 6- or 3-position of the anhydroglucose unit has taken place.

EC specifications: E 1422 Acetylated distarch adipate [1].
Assay: -
Acetyl groups: Not more than 2.5%.
Adipate groups: Not more than 0.135%.
In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

JECFA specifications: Modified starches - Acetylated distarch adipate [2].
Assay: -
Acetyl groups: Not more than 2.5%.
Adipate groups: Not more than 0.135%.
In addition the specification includes purity criteria on Sulphur dioxide and Lead.

Hydroxypropyl starch
Manufacture: Hydroxypropyl starch is obtained from food grade starches by esterification with propylene oxide.

Definition: Hydroxypropyl starch consists of starch in which a partial substitution with hydroxypropyl groups in the 2-, 6- or 3-position of the anhydroglucose unit has taken place.

EC specifications: E 1440 Hydroxypropyl starch [1].
Assay: -
Hydroxypropyl groups: Not more than 7.0%.
Propylene chlorohydrin: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

JECFA specifications: Modified starches - Hydroxypropyl starch [2].
Assay: -
Hydroxypropyl groups: Not more than 7.0%.
Propylene chlorohydrin: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Sulphur dioxide and Lead.

**Hydroxypropyl distarch phosphate**

**Manufacture:** Hydroxypropyl distarch phosphate is obtained from food grade starches by cross-linking with sodium trimetaphosphate or phosphorous oxychloride and esterification with propylene oxide.

**Definition:** Hydroxypropyl distarch phosphate consists of starch cross-linked with phosphate groups. In addition a partial substitution with hydroxypropyl groups in the 2-, 6- or 3-position of the anhydroglucose unit has taken place.

**EC specifications:** E 1442 Hydroxypropyl distarch phosphate [1].
Assay: -
Hydroxypropyl groups: Not more than 7.0%.
Propylene chlorohydrin: Not more than 1 mg/kg.
Residual phosphate: Not more than 0.14% for wheat and potato starch.
Not more than 0.04% for other starches.
In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

**JECFA specifications:** Modified starches - Hydroxypropyl distarch phosphate [2].
Assay: -
Hydroxypropyl groups: Not more than 7.0%.
Propylene chlorohydrin: Not more than 1 mg/kg.
Residual phosphate: Not more than 0.14% for wheat and potato starch.
Not more than 0.04% for other starches.
In addition the specification includes purity criteria on Sulphur dioxide and Lead.

**Starch sodium octenyl succinate**

**Manufacture:** Starch sodium octenyl succinate is obtained from food grade starches esterification with octenyl succinic anhydride.

**Definition:** Starch sodium octenyl succinate consists of starch in which a partial substitution with hydroxypropyl groups in the 2-, 6- or 3-position of the anhydroglucose unit has taken place.

**EC specifications:** E 1450 Starch sodium octenyl succinate [1].
Assay: -
Octenylsuccinyl groups: Not more than 3%.
Octenysicinic acid residue: Not more than 0.3%.
In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

**JECFA specifications:** Modified starches - Starch sodium octenyl succinate [2].
Assay: -
Octenylsuccinyl groups: Not more than 3%.
Octenysicinic acid residue: Not more than 0.3%.
In addition the specification includes purity criteria on Sulphur dioxide and Lead.
Acetylated oxidised starch

**Manufacture:** Acetylated oxidised starch is obtained from food grade starches by treating with sodium hypochlorite and esterification with acetic anhydride.

**Definition:** Acetylated oxidised starch consists of starch with a certain amount of carboxylic groups. In addition a partial substitution with acetyl groups in the 2-, 6- or 3-position of the anhydroglucose unit has taken place.

**EC specifications:** E 1451 Acetylated oxidised starch [1].

**Assay:**
Carboxyl groups: Not more than 1.3%
Acetyl groups: Not more than 2.5%

In addition the specification includes purity criteria on Loss on drying, Sulphur dioxide, Arsenic, Lead and Mercury.

**JECFA specifications:** No JECFA specification had been prepared at closing date. Specification has been prepared at 57th meeting 2001

**Exposure:** The modified starches are permitted generally in foodstuffs except those where additives are not permitted. No upper levels are specified and an exposure estimate is, therefore, not possible. ADI is “not specified” and the substance was for that reason not included in the EU monitoring system (tier 0). This is in contrast to the SCF request to follow the use of these modified starches to see whether uses will significantly exceed what was the assumed exposure at the time of the evaluation.

Except for E1440-2 also permitted up to 5 % in some foods for infants and young children in good health.

**SCF/JECFA evaluation:**

**SCF status:** The products E1404; E1410; E1412; E1413; E1414; E1420; E1422; E1440; E1442 were, together with some other products, evaluated for the first time in 1976 when the Committee classified the starches in three categories from A to C [3]. In group A were classified those starches modified with “mild” means e.g. acid and enzymes and the Committee found them acceptable without special restrictions and they are therefore not considered as food additives. In group B were classified those substances which were found temporarily acceptable in food including food for infants up to 5%. For the products classified in group C special questions were raised concerning residues of by products of modifying agents, especially the chlorohydrins. Also these products were found temporarily acceptable, but not to food for infants.

The Committee considered it unnecessary to establish individual ADIs, provided technological usage remains at present-day levels. The Committee requested that this aspect should be kept under review by the Commission.

In 1981 the Committee reviewed the products in the light of new information and found the substances in group B fully acceptable. Two of the substances in group C, E1440 and E1442, were also found acceptable, except for food especially prepared for infants and young children, provided the residual level of propylene chlorohydrin did not exceed 0.1 mg/kg [4]. This advise has not been followed in the specifications where the maximum level is set at 1 mg/kg. The other substances in group C were no longer used and the Committee withdrew the acceptance.
E1450: Based on new long-term study and previous presented data the Committee in 1990 [5] found this additive acceptable for use in food together with other modified starches classified in group B presented in 1976 [3].

E1451: In 1995 [6], the Committee agreed that acetylated oxidised starch (E1451) is acceptable from a safety point of view and that it can be placed with the other modified starches similarly considered acceptable [4] for which it was not necessary to establish ADI’s.

**JECFA status:** An ADI “not specified” was established for most of the additives in 1973 and 1974 [7;8], and confirmed in 1982 [9]. At the latter occasion also E1450 was included in the ADI.

E1451: This additive had not been evaluated by JECFA when closing for addition of new data, but later, in 2001 at its 57th meeting, the Committee included also this additive in the ADI “not specified” allocated for the other modified starches.

**Background data:**

**Subacute/subchronic toxicity:** Short-term studies were available to SCF on substances in group B and C [4] [3]: No dose-response relationship was found. For E1450 data were available from short-term and 90-day studies. However, no data were specified [5]. For E1451 a 90-day study did not indicate any specific adverse effect with the dual treatment and it was possible to establish a NOEL on 10% in the diet [6].

Short-term studies were available to JECFA on (E1404: rats; E1412: rat, pig; E1413: rat, dog, pig; E1420: rat; E1422, rat; E1440: rat; E1442: rat; E1450: rat). No adverse effects were noticed [10]. A 90-day study showed no serious toxic effects at the 25% dietary level, the highest level tested. Short-term toxicity studies are available on E1412, without showing any adverse effect. Studies on E1414 showed no adverse effect in rat, hamster, or pig [10].

**Genotoxicity:** According to SCF no mutagenic effect was seen for E1450, however, no data were specified [4].

**Chronic toxicity/Carcinogenicity:** No evidence of carcinogenicity.

Long-term studies were available to SCF on substances in group B or C: No dose-response relationship was found [4]. Data were available from long-term studies in rats on E1450. However, no data were specified [5].

Long-term studies, considered by JECFA, on E1413 (rat), E1414 (rat), and 1420 (mouse, rat) did not reveal any significant effects [10]. In a lifetime study on E1422 in rats there were no consistent adverse effects but renal epithelial hyperplasia in females [10].

**Reproduction toxicity:** No effects reported on reproductive performance.

Reproduction studies are available on starches in group B or C [4]: No dose-response relationship was found [4].

Reproduction studies in rats on E1413, E1414, and E1420 did not reveal any significant effects [10]. A multi-generation reproduction study in rats on E1422 did not show any adverse effect on reproductive performance [10].
Effect in humans: Digestibility of starches are available:

-Adults digest starches mainly by action of pancreatic amylase [4].

-Newborns have virtually zero pancreatic amylase activity. Salivary amylase activity is low, but increases rapidly to two-thirds of adult values by 3 months [5].

-Infants have very low activity of pancreatic amylase, instead mucosal glucoamylase and salivary amylase are sufficient in some infants to digest long-chain glucose-polymers. Infants are also capable of digesting cooked native starches from 1 month of life. Large amounts of starches (40g/day) in diet to one-month old infants resulted in malabsorption and fermentative diarrhoea [6].

E1450: Data are available on caloric utilisation in rats and from in vitro enzyme digestibility studies. However, no data were specified [4].

E1413, E1414, and E1420 have been studied in human volunteers taking doses of 60g/day for 4 successive days of each. No adverse effects were noted due to any of these additives [10].

Other: Biochemical aspects: In vitro studies on human and rabbit pancreatic amylases and in vivo studies in adult rabbits showed that the digestibility of corn distarch phosphate (E1412) and native starches is comparable [6]. Data on the caloric utilisation and in vitro digestibility of E1450 are available, but no results are specified [5].

The digestibility of E1404 has been investigated in vivo and found to be similar to that of unmodified starch. An adequate metabolic study showed that modification did not affect the digestibility of E1410. Studies on the metabolic behaviour of E1412 were not available to JECFA. In vitro digestibility studies on E1413 showed a somewhat reduced rate in one study and unchanged rate in another as compared with unmodified starch [10]. Feeding studies in rats showed that E1414 is well utilised and in vitro digestibility studies (E1414, E1420) show breakdown comparable to that of unmodified starch [10]. Metabolic studies on E1422 in rats show that the adipic acid moiety enters the metabolic pool more slowly but follows the normal pathways of free adipic acid, and there seems not to be any difference in the caloric value between E1422 and unmodified starches [10]. A metabolic study in rats on E1440 shows that most of the hydroxypropyl-containing moiety is excreted in faeces [10]. The caloric utilisation of E1442 and E1450 is in the range of that of unmodified starch [10].

In conclusion, modified starches are degraded into their basic components following ingestion and enter common intermediary metabolism. The degradation may be total or partial. Not degraded modified starch will be excreted in faeces.

Prior problems: SCF and JECFA have considered the kidney lesions in rats fed high levels of modified starches and concluded that the rat is a particularly sensitive species for pelvic nephrocalcinosis (PN) and that this effect has little relevance for safety evaluation of modified starches in man. [4;9] The incidence increased apparently with the age of the animals when first exposed [4]. PN is much rarer in mice and not present in hamster [4]. The mechanism seems to be increased calcium absorption in the lower intestine caused by the formation of absorbable breakdown products in the lower intestine [4].
Conclusion:
The parent compound: starch, is a natural component of all plants and has been eaten as a main feedstock by man throughout evolution and there appears to be no reason to expect that the use of modified starches should give any reason for concern.

SCF in 1982 [4] considered it unnecessary to establish individual ADIs, provided technological usage remains at present-day levels. The Committee requested that this aspect should be kept under review by the Commission. This has not been the case.

Modified starches as defined by the specifications are not covered by the toxicological evaluation by SCF with respect to the content of residual propylene chlorohydrin in E1440 and E 1442.

References:


TRIETHYL CITRATE

E number: E 1505

Recommendation: No action needed.

Chemical name/synonyms: Triethyl-2-hydroxypropan-1,2,3-tricarboxylate/ ethyl citrate.

Chemical formula: C$_{12}$H$_{20}$O$_{7}$

EINECS number: 201-070-7

CAS number: 77-93-0

Functional Class: Carrier.

Specification:

Manufacture: No information on manufacturing processes for food grade triethyl citrate.

Definition: Triethyl citrate is the triethyl ester of citric acid. It is slightly soluble in water and miscible with ethanol.

EC specifications: E 1505 Triethyl citrate [1].
Assay: Not less than 99.0%.
The specification includes purity criteria on Water, Acidity, Arsenic and Lead.

JECFA specifications: Triethyl citrate (INS 1519) [2].
Assay: Not less than 99%.
The specification includes purity criteria on Water, Acidity, Arsenic and Heavy metals.

Exposure: Triethyl citrate is only permitted in dried egg whites so even if there is no upper limit, the exposure for certain will be well below the ADI.

In the EU monitoring system the substance has been moved to tier 3, as it cannot be examined at tier 1 and 2. This, however, seems unnecessary because of the limited use.

SCF/JECFA evaluation:

SCF status: Latest evaluation 1990. ADI 20 mg/kg bw. based on the JECFA evaluation [3].

JECFA status: Latest evaluation 1984. ADI 20 mg/kg bw based on the long-term rat study mentioned below and metabolic studies showing that both liver and blood serum have enzymes capable of hydrolysing triethyl citrate into ethanol and citric acid [4].

Background data:

Subacute/subchronic toxicity: Cats receiving daily doses of 280 mg/kg bw (way of administration not mentioned) for eight weeks experienced weakness, ataxia and depression. After treatment was discontinued the animals recovered [5].
**Genotoxicity:** No mutagenicity in Ames bacterial test or in yeast with and without metabolic activation [5].

**Chronic toxicity/carcinogenicity:** Groups of 15 male and 15 female were given feed containing 0.33, 1.0 and 3.0 % triethyl citrate for two years (initial doses from 0.2 to 2 g/kg bw/day). Weight gain and food intake were reduced with increased doses but no adverse effects of haematologic, urinanalysis, survival, gross or histopathologic parameters could be attributed to triethyl citrate [5].

**Reproduction toxicity:** At doses ranging from 0.5 to 10 mg/kg bw triethyl citrate was nonteratogenic in the chicken embryo [5].

**Other:** Metabolic studies on blood serum from rat and human show that triethyl citrate is hydrolysed to ethanol and citric acid [6]. Studies on neurological activity on rat and rabbit did demonstrate an effect when the substance was given intraperitoneally or intravenously [5]. Triethyl citrate is not an irritant to the skin of humans and laboratory animals [7].

**Conclusion:** Due to the fact that triethyl citrate is hydrolysed to ethanol and citric acid and the fact that exposure is very limited there is no need for further examination.

**References:**


GLYCERYL TRIACETATE (TRIACETIN)

**E number:** E 1518

**Recommendation:** No need for a re-evaluation.

**Chemical name/synonyms:** Glyceryl triacetate/ triacetin.

**Chemical formula:** C₉H₁₄O₆

**EINECS number:** 203-051-9

**CAS number:** 102-76-1

**Functional Class:** Humectant, solvent.

**Specification:**
**Manufacture:** No information on manufacturing processes for food grade glyceryl triacetate.

**Definition:** Glyceryl triacetate is the triacetic acid ester with glycerol. It is sparingly soluble in water and soluble in ethanol.

**EC specifications:** E 1518 Glyceryl triacetate [1].
Assay: Not less than 98.0%.
The specification includes purity criteria on Water, Sulphated ash, Arsenic and Lead.

**JECFA specifications:** Glyceryl triacetate [2].
Assay: Not less than 98.5%.
The specification includes purity criteria on Refractive index, Specific gravity, Distillation range, Water, Sulphated ash, Acidity, Unsaturated compounds and Heavy metals.

**Exposure:** Glyceryl triacetate is permitted only to chewing gum and as a carrier solvent for food additives. Exposure is likely to be limited.

**SCF/JECFA evaluation:**
**SCF status:** Latest evaluation in 1990 when an ADI “not specified” was allocated based on the fact that this ester is readily hydrolysed to glycerol and acetic acid [3].

**JECFA status:** Latest evaluation 1975. ADI not specified without specific toxicity data on glyceryl triacetate because the substance is readily hydrolysed [4].

**Background data:**
**Subacute/subchronic toxicity:** -

**Genotoxicity:** -

**Chronic toxicity/carcinogenicity:** -
Reproduction toxicity: -

Other: Numerous studies have shown that triacetin is rapidly hydrolysed in vitro by all tissues of the organism including the gastrointestinal tract [5]

Conclusion: Glyceryl triacetate is hydrolysed to the normal body constituents acetic acid and glycerol and although no formal toxicity studies exist this substance can be considered safe as a food additive.

References:


**PROPANE-1,2-DIOL**

**E number:** E 1520

**Recommendation:** A re-evaluation is not needed. However, a survey to estimate the likely exposure of propane-1,2-diol is recommended.

**Chemical name/synonyms:** 1,2-dihydroxypropane/ propylene glycol

**Chemical formula:** C₃H₈O₂

**EINECS number:** 200-338-0

**CAS number:** 57-55-6

**Functional Class:** Carrier.

**Specification:**

**Manufacture:** No information on manufacturing processes for food grade propane-1,2-diol.

**Definition:** Propane-1,2-diol is soluble in water and in ethanol.

**EC specifications:** E 1520 Propane-1,2-diol [1].
Assay: Not less than 99.5% on the anhydrous basis.
The specification includes purity criteria on Distillation range, Sulphated ash, Water and Lead.

**JECFA specifications:** Propylene glycol [2].
Assay: Not less than 99.5% on the anhydrous basis.
The specification includes purity criteria on Distillation range, Specific gravity, Sulphated ash, Water Free acid and Heavy metals.

**Exposure:** Propane-1,2-diol is permitted as a carrier solvent with a maximum use level in final food of 1 g/kg. Calculations according to the Budget method indicate that there is a theoretical possibility for exceeding the ADI, which would suggest a more detailed survey. However in the EU monitoring system the substance was not examined with the explanation that is permitted as a carrier and not as a food additive as such. As this in itself does not exclude that the ADI is exceeded, the substance should be examined at tier 3 level.

Furthermore Danish control examinations on use levels of propane-1,2-diol have shown that the legal limit of 1 g/kg in several cases have been exceeded. For example levels of up to 28 g/kg have been found in cakes, indicating that the substance is, illegally, used for also technological purposes.

**SCF/JECFA evaluation:**

**SCF status:** Latest evaluation in 1996 where the temporary ADI of 25 mg/kg bw was made full after the Committee had received further data on genotoxicity [3].

**JECFA status:** Latest evaluation 1973: ADI 25 mg/kg bw. Based on long-term studies in rat and dog [4]. At its meeting in 1993, when discussing propylene glycol alginate, JECFA expressed a
wish to re-evaluate propylene glycol in the light of the new data published since the evaluation in 1973. Propylene glycol was on the agenda as a flavouring agent at the 57th meeting in 2001. A report from the meeting was not available when this monograph was finalized.

Background data:

Subacute/subchronic toxicity: Rats tolerated up to 10% of propylene glycol in the drinking water for one-eighth of their normal lifespan [5]. When groups of 10 rats were given 10% propane-1,2-diol there was a significant increase in liver weight [5]. In rats given feed where 13% of the carbohydrates was replaced by propylene glycol for 5 months weight gain was slower but mortality were not increased [5]. When dogs were given 5% of propane-1,2-diol in their drinking water for 5 to 9 months no adverse effects were seen [5].

Genotoxicity: Several in vitro test with and without metabolic activation did not indicate genotoxicity except for some recombinogenic activity shown in S. cerevisiae. In vivo test in mice did not indicate any genotoxicity. Although an in vitro test with mammalian gene has not been performed SCF concluded propane-1,2-diol does not pose a significant concern for genotoxic potential [3].

Chronic toxicity/carcinogenicity: No adverse effects were seen when 30 male and 30 female rats were fed diets containing up to 2500 mg/kg bw. for two years [5]. Groups of 5 male and 5 female dogs were given 0.0, 2.0 and 5.0 g/kg bw for 2 years. In the high dose groups there were effects on haematological parameters but no effects were seen in the low dose group [5].

Reproduction toxicity: In a multigeneration study in mice with concentrations of 0.0, 1.0, 2.5, 5.0% propane-1,2-diol in the drinking water no adverse effects were seen in any of the treated generations [6].

Other: Propane-1,2-diol is rapidly absorbed from the gastro-intestinal tract of mammals, quickly distributes in the whole body water, and is partially rapidly excreted and partially metabolised to lactic acid, pyruvic acid and carbon dioxide, well-known intermediates of mammalian carbohydrate metabolism [7].

Conclusion: There is no need for a reevaluation of propane-1,2-diol. However as the substance was not included in the EU monitoring system (tier 0), the potential exposure should be assessed at tier 3 level.

References:


4. [1973, NMRS 53/TRS 539-JECFA 17]
Toxicological evaluation of certain food additives with a review of general principles and of specifications (Seventeenth report of the Joint FAO/WHO Expert Committee on Food

5. *[1973, FAS 5/NMRS 53A-JECFA 17]*


POLYETHYLENEGLYCOL 6000 (PEG 6000)

E number: No E number; INS (for PEG 200-9500): 1521

Recommendation: No need for a re-evaluation.

Chemical name/synonyms: PEG 6000, Macrogol 6000

Chemical formula: \((\text{C}_2\text{H}_4\text{O})_{n+1}\text{H}_2\text{O}\)

EINECS number: -

CAS number: 25322-68-3

Functional Class: Carrier (tablet disintegrant).

Specification:
Definition: Polyethylene glycol 6000 is a mixture of polymers with the general formula \(\text{H}-(\text{OCH}_2\text{-CH})-\text{OH}\) corresponding to an average relative molecular mass of approximately 6000.

EC specifications: Polyethyleneglycol 6000 [1].
Assay: Polyethyleneglycol 6000: Not less than 90.0 % and not more than 110.0 %.
Ethylene oxide: Not more than 1 mg/kg.
In addition the specification includes purity criteria on Viscosity, Hydroxyl value, Sulphated ash, Arsenic and Lead.

JECFA specifications: INS 1521 Polyethylene glycols (covers a whole range from 200-9500)
1,4-Dioxane: Not more than 10 mg/kg.
Ethylene oxide: Not more than 0.02%.
Ethylene glycol and diethylene glycol: Total not more than 0.25% w/w individually or in combination.
In addition the specification includes purity criteria on Viscosity, Acidity, Sulfated ash, Arsenic and Heavy metals.

Exposure: Only permitted as carrier for sweeteners so exposure is likely to be very low.

SCF/JECFA evaluation:
SCF status: Taken into account its low resorption, the absence of known toxic manifestations and the limited exposure which could result from the recommended use SCF accepted the use of Polyethyleneglycol 6000 [2].

JECFA status: An ADI of 10 mg/kg bw was allocated in 1979 for polyethylene glycols with molecular weights between 200 and 10000 [3]

Background data:
Subacute/subchronic toxicity: No adverse effect were seen in a 90 day rat study with Polyethyleneglycol 6000 [2]. In another 90 day rat study with 5 males and 5 females in each group
the NOEL was 16% in the diet. The adverse effects at higher doses was increased kidney weight and decreased body weight [3].

**Genotoxicity:** -

**Chronic toxicity/Carcinogenicity:** No adverse effects were seen when rats were given 4% PEG 4000 for 2 years [3]. When dogs where fed 2% in the diet for one year no adverse effects were seen [3].

**Reproduction toxicity:** -

**Other:** No absorption of polyethylene glycol 6000 from the G.I in rats was seen over a five hour period (dose not given) [3]. When polyethylene glycol 6000 were given intravenously into six human subjects, 96% was excreted in the urine in 12 hours [3]. When 10 g were given orally to five humans nothing was found in the urine within the following 24 hours [3].

**Conclusion:** The long-term study on PEG 4000 indicate that the long-term toxicity of polyethylene glycols with hig molecular weight is low. The toxicity of PEG 6000 is probably at the same magnitude as the toxicity of PEG 4000. The metabolic studies show that PEG 6000 is not absorbed and if it enter the bloodstream it will be excreted fast. Beside these studies only very few other studies on polyethylenglycol 6000 as such are available. These results combined with the very limited intake of PEG 6000 are the background for the conclusion that there is no need for further evaluation of this substance.

**References:**


## Annex II

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<td>Column 7</td>
<td>Priority system for re-evaluation or other actions. The system has been used to facilitate a quick overview. The comments in column 6 gives the main reasons, but monographs should be consulted for the explanation for priority. Following priorities have been used:</td>
</tr>
<tr>
<td></td>
<td>- = The substance is presently on the agenda of the SCF and no further action warranted.</td>
</tr>
<tr>
<td></td>
<td>0 = No need for any action</td>
</tr>
<tr>
<td></td>
<td>1 = Some (usual minor) matters to be clarified</td>
</tr>
<tr>
<td></td>
<td>2 = Update of evaluation recommended. Often this priority has been used if there seems no reason to change present ADI, but new data has been published which preferably should be included in the evaluation.</td>
</tr>
<tr>
<td></td>
<td>3 = Some priority for a re-evaluation or other action.</td>
</tr>
<tr>
<td></td>
<td>4 = Priority for a re-evaluation or other action.</td>
</tr>
<tr>
<td></td>
<td>5 = High priority for a re-evaluation or other action (e.g. modification of present legislation).</td>
</tr>
</tbody>
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*Priorities: 0 = no need for any action; 1 = matters to be clarified; 2 = update of evaluation; 3 = some priority for re-evaluation 4 = priority for re-evaluation; 5 = high priority for re-evaluation; - = on the agenda of SCF, no need for further action*
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<tr>
<td>100</td>
<td>Curcumin</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier0: exposure not examined Exposure should be monitored</td>
<td>SCF: &quot;acceptable&quot; if from food sources and if low exposure (1R 1975) JECFA: t-ADI=1 mg/kg bw (51R 1998)</td>
<td>Needed: Studies on carcinogenicity and reproductive toxicity; Specification; Exposure data</td>
</tr>
<tr>
<td>101</td>
<td>Riboflavin</td>
<td>Riboflavin-5'-phosphate All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable&quot; (1R 1975) + GMO Dec. 2000 JECFA: ADI= 0.5 mg/kg bw (25R 1981)+GMO 51R 1998</td>
<td>-</td>
</tr>
<tr>
<td>102</td>
<td>Tartrazine</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake for children: 50% of ADI</td>
<td>SCF: ADI= 7.5 mg/kg bw (14R 1983) JECFA: ADI= 7.5 mg/kg bw (8R 1964)</td>
<td>Update evaluation to include new data</td>
</tr>
<tr>
<td>104</td>
<td>Quinoline Yellow</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake for children: 20% of ADI</td>
<td>SCF: ADI= 10 mg/kg bw (14R 1983) JECFA: ADI= 10 mg/kg bw (28R 1984)</td>
<td>Clarify apparent discrepancy on safety factors</td>
</tr>
<tr>
<td>110</td>
<td>Sunset Yellow FCF</td>
<td>All &quot;colourable&quot; foods: soft drinks 50 mg/litre/solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake 2-26%; for children 80% of ADI</td>
<td>SCF: ADI=2,5 mg/kg bw (14R 1983) JECFA: ADI=5 mg/kg bw (26R 1982)</td>
<td>Re-evaluation because of inadequate reporting and new data</td>
</tr>
<tr>
<td>120</td>
<td>Cochineal, Carminic acid, Carmines</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake 3-22%; for children 80% of ADI</td>
<td>SCF: ADI=5 mg/kg bw (26R 1982)</td>
<td>Re-evaluation because of reports on allergy and new reproduction data</td>
</tr>
<tr>
<td>122</td>
<td>Azorubine, Carmoisine</td>
<td>All &quot;colourable&quot; foods: soft drinks 50 mg/litre solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake 3-16%, for children 50% of ADI</td>
<td>SCF: ADI=4 mg/kg bw (14R 1983) JECFA: ADI=4 mg/kg bw (27R 1983)</td>
<td>-</td>
</tr>
<tr>
<td>123</td>
<td>Amaranth</td>
<td>Only Americano, Bitter soda, Bitter vino aperitif wine 100 ml, aperitif wine 30 ml/l, fish roe 30 mg/kg</td>
<td>480 ml Americano etc. or 1.6 litre aperitif wine or 1.6 kg roe to reach ADI. Tier1: ADI not exceeded</td>
<td>SCF: ADI=0.8mg/kg bw (14R 1983) JECFA: ADI= 0.5mg/kg bw (28R 1984)</td>
<td>Low exposure. Update to clear discrepancy between ADI's and to include new data</td>
</tr>
<tr>
<td>124</td>
<td>Ponceau 4R</td>
<td>All &quot;colourable&quot; foods: soft drinks 50 mg/litre solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake 3-16%; for children 50% of ADI</td>
<td>SCF: ADI=4 mg/kg bw (14R 1983) JECFA: ADI=4 mg/kg bw (27R 1983)</td>
<td>Clarify basis for ADI and safety factors used</td>
</tr>
<tr>
<td>127</td>
<td>Erythrosine</td>
<td>Cock-tail chemies + other special chemies only, 150-200 mg/kg, 30 g cock-tail chemies to reach ADI</td>
<td>Tier2: Calculated intake 0% of ADI</td>
<td>SCF: ADI=0.1 mg/kg bw (21R 1987) JECFA: ADI=0.1 mg/kg bw (15R 1990)</td>
<td>-</td>
</tr>
<tr>
<td>128</td>
<td>Red 2G</td>
<td>Breakfast sausages and burger meat only, 20 mg/kg</td>
<td>300 g sausage or burger to reach ADI Tier2: Calculated intake 2-20%; for children 40% of ADI</td>
<td>SCF: ADI=0.1 mg/kg bw (1R 1975) JECFA: ADI=0.1 mg/kg bw (25R 1981)</td>
<td>Albeit low theoretical exposure re-evaluation recommended if colour is still used</td>
</tr>
<tr>
<td>129</td>
<td>Allura Red AC</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake for children 50% of ADI</td>
<td>SCF: ADI=7 mg/kg bw (21R 1987) JECFA: ADI=7 mg/kg bw (25R 1981)</td>
<td>Update to include new data</td>
</tr>
<tr>
<td>131</td>
<td>Patent Blue V</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg, Tier2: Calculated intake for children 13% of ADI</td>
<td>SCF: ADI= 15 mg/kg bw (14R 1983) JECFA: No ADI (18R 1974)</td>
<td>Clarify basis for ADI and discrepancy between SCF and JECFA</td>
<td></td>
</tr>
<tr>
<td>132</td>
<td>Indigotine, Indigo Carmine</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake 2-13%; for children 40% of ADI</td>
<td>SCF: ADI=4 mg/kg bw (18R 1974) JECFA: ADI=4 mg/kg bw (18R 1974)</td>
<td>Update to include new data</td>
</tr>
<tr>
<td>133</td>
<td>Brilliant Blue FCF</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake for children 38% of ADI</td>
<td>SCF: ADI=10 mg/kg bw (13R 1969) JECFA: ADI=12.5 mg/kg bw (13R 1969)</td>
<td>Update to include new data</td>
</tr>
<tr>
<td>140</td>
<td>Chlorophylls and Chlorophyllins</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable&quot; if from food sources and if low exposure (1R 1975) JECFA: ADI=&quot;not specified&quot; (13R 1969)</td>
<td>Clarify present uses</td>
</tr>
<tr>
<td>141</td>
<td>Copper complexes of chlorophylls and of chlorophyllins</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=15 mg/kg bw (1R 1975) JECFA: ADI=15 mg/kg bw (13R 1969)</td>
<td>Re-evaluation to clarify significance of Cu-content and cancer promoting effect</td>
</tr>
<tr>
<td>142</td>
<td>Green S</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake 3-20%, for children 76% of ADI</td>
<td>SCF: ADI=5 mg/kg bw (14R 1983) JECFA: No ADI (18R 1974)</td>
<td>Update to include new data.</td>
</tr>
<tr>
<td>150a</td>
<td>Plain caramel</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: &quot;Acceptable&quot; (21R 1987) JECFA: ADI=&quot;not specified&quot; (28R 1985)</td>
<td>-</td>
</tr>
</tbody>
</table>

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<tr>
<td>150b</td>
<td>Caustic sulphite caramel</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=200 mg/kg bw (76M Dec.1990). Group with 150d JECFA: ADI=160 mg/kg bw (55R 2000)</td>
<td>-</td>
</tr>
<tr>
<td>150c</td>
<td>Ammonia caramel</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=200 mg/kg bw (36R 1998) JECFA: ADI=200 mg/kg bw (29R 1985)</td>
<td>Further discussion on lymphocyte-suppressing activity. Specification question</td>
</tr>
<tr>
<td>150d</td>
<td>Sulphite ammonia caramel</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=200 mg/kg bw (21R 1987). Group with 150b JECFA: ADI=200 mg/kg bw (29R 1985)</td>
<td>-</td>
</tr>
<tr>
<td>151</td>
<td>Brilliant Black BN, Black PN</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake 3-20%; for children 76% of SCF ADI</td>
<td>SCF: ADI=5 mg/kg bw (14R 1987) JECFA: ADI=1 mg/kg bw (25R 1981)</td>
<td>Clarify discrepancy between SCF and JECFA ADI's. JECFA ADI may be exceeded so exposure should be investigated further</td>
</tr>
<tr>
<td>153</td>
<td>Vegetable carbon</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier1: ADI not exceeded</td>
<td>SCF: &quot;acceptable&quot; (1R 1975) JECFA: no ADI as food colour (31R 1987). &quot;Not specified&quot; as clarifying agent (21R 1977)</td>
<td>-</td>
</tr>
<tr>
<td>154</td>
<td>Brown FK</td>
<td>Kippers only 20 mg/kg</td>
<td>450 g kippers to reach ADI Tier1: ADI not exceeded</td>
<td>SCF: ADI=0.15 mg/kg bw (14R 1983) JECFA: ADI withdrawn (29R 1985)</td>
<td>Albeit low exposure re-evaluation recommended if colour still used</td>
</tr>
<tr>
<td>155</td>
<td>Brown HT</td>
<td>All &quot;colourable&quot; foods: soft drinks 50 mg/litre solid foods 50-500 mg/kg</td>
<td>Tier2: Calculated intake 3-22%; for children 67% of ADI</td>
<td>SCF: ADI=3 mg/kg bw (14R 1983) JECFA: ADI=1.5 mg/kg bw (28R 1984)</td>
<td>Clarify discrepancy between SCF and JECFA ADI's. Question on organ disposition should be elucidated</td>
</tr>
<tr>
<td>150e</td>
<td>160a i) Mixed carotenones</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: mixed carotenones: “acceptable” if from food sources and if low exposure (1R 1975) Algal carotene “acceptable” (43R 1997) beta-carotene: Previous group ADI of 5 mg/kg bw (1R 1975) withdrawn. No ADI but limited use “acceptable” (Sep, 2000) JECFA: ADI=5mg/kg bw (group with 160e+f) (18R 1974)</td>
<td>On SCF agenda</td>
</tr>
<tr>
<td></td>
<td>ii) beta-carotene</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>160b</td>
<td>Annatto, Bixin, Norbixin</td>
<td>Not in beverage in some solid foods 10-50 mg/kg</td>
<td>Tier2: Calculated intake 0-62%, for children 108-170% of ADI Tier3: further examination needed</td>
<td>SCF: ADI= 2.5 mg/kg bw as an extract containing 2.6% bixin based on highest dose level = NEL. From this an ADI of 0.065 mg/kg bw as bixin has been calculated (8R 1979) JECFA: ADI=0.065 mg/kg bw (as bixin) (26R 1982)</td>
<td>Re-evaluation as previous evaluation old and based on products differing significantly from products used today and as present ADI may be exceeded</td>
</tr>
<tr>
<td>160c</td>
<td>Paprika extract (capsanthin, capsorubin)</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: not evaluated JECFA: no ADI (55R 2000)</td>
<td>Should be evaluated. Significant differences between EU and JECFA specifications.</td>
</tr>
<tr>
<td>160d</td>
<td>Lycopene</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier0: exposure not examined If used according to permitted conditions exposure will vastly exceed exposure from normal food sources</td>
<td>SCF: “acceptable” if from food sources and if low exposure (1R 1975, confirmed 21R 1987). Does not cover synthetic lycopene (Dec. 1999) JECFA 77: decision postponed</td>
<td>Exposure should be monitored, and if exceeding normal exposure new evaluation</td>
</tr>
<tr>
<td>160e</td>
<td>Beta-apo-8'-carotenal(C30)</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Exposure not calculated Tier3: further examination needed</td>
<td>SCF: Previous group ADI of 5 mg/kg bw (1R 1975) withdrawn. No ADI but limited use “acceptable” (Sep. 2000) JECFA: ADI=5 mg/kg bw (group with 160ai) (18R 1974)</td>
<td>Should be re-evaluated together with beta-carotene.</td>
</tr>
<tr>
<td>160f</td>
<td>Ethyl ester of beta-apo-8'-carotenonic acid (C30)</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Exposure not calculated Tier3: further examination needed</td>
<td>SCF: Previous group ADI of 5 mg/kg bw (1R 1975) withdrawn. No ADI but limited use “acceptable” (Sep. 2000) JECFA: ADI=5 mg/kg bw (group with 160ai) (18R 1974)</td>
<td>Should be re-evaluated together with beta-carotene.</td>
</tr>
</tbody>
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<td>161b</td>
<td>Lutein</td>
<td>All &quot;colourable&quot; foods: soft drinks 100 mg/litre; solid foods 50-500 mg/kg</td>
<td>Tier0: exposure not examined If used according to permitted conditions exposure will vastly exceed exposure from normal food sources</td>
<td>SCF: &quot;acceptable&quot; if from food sources and if low exposure compared with lutein from natural sources (1R 1975) When evaluating antheraxanthin from Aztec Marigold (Tagetes) the Committee recommended that this colour should not be used to colour food, however part of specification (4R) JECFA: not evaluated</td>
<td>Exposure should be monitored. Specification examined.</td>
</tr>
<tr>
<td>161g</td>
<td>Canthinaxanthin</td>
<td>Saucisses de Strassbourg only 15 mg/kg (NB: occurs also as residues from animal feed)</td>
<td>200 g product to reach ADI Tier2: Calculated intake 0%, for children 0% of ADI</td>
<td>SCF: ADI= 0.03 mg/kg bw (43R 1997) JECFA: ADI=0.03 mg/kg bw (44R 1995)</td>
<td>-</td>
</tr>
<tr>
<td>162</td>
<td>Beetroot Red, Betanin</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable&quot; if from food sources and if low exposure (1R 1975) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Exposure should be monitored and if significant, toxicology should be examined</td>
</tr>
<tr>
<td>163</td>
<td>Anthocyanins</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable&quot; if from food sources and if low exposure (1R 1975) JECFA: ADI=2.5 mg/kg bw (grape skin extract) (26R 1982)</td>
<td>Exposure should be monitored.</td>
</tr>
<tr>
<td>170</td>
<td>Calcium carbonates</td>
<td>See E 500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>171</td>
<td>Titanium dioxide</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable&quot; (4R 1977) JECFA: ADI=&quot;not specified&quot; (13R 1969)</td>
<td>-</td>
</tr>
<tr>
<td>172</td>
<td>Iron oxides and hydroxides</td>
<td>All &quot;colourable&quot; foods q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=&quot;not specified&quot; (1R 1975) JECFA 79: ADI=0.5 mg/kg bw (not expressed as Iron)</td>
<td>Basis for evaluations unclear</td>
</tr>
<tr>
<td>173</td>
<td>Aluminim</td>
<td>External coating of sugar confectionery for the decoration of cakes and pastries only; q.s.</td>
<td>Likely to be small Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable for external colouring&quot; (1R 1975) JECFA: no ADI, but use for decoration &quot;not considered to present a hazard&quot;</td>
<td>Aluminium from all sources should be re-evaluated See also E 520-3, 541, 554-9 and 558</td>
</tr>
<tr>
<td>174</td>
<td>Silver</td>
<td>External coating of confectionery, decoration of chocolates and liqueurs only; q.s.</td>
<td>Likely to be small Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable for external colouring&quot; * (1R 1975) JECFA: decision postponed (21R 1977)</td>
<td>-</td>
</tr>
<tr>
<td>175</td>
<td>Gold</td>
<td>External coating of confectionery, decoration of chocolates and liqueurs only; q.s.</td>
<td>Likely to be small Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable for external colouring&quot; (1R 1975) JECFA: no ADI but &quot;the limited use is not considered to present a hazard&quot; (21R 1977)</td>
<td>-</td>
</tr>
<tr>
<td>180</td>
<td>Litholrubine BK</td>
<td>Edible cheese rind only; q.s.</td>
<td>Likely to be small Tier0: further examination needed</td>
<td>SCF: ADI=1.5 mg/kg bw (14R 1983) JECFA: no ADI (30R 1986)</td>
<td>Albeit low exposure re-evaluation recommended if still used</td>
</tr>
<tr>
<td>200</td>
<td>Sorbic acid</td>
<td>To a variety of foods; only in marginal products exceeding 2 g/kg. Beverages 300 mg/litre</td>
<td>Tier2: Calculated intake for children: 76% of ADI</td>
<td>SCF: ADI=25 mg/kg bw (35R 1994) JECFA: no ADI (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>202</td>
<td>Potassium sorbate</td>
<td>Calcium sorbate</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>203</td>
<td>Sodium benzoate</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>210</td>
<td>Benzoic acid</td>
<td>Sodium benzoate</td>
<td>Tier2: Calculated intake 6-54%, for children 17-96% of ADI Tier3: further examination needed</td>
<td>SCF: t-ADI = 5 mg/kg bw (35R 1994) JECFA: ADI=5 mg/kg bw; group with alcohol and aldehyde and ester (46R 1996)</td>
<td>On SCF agenda Exposure data needed</td>
</tr>
<tr>
<td>211</td>
<td>Propyl-p-hydroxybenzoate</td>
<td>Only jelly coatings of meat products and paté 1000 mg/kg, surface treatment of dried meat products q.s. cereal or potato-based snacks and coated nuts and confectionary 300 mg/kg, liquid dietary supplements 2000mg/kg. Not in beverages</td>
<td>600 g jelly coating a day or 2 kg snack or confectionary to reach ADI Tier1: ADI not exceeded</td>
<td>SCF: t-ADI=10 mg/kg bw (group) (35R 1994) JECFA: ADI=10 mg/kg bw (group) (17R 1973, sodium salts not considered)</td>
<td>On SCF agenda</td>
</tr>
<tr>
<td>214</td>
<td>Ethyl-p-hydroxybenzoate</td>
<td>Propyl-p-hydroxybenzoate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>215</td>
<td>Sodium ethyl-p-hydroxybenzoate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>216</td>
<td>Sodium propyl-p-hydroxybenzoate</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>217</td>
<td>Methyl-p-hydroxybenzoate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>218</td>
<td>Sodium methyl-p-hydroxybenzoate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>219</td>
<td></td>
<td></td>
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<tr>
<td>220</td>
<td>Sulphur dioxide</td>
<td>To a wide variety of foods among which burger meat and breakfast sauages 450 mg/kg, dehydrated</td>
<td>The ADI for a 30 kg person can be reached by consuming e.g. 10 g dried apricot (or peach, grape, prune, or fig) Tier2: Calculated intake 20-266%; for children 83-1227% of ADI</td>
<td>SCF: ADI=0.7 mg/kg bw (35R 1994). Special warning for sensitive individuals recommended. JECFA confirmed ADI=0.7 mg/kg bw (51R 1998)</td>
<td>ADI likely to be exceeded, and keeping the allergy aspect in mind limitations in permitted uses should be considered. EU specification for E 221 should be reconsidered.</td>
</tr>
<tr>
<td>221</td>
<td>Sodium sulphite</td>
<td></td>
<td></td>
<td>SCF: Not evaluated JECFA: ADI=0.05 mg/kg bw (8R 1964) JMPR ADI=0.125 (1967)</td>
<td>Should be evaluated by SCF</td>
</tr>
<tr>
<td>222</td>
<td>Sodium hydrogen sulphite</td>
<td></td>
<td></td>
<td>SCF: Not evaluated JECFA: ADI=0.2 mg/kg bw (8R 1964) JMPR: ADI=0.4 (1999)</td>
<td>Should be evaluated by SCF</td>
</tr>
<tr>
<td>223</td>
<td>Sodium metabisulphite</td>
<td></td>
<td></td>
<td>SCF: Acceptable for surface treatment of whole pressed cheese (semi hard) and on the casings of certain sausages requiring maturation before marketing provided residues do not exceed 1 mg/dm² of surface and not present at a depth greater than 5 mm. (9R 1979) JECFA 76: ADI=0.3 mg/kg bw 12R 1968</td>
<td>On the agenda of SCF for possibility for induction of microbial resistance</td>
</tr>
<tr>
<td>224</td>
<td>Calcium sulphite</td>
<td></td>
<td></td>
<td>SCF: Only indirectly evaluated by SCF (4R 1977) JECFA: ADI = 0.15 mg/kg bw (17R 1973)</td>
<td>Albeit low exposure a re-evaluation is recommended if still used</td>
</tr>
<tr>
<td>225</td>
<td>Calcium hydrogen sulphite</td>
<td></td>
<td></td>
<td>SCF: Treatment acceptable up to 250 mg/litre (26R 1990) JECFA: “acceptable” (max 250 mg/l) (37 1990)</td>
<td>-</td>
</tr>
<tr>
<td>226</td>
<td>Potassium metabisulphite</td>
<td></td>
<td></td>
<td>SCF: ADI=5 mg/kg bw expressed as sodium nitrate. &quot;Efforts should be made to change production methods in order to reduce and, where feasible, to abandon the combined use of nitrate and nitrite&quot; (26R 1990, confirmed 38R 1995) JECFA: ADI=5 mg/kg bw expressed as sodium nitrate (44R 1995)</td>
<td>-[monografi ikke færdig]</td>
</tr>
<tr>
<td>227</td>
<td>Sodium nitrate</td>
<td></td>
<td></td>
<td>SCF: ADI=0.06 mg/kg bw expressed as nitrite ion (38R 1995) JECFA: ADI=0.06 mg/kg bw expressed as nitrite ion (44R 1995)</td>
<td>-[monografi ikke færdig]</td>
</tr>
<tr>
<td>228</td>
<td>Potassium nitrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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<tr>
<td>260</td>
<td>Acetic acid</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (25R 1990)</td>
<td>-</td>
</tr>
<tr>
<td>261</td>
<td>Potassium acetate</td>
<td></td>
<td></td>
<td>JECFA: ADI=&quot;not specified&quot; (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>262</td>
<td>Sodium acetates</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>263</td>
<td>Calcium acetate</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>270</td>
<td>Lactic acid</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (25R 1990)</td>
<td>-</td>
</tr>
<tr>
<td>325</td>
<td>Sodium lactate</td>
<td></td>
<td></td>
<td>JECFA: ADI=&quot;not specified&quot; (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>326</td>
<td>Calcium lactate</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>327</td>
<td>Calcium lactate</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>270</td>
<td>Propionic acid</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (25R 1990)</td>
<td>Consider the request from SCF</td>
</tr>
<tr>
<td>280</td>
<td>Sodium propionate</td>
<td></td>
<td></td>
<td>JECFA: ADI=&quot;not specified&quot; (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>281</td>
<td>Calcium propionate</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>282</td>
<td>Propionic acid</td>
<td>Prepacked bread and fine bakery ware + christmas pudding. Max 1-3 g/kg</td>
<td>Tier0: exposure not examined</td>
<td>SCF: &quot;No adverse health consequences from present uses. Comparative studies with other short chain fatty acids and their salts desirable&quot;. (26R 1990)</td>
<td>-</td>
</tr>
<tr>
<td>283</td>
<td>Potassium propionate</td>
<td></td>
<td></td>
<td>JECFA: ADI=&quot;not specified&quot; (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>284</td>
<td>Boric acid</td>
<td>Sturgeons' eggs (caviar) max 4 g/kg (equivalent to ~ 700 mg B/kg)</td>
<td>~ 10 g caviar to reach the TDI for boron</td>
<td>SCF: &quot;Only acceptable for real caviar&quot; (26R 1990). (TDI for boron 0.1 mg/kg bw (1996))</td>
<td>Present very restricted uses probably of no concern. No need for a re-evaluation</td>
</tr>
<tr>
<td>290</td>
<td>Carbon dioxide</td>
<td>q.s.</td>
<td></td>
<td>SCF: ADI=&quot;not specified&quot; (25R 1990)</td>
<td>-</td>
</tr>
<tr>
<td>306</td>
<td>Malic acid</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (25R 1990)</td>
<td>-</td>
</tr>
<tr>
<td>350</td>
<td>Sodium malates</td>
<td></td>
<td></td>
<td>JECFA: ADI=&quot;not specified&quot; (13R 1969)</td>
<td>-</td>
</tr>
<tr>
<td>351</td>
<td>Potassium malate</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>352</td>
<td>Calcium malates</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>297</td>
<td>Fumaric acid</td>
<td>Only fillings and toppings for fine bakery wares 2.5 g/kg, sugar confectionary 1 g/kg, some desserts 4 g/kg, chewing gum 2 g/kg, instant powders for fruit based drinks and instant tea powder 1000 mg/litre. Also authorized in some imported wines.</td>
<td>360 ml drink/tea or 90 g dessert to reach ADI (60 kg person) Tier2: Calculated intake 1-17%; for children 6-66% of ADI</td>
<td>SCF: ADI=6 mg/kg bw (25R 1990)</td>
<td>-</td>
</tr>
<tr>
<td>301</td>
<td>Sodium ascorbate</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>302</td>
<td>Calcium ascorbate</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>304</td>
<td>(i) Ascorbyl palmitate</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: &quot;acceptable&quot; ( steerate not mentioned in evaluation) (22R 1987)</td>
<td>Needed: metabolism, bioavailability and possibly reproduction studies Exposure data</td>
</tr>
<tr>
<td></td>
<td>(ii) Ascorbyl stearate</td>
<td></td>
<td></td>
<td>JECFA: ADI=1.25 mg/kg bw (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>306</td>
<td>Tocopherol-rich extract</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: &quot;acceptable&quot; (assuming that intake from natural sources normally far will exceed that from processed foods containing tocopherol as an antioxidant) (22R 1987). NB gamma- and delta-tocopherols not included in evaluation JECFA: ADI=2 mg/kg bw (only alpha-form) (30R 1988)</td>
<td>-</td>
</tr>
<tr>
<td>307</td>
<td>Alpha-tocopherol</td>
<td></td>
<td></td>
<td>JECFA: ADI for the others were withdrawn (46R1996)</td>
<td>-</td>
</tr>
<tr>
<td>308</td>
<td>Gamma-tocopherol</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>309</td>
<td>Delta-tocopherol</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>310</td>
<td>Propyl gallate</td>
<td>Fats and oils for the professional manufacture of heat treated foodstuffs, frying oil and frying fat, lard, fish oil, and beef, poultry and sheep fat, and some fat containing products 200 mg/kg expressed on fat. Dehydrated granulated potatoes 25 mg/kg, chewing gum and dietary supplements 400 mg/kg</td>
<td>150 g fat (direct and indirect) a day to reach ADI (60 kg person) or 75 g chewing gum/dietary supplement Tier2: Calculated intake 12-34%; for children 17-70% of ADI</td>
<td>SCF: ADI=0.5 mg/kg bw (group for all) (22R 1987)</td>
<td>Clarify discrepancy between SCF and JECFA ADI's</td>
</tr>
<tr>
<td>311</td>
<td>Octyl gallate</td>
<td></td>
<td></td>
<td>JECFA: ADI=1.4 mg/kg bw for propyl gallate ADI for the others were withdrawn (46R1996)</td>
<td>-</td>
</tr>
<tr>
<td>312</td>
<td>Dodecyl gallate</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
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<td>315</td>
<td>Erythorbic acid (isoascorbic acid) Sodium erythorbate</td>
<td>Semi-preserved and preserved meat products max 500 mg/kg. Preserved and semi-preserved fish products and frozen and deep-frozen fish with red skin max 1500 mg/kg. Not in beverages</td>
<td>720 g meat product a day or 240 g fish product a day to reach ADI (60 kg person)</td>
<td>SCF: ADI=6 mg/kg bw (26R 1987; confirmed 36R 1995). JECFA: ADI=&quot;not specified&quot; (37R 1990)</td>
<td>Need for reproductive study should be discussed</td>
</tr>
<tr>
<td>320</td>
<td>Butylated hydroxyanisole</td>
<td>Fats and oils for the professional manufacture of heat treated foodstuffs, frying oil and frying fat, lard, fish oil, and beef, poultry and sheep fat, and some fat containing products 200 mg/kg expressed on fat. Dehydrated granulated potatoes 25 mg/kg, chewing gum and dietary supplements 400 mg/kg</td>
<td>150 g fat (direct and indirect) a day to reach SCF ADI (60 kg person) or 75 g chewing gum/dietary supplement</td>
<td>SCF: ADI=0.5 mg/kg bw (22R 1987) JECFA: ADI=0.5 mg/kg bw (33R 1988)</td>
<td>Re-evaluation to remove temporary status. Need for studies on multi-generation and possible accumulation should be discussed</td>
</tr>
<tr>
<td>321</td>
<td>Butylated hydroxytoluene</td>
<td>Fats and oils for the professional manufacture of heat treated foodstuffs, frying oil and frying fat, lard, fish oil, and beef, poultry and sheep fat 100 mg/kg expressed on fat, chewing gum and dietary supplements 400 mg/kg</td>
<td>30 g fat (direct and indirect) a day to reach SCF ADI (60 kg person) or 7.5 g chewing gum/dietary supplement</td>
<td>SCF: ADI=0.05 mg/kg bw (22R 1987) JECFA: ADI=0.3 mg/kg bw (44R 1995)</td>
<td>Clarify discrepancy between SCF and JECFA ADI's</td>
</tr>
<tr>
<td>322</td>
<td>Lecithins</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: Not formally evaluated (has, however, been accepted for infant formulae and baby food (24R 1990)) JECFA: ADI=&quot;not specified&quot; 17R 1973</td>
<td>-</td>
</tr>
<tr>
<td>325</td>
<td>Lactates</td>
<td>See E 270</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>330</td>
<td>Citric acid Sodium citrates</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=&quot;not specified&quot; (25R 1990) JECFA ADI=&quot;not specified&quot; (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>334</td>
<td>Tartaric acid Sodium tartrates</td>
<td>q.s.</td>
<td>Not possible Tier3: further examination needed</td>
<td>SCF: ADI=30 mg/kg bw (25R 1990) JECFA: ADI=30 mg/kg bw (21R 1977)</td>
<td>Exposure</td>
</tr>
<tr>
<td>338</td>
<td>Phosphoric acid Sodium phosphates</td>
<td>In a wide variety of foods in amounts from 1-20 g/kg. Permitted in some beverages up to 2 g/litre (vegetable protein drinks up to 20 g/litre) Expressed as P₂O₅</td>
<td>Tier2: Calculated intake for children 53-172% of ADI Tier3: further examination needed for children</td>
<td>SCF: MTDI=70 mg/kg bw as P from all sources (equivalent to 160 mg P₂O₅) (25R 1990) JECFA: MTDI=70 mg/kg bw as P from all sources (26R 1982)</td>
<td>As MTDI is expressed as intake from all sources a more detailed exposure assessment is desirable (preferably together with estimates of calcium exposure)</td>
</tr>
<tr>
<td>350-52</td>
<td>Malates</td>
<td>See E 296</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>353</td>
<td>Metatartaric acid</td>
<td>In wine according to regulations Made wine 100 mg/l</td>
<td>SCF: “acceptable in wine” up to 100 mg/litre (25R 1990) JECFA: not evaluated</td>
<td>How much is it actually used?</td>
<td></td>
</tr>
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<tr>
<td>355</td>
<td>Adipic acid</td>
<td>Only fillings and toppings for fine bakery wares 2g/kg, dry powdered dessert mixes 1 g/kg, gel-like desserts 6 g/kg, fruit-flavoured desserts 1 g/kg and powders for home preparation of drinks 10 g/litre</td>
<td>Only 50 g dessert or 30 ml drink to reach ADI (if limit means ready to consume product) Tier2: Calculated intake 2-20%; for children 3-7% of ADI</td>
<td>SCF: ADI=5 mg/kg bw (25R 1990) JECFA: ADI=5 mg/kg bw (21R 1977)</td>
<td>Clarification of limit in powders for drinks and if limit refers to ready to consume products an exposure estimate should be performed</td>
</tr>
<tr>
<td>356</td>
<td>Sodium adipate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>357</td>
<td>Potassium adipate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>363</td>
<td>Succinic acid</td>
<td>Only desserts 6 g/kg, soups and broths 5 g/kg and powders for home preparation of drinks 3 g/litre. Tier0: exposure not examined</td>
<td>SCF: ADI=&quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (29R 1985)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>380</td>
<td>Triammonium citrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>385</td>
<td>Calcium disodium ethylene diamine tetra-acetate (Calcium disodium EDTA)</td>
<td>Only emulsified sauces, canned and bottled fish, crustaceans and molluscs and frozen crustaceans 75 mg/kg. Minarine 100 mg/kg and canned and bottled pulses, legumes, mushrooms and artichokes 250 mg/kg. Not in beverages</td>
<td>Tier1: ADI not exceeded Restricted uses so exposure likely to be well below ADI</td>
<td>SCF: ADI=2.5 mg/kg bw (26R 191990) JECFA: ADI=2.5 mg/kg bw (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>400</td>
<td>Alginic acid</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=&quot;not specified&quot; (32R 1990) JECFA: ADI=&quot;not specified&quot; (39R 1992)</td>
<td>-</td>
</tr>
<tr>
<td>401</td>
<td>Sodium alginate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>402</td>
<td>Potassium alginate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>403</td>
<td>Ammonium alginate</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>404</td>
<td>Calcium alginate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>405</td>
<td>Propane-1,2-diol alginate</td>
<td>Allowed in various defined foods from 1 to 10 g/kg. In beer 100 mg/litre and non-alcoholic flavoured drinks 300 mg/litre. Also permitted as carrier</td>
<td>Tier1: ADI not exceeded</td>
<td>SCF: ADI=25 mg/kg bw expressed as propylene glycol (i.e. the &quot;real&quot; ADI is higher). (32R 1990) JECFA: ADI=70 mg/kg bw (corrected for the propylene glycol content) (41R 1993)</td>
<td>-</td>
</tr>
<tr>
<td>406</td>
<td>Agar</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=&quot;not specified&quot; (21R 1988) JECFA: ADI=&quot;not specified&quot; (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>407a</td>
<td>Processed Eucheuma Seaweed</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined as &quot;new&quot; additive</td>
<td>SCF: ADI=75mg/kg bw (group with E407) (35R 1994) JECFA: included in group ADI &quot;not specified&quot; for E407 (57R 2001)</td>
<td>On SCF agenda for re-evaluation</td>
</tr>
<tr>
<td>410</td>
<td>Locust bean gum (carob bean gum)</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: Not formally evaluated by SCF but accepted in food for special medical purposes (43R 1997) JECFA: ADI = &quot;not specified&quot; (25R 1981)</td>
<td>Update to include new data</td>
</tr>
<tr>
<td>412</td>
<td>Guar gum</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=&quot;not specified&quot; (7R 1977) JECFA: ADI=&quot;not specified&quot; (19R 1975)</td>
<td>Clarify allergy aspect</td>
</tr>
<tr>
<td>413</td>
<td>Tragacanth</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI=&quot;not specified&quot; (21R 1988) JECFA: ADI=&quot;not specified&quot; (29R 1985)</td>
<td>Clarify allergy aspect</td>
</tr>
<tr>
<td>414</td>
<td>Acacia gum (gum arabic)</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: Not formally evaluated by SCF (accepted in small amounts in some baby food (43R 1997) JECFA: ADI = &quot;not specified&quot; (35R 1989)</td>
<td>Formal SCF evaluation desirable. Questions on allergy and specifications should be clarified</td>
</tr>
</tbody>
</table>

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<tr>
<td>415</td>
<td>Xanthan gum</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (26R 1990). Accepted to certain kind of baby food (43R 1997) JECFA: ADI=&quot;not specified&quot; (30R 1986)</td>
<td>Exposure needed as evaluation linked to exposure estimates</td>
</tr>
<tr>
<td>416</td>
<td>Karaya gum</td>
<td>Only in some snacks, nut coatings, fillings, toppings and coatings for fine bakery wares, desserts, emulsified sauces, egg-based liqueurs and chewing gum 5-10 g/kg. Dietary supplements q.s. 150 g snack, filling or dessert a day to reach ADI (60 kg person) or 75 g nut, sauce or liqueur. Tier2: Calculated intake 0-16%; for children 17-48% of ADI.</td>
<td>SCF: ADI=12.5 mg/kg bw (21R 1988) JECFA: ADI=&quot;not specified&quot; (33R 1988)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>417</td>
<td>Tara gum</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (26R 1990) (use levels normally in the range of 0.5-1 %) JECFA: ADI=&quot;not specified&quot; (30R 1986)</td>
<td>Exposure needed as evaluation linked to exposure estimates</td>
</tr>
<tr>
<td>418</td>
<td>Gellan gum</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (not covering specific dietary purposes) (26R1990) JECFA: ADI&quot;not specified&quot; (37R 1990)</td>
<td>-</td>
</tr>
<tr>
<td>420</td>
<td>Sorbitol; Sorbitol syrup</td>
<td>Allowed (together with E 421 + E 953 + 965-7 q.s. for non sweetener purposes in food in general except beverages. Allowed as sweetener q.s. in desserts, edible ices, confectionery, breakfast cereals, sauces, mustard etc. Not permitted in beverages. Tier0: exposure not examined</td>
<td>SCF found this polyol &quot;acceptable&quot; with the warning that laxation may be observed at high intakes (&gt;20g/person). (16R 1984) JECFA: ADI=&quot;not specified&quot; (26R 1982)</td>
<td>Exposure data of this and the other polyols needed</td>
<td></td>
</tr>
<tr>
<td>421</td>
<td>Mannitol</td>
<td>Allowed (together with E 420 + E 953 + 965-7 q.s. for non sweetener purposes in food in general except beverages. Allowed as sweetener q.s. in desserts, edible ices, confectionery, breakfast cereals, sauces, mustard etc. Not permitted in beverages. Tier0: exposure not examined</td>
<td>SCF found this polyol &quot;acceptable&quot; with the warning that laxation may be observed at high intakes (&gt;20g/person). (16R 1984) JECFA: ADI=&quot;not specified&quot; (30R 1986)</td>
<td>Exposure data of this and the other polyols needed</td>
<td></td>
</tr>
<tr>
<td>422</td>
<td>Glycerol</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (11R 1981). Not acceptable as sweetener (43R 1997) JECFA: ADI=&quot;not specified&quot; (20R 1976)</td>
<td>Exposure should be monitored to ensure that glycerol is not used as sweetener</td>
</tr>
<tr>
<td>425i</td>
<td>Konjac glucomannane</td>
<td>Foodstuffs in general 10 g/kg</td>
<td>Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable&quot; up to 1% in food. Exposure should not exceed 3/person/day (41R 1996) JECFA: ADI=&quot;not specified&quot; for konjac flour (46R 1996)</td>
<td>-</td>
</tr>
<tr>
<td>431</td>
<td>Polyoxyethylene(40)steartate</td>
<td>May be present in some imported wines otherwise not authorized</td>
<td>Tier0: exposure not examined</td>
<td>SCF: &quot;Not acceptable&quot; (lack of data) (15R 1983) JECFA: ADI=25 mg/kg bw (Group with E432-6)</td>
<td>Re-evaluation if use is continued</td>
</tr>
<tr>
<td>432</td>
<td>Polyoxyethylene sorbitan monolaurate (polysorbate 20)</td>
<td>Limited number of foods among which fine bakery wares, desserts 3 g/kg, edible ices, confectionery and soups 1 g/kg. &quot;Milk and cream analogues&quot; 5 g/kg. Dietary supplements q.s. Not in beverages unless &quot;milk analogues&quot; may also be intended for drinking; Also permitted as carriers for antifoaming agents, colours and fat soluble antioxidants.</td>
<td>Tier2: Calculated intake 2-78%; for children 47-107% of ADI Tier3: further examination needed</td>
<td>SCF: ADI= 10 mg/kg bw (group)(15R 1983; confirmed for polysorbate in 34R 1993) JECFA: ADI=25 mg/kg bw (17R 1973)</td>
<td>Update of evaluation recommended if exposure significant. SCF is currently evaluating the question of residual ethylene oxide</td>
</tr>
<tr>
<td>433</td>
<td>Polyoxyethylene sorbitan monooleate (polysorbate 80)</td>
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<tr>
<td>434</td>
<td>Polyoxyethylene sorbitan monopalmitate (polysorbate 40)</td>
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<tr>
<td>435</td>
<td>Polyoxyethylene sorbitan monostearate (polysorbate 60)</td>
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<tr>
<td>436</td>
<td>Polyoxyethylene sorbitan tristearate (polysorbate 85)</td>
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</tr>
<tr>
<td>440</td>
<td>Pectin and amidated pectin</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (15R 1983) JECFA: ADI=&quot;not specified&quot; (25R 1981)</td>
<td>-</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td>442</td>
<td>Ammonium phosphatides</td>
<td>Only cocoa and chocolate products and cocoa-based confectionery 10 g/kg Also permitted as carrier for antioxidants</td>
<td>Tier2: Calculated intake 1-11%, for children 8-26% of ADI</td>
<td>SCF: ADI=30 mg/kg bw (7R 1978)</td>
<td>-</td>
</tr>
<tr>
<td>444</td>
<td>Sucrose acetate isobutyrate</td>
<td>Only in non-alcoholic flavoured cloudy drinks 300 mg/litre</td>
<td>Tier2: Calculated intake for children 14% of SCF ADI</td>
<td>SCF: ADI=10 mg/kg bw (32R 1992)</td>
<td>-</td>
</tr>
<tr>
<td>445</td>
<td>Glycerol esters of wood rosin</td>
<td>Only in non-alcoholic flavoured cloudy drinks 100 mg/litre and on citrus fruits 50 mg/kg</td>
<td>Tier1: ADI not exceeded</td>
<td>SCF: ADI=12.5 mg/kg bw (32R 1992)</td>
<td>-</td>
</tr>
<tr>
<td>448</td>
<td>Diphosphates</td>
<td>See E 338</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>451</td>
<td>Triphosphates</td>
<td>See E 338</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>452</td>
<td>Polyphosphates</td>
<td>See E 338</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>459</td>
<td>beta-Cyclodextrin</td>
<td>Permitted as carrier. Max. level 1g/kg additive</td>
<td>Tier0: exposure not examined as &quot;new&quot; additive</td>
<td>SCF: ADI=5 mg/kg bw (41R 1996)</td>
<td>-</td>
</tr>
<tr>
<td>460</td>
<td>i) Microcrystalline cellulose</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (44R 1997)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ii) Powdered cellulose</td>
<td>q.s.</td>
<td>Not possible</td>
<td>JECFA: ADI=&quot;not specified&quot; according to revised specification (49R 1997)</td>
<td>-</td>
</tr>
<tr>
<td>461</td>
<td>Methyl cellulose</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (44R 1997)</td>
<td>-</td>
</tr>
<tr>
<td>463</td>
<td>Hydroxypropyl cellulose</td>
<td>q.s.</td>
<td>Not possible</td>
<td>JECFA: ADI=&quot;not specified&quot; (44R 1997)</td>
<td>-</td>
</tr>
<tr>
<td>464</td>
<td>Ethyl methyl cellulose</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (44R 1997)</td>
<td>-</td>
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<tr>
<td>465</td>
<td>Carboxy methyl cellulose</td>
<td>q.s.</td>
<td>Not possible</td>
<td>JECFA: ADI=&quot;not specified&quot; (44R 1997)</td>
<td>-</td>
</tr>
<tr>
<td>466</td>
<td>Sodium carboxy methyl cellulose</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (44R 1997)</td>
<td>-</td>
</tr>
<tr>
<td>467</td>
<td>Enzymatically hydrolysed cellulose</td>
<td>q.s.</td>
<td>Not possible</td>
<td>JECFA: ADI=&quot;not specified&quot; (44R 1997)</td>
<td>-</td>
</tr>
<tr>
<td>468</td>
<td>Cross linked carboxy methyl cellulose</td>
<td>Only permitted as carrier for sweeteners and food supplements</td>
<td>Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable&quot; as disintegrant in sweeteners (35R 1994) and dietary supplements (110M Jan. 1998)</td>
<td>-</td>
</tr>
<tr>
<td>469</td>
<td>Enzymatically hydrolysed cellulose</td>
<td>See 461</td>
<td></td>
<td>JECFA: not evaluated</td>
<td></td>
</tr>
<tr>
<td>470</td>
<td>Sodium, potassium, calcium and magnesium salts of fatty acids</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (25R 1990)</td>
<td>Questions on specification should be clarified</td>
</tr>
<tr>
<td>570</td>
<td>Fatty acids</td>
<td>q.s.</td>
<td>Not possible</td>
<td>JECFA: ADI=&quot;not specified&quot; (29R 1985)</td>
<td>1</td>
</tr>
<tr>
<td>471</td>
<td>Mono- and diglycerides of fatty acids</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: Not formally evaluated but accepted in certain baby food (43R 1997)</td>
<td>-</td>
</tr>
<tr>
<td>472a</td>
<td>Acetic acid esters of mono- and diglycerides of fatty acids</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (7R 1977)</td>
<td>-</td>
</tr>
<tr>
<td>472b</td>
<td>Lactic acid esters of mono- and diglycerides of fatty acids</td>
<td>q.s.</td>
<td>Not possible</td>
<td>JECFA: ADI=&quot;not specified&quot; (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>472c</td>
<td>Citric acid esters of mono- and diglycerides of fatty acids</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (7R 1977)</td>
<td>-</td>
</tr>
<tr>
<td>472d</td>
<td>Tartaric acid esters of mono- and diglycerides of fatty acids</td>
<td>q.s.</td>
<td>Not possible</td>
<td>JECFA: ADI=&quot;not specified&quot; (17R 1973)</td>
<td>-</td>
</tr>
<tr>
<td>472e</td>
<td>Mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=50 mg/kg bw (7R 1977; changed to 25 mg/kg bw (temp.) at 107M June 1997)</td>
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<tr>
<td>472f</td>
<td>Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids</td>
<td>Series of foods including fine bakery wares and sauces 10 g/kg, edible ices, confectionary and desserts 5 g. Also to dietetic food to replace meals (5g/kg). In some non alcoholic beverages 5 g/litre. Also permitted as carrier for colours and fat soluble antioxidants</td>
<td>Tier2: Calculated intake 4-138%; for children 226-374% of ADI Tier3: further examination needed.</td>
<td>SCF: ADI= “not specified” (7R 1977) JECFA: included in E472e</td>
<td>Clarify possible identity with E 472e and monitor exposure 1</td>
</tr>
<tr>
<td>473</td>
<td>Sucrose esters of fatty acids Sucroglycerides</td>
<td>Series of foods 2-10 g/kg. Not in beverages unless &quot;milk and cream analogues&quot; may also be intended for drinking (5 g/kg). Also permitted as carrier for colours and fat soluble antioxidants</td>
<td>Tier2: Calculated intake 3-53%; for children 114-160% of ADI Tier3: further examination needed</td>
<td>SCF: ADI=25 mg/kg bw (7R 1978) JECFA: ADI=25 mg/kg bw (17R 1973)</td>
<td>Exposure data desirable 1</td>
</tr>
<tr>
<td>474</td>
<td>Polyglycerol esters of fatty acids</td>
<td>Series of foods 2-10 g/kg. Not in beverages unless &quot;milk and cream analogues&quot; may also be intended for drinking (5 g/kg). Also permitted as carrier for colours and fat soluble antioxidants</td>
<td>Tier2: Calculated intake 3-53%; for children 114-160% of ADI Tier3: further examination needed</td>
<td>SCF: ADI=25 mg/kg bw (7R 1978) JECFA: ADI=25 mg/kg bw (17R 1973)</td>
<td>Exposure data desirable 1</td>
</tr>
<tr>
<td>476</td>
<td>Polyglycerol polyricinoleate</td>
<td>Only low fat spreads and dressings 4 g/kg, cocoa-based confectionary including chocolate 5 g/kg. Not in beverages (0).</td>
<td>Tier2: Calculated intake 4-33%; for children 49-53% of ADI</td>
<td>SCF: ADI=7.5 mg/kg bw (7R 1978) JECFA: ADI=7.5 mg/kg bw (17R 1973)</td>
<td>- 0</td>
</tr>
<tr>
<td>477</td>
<td>Propane-1,2-diol esters of fatty acids</td>
<td>Series of foods 5-30 g/kg. Not in beverages unless &quot;milk and cream analogues&quot; may also be intended for drinking (5 g/kg).</td>
<td>Tier1: ADI not exceeded Tier2: Calculated intake 1-10%; for children 5% of ADI Tier3: further examination needed</td>
<td>SCF: ADI=25 mg/kg bw expressed as propylene glycol (i.e. the &quot;real&quot; ADI is higher). (7R 1977) JECFA: ADI=25 mg/kg bw expressed as propylene glycol (17R 1973)</td>
<td>Status for data requested by SCF 1</td>
</tr>
<tr>
<td>479b</td>
<td>Thermally oxidized soya bean oil</td>
<td>Only fat emulsions for frying purposes 5 g/kg</td>
<td>Tier2: Calculated intake 1-10%; for children 5% of ADI</td>
<td>SCF: ADI=25 mg/kg bw (2R 1988) JECFA: ADI=30 mg/kg bw (39R 1992)</td>
<td>- 0</td>
</tr>
<tr>
<td>495</td>
<td>Sodium stearoyl-2-lactylate</td>
<td>Several foods including bread, breakfast cereals 2-5 g/kg. In beverages only in some alcoholic beverages (8 g/litre) and in powders for the preparation of hot beverages 2 g/litre</td>
<td>Tier2: Calculated intake 2-114%; for children 136-268% of ADI Tier3: further examination needed</td>
<td>SCF: ADI=25 mg/kg bw (5R 1978; not reported in any detail) JECFA: accepts 500 mg/kg flour as dough strengthening agent (9R 1965); request for new data (55R 2000)</td>
<td>Data on hydrolysis needed 3</td>
</tr>
<tr>
<td>482</td>
<td>Stearyl tartrate</td>
<td>Only bakery wares 4 g/kg and desserts 5 g/kg</td>
<td>Tier2: Calculated intake 1-98%; for children 49-112% of ADI Tier3: further examination needed</td>
<td>SCF: ADI=20 mg/kg bw (5R 1978; not reported in any detail) JECFA: accepts 500 mg/kg flour as dough strengthening agent (9R 1965); request for new data (55R 2000)</td>
<td>Data on hydrolysis needed 3</td>
</tr>
<tr>
<td>491</td>
<td>Sorbitan monostearate Sorbitan tristearate Sorbitan monopalmitate</td>
<td>Together with E491-2+495: Several foods 5-25 g/kg. Beverages only tea concentrates (including fruit and herbal) 0.5 g/litre Also permitted as carriers for colours and anti-foaming agents</td>
<td>Tier2: Calculated intake 3-75%; for children 150-190% of ADI Tier3: further examination needed</td>
<td>SCF: ADI=25 mg/kg bw (7R 1978) JECFA: ADI=25 mg/kg bw (17R 1973) (group including also E491 and E494)</td>
<td>Exposure estimates and re-evaluation 4</td>
</tr>
<tr>
<td>492</td>
<td>Sorbitan monolaurate</td>
<td>Together with E491-2+495: Several foods 5-25 g/kg. Beverages only tea concentrates (including fruit and herbal) 0.5 g/litre Also permitted as carriers for colours and anti-foaming agents</td>
<td>Tier2: Calculated intake 16-354%; for children 657-803% of ADI Tier3: further examination needed</td>
<td>SCF: ADI=5 mg/kg bw (7R 1977) JECFA: ADI=25 mg/kg bw (26R 1982) (group including also E491, E 492 and E495)</td>
<td>Exposure estimates and re-evaluation 4</td>
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<td>170</td>
<td>Calcium carbonates</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI= “not specified” (25R 1990) JECFA: ADI=&quot;not specified&quot; (29R 1985)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sodium carbonates</td>
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<td>Potassium carbonates</td>
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<td></td>
<td>Ammonium carbonates</td>
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<td></td>
<td>Magnesium carbonates</td>
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<tr>
<td>501</td>
<td>Hydrochloric acid</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA ADI=&quot;not specified&quot; (29R 1985)</td>
<td>-</td>
<td>0</td>
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<tr>
<td>502</td>
<td>Potassium chloride</td>
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<tr>
<td>503</td>
<td>Calcium chloride</td>
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<tr>
<td>504</td>
<td>Magnesium chloride</td>
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<tr>
<td>507</td>
<td>Stannous chloride</td>
<td>Only canned and bottled white asparagus 25 mg/kg as Sn</td>
<td>Tier0: exposure not examined PMTDI cannot be reached</td>
<td>SCF: PMTDI = 2 mg/kg bw as Sn. “Acceptable as colour stabilizing agent for white vegetables” (25R 1990) JECFA: PTWI = 14 mg/kg bw as Sn (55R 2000)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>511</td>
<td>Silicic acid</td>
<td>Only egg white 30 mg/kg, candied, crystallized and glazed fruits and vegetables 200 mg/kg (as Al)</td>
<td>Tier3: further examination needed for all aluminium containing additives</td>
<td>SCF: PTWI=7 mg/kg bw (as Al from all sources) (25R 1990). JECFA: PTWI=7 mg/kg bw (as Al from all sources (33R 1988)</td>
<td>Aluminium from all sources should be re-evaluated. See also E 173, 541, 554-9 and 558</td>
<td>4</td>
</tr>
<tr>
<td>512</td>
<td>Sulphuric acid</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (29R 1985)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>513</td>
<td>Sodium hydroxide</td>
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<tr>
<td>514</td>
<td>Potassium hydroxide</td>
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<tr>
<td>515</td>
<td>Aluminium hydroxide</td>
<td></td>
<td></td>
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<tr>
<td>516</td>
<td>Magnesium hydroxide</td>
<td></td>
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<tr>
<td>517</td>
<td>Ammonium hydroxide</td>
<td></td>
<td></td>
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<tr>
<td>518</td>
<td>Ammonium sulphate</td>
<td>Only as carrier</td>
<td></td>
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<tr>
<td>521</td>
<td>Sulphate</td>
<td></td>
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<tr>
<td>522</td>
<td>Potassium sulphate</td>
<td></td>
<td></td>
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<tr>
<td>523</td>
<td>Calcium sulphate</td>
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<tr>
<td>524</td>
<td>Sodium ferrocyanide</td>
<td>Salts and its substitutes 20 mg/kg</td>
<td>75 g salt or substitute a day to reach ADI (60 kg person) ADI cannot be exceeded</td>
<td>SCF: ADI=0.025 mg/kg bw (25R 1990) JECFA: ADI=0.025 mg/kg bw (18R 1974)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>525</td>
<td>Potassium ferrocyanide</td>
<td></td>
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<tr>
<td>526</td>
<td>Aluminium ferricyanide</td>
<td></td>
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<tr>
<td>527</td>
<td>Magnesium hydroxide</td>
<td>Only scones and sponge wares, 1 g/kg expressed as Al</td>
<td>Tier3: further examination needed for all aluminium containing additives</td>
<td>SCF: PTWI=7 mg/kg bw (as Al from all sources) (25R 1990). JECFA: PTWI=7 mg/kg bw (as Al from all sources (33R 1988)</td>
<td>Aluminium from all sources should be re-evaluated. See also E 173, 520-3, 554-9 and 558</td>
<td>4</td>
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<tr>
<td>528</td>
<td>Calcium ferricyanide</td>
<td></td>
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<tr>
<td>530</td>
<td>Sodium ferricyanide</td>
<td></td>
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<tr>
<td>531</td>
<td>Magnesium silicate</td>
<td></td>
<td></td>
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<tr>
<td>532</td>
<td>Silicon dioxide</td>
<td>Dried powdered foodstuffs, salt and salt substitutes, sliced hard cheese and sliced processed cheese 10 g/kg Dietary supplements q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (29R + 30R 1985 + 1986) (including aluminium silicates)</td>
<td>The use of talc needs re-evaluation. No priority for the other silicates</td>
<td>4</td>
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<tr>
<td>533</td>
<td>Sodium aluminium phosphate, acid</td>
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<tr>
<td>534</td>
<td>Calcium silicate</td>
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<tr>
<td>535</td>
<td>Magnesium silicate</td>
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<tr>
<td>536</td>
<td>Magnesium trisilicate</td>
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<tr>
<td>538</td>
<td>Talcum</td>
<td></td>
<td></td>
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</tr>
</tbody>
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<th>Comments/recommendations</th>
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</thead>
<tbody>
<tr>
<td>554</td>
<td>Sodium aluminium silicate</td>
<td>Dried powdered foodstuffs, salt and salt substitutes, sliced hard cheese and sliced processed cheese 10 g/kg</td>
<td>24 g of the foodstuffs in question could reach the PTWI (calculating with $\frac{1}{2}$ Al in the salts and full availability) Tier3: further examination needed for all aluminium containing additives</td>
<td>SCF: PTWI = 7 mg/kg bw (as Al from all sources), <em>Although there is reason to believe that Al from these substances is less absorbed than form other Al salts this needs to be documented.</em> (25R 1990) JECFA: ADI=&quot;not specified&quot; (29R 1985)</td>
<td>Needed: data on bioavailability See also E 173, 520-3, 541, and 558 3</td>
</tr>
<tr>
<td>555</td>
<td>Potassium aluminium silicate</td>
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<tr>
<td>556</td>
<td>Calcium aluminium silicate</td>
<td>Some of the substances also permitted as carriers</td>
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<tr>
<td>557</td>
<td>Aluminium silicate</td>
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<tr>
<td>558</td>
<td>Bentonite</td>
<td>Only carrier for colours max 5.6%</td>
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<tr>
<td>570</td>
<td>Fatty acids</td>
<td>See E 470</td>
<td></td>
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<tr>
<td>574</td>
<td>Gluconic acid</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (5IR 1998)</td>
<td>-</td>
</tr>
<tr>
<td>574</td>
<td>Glucono-delta-lactone</td>
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<tr>
<td>575</td>
<td>Sodium gluconate</td>
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<tr>
<td>576</td>
<td>Potassium gluconate</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>577</td>
<td>Calcium gluconate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>579</td>
<td>Ferrous gluconate</td>
<td>Only olives darkened by oxidation 150 mg/kg as Fe</td>
<td>Exposure insignificant compared with other sources of Fe</td>
<td>SCF: &quot;acceptable as colour stabilizing agent in olives” (based on PMTDI=0.8 mg/kg bw as iron (25R 1990) JECFA: Included in PMTDI=0.8 mg/kg bw as iron (31R 1987)</td>
<td>-</td>
</tr>
<tr>
<td>585</td>
<td>Ferrous lactate</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>592</td>
<td>Fatty acids</td>
<td>See E 470</td>
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<td></td>
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<tr>
<td>602</td>
<td>Gluconic acid</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>602</td>
<td>Monosodium glutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>602</td>
<td>Monopotassium glutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>602</td>
<td>Calcium diglutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>602</td>
<td>Monoammonium glutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>602</td>
<td>Magnesium diglutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>619</td>
<td>Gluconic acid</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>619</td>
<td>Monosodium glutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>619</td>
<td>Monopotassium glutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>619</td>
<td>Calcium diglutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>619</td>
<td>Monoammonium glutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
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<tr>
<td>619</td>
<td>Magnesium diglutamate</td>
<td>All foods except those where additives are not permitted, 10g/kg condiments and seasonings q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; (25R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>Update of evaluation to include new data 1</td>
</tr>
<tr>
<td>640</td>
<td>Glycine and its sodium salt</td>
<td>q.s.</td>
<td>Not possible Tier0: exposure not examined</td>
<td>SCF: ADI= &quot;not specified&quot; when used as acidity regulator, flavour modifier and humectant. Use as sweetener not included in evaluation. (25R 1990) JECFA: not evaluated</td>
<td>-</td>
</tr>
<tr>
<td>900</td>
<td>Dimethyl polysiloxane</td>
<td>Only few foods including beverages 10 mg/kg or litre</td>
<td>Tier1: ADI not exceeded</td>
<td>SCF: ADI=1.5 mg/kg bw (based on JECFA) (25R 1990) JECFA: ADI=1.5 mg/kg bw (18R 1974)</td>
<td>Clarification of specification 1</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>901</td>
<td>Bees wax, white and yellow</td>
<td>As glazing agents only for confectionery including chocolate, small products of fine bakery wares coated with chocolate, snacks, nuts, coffee beans, dietary food supplements, fresh citrus fruits, melons, apples, peaches, pineapples and pears. q.s.</td>
<td>Tier0: exposure not examined</td>
<td>SCF: temporarily acceptable as glazing agent (26R 1990) JECFA: “acceptable” (food constituent; present uses of no toxicological concern) (39R 1992)</td>
<td>temporary SCF status 2</td>
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<tr>
<td>902</td>
<td>Candelilla wax</td>
<td></td>
<td></td>
<td>SCF: temporarily acceptable as glazing agent (26R 1990) JECFA: no data but “acceptable” (present uses of no toxicological concern) (39R 1992)</td>
<td>temporary SCF status 2</td>
</tr>
<tr>
<td>903</td>
<td>Carnauba wax</td>
<td></td>
<td></td>
<td>SCF: “acceptable” as glazing agent up to 200 mg/kg (128M Jul. 2001) JECFA: ADI=7 mg/kg bw (39R 1992)</td>
<td>-</td>
</tr>
<tr>
<td>904</td>
<td>Shellac</td>
<td></td>
<td></td>
<td>SCF: temporarily acceptable as glazing agent (26R 1990) JECFA: “acceptable” (present uses of no toxicological concern) (39R 1992)</td>
<td>temporary SCF status 2</td>
</tr>
<tr>
<td>905</td>
<td>Microcrystalline wax</td>
<td>q.s. as surface treatment of confectionery (excluding chocolate), chewing gum and melons, papaya, mango and avocado</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI=20 mg/kg bw (37R 1995) JECFA: ADI=20 mg/kg bw (44R 1995)</td>
<td>-</td>
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<tr>
<td>912</td>
<td>Montan acid esters</td>
<td>q.s. on fresh citrus fruits, melon, mango, papaya, avocado and pineapple</td>
<td>Tier0: exposure not examined</td>
<td>SCF: temporarily acceptable as glazing agent up to 140 mg/kg (26R 1990) JECFA: not evaluated (on agenda for 49M 1999, but removed as no data were submitted)</td>
<td>on SCF agenda 1</td>
</tr>
<tr>
<td>914</td>
<td>Oxidized polyethylene wax</td>
<td>q.s. on fresh citrus fruits, melon, mango, papaya, avocado and pineapple</td>
<td>Tier0: exposure not examined</td>
<td>SCF: temporarily acceptable as glazing agent up to 140 mg/kg (26R 1990) JECFA: not evaluated</td>
<td>temporary SCF status 2</td>
</tr>
<tr>
<td>920</td>
<td>L-Cysteine</td>
<td>may be used q.s. as a flour treatment agent only</td>
<td>Tier0: exposure not examined</td>
<td>SCF: “acceptable” as flour treatment agent (25R 1990) JECFA: not evaluated</td>
<td>-</td>
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<tr>
<td>927b</td>
<td>Carbamide</td>
<td>Sugar-free chewing gum 30 g/kg</td>
<td>Tier0: exposure not examined</td>
<td>SCF: acceptable for use in sugar-free chewing gum at a level up to 3% (81st meeting 9-10/12/91 JECFA: acceptable (3% in chewing gum) as texturizer (41R 1993)</td>
<td>-</td>
</tr>
<tr>
<td>938</td>
<td>Argon</td>
<td>q.s.</td>
<td></td>
<td>SCF: Toxicologically acceptable as packaging gases and propellants (Helium not included in evaluation) (25R 1990) JECFA (for nitrogen): no ADI necessary (24R 1980) (for nitrous oxide): acceptable as propellant (29R 1995) Others not evaluated</td>
<td>-</td>
</tr>
<tr>
<td>950</td>
<td>Acesulfame K</td>
<td>Beverages: 350 mg/litre Solid foods: 350-1000 mg/kg</td>
<td>Tier2: Calculated intake 2-37%; for children 3-107% of ADI Tier3: further examination needed</td>
<td>SCF: ADI= 9 mg/kg bw (16R 1984; confirmed at 120M March 2000) JECFA: ADI=15 mg/kg bw (37M 1990)</td>
<td>-</td>
</tr>
<tr>
<td>951</td>
<td>Aspartame</td>
<td>Beverages: 600 mg/litre Solid foods: 350-2000 mg/kg</td>
<td>Tier2: Calculated intake for children 1-40% of ADI</td>
<td>SCF: ADI= 40 mg/kg bw (21R 1988; confirmed at 107M June 97) JECFA: ADI=40 mg/kg bw (25M 1981)</td>
<td>On the agenda of SCF</td>
</tr>
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<tr>
<td>952</td>
<td>Cyclamic acid and its sodium and calcium</td>
<td>Beverages: 400 mg/litre Solid foods: 250-1000</td>
<td>Tier2: Calculated intake 0-10%; for children 1-74% of old ADI (11 mg/kg)</td>
<td>SCF: ADI=7 mg/kg bw (120M March 2000)</td>
<td>Exposure data and possibly reduction in use levels</td>
<td>1</td>
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<tr>
<td></td>
<td>salts</td>
<td></td>
<td></td>
<td>JECFA: ADI=11 mg/kg bw (26R 1982)</td>
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<tr>
<td>953</td>
<td>Isomalt</td>
<td>Allowed (together with E 420-1 + E 965-7) q.s. for non sweetener purposes in food in general except beverages. Allowed as sweetener q.s. in desserts, edible ices, confectionery, breakfast cereals, sauces, mustard etc. Not permitted in beverages.</td>
<td>Tier0: exposure not examined</td>
<td>SCF found this polyol &quot;acceptable&quot; with the warning that laxation may be observed at high intakes (&gt;20g/person). (16R 1984; confirmed in 21R 1988) JECFA: ADI=&quot;not specified&quot; (29R 1985)</td>
<td>Exposure data of this and the other polyols needed</td>
<td>1</td>
</tr>
<tr>
<td>954</td>
<td>Saccharin and its sodium, potassium and calcium salts</td>
<td>Beverages: 80-100 mg/litre Solid foods: 100-500 mg/kg</td>
<td>Tier2: Calculated intake for children 2-51% of ADI</td>
<td>SCF: ADI=5 mg/kg bw (97M 2 June 1995)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>957</td>
<td>Thaumatin</td>
<td>Confectionary: 50 mg/kg</td>
<td>Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable&quot; (21R 1988) JECFA: ADI=&quot;not specified&quot; (29R 1985)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>959</td>
<td>Neohesperidine dihydrochalcone (NHDC)</td>
<td>As sweetener: Beverages: 30-50 mg/litre Solid foods: 50-150 mg/kg</td>
<td>Tier2: Calculated intake for children 1-18% of ADI</td>
<td>SCF: ADI= 5 mg/kg bw (21R 1988) JECFA: not evaluated</td>
<td>Exposure data of this and the other polyols needed</td>
<td>2</td>
</tr>
<tr>
<td>955</td>
<td>Maltitol; Maltitol syrup</td>
<td>Allowed (together with E 420-1 + E 953 + E 966-7) q.s. for non sweetener purposes in food in general except beverages. Allowed as sweetener q.s. in desserts, edible ices, confectionery, breakfast cereals, sauces, mustard etc. Not permitted in beverages.</td>
<td>Tier0: exposure not examined</td>
<td>SCF found this polyol &quot;acceptable&quot; with the warning that laxation may be observed at high intakes (&gt;20g/person). (16R 1984; new spec 119M Dec. 1999) JECFA: ADI=&quot;not specified&quot; (49R 1997)</td>
<td>Exposure data of this and the other polyols needed</td>
<td>1</td>
</tr>
<tr>
<td>956</td>
<td>Lactitol</td>
<td>Allowed (together with E 420-1 + E 953 + E 965+7) q.s. for non sweetener purposes in food in general except beverages. Allowed as sweetener q.s. in desserts, edible ices, confectionery, breakfast cereals, sauces, mustard etc. Not permitted in beverages.</td>
<td>Tier0: exposure not examined</td>
<td>SCF found this polyol &quot;acceptable&quot; with the warning that laxation may be observed at high intakes (&gt;20g/person). (16R 1984; new spec 119M Dec. 1999) JECFA: ADI=&quot;not specified&quot; (27R 1983)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>957</td>
<td>Xylitol</td>
<td>Allowed (together with E 420-1 + E 953 + E 965-6) q.s. for non sweetener purposes in food in general except beverages. Allowed as sweetener q.s. in desserts, edible ices, confectionery, breakfast cereals, sauces, mustard etc. Not permitted in beverages.</td>
<td>Tier0: exposure not examined</td>
<td>SCF found this polyol &quot;acceptable&quot; with the warning that laxation may be observed at high intakes (&gt;20g/person). (16R 1984) JECFA: ADI=&quot;not specified&quot; (27R 1983)</td>
<td>Exposure data of this and the other polyols needed</td>
<td>1</td>
</tr>
<tr>
<td>999</td>
<td>Quillaia extract</td>
<td>Water-based flavoured non-alcoholic drinks 200 mg/litre calculated as anhydrous extract</td>
<td>Tier2: Calculated intake for children 1-71% of ADI</td>
<td>SCF: ADI=5 mg/kg bw (7R 1978) JECFA: ADI= 5 mg/kg bw (29R 1985)</td>
<td>Exposure data and possibly re-evaluation</td>
<td>2</td>
</tr>
<tr>
<td>1103</td>
<td>Invertase</td>
<td>q.s.</td>
<td>Only requested for sweets so exposure likely to be small</td>
<td>SCF: &quot;acceptable&quot; when derived from Saccharomyces cerevisiae (32R 1996) JECFA: &quot;acceptable&quot; from S. cerevisiae (57M 2001)</td>
<td>-</td>
<td>0</td>
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<tr>
<td>1105</td>
<td>Lysozyme</td>
<td>q.s. in ripened cheese</td>
<td>Exposure small</td>
<td>SCF: &quot;acceptable&quot; as egg for cheese making (80M Oct 1991) JECFA: &quot;acceptable&quot; as derived from edible animal tissue commonly used as food (39R 1992)</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

*Priorities: 0 = no need for any action; 1 = matters to be clarified; 2 = update of evaluation; 3 = some priority for re-evaluation 4 = priority for re-evaluation; 5 = high priority for re-evaluation; - = on the agenda of SCF, no need for further action
<table>
<thead>
<tr>
<th>E No</th>
<th>Name</th>
<th>Main uses according to directives</th>
<th>Intake estimate &amp; comments</th>
<th>SCF and JECFA evaluation</th>
<th>Comments/recommendations</th>
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<tr>
<td>1200</td>
<td>Polydextrose</td>
<td>q.s.</td>
<td>Not possible</td>
<td>SCF: ADI=&quot;not specified&quot; (keeping laxative effect in mind) (26R 1990) JECFA: ADI=&quot;not specified&quot; (31R 1987)</td>
<td>-</td>
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<tr>
<td>1201</td>
<td>Polyvinyl pyrrolidone</td>
<td>Dietary food supplements in tablet and coated tablet form. Also permitted as carrier for sweeteners</td>
<td>Tier0: exposure not examined</td>
<td>SCF: &quot;acceptable&quot; as excipient (26R 1990) JECFA: ADI=50 mg/kg bw (30R 1986)</td>
<td>Specification should ensure low residual levels of N-vinyl pyrrolidone</td>
</tr>
<tr>
<td>1202</td>
<td>Polyvinyl polypyrrolidone</td>
<td>Tier0: exposure not examined</td>
<td>SCF: Acceptable as disintegrating agent in tablets (26R 1990) JECFA: ADI=&quot;not specified&quot; (27R 1983)</td>
<td>Specification should ensure low residual levels of N-vinyl pyrrolidone</td>
<td>1</td>
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<tr>
<td>1404</td>
<td>Oxidized starch</td>
<td>q.s.</td>
<td>SCF: The Committee considered it unnecessary to establish individual ADIs provided technological usage remains at present-day levels. The Committee requested that this aspect should be kept under review by the Commission. (2R 1976 +13R 1981)</td>
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<td>1410</td>
<td>Monostarch phosphate</td>
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<td>1412</td>
<td>Distarch phosphate</td>
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<td>1413</td>
<td>Phosphated distarch phosphate</td>
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<td>1414</td>
<td>Acetylated distarch phosphate</td>
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<td>Acetylated starch</td>
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<td>1422</td>
<td>Acetylated distarch adipate</td>
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<tr>
<td>1440</td>
<td>Hydroxy propyl starch</td>
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<td></td>
<td></td>
<td>The specification concerning residual propylene chlorohydrin should be compared with the SCF recommendation and exposure estimates considered</td>
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<tr>
<td>1442</td>
<td>Hydroxy propyl distarch phosphate</td>
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<td>1450</td>
<td>Starch sodium octenyl succinate</td>
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<td>SCF: included (32R 1990) JECFA: included (26R 1982)</td>
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<tr>
<td>1451</td>
<td>Acetylated oxidized starch</td>
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<td></td>
<td>SCF: included (36R 1995) JECFA: included (57M2001)</td>
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<tr>
<td>1505</td>
<td>Triethyl citrate</td>
<td>Dried egg white and as carrier</td>
<td>Tier3: further examination initiated</td>
<td>SCF: ADI=20 mg/kg bw (26R 1990) JECFA: ADI=20 mg/kg bw (28R 1984)</td>
<td>-</td>
</tr>
<tr>
<td>1518</td>
<td>Glyceryl triacetate (triacetin)</td>
<td>Chewing gum and as carrier</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI=&quot;not specified&quot; (26R 1990) JECFA: ADI=&quot;not specified&quot; (18R 1975)</td>
<td>-</td>
</tr>
<tr>
<td>1520</td>
<td>Propane-1,2-diol (Propylene glycol)</td>
<td>Only as carrier for colours, emulsifiers, antioxidants and enzymes. Maximum 1 g/kg in the foodstuffs</td>
<td>Tier0: exposure not examined</td>
<td>SCF: ADI=25 mg/kg bw (40R 1996) JECFA: ADI=25 mg/kg bw (17R 1973)</td>
<td>Exposure estimates desirable</td>
</tr>
<tr>
<td>-</td>
<td>Polyethylene glycol 6000</td>
<td>Carrier for sweeteners</td>
<td>-</td>
<td>SCF: &quot;acceptable&quot; as excipient for sweetener tablets (36R 1994) JECFA: ADI=10 mg/kg bw (23R 1979)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Priorities: 0 = no need for any action; 1 = matters to be clarified; 2 = update of evaluation; 3 = some priority for re-evaluation 4 = priority for re-evaluation; 5 = high priority for re-evaluation; - = on the agenda of SCF, no need for further action
### Annex III Abbreviations, definitions and useful links

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ADI</td>
<td>Acceptable Daily Intake. A measure for the innocuousness of a substance. It is the amount of a food additive, expressed on a mg/kg body weight basis, that can be ingested daily over a lifetime without incurring any appreciable health risk, and is based on an evaluation of available toxicological data.</td>
</tr>
<tr>
<td>ADI not limited</td>
<td>A phrase which by the expert committees has been replaced by “ADI not specified” to avoid the misunderstanding that any dose would be safe.</td>
</tr>
<tr>
<td>ADI not specified</td>
<td>Is the term used when on the basis of the available toxicological, biochemical and clinical data, the total daily intake of the substance, arising from its natural occurrence and/or its present use or uses in food at the levels necessary to achieve the desired technological effect, will not represent a hazard to health. For this reason, the establishment of a numerical ADI is not considered necessary for these substances. It should be noted that any amount of such substances would not necessarily be toxicologically acceptable. Any additive allocated an “ADI not specified” must be used according to good manufacturing practice, i.e. it should be technologically efficacious, should be used at the lowest level necessary to achieve its technological effect, should not conceal inferior food quality or adulteration, and should not create a nutritional imbalance.</td>
</tr>
<tr>
<td>AFB1</td>
<td>Aflatoxin B1.</td>
</tr>
<tr>
<td>BIBRA</td>
<td>The British Industrial Biological Research Association.</td>
</tr>
<tr>
<td>bw</td>
<td>Body weight.</td>
</tr>
<tr>
<td>CA</td>
<td>Chromosome Aberration (test).</td>
</tr>
<tr>
<td>CAS-number</td>
<td>Chemical Abstract Service Registry Number.</td>
</tr>
<tr>
<td>CHO cells</td>
<td>Chinese Hamster Ovary cells.</td>
</tr>
<tr>
<td>CI</td>
<td>Colour Index.</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System.</td>
</tr>
<tr>
<td>Colourable foods</td>
<td>Term used in the monographs in this report for those foods, which may be added a series of, mostly, synthetic colours. They include non-alcoholic flavoured drinks and some alcoholic drinks, confectionery, fine bakers wares and desserts including ices and flavoured milk products. Other categories are special fish products and fish and meat analogues, snacks, mustard, cheese rind, sauces and soups, as well as various foods for special dietary purposes.</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid.</td>
</tr>
<tr>
<td>EINECS</td>
<td>European Inventory of Existing Commercial Chemical Substances</td>
</tr>
<tr>
<td>EPA</td>
<td>Environmental Protection Agency (USA).</td>
</tr>
<tr>
<td>EU</td>
<td>European Union.</td>
</tr>
<tr>
<td>EU monitoring system</td>
<td>The EU monitoring system is based on the recommendations given in the report of the working group on “Development of methods for monitoring intake of food additives in the European Union”, task 4.2 of the Scientific Co-operation (SCOOP) on questions relating to food. See also section 3.3. (Published on the Commission website: <a href="http://europa.eu.int/comm/food/fs/sfp/addit_flavor/flav15_en.pdf">http://europa.eu.int/comm/food/fs/sfp/addit_flavor/flav15_en.pdf</a>).</td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agriculture Organization (United Nations).</td>
</tr>
<tr>
<td>GALT</td>
<td>Gut-Associated Lymphoid Tissue.</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice.</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer (WHO).</td>
</tr>
<tr>
<td>im</td>
<td>Intramuscularly.</td>
</tr>
<tr>
<td>in vitro</td>
<td>Experiments in cell cultures and bacteria.</td>
</tr>
<tr>
<td>in vivo</td>
<td>Experiments in intact animals.</td>
</tr>
<tr>
<td>ip</td>
<td>Intraperitoneal.</td>
</tr>
<tr>
<td>IPCS</td>
<td>International Programme on Chemical Safety (WHO).</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry.</td>
</tr>
<tr>
<td>iv</td>
<td>Intravenous.</td>
</tr>
<tr>
<td>JECFA</td>
<td>Joint FAO/WHO Expert Committee on Food Additives.</td>
</tr>
<tr>
<td>JMPR</td>
<td>Joint FAO/WHO Meeting on Pesticide Residues.</td>
</tr>
<tr>
<td>LD₅₀</td>
<td>Lethal Dose, median.</td>
</tr>
<tr>
<td>LO(A)EL</td>
<td>Lowest Observed (Adverse) Effect Level.</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximum Tolerated Dose.</td>
</tr>
<tr>
<td>NEL</td>
<td>No Effect Level.</td>
</tr>
<tr>
<td>NNT</td>
<td>Nordic Working Group on Food Toxicology and Risk Assessment.</td>
</tr>
<tr>
<td>NO(A)EL</td>
<td>No Observable (Adverse) Effect Level.</td>
</tr>
<tr>
<td>NOC</td>
<td>N-nitroso compounds.</td>
</tr>
<tr>
<td>NTP</td>
<td>National Toxicology Programme (USA).</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development.</td>
</tr>
<tr>
<td>PMTDI</td>
<td>Provisional Maximum Tolerable Daily Intake. Term used like TDI.</td>
</tr>
<tr>
<td>po</td>
<td>Per os (by mouth).</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million.</td>
</tr>
<tr>
<td>PTWI</td>
<td>Provisional Tolerable Weekly Intake. Term used like TDI for substances, normally metals, which shows potential for accumulation.</td>
</tr>
<tr>
<td>RTCS</td>
<td>Registry of Toxic Chemical Substances.</td>
</tr>
<tr>
<td>se</td>
<td>Subcutaneous.</td>
</tr>
<tr>
<td>SCF</td>
<td>Scientific Committee on Food (previously for food).</td>
</tr>
<tr>
<td>SCOOP</td>
<td>Scientific COOPeration in EU (see above under EU monitoring system).</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum glutamate-oxalatetrasaminase.</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum Glutamate.PyruvateTransaminase.</td>
</tr>
<tr>
<td>SOS chromotest</td>
<td>DNA repair test.</td>
</tr>
<tr>
<td>TDI</td>
<td>Tolerable Daily Intake. Term, which in contrast to ADI, is used for substances that are normally not added deliberately to food.</td>
</tr>
<tr>
<td>Tier system</td>
<td>Used in connection with the EU monitoring system as described above and in section 3.3. In tier 0 it is decided whether to perform an exposure estimate at all. In tier 1 a rough estimate is performed on permitted levels and assuming high consumption (budget calculation). In tier 3 the maximum permitted levels are compared with national food consumption surveys. Tier 3 has not been performed yet, but will consist of a more close exposure estimate for those additives where tier 2 shows a potential for high intake compared with the ADI.</td>
</tr>
<tr>
<td>TMDI</td>
<td>Theoretical Maximum Daily Intake</td>
</tr>
<tr>
<td>VFA</td>
<td>Volatile Fatty Acids.</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization (United Nations).</td>
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</table>
Useful links:
- EU food additives: http://europa.eu.int/comm/food/fs/sfp/addit_flavor/additives/index_en.html
- Colours: http://europa.eu.int/comm/food/fs/sfp/addit_flavor/flav08_en.pdf
- Sweeteners: http://europa.eu.int/comm/food/fs/sfp/addit_flavor/flav10_en.pdf
- SCF outcome (reports): http://europa.eu.int/comm/food/fs/sc/scf/outcome_en.html
- JECFA main: http://www.who.int/pcs/jecfa/jecfa.htm
- JECFA summaries: http://jecfa.ilsi.org/
- JECFA toxicological monographs: http://www.inchem.org/pages/jecfa.html
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<tr>
<th>Name</th>
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<th>See E no</th>
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<td>Acacia gum (gum arabic)</td>
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<td>Acesulfame K</td>
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<td>Acetic acid</td>
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<td>Acetic acid esters of mono- and diglycerides of fatty acids</td>
<td>472a</td>
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<td>Acetylated distarch adipate</td>
<td>1422</td>
<td>See 1404</td>
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<td>Acetylated distarch phosphate</td>
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<td>See 1404</td>
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<td>Anthocyanins</td>
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<td>Aspartame</td>
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<td>Azorubine</td>
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<td>Bees wax, white and yellow</td>
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<td>Beetroot Red</td>
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<td>Bentonite</td>
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<td>beta-Apo-8'-carotenal(C30)</td>
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<td>beta-carotene</td>
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<td>beta-Cyclodextrin</td>
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<td>Betanin</td>
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<tr>
<td>Biphenyl, Diphenyl</td>
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### Annex IV Index of substances in alphabetical order

<table>
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<tr>
<th>Name</th>
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<td>Borax</td>
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<td>Brown HT</td>
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<td>Calcium aluminium silicate</td>
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<td>See 554</td>
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<td>Calcium ascorbate</td>
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<td>See 300</td>
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<tr>
<td>Calcium benzoate</td>
<td>213</td>
<td>See 210</td>
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<tr>
<td>Calcium carbonates</td>
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<td>See 500</td>
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<td>Calcium chloride</td>
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<td>See 507</td>
</tr>
<tr>
<td>Calcium citrates</td>
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<td>See 330</td>
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<tr>
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