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Review of the regulation and safety assessment of food substances in various countries and jurisdictions

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This review compares the regulations, definitions and approval processes for substances intentionally added to or unintentionally present in human food in the following specific countries/jurisdictions: Argentina, Australia, Brazil, Canada, China, the European Union, Japan, Mexico, New Zealand, and the United States. This includes direct food additives, food ingredients, flavouring agents, food enzymes and/or processing aids, food contact materials, novel foods, and nanoscale materials for food applications. The regulatory authority of each target jurisdiction/country uses its own regulatory framework and although the definitions, regulations and approval processes may vary among all target countries, in general there are many similarities. In all cases, the main purpose of each authority is to establish a regulatory framework and maintain/enforce regulations to ensure that food consumed and sold within its respective countries is safe. There is a move towards harmonisation of food regulations, as illustrated by Australia and New Zealand and by Mercosur. The European Union has also established regulations, which are applicable for all member states, to establish a common authorisation procedure for direct food additives, flavourings and enzymes. Although the path for approval of different categories of food additives varies from jurisdiction to jurisdiction, there are many commonalities in terms of the data requirements and considerations for assessment of the safety of use of food additives, including the use of positive lists of approved substances, pre-market approval, and a separation between science and policy decisions. The principles applied are largely reflective of the early work by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) committees and JECFA assessments of the safety of food additives for human and animal foods.

Keywords: food additives; novel food; food contact substances; flavouring agents; enzymes; processing aids; nanoscale materials; regulatory framework

Introduction

The purpose of this review is to present an overview and comparison of the regulation of substances added to foods in a number of different countries/jurisdictions, as well as the efforts of internationally recognised scientific and advisory bodies, such as the Codex Alimentarius Commission (CAC) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) with respect to the safety assessment of these substances.

The specific countries/jurisdictions addressed are Argentina, Australia, Brazil, Canada, China, the European Union (EU), Japan, Mexico, New Zealand, and the United States (herein referred to as the "target countries"). The choice of jurisdictions to be included was based on a number of factors, and was intended to include both of well-established and emerging regulatory systems. The substances added to human food that are included in this review are direct food additives, common food ingredients such as sugar, food contact materials, flavouring agents, food enzymes, and/or processing aids. In addition, information pertaining to the development of regulations for nanomaterials falls under the scope of this review. Pesticide residues, drug residues or contaminants (e.g. lead) are not addressed in detail. A full list of included substances and their definitions according to each target country is provided. It should be noted that regulatory information for each country may be updated frequently and this report was written as an overview of the regulatory framework for each country. To the best of our knowledge, regulatory information is current as of June 2012. It is recognised that the definitions of terms used in this document may vary by organisation.

International scientific and advisory committees

The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) established the CAC

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jointly in 1962 to address safety and nutritional quality of foods, and develop international standards to promote trade (Codex Alimentarius Commission 2006). The CAC is an intergovernmental body composed of delegations from FAO and WHO member states that participate in developing food standards. The CAC develops standards on the basis of sound scientific evidence provided by independent FAO/WHO scientific committees. JECFA, established prior to the CAC in 1956, is the oldest and most active of these. Primary roles of the CAC include establishing international food standards for approved food additives providing maximum levels in foods, maximum limits for contaminants and toxins, maximum residue limits for pesticides and for veterinary drugs used in veterinary animals, and establishing hygiene and technological function practice codes (Codex Alimentarius Commission 2006). The collection of these standards, codes of practice, guidelines and recommendations, constitute what is known as the Codex Alimentarius, a substantial and useful reference. While the standards set by the CAC serve as guidelines to nations, the CAC has no regulatory authority and their standards are not enforceable unless they have been adopted into the regulatory framework for a nation or otherwise indicated (Codex 2011). For example, the World Trade Organization (WTO) refers to the Codex Alimentarius Sanitary and Phytosanitary practice codes in the SPS Agreement for member country food safety purposes.

Expert scientific advice is provided to the CAC by JECFA. Independent scientific committee members are appointed as experts in their own right and not as representatives of their governments or employers. Initially developed by WHO and FAO to address the safety of food additives, JECFA also has extended its activities to evaluate the safety of contaminants and veterinary drug residues in food. Although the outcome of JECFA's evaluations does not have any direct bearing on the regulatory approval of use of a food additive in any specific country, its evaluations are widely recognised and may affect an application for approval for a new food additive in a particular country.

The Joint FAO/WHO Committee on Food Additives (JECFA)

The initial steps of the Committee were to establish general principles regarding the technical purpose of food additives as well as principles for safe use for these substances. Regarding the matter of technical purpose the Committee noted that food additives could serve a valuable technical function in food: (1) to maintain the nutritional quality of food; (2) to enhance keeping quality or stability, with resulting reductions in food wastage; (3) to make food attractive to consumers; and (4) to provide essential aids to processing.

The Committee established the following situations in which food additives should not be used: (1) to deceive the consumer; (2) to result in substantial reduction of the nutritional value of food; (3) when the desired effect can be obtained by good manufacturing practices; or (4) to disguise the use of faulty processing or handling techniques.

With respect to safety evaluation of food additives the Committee again established sound key general principles. They were: (1) it is impossible to establish absolute proof of non-toxicity for all members of the human population; (2) critically designed animal studies can provide a reasonable basis for evaluating the safety of food additives; (3) the decision as to a safe level for a food additive should be based on knowledge of the minimum dietary level that produces no unfavourable response in test animals; (4) decisions on the use of food additives must be based on the considered judgment of properly qualified scientists that the intake of the additive will be below any level which could be harmful to consumers; (5) the fate of the additive during food processing and preparation should be considered because of the possible formation of toxic substances and interaction of the food additive with components of food or other food additives; and (6) consideration should be given to groups within the population who for medical reasons may be especially vulnerable to certain food additives. The Committee went on to recommend that when a food additive is proposed for use, considerations should be given:

- to determine if there is a demonstrated benefit to consumers;
- to limit the use of food additives in the diets of infants and young children;
- to assess whether there are adequate data to derive specifications for identify and purity of the food additive; and
- to limit the level of use of food additives to the minimum required to achieve the desired technical effect.

The Committee also noted that permitted lists of food additives should be drawn up because the use of prohibited lists could entail several years of exposure to potentially harmful food additives before sufficient evidence was accumulated to place it on the prohibited list. The use of permitted lists would eliminate this danger. The Committee also agreed with the principle that consumers should be made aware of the presence of food additives in their food and noted that label declaration is the most effective method of achieving this result. With respect to regulatory control at the national level, the Committee noted that methods must be available to measure food additives in foods and that enforcement of levels of use through appropriate food legislation provided a reliable way of governing the use of food additives.

JECFA also established principles and procedures for the testing of food additives to establish the safety of food additive use (JECFA 1958). The Committee noted that food additives may be consumed over a substantial proportion of lifetime and emphasised the need for studies in appropriate animal species that would reflect the conditions of human exposure. The Committee further noted that no single pattern of tests could adequately cover the testing requirements of substances of such diverse structure and function as food additives and therefore the Committee strongly emphasised that the establishment of a uniform set of experimental procedures that would be standardised and obligatory was undesirable. For this reason, which still holds true today, the Committee decided that it was only possible to formulate general recommendations on testing procedures.

The general principles regarding the testing of food additives were identified including: (1) the selection of animal species for testing indicating that background information on species/strain, natural disease rates, tumour incidence, and duration of life was essential for proper interpretation of experimental results; (2) the importance of animal housing, diets, control groups and statistical procedures for the design of studies, and their interpretation; (3) the importance of dose selection emphasising the need to magnify the dose in experimental animals to overcome statistical limitations of the test design and to provide a means of studying dose–response relationships; (4) the need for biochemical mechanistic investigations to detect subtle physiological changes and to assist in data interpretation; and (5) the need to examine the potential for food additives to induce carcinogenesis, stating that no proven carcinogen should be considered suitable for use as a food additive in any amount (JECFA 1958). The results of the toxicological evaluations are the basis for the allocation of an acceptable daily intake (ADI) or tolerable intake for contaminants the Committee considered unavoidable.

The Committee also discussed the pivotal issue relating to the extrapolation of animal studies to humans noting that in most instances a dosage level can be identified that causes no demonstrable effect in animals. It also noted that a margin of safety of 100 could be applied in extrapolating animal data to humans to account for species differences in susceptibility, numerical differences in population ranges between the test animals and the human population, the greater variety of complicating disease processes in the human population, and the possibility of synergistic action among food additives. The Committee noted that application of a 100-fold margin of safety would limit the use of some food additives yet was an adequate margin of safety for most substances proposed for use as food additives at the time.

Additionally, the Committee established specifications for the identity and purity of food additives. From the viewpoint of industry the specifications of the substance/compound helped define suitability for use in food. Items included in the specifications document were: title or name in common usage; synonyms; chemical name (IUPAC); empirical (organic compounds) or chemical formula (inorganic compounds); structural formula; molecular weight; definition (percentage of the stated substance that should be present origin of the material if necessary); description (appearance, taste, odour and other general properties); identification tests; and purity tests (tests for impurities and their nature).

In the early 1990s the CAC recognised the need to formalise the risk analysis process. A definition of risk analysis was developed, through a series of consultations, that embodies risk assessment, risk management and risk communication (CAC 2005). Scientific committees such as JECFA are responsible for risk assessment, which includes hazard identification, hazard characterisation, exposure assessment and risk characterisation. In response to formalisation of the risk assessment process, JECFA has increased its emphasis on exposure assessment, which includes predicted intake for substances new to the market or for which few relevant data exist and estimated intake of food additives and contaminants for which sufficient information exists for such an analysis. Within each jurisdiction, responsibility for each of the three components of risk analysis is often divided among different divisions of the regulatory agencies or to separate bodies. For example, in the EU, the Directorate General for Health and Consumers has risk management responsibility whereas the European Food Safety Authority (EFSA) is an independent body with risk assessment and risk communication responsibilities. Further discussion of the process of risk analysis of components in foods, including risk management and risk communication, is outside the scope of this review.

When one looks back at this early work of the Committee, it is clear that JECFA has played a leading role in setting the worldwide agenda for how food additives, contaminants and adventitious substances in food should be evaluated. Although these deliberations occurred 50 years ago, the general principles and procedures elaborated by JECFA in early meetings have stood the test of time and are still used by the Committee at the present time. The credit for this lies with the early Committee members most of whom were outstanding research scientists and widely recognised experts in their discipline. The early work of JECFA also brought harmonisation of the approach to safety assessment of food additives on a worldwide basis. This resulted in a tremendous advantage to national governments that looked to JECFA for guidance and continue to do so. There can be no doubt that JECFA is the preeminent body dealing with food safety issues internationally.

The International Programme on Chemical Safety (IPCS)

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the WHO. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. In 1987, in response to numerous recommendations by JECFA, the IPCS convened a Task Force to review current knowledge and advances in toxicological science, and to develop criteria for testing and evaluation of the safety of food additives and contaminants. Thus, in 1987, the Environmental Health Criteria 70 (EHC70) was published, entitled *Principles for the Safety Assessment of Food Additives and Contaminants in Food*. This document was subsequently updated by the IPCS in 2009, with the publication of EHC240, entitled *Principles and Methods for the Risk Assessment of Chemicals in Food* (WHO 2009).

These guidelines provide a comprehensive current review of the key issues considered by JECFA during their risk assessments of food chemicals. Topics addressed include the risk assessment paradigm, chemical characterisation and specifications for food chemicals, toxicological studies used for hazard identification and characterisation, dose–response assessments, derivation of health-based guidance values such as ADI, assessment of dietary exposure to chemicals in food, risk characterisation, determination of maximum residue limits for pesticides and veterinary drugs, and approaches for assessment of specific groups of substances such as flavours and novel foods.

Regulations in different jurisdictions

To obtain an understanding of the global regulation of substances intentionally added to food, the regulatory systems and laws pertaining to their safety were reviewed and tabulated for ease of presentation and comparison. The countries that were chosen included: Argentina, Australia, Brazil, Canada, China, the EU, Japan, Mexico, New Zealand, and United States. These countries include both those with well-established regulatory systems (i.e. Australia, Canada, Japan, New Zealand, and the EU and US) and several that are currently in the process of changing and/or modernising their food regulatory systems (i.e. Argentina, Brazil, China and Mexico). Although it is acknowledged that there are many other jurisdictions that were worthy of inclusion in this review, limited resources required selection of those for which we had expertise in, and English versions or translations of regulations.

For each target country, the following information was sought and is summarised in table format (Tables 1–9):

- A brief historical overview of the main regulatory body/scientific advisory body and highlight roles and responsibilities concerning the regulation of chemicals added to food.
- A discussion of the regulatory framework.
- Pertinent regulations.
- Submission requirements/process for the approval of new food substances.
- Any pending or recent changes and the reason for the changes.

Comparison of the regulatory systems and regulations for food substances in the different jurisdictions

Overview

In general, each of the target countries has a regulatory system in place for the scientific evaluation and approval of food additives, food ingredients, and food contact substances; however, several are undergoing change, refinement and working towards harmonisation with other countries. The EU has recently adopted new regulations, which establish a common authorisation procedure for food additives and, for the first time, food enzymes and flavouring agents. Prior to the implementation of these new regulations, food enzymes and flavourings were regulated at the national level for each member state.

Similar to the EU, other regional bodies representing multiple nations have been established and are working to harmonise food standards for member countries. Australia and New Zealand have harmonised their food standards, which are maintained by Food Standards Australia New Zealand (FSANZ). Thus, Australia and New Zealand (NZ) have joint labelling and compositional standards under the Australia NZ Food Standard Code; however, there are separate standards that are not part of the joint food standards setting system, covering food safety, agricultural compounds and veterinary medicines, and primary food production and processing. These are covered in the Code but apply to Australia only. Equivalent NZ standards are developed and administered by the NZ Ministry for Primary Industries (MPI) (formerly MAF). MPI is responsible for implementation and enforcement of food standards and requirements for exported foods. Furthermore, in NZ there is a standard for supplemented foods allowing foods to be modified in a way that is beyond what is permitted under the Food Standards Code. The Supplemented Food Standard was introduced in March 2010 to regulate food type products previously sold under the NZ Dietary Supplements Regulations. However, supplemented foods must comply with most sections of the Code including the food additive requirements.

In South America, the South American Common Market, known as Mercosur, represents Brazil, Argentina, Uruguay, Paraguay and Venezuela. While these nations do

Table 1. Regulatory framework of chemicals added to food in Argentina.

Regulatory authority	*Name*: Ministry of Health (Ministerio de Salud) and The National Administration of Drugs, Foods, and Medical Technology (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica – ANMAT)
	Website: • Ministry of Health: http://www.msal.gov.ar/ (Ministerio de Salud 2011) • ANMAT: http://www.anmat.gov.ar/alimentos/normativas_alimentos_caa.asp (ANMAT 2010) • Mercosur: http://www.puntofocal.gov.ar/mercosur_sgt_alimentos.htm (Mercosur 2010)
	Historical overview: ANMAT was created by Presidential Decree 1490/92 (ANMAT 1992) (http://www.anmat.gov.ar/webanmat/Legislacion/NormasGenerales/Decreto_1490-1992.pdf)
	Role/responsibility: ANMAT is a decentralised body of the National Public Administration, established by Decree 1490/92. It assists in the protection of human health, ensuring the quality of products within its jurisdiction: drugs, food, medical products, diagnostic reagents, cosmetics, dietary supplements and household products. Its jurisdiction covers the entire country. It was created in August 1992. Since then, a body of professionals and technicians work with modern technology effectively to implement the processes of authorisation, registration, regulation, monitoring and control products used in medicine, human food and cosmetics. It depends both technically and scientifically on the norms and directives given to it by the Secretary for Policies, Regulations and Institutions of the Ministry of Health, with a system of economic and financial autarchy. In this context, ANMAT's main objective is "to ensure that medicines, food and medical devices available to the population, have proven effectiveness (achieving the therapeutic, diagnostic or nutrition targets) safety (high ratio benefit/risk) and quality (responding to the needs and expectations of citizenship) …"
Advisory scientific body	*Name*: National Committee of Food (CONAL)
	Website: http://www.conal.gov.ar (CONAL 2011)
	Historical overview: Created by Presidential Decree 815/99 (http://www.conal.gov.ar/Documentos/Decreto_815/815-99.htm) (CONAL 1999)
	Role/responsibility: CONAL functions as an advisory body that provides support and monitoring to the National Food Inspection System (Sistema Nacional de Control de Alimentos – SNCA), which enforces the Argentine Food Code (also known as Codigo Alimentario Argentino – CAA) (http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Food%20and%20Agricultural%20Import%20Regulations%20and%20Standards%20-%20Narrative_Buenos%20Aires_Argentina_12-22-2011.pdf) (USDA 2010a). CONAL reviews all the petitions for incorporation to the CAA of new ingredients, food additives and processing aids, as well as materials in contact with foods, etc. When pertinent because of harmonisation requirements with Mercosur, CONAL requests treatment of the matter at the Mercosur level.
Framework regulations	The CAA regulates local food production; however, as harmonised Mercosur regulations become available, the CAA incorporates those regulations into the CAA through *Resoluciones Conjuntas* issued by the Ministry of Health and the Ministry of Agriculture, Livestock and Fisheries (http://www.anmat.gov.ar/alimentos/normativas_alimentos_caa.asp). The CAA is a set of sanitary provisions, analytical standards and rules for commercial identification of products. It has more than 1400 articles divided into 20 chapters that include general provisions related to food factories and food trade, conservation and food processing, use of utensils, containers, packaging, standards for labelling and advertising of food, technical specifications of the different types of foods and beverages, processing aids, and food additives.
	Historical overview: The Argentine Food Code was put into force by Law 18,284, regulated by Decree 2126/71, of which Annex I is the text of CAA. It is a regularly updated technical regulation that establishes sanitary standards, analytical standards, and authenticity and quality standards to be complied by companies and individuals, production facilities, and food products that fall into their orbit. This legislation is primarily aimed at protecting the health of the population, and reliance in commercial transactions.
Part of an overarching international organisation	Argentina has been a member of the World Trade Organization since 1995. It is a member of the Codex Alimentarius Commission as well as a member of Mercosur.
Recent and/or pending changes	None known

(*continued*)

Table 1. Continued.

Regulatory overview of specific food chemical groups	
Food ingredients	*Definition*: As per GRUPO MERCADO COMUN (GMC) 26/03, food ingredients are defined as all substances, including the food additives, which are used in the manufacture or preparation of foods and which are present in the final product in its original or modified form. *Novel foods*: CAA does not define novel foods. Mercosur does not have a definition of novel foods either; however, novel foods are recognised in practice.
	Regulation: Currently, there are no novel food regulations in the CAA
	Guidance document: GMC 26/03
	Approval process for a new substances (http://www.conal.gov.ar). New food ingredients, novel foods and food additives as well as any request for modification of the CAA should be done according to this guidance. However, if the product requested is considered a novel food in Europe, its inclusion will be delayed until the novel foods chapter of the CAA is written, approved and incorporated into the CAA.
Direct food additives	*Definition*: Food additives are defined according to GMC 26/03 as any ingredient that is added to foods intentionally, without intent to nurture, in order to modify the physical, chemical, biological or sensory characteristics of foods during its manufacture, processing, preparation, processing, packaging, conditioning, storage, transport or during food handling; it will have, or it can be reasonably expected to have (directly or indirectly) as a result, that the additive itself or its by-products become part of that food. This term does not include contaminants, or nutrients that are incorporated into a food in order to maintain or improve its nutritional properties. GMC 26/03 is currently under revision by the Sub Work Group #3 (SGT#3) Mercosur and a new Definition 2 continues to be discussed and should be gazetted during 2012.
	Regulation: • GMC 11/06 – List of permitted food additives available in Spanish and Portuguese (http://www.mercosur.int/msweb/Normas/normas_web/Resoluciones/ES/GMC_2006_RES-011_ES_RTM-Aditivos%20Alimentarios.pdf) (Mercosur 2006) • GMC 34/07 – List of food additives not permitted for use (http://www.puntofocal.gov.ar/doc/r_gmc_34-07.pdf) (Mercosur 2007) Two new regulations for Mercosur, GMC 34/10 and GMC 35/10; however, not all member states have adopted these regulations yet: • GMC 34/10 – List of food additives according to good manufacturing practices (http://www.puntofocal.gov.ar/doc/r_gmc_34-10.pdf) • GMC 35/10 – List of food additives permitted for use at maximum levels (http://www.puntofocal.gov.ar/doc/r_gmc_35-10.pdf) From the CAA: Article 2 of Decree §2092 of October 1991, states the following: all foods, condiments, beverages, or their raw material and food additives which are manufactured, fractioned, preserved, transported, sold or exposed, must comply with the CAA requirements. When one of those is imported, the CAA requirements will be applied. The Argentine Government also considers products from countries which have food controls comparable to those of Argentina, or when they use the Codex Alimentarius (FAO/OMS) standards, to be in compliance with Argentine standards. (http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Food%20and%20Agricultural%20Import%20Regulations%20and%20Standards%20-%20Narrative_Buenos%20Aires_Argentina_12-22-2011.pdf)
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: All food additives that are not listed in the GMC11/06 can be submitted for evaluation to CONAL who will then submit a request to the Mercosur Sub Work Group #3 to consider the revision of 11/06 and to proceed to its incorporation. Revision of GMC 11/06 is expected in 2013. Submissions dossier should be addressed to CONAL following the general guidelines set forth at: http://www.conal.gov.ar

(*continued*)

Table 1. Continued.

Food contact substances (e.g. components of packaging materials)	*Definition*: According to GMC, food contact substances are defined as any primary container or primary wrapping or container (one that is in direct contact with food).
	Regulation: GMC 32/07. There is a positive list of substances (in Appendix 1 of regulation GMC 32/07) that are added to plastics to achieve a technical effect in the final product (additives) such as antioxidants, antistatic, foaming, defoaming, fillers, impact modifiers, plasticisers, lubricants, stabilisers, UV protectants, preservatives, hardeners, etc. Included within this list are the substances used to provide a suitable medium polymerisation (e.g. emulsifiers, surfactants, buffers pH, solvents).
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: Same as direct food additives
Flavouring agents	*Definition*: Flavouring agents are substances or mixtures of substances with odoriferous and/or flavour properties that are able to confer or enhance the aroma and/or taste of food. For the purpose of this Technical Regulation, flavourings/flavourings are classified as either natural or synthetic
	Regulation: Under Mercosur, GMC 10/06. A specified list of flavouring agents (natural or synthetic), including colourants is permitted. Exclusions from the technical regulations include: • Substances that give only sweet, salty or sour • Substances and food products with odoriferous and/or sapid consumed without processing, with or without reconstitution • Substances of plant or animal origin having inherent flavours/flavouring properties, where they are used as sources of flavourings
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: Submission to CONAL and subsequent submission to Mercosur. General guidelines (http://www.conal.gov.ar)
Enzymes	*Definition*: Enzymes or enzyme preparations are defined as substances of animal, plant or microbial origin that act by promoting the desirable chemical reactions
	Regulation: CAA, Chapter XVI, Articles 1261, 1262 and 1263. Enzymes regulations are not harmonised in Mercosur
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: General guidelines (http://www.conal.gov.ar)
Processing aids	*Definition*: A processing aid is any substance, excluding equipment and utensils, that is not consumed by itself as a food ingredient and which is intentionally used in the processing of raw materials, foods or ingredients, for a technological purpose during treatment or processing. It must be removed from the food or inactivated; the presence of traces of the substances or their derivatives may be admitted in the final product.
	Regulation: • GMC 18/93 Modificación RES • GMC 31/92 "Definición y Principios fundamentales referente a empleo de aditivos, ingredientes, coadyuvante de elaboración, contaminantes". Resolución GMC No. 84/93, incorporated into the CAA by Resolución MSyAS No. 003 dated 11 January 1995 defines the functions of processing aids. Processing aids are not harmonised in Mercosur; the only harmonised regulation is GMC 84/93 which establishes the definitions of the functions of processing aids. Certain processing aids are listed under Chapter XVI of the CAA, but this list is not comprehensive.
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: General guidelines (http://www.conal.gov.ar)
Nanoscale materials	*Definition*: No authoritative statement found
	Regulation: No authoritative statement found
	Guidance document: No authoritative guidance information found
	Approval process for a new substances: No authoritative statement found

(*continued*)

Table 1. Continued.

	Efforts towards developing standards and regulations (Locascio et al. 2011): • A Working Group for "the development of standards in the areas of health, safety and environmental aspects of nanotechnologies" (http://www.iram.org.ar/): methodologies and data quality analysis for risk assessment. • El Centro Cientifico Tecnologico, Consejo Nacional de Investigaciones Cientificas y Tecnicas (CONICET) – Mendoza (Cientificas y Tecnicas (CONICET) – Mendoza (http://www.cricyt.edu.ar) developing assays for acute toxicity and distribution of nanostructured alumina in mammals and toxicity of nanostructured alumina in vertebrates.

Table 2. Regulatory framework of chemicals added to food in Australia/New Zealand.

Regulatory authority	*Name*: Food Standards Australia New Zealand (FSANZ)
	Website: http://www.foodstandards.gov.au (FSANZ 2011c)
	Historical overview: • The first national agency to regulate food in Australia (National Food Authority) was established in June 1991. This became the Australia New Zealand Food Authority in July 1996, and FSANZ was established on 1 July 2002 • FSANZ is a statutory authority operating under the Food Standards Australia New Zealand Act 1991 (Commonwealth of Australia 2007). The act provides a focus for cooperation between governments, industry, and the community to establish and maintain uniform food regulation in Australia and New Zealand • FSANZ establishes food standards for Australia and New Zealand. There is an agreement (established in July 1996) between the governments of Australia and New Zealand that establishes FSANZ's role in setting joint food standards, i.e. standards that apply in both countries • The agreement does not cover some areas, such as maximum residue limits, food hygiene provisions and export requirements relating to third country trade. It also contains provisions that allow New Zealand to opt out of a joint standard for exceptional reasons relating to health, safety, environmental concerns or cultural issues. In such cases, FSANZ may be asked to prepare a variation to a standard to apply only in New Zealand • In Australia only, FSANZ develops standards for primary production and processing and for food hygiene, as well as setting residue limits for agricultural and veterinary products. Equivalent New Zealand standards are developed and administered by the New Zealand Ministry for Primary Industries (MPI), formerly MAF. MPI is also responsible for implementation and enforcement of food standards and requirements for exported foods
	Role/responsibility: • FSANZ is responsible for developing and administering the Australia New Zealand Food Standards Code (the Code) – see below • FSANZ is governed by a Board with a wide range of expertise and experience in food matters, with members drawn from Australia and New Zealand • As of February 2001, the Legislative and Governance Forum on Food Regulation (the Forum) is primarily responsible for the development of domestic food regulatory policy and guidelines for setting domestic food standards. The Forum also has the capacity to adopt, amend or reject standards and to request that these be reviewed • FSANZ recently implemented the Code Interpretation Service (CIS) on a cost-recovery basis to provide coordinated guidance on Chapters 1 and 2 of the Australia New Zealand Food Standards Code • In Australia, enforcing compliance with the Code for all foods is the responsibility of State/Territory Health Departments within Australia. For imported foods, enforcing compliance is the responsibility of the Australian Quarantine Inspection Service (AQIS) • In New Zealand, enforcing compliance with the Code for all foods is the responsibility of the New Zealand Ministry for Primary Industries (MPI), formerly MAF

(*continued*)

Table 2. Continued.

Advisory scientific body	• FSANZ Board: The FSANZ Board is selected by the Australian Minister for Health and Aging in Consultation with the Food Regulation Ministerial Council and must include qualified people from a wide range of expertise. Members of the Board have been drawn from specialist areas – public health, food science, human nutrition, consumer affairs, food allergy, medical science, microbiology, food safety, biotechnology, veterinary science, primary food production, the food industry, food processing or retailing, small business, international trade, food regulation, consumer rights and consumer affairs policy, the National Health and Medical Research Council (NHMRC) and government • FSANZ Fellows: FSANZ Fellows provide expert advice on applications, proposals and other risk assessment activities of the agency. FSANZ Fellows, within their relevant areas of expertise, also peer review FSANZ work and provide training to FSANZ staff • Scientific Advisory Groups (SAG): These ad hoc advisory groups are set up to advise FSANZ on particular scientific issues, e.g. health claims, iodine and folic acid fortification and dairy primary production and processing
	Role/responsibility: See above
Framework regulations	Australia New Zealand Standards Code (the Code): The Code regulates all aspects of food including labelling, the addition of food additives, processing aids, nutritive substances, levels of contaminants, approval of new foods (novel foods, genetically modified (GM) foods and irradiated foods), composition of standardised and special purpose foods, and applying in Australia only, food safety programmes and food processing and primary production (http://www.foodstandards.gov.au) (FSANZ 2011a)
Part of an overarching international organisation	Australia and New Zealand are both members of the World Trade Organization since 1995, and they are both members of the Codex Alimentarius Commission
Recent and/or pending changes	No major changes to the regulatory framework anticipated. Refer to the new Science Strategy above
Regulatory overview of specific food chemical groups	
Food ingredients	Food ingredients as such are not defined under the Australia New Zealand food regulations. Ingredients are generally considered to be either foods or substances added to food. FSANZ is reviewing the regulation of novel foods and nutritive substances as of March 2012. Due to problems with the definition of these terms a new approach is being considered based on criteria for "eligible foods" (i.e. foods in the wider sense including ingredients, additives and other substances added to food). Any non-eligible foods would be prohibited and will require appropriate safety assessment. Novel foods (including novel food ingredients): • Novel foods are defined as a non-traditional food with no history of safe use and the food requires an assessment of the public health and safety considerations having regard to: o the potential for adverse effects in humans; or o the composition or structure of the food; or o the process by which the food has been prepared; or o the source from which it is derived; oro patterns and levels of consumption of the food; or o any other relevant matters. • A non-traditional food is defined as: o a food that does not have a history of human consumption in Australia/New Zealand; or o a substance derived from a food where that substance does not have a history of human consumption in Australia/New Zealand other than as a component of that food; or o any other substance, where that substance, or the source from which it is derived, does not have a history of human consumption as a food in Australia/New Zealand. • Categories of novel foods may include but are not limited to: o plants or animals and their components; o plant or animal extracts; o herbs, including extracts; o dietary macro-components; o single chemical entities;

(*continued*)

Table 2. Continued.

	○ microorganisms, including probiotics; and ○ foods produced from new sources, or by a process not previously applied to food. Foods produced using gene technology or irradiated foods are regulated separately from novel foods and will be not discussed further within this report
	Regulation: • Novel foods and novel food ingredients are regulated under Food Standard 1.5.1. This standard prohibits the sale of these foods unless they are listed in the table to Clause 2 under Food Standard 1.5.1 and comply with any special conditions of use in that table • Food Standard 1.3.4 describes standards for the identity and purity of novel food ingredients
	Guidance document: Application Handbook (http://www.foodstandards.gov.au): • General application requirements are provided in Sections 2 and 3.1 • Specific requirements for novel foods are provided in Section 3.5.2
	Approval process for a new substances: An application to vary the code is required to approve the use of a novel food ingredient or a novel food. All application forms must conform to the general requirements (under Section 3.1 of the Application Handbook). Section 3.5.2 Novel Foods (within the handbook) lists additional requirements specific to novel foods. A summary of the requirements are listed below: • Indicate whether the applicant is requesting for exclusive permission for the novel food (if applicable): ○ Will need to indicate the specific class of food and brand of the food • Technical information on novel food: ○ Description of novel food (if it falls under one of the major categories listed below) ○ Physical and chemical properties ○ Impurity profile ○ Manufacturing process ○ Specification for identity and purity ○ Analytical method for detection • Safety information of novel food: ○ Depending on which major category that novel foods falls below (plants or animals and their components; plant or animal extracts; herbs (both non-culinary and culinary) including extracts; single chemical entities; dietary macro-components; micro-organisms (including probiotics); food ingredients derived from new sources; or foods produced by a process not previously applied to food), different requirements are specified (see Section 3.5.2 of handbook) • Dietary exposure to novel food: ○ List of the foods or food groups proposed to contain the novel food ○ Proposed use level of novel food for each food or food group ○ Percentage of the food group in which the novel food is proposed to be used or the percentage of the market likely to use the novel food ingredient ○ Data to indicate whether the food or the food in which the novel food ingredient is used, is likely to replace another food from the diet (if applicable) ○ Information regarding the use of the novel food/novel food ingredient in other countries (if applicable) • Nutritional impact of the novel food • Information related to potential impact on consumer understanding and behaviour • Information related to impact on the food industry (industry applicants only)
Nutritive substances	*Definition*: Nutritive substance means a substance not normally consumed as a food in itself and not normally used as an ingredient of food, but which, after extraction and/or refinement or synthesis, is intentionally added to a food to achieve a nutritional purpose, and includes vitamins, minerals, amino acids, electrolytes and nucleotides
	Regulation: Nutritive substances cannot be added to certain special purpose foods without express permission. These are: • Standard 2.9.1 Infant Formula Products • Standard 2.9.2 Food for Infants • Standard 2.9.3 Formulated Meal Replacements and formulated supplementary foods • Vitamins and minerals are regulated under Standard 1.3.2
	Guidance document: Application Handbook: • General application requirements are provided in Sections 2 and 3.1. • Specific requirements for nutritive substances are provided in Section 3.3.3.

(*continued*)

Table 2. Continued.

	Approval process for a new substances: An application to vary the code is required to approve the use of a nutritive substance or to change the permissions of a currently used nutritive substance. All application forms must conform to the general requirements (under Section 3.1 of the Application Handbook). A summary of the requirements are listed below:
	• General information on the application
	• Technical information on the nutritive substance:
	  ○ Identity of the nutritive substance
	  ○ Chemical and physical properties
	  ○ Impurity profile
	  ○ Manufacturing process
	  ○ Specifications for identity and purity
	  ○ Analytical method for detection
	• Information related to the safety of the nutritive substance:
	  ○ Toxicokinetics or metabolism of the nutritive substance
	  ○ Studies in animals or humans that is relevant to the toxicity of the nutritive substance
	• Information on dietary exposure to the nutritive substance:
	  ○ A list of food groups or foods proposed to contain the nutritive substance
	  ○ The maximum proposed level of the nutritive substance for each food group or food
	• Information related to the nutritive impact of a nutritive substance other than vitamins and minerals:
	  ○ Nutritional purpose of adding the nutritive substance to each food
	• Information related to the nutritive impact of a vitamin or mineral:
	  ○ Information to demonstrate a need to permit the addition of a vitamin or mineral
	  ○ Information to demonstrate the permitted addition of a vitamin or mineral has the potential to address a deficit or deliver a health benefit
	• Information related to the potential impact on consumer understanding and behaviour:
	  ○ Information to demonstrate consumer awareness and understanding
	  ○ Information to demonstrate consumer awareness and understanding
	  ○ Information on the actual and/or potential behaviour of consumers in response to proposed foods
	  ○ Information that the nutritive substance will not adversely affect any subpopulation
	• Information related to impact on the food industry:
	  ○ Data on the projected impact on the food industry

Direct food additives	*Definition*: • Direct food additive is not a term used in Australia/New Zealand • A food additive is any substance not normally consumed as a food in itself and not normally used as an ingredient of food, but which is intentionally added to a food to achieve one or more of the technological functions specified in Schedule 5. It or its by-products may remain in the food. Food additives are distinguishable from processing aids and vitamins and minerals added to food for nutritional purposes
	Regulation: • Food additives may only be added to food where expressly permitted in Food Standard 1.3.1. Additives can only be added to food in order to achieve an identified technological function according to good manufacturing practice (GMP). Some additives have specific permissions and maximum use levels allowed in food and other additives are limited to GMP (see Schedules 1–5 below). Specific flavourings, sweeteners and colouring agents are regulated as food additives • Schedule 1 of Standard 1.3.1 contains information on the permitted uses of food additives (including sweeteners) by food type • Schedule 2 of Standard 1.3.1 contains miscellaneous food additives permitted according to GMP in processed foods specified in Schedule 1 • Schedules 3 and 4 of Standard 1.3.1 contain colouring agents permitted to GMP and to specified levels in processed foods specified in Schedule 1 • Schedule 5 lists the technological functions that may be performed by food additives • Standard 1.3.4 describes standards for the identity and purity of food additives
	Guidance document: Application Handbook: • General application requirements are provided in Sections 2 and 3.1 • Specific requirements for food additives are provided in Section 3.3.1

(*continued*)

Table 2. Continued.

	Approval process for a new substances: Application to vary the code is required to approve the use of a new food additive or to change the permissions of a currently used food additive. The following information are required: • Technical information on food additive: o Nature and technological function o Identification of food additive o Chemical and physical properties of food additive o Impurity profile o Manufacturing process o Specification for identity and purity o Food labelling information o Analytical method for detection • Safety information of food additive: o Toxicokinetics and metabolism of food additive and if applicable, its degradation products and/or major metabolites o Information on the toxicity of food additive and if applicable, its degradation products and major metabolites o Safety assessment reports prepared by international agencies or other national government agencies, if available • Dietary exposure to food additive: o List of food groups or foods proposed to contain food additive, or changes to currently permitted foods o Maximum proposed level or concentration range of food additive for each food group or food, or proposed changes to the currently permitted levels o Percentage of the food group in which the food additive is proposed to be used or the percentage of the market likely to use the food additive o Information regarding the use of the food additive in other countries (if applicable)
Food contact substances (e.g. components of packaging materials)	*Definition*: • Food contact substances are defined as any materials in contact with food, including packaging material, which may include materials such as moisture absorbers, mould inhibitors, oxygen absorbers, promotional materials, writing or other graphics • Food contact substances may be placed in contact with food, provided such articles or materials, if taken into the mouth, are not capable of being swallowed or of obstructing any alimentary or respiratory passage and are not otherwise likely to cause bodily harm, distress or discomfort
	Regulation: • Food Standard 1.4.3 • Food Standard 1.4.1
	Guidance document: • Food Standard 1.4.3 deals with food contact materials in general terms, and does not specify individual packaging materials for food contact or how they should be produced or used. However, with respect to plastic packaging products, the standard refers to the Australian Standard for Plastic Materials for Food Contact Use, AS 2070-1999. This Standard provides a guide to industry about the production of plastic materials for food contact use. AS 2070, in turn, refers to regulations of the United States and European Economic Community directives relevant to the manufacture and use of plastics • Standard 1.4.1 – Contaminants and Natural Toxicants of the Food Standard Code regulates the levels of these substances that can be present in food from any source, including as a result of contact with food packaging materials. Even if a specific contaminant or toxicant is not listed in the standards, it sets out an expectation that all other contaminants and toxicants be kept to levels as low as reasonably achievable
	Approval process for a new substances: • Applications for food packaging materials are generally unnecessary if there is approval in the European Union or United States. At present it is voluntary that plastic materials for food contact use comply with the Australian Standard AS 2070-1999 • FSANZ has been considering its approach to chemicals that migrate from packaging into food for several years now, and it is envisaged that their approach may change to become more prescriptive and mandatory. Thus, in future, it may become mandatory to comply with either EU or US regulations under the Standard Code pending discussions with stakeholders

(*continued*)

Table 2. Continued.

Flavouring agents	*Definition*: • Flavouring agents, as such, are not defined in the Food Standards Code • Flavourings are defined as intense preparations which are added to foods to impart taste and/or odour, which are used in small amounts and are not intended to be consumed alone, but do not include herbs, spices and substances which have an exclusively sweet, sour or salt taste • Some flavourings are listed on the approved list of food additives with limitations • "Permitted flavouring substances are those which are either: a) listed in at least one of the following publications: o *Food Technology, A Publication of the Institute of Food Technologists*, Generally Recognized as Safe (GRAS) lists of flavoring substances published by the Flavor and Extract Manufacturers" Association of the United States from 1960 to August 2007; or o Chemically defined flavoring substances, Council of Europe, November 2000; or o United States *Code of Federal Regulations,* 2007, 21 CFR Part 172.515; or (b) a substance that is a single chemical entity obtained by physical, microbiological, enzymatic, synthetic or chemical processes, from material of vegetable or animal origin either in its raw state or after processing by traditional preparation process including drying, roasting, and fermentation"
	Regulation: Food Standard 1.3.1 Section 11
	Guidance document: An application is generally not required for flavourings and therefore no guidance is provided in the Application Handbook
	Approval process for a new substances: Flavourings are regarded as food additives. An application is generally not required for flavourings
Enzymes	*Definition*: • Enzymes, as such, are not specifically defined in the Food Standards Code • Enzymes are considered to be processing aids. They may be used in the course of manufacture of any food, provided the enzyme is derived from the corresponding source or sources specified in the tables of Sections 15, 16, and 17 of Food Standard 1.3.3. Refer to processing aids (below)
	Regulation: Enzymes are regulated as processing aids (below)
	Guidance document: Refer to processing aids (below)
	Approval process for a new substances: Refer to processing aids (below)
Processing aids	*Definition*: Processing aid means a substance listed in clauses 3–19 [of Standard 1.3.3] where: • the substances used in the processing of raw materials, foods or ingredients, to fulfil a technological purpose relating to treatment or processing but does not perform a technological function in the final food; and • the substance is used in the course of manufacture of a food at the lowest level necessary to achieve a function in the processing of that food, irrespective of any maximum permitted level specified
	Regulation: Food Standard 1.3.3 – Processing aids
	Guidance document: • Refer to the Application Handbook • General application guidelines are provided in Sections 2 and 3.1 • Specific requirements for processing aids are provided in Section 3.3.2
	Approval process for a new substances: Application to vary the code is required to approve the use of a new processing aid or to change the permissions of a currently used processing aid. The following information are required in the application: • Technical information on processing aid: o Information on the type of processing aid o Identification of processing aid o Chemical and physical properties of processing aid

(*continued*)

Table 2. Continued.

	○ Manufacturing process ○ Specification for identity and purity ○ Analytical method for detection • Safety information of a chemical processing aid: ○ General information on the industrial use of the chemical ○ General information on the use of the chemical as a food processing aid in other countries ○ Toxicokinetic and metabolism data on the processing aid, and if necessary its metabolites ○ Information on the toxicity of the processing aid, and if necessary its major metabolites ○ Safety assessment reports prepared by international agencies or other national government agencies, if available • Safety information of an enzyme processing aid: ○ General information on the use of the enzyme as a food processing aid in other countries ○ Toxicity information of the enzyme processing aid ○ Information on the potential allergenicity of the enzyme processing aid ○ Safety assessment reports prepared by international agencies or other national government agencies, if available • Additional information related to the safety of an enzyme processing aid derived from a microorganism: ○ Information regarding the source microorganism ○ Information regarding the pathogenicity and toxicity of the source microorganism ○ Information on the genetic stability of the source organism • Additional information related to the safety of a processing aid derived from a genetically modified microorganism: ○ Information on the methods used in the genetic modification of the source organism • Dietary exposure to the processing aid: ○ List of foods or food groups likely to contain the processing aid or its metabolites ○ Levels of residues of the processing aid or its metabolites for each food or food group ○ Percentage of the food group in which the processing aid is likely to be present or the percentage of the market likely to use the processing aid ○ Information relating to the levels of residues in foods in other countries
Nanoscale materials	*Definition*: The term "nanotechnology" is usually applied to the process of controlling the size and shape of materials at the atomic and molecular scale. Generally, the term is defined as deliberately engineered matter less than 100 nm in size in one dimension (http://www.foodstandards.gov.au/consumerinformation/nanotechnologyandfoo4542.cfm)
	Regulation: No authoritative statement found for food applications
	Guidance document: No specific guidance document found for food applications
	Approval process for a new substances: • Any new food substances that are manufactured using nanotechnologies that may present safety concerns will have to undergo a comprehensive scientific safety assessment under the appropriate standard before they can be legally supplied in Australia (http://www.foodstandards.gov.au/consumerinformation/nanotechnologyandfoo4542.cfm) • Applications for food additives, processing aids, novel foods and nutritive substances must include particle size, size distribution and morphology, where the substance(s) is particulate in nature and will remain so in the final food
	Efforts towards developing standards and regulations (Locascio et al. 2011): National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (http://www.nicnas.gov.au): • Active role in international activities to develop best-practice testing protocols and risk assessment methodologies • Focused on industrial chemicals that are in the form of nanomaterials

Table 3. Regulatory framework of chemicals added to food in Brazil.

Regulatory authority	*Name*: Ministry of Health (Ministério da Saude) through its regulatory agency Agencia Nacional de Vigilancia Sanitária (ANVISA – National Agency of Sanitary Surveillance)
	Website: • Ministry of Health: http://portal.saude.gov.br/portal/saude/default.cfm (Ministerio da Saude 2011) • ANVISA: http://portal.anvisa.gov.br/wps/portal/anvisa/home/(ANVISA 2009). ANVISA website in English: http://www.anvisa.gov.br/eng/legis/index.htm (ANVISA 2003) • Mercosur: http://www.mercosul.gov.br (Mercosur 2011)
	Historical overview: ANVISA was established by Law 9.782, as of 26 January 1999
	Role/responsibility: The institutional purpose of the agency is to foster protection of the health of the population by exercising sanitary control over production and marketing of products and services subject to sanitary surveillance. The latter embraces premises and manufacturing processes, as well as the range of inputs and technologies concerned with the same. In addition, the agency exercises control over ports, airports and borders and also liaises with the Brazilian Ministry of Foreign Affairs and foreign institutions over matters concerning international aspects of sanitary surveillance
Advisory scientific body	*Name*: ANVISA is designated an autonomous agency operating under a special regime. This means that it is an independently administered, financially autonomous regulatory agency with security of tenure for its directors during the period of their mandates. It is managed by a Collegiate Board of Directors, comprised of five members
	Website: http://portal.anvisa.gov.br/wps/portal/anvisa/home
	Historical overview: No authoritative statement found
	Role/responsibility: ANVISA's function is to evaluate the safety of use of food additives and ingredients in foods. There are specific work groups, comprised of university professors who give technical support if needed. These groups work mainly in the approval of novel foods and novel food ingredients with functional health claims
Framework regulations	No authoritative statement found
Part of an overarching international organisation	• Mercosur (which was established in 1991 and encompasses Argentina, Brazil, Uruguay, Paraguay, and as of 2006, Venezuela) • Mercosur standards are influenced by the European Union, the Codex Alimentarius Commission, and the USFDA • Brazil has been a member of the World Trade Organization since 1995 • Brazil also is a member of the Codex Alimentarius Commission. There is also the Codex Alimentarius Group of Brazil, formed by entities and professors, whose function is to meet the demands of the Codex Committee
Recent and/or Pending changes	None known
Regulatory overview of specific food chemical groups	
Food ingredients	*Definition*: As per GMC 26/03, food ingredients are defined as all substances, including food additives, which are used in the manufacture or preparation of foods and which are present in the final product in its original or modified form.
	Novel foods: These are the criteria for classification of novel foods: 1 – The following foods must be registered in the category of novel food, if they do not bear functional and/or health claims, given the criteria set out in Resolution No. 16/99: 1.1 – foods with no history of use in the country; 1.2 – foods containing novel ingredients, except those listed in Table 1; 1.3 – foods containing substances already consumed that may be added or used at levels much higher than those currently observed in the foods that constitute part of a regular diet; and 1.4 – food offered in the form of capsules, pills, tablets and the like

(*continued*)

Table 3. Continued.

	Regulation: Brazil has a specific regulation for the approval of novel ingredients or novel foods. Novel foods (Resolution No. 16): • List of novel foods approved by ANVISA (http://www.anvisa.gov.br/alimentos/comissoes/novos_alimentos.htm) • List of novel ingredients approved by ANVISA (http://www.anvisa.gov.br/alimentos/comissoes/novos_ingredientes.htm) *Guidance document*: No authoritative guidance document found
	Approval process for a new substances: Pre-market application is required prior to sale (http://portal.anvisa.gov.br/wps/portal/anvisa/home)
Direct food additives	*Definition*: Defined by GMC 26/03, as any ingredient which added to foods intentionally, without intent to nurture, in order to modify the physical, chemical, biological or sensory characteristics of foods, during its manufacture, processing, preparation, processing, packaging, conditioning, storage, transport or during food handling: it will have, or it can be reasonably expected to have (directly or indirectly) as a result, that the additive itself or its by-products becomes part of that food. This term does not include contaminants or nutrients that are incorporated into a food in order to maintain or improve its nutritional properties. GMC 26/03 is currently under revision by Sub Work Group #3 (SGT#3) Mercosur and continues to be discussed and should be gazetted during 2012
	Regulation: • GMC 11/06 – List of permitted food additives available in Spanish and Portuguese (http://www.mercosur.int/msweb/Normas/normas_web/Resoluciones/ES/GMC_2006_RES-011_ES_RTM-Aditivos%20Alimentarios.pdf) (Mercosur 2006) • GMC 34/07 – List of food additives not permitted for use • Two new regulations for Mercosur, GMC 34/10 and GMC 35/10; however, not all member states have adopted these regulations • GMC 34/10 – List of food additives according to good manufacturing practices (already internalised in Brazil by means of Resolução RDC 45 dated 3 November 2010) (http://portal.anvisa.gov.br/wps/wcm/connect/11707300474597459fc3df3fbc4c6735/Resolu%C3%A7%C3%A3o±da±Diretoria±Colegiada±±RDC±n±±45±de±03±de±novembro±de±2010.pdf?MOD=AJPERES) • GMC 35/10 – List of food additives permitted for use at maximum levels, internalised in Brazil by means of Resolução RDC 46 dated 3 November 2010. Website (http://portal.anvisa.gov.br/wps/wcm/connect/3664e600474597459fc4df3fbc4c6735/RESOLU%C3%87%C3%83O±RDC±N±±46±DE±3±DE±NOVEMBRO±DE±2010±.pdf?MOD=AJPERES) • Revision of GMC 11/06 is expected in 2013
	Guidance document: http://www.anvisa.gov.br/alimentos/guia_pedidos.pdf
	Approval process for a new substances: All food additives that are not listed in GMC11/06 can be submitted for evaluation to ANVISA, who will then submit a request to the Mercosur Sub Work Group #3 to consider the revision of 11/06 and to proceed to its incorporation. Requests must be sent first for evaluation to ANVISA and comply with the guidance document listed on the website (http://www.anvisa.gov.br/alimentos/guia_pedidos.pdf)
Food contact substances (e.g. components of packaging materials)	*Definition*: According to GMC 26/03, food contact substances are defined as the primary container or primary wrapping or container (container that is in direct contact with food)
	Regulation: GMC 32/07: • There is a positive list of substances (in Appendix 1 of regulation GMC 32/07) that are added to plastics to achieve a technical effect in the final product (additives) such as antioxidants, antistatic, foaming, defoaming, fillers, impact modifiers, plasticisers, lubricants, stabilisers, UV protectants, preservatives, hardeners, etc. • Included within this list are the substances used to provide a suitable medium polymerisation (e.g. emulsifiers, surfactants, buffers pH, solvents)
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: Same as direct food additives
Flavouring agents	*Definition*: Flavouring agents are substances or mixtures of substances with odoriferous and/or flavour properties that are able to confer or enhance the aroma and/or taste of food. For the purpose of this Technical Regulation, flavourings/flavourings are classified as either natural or synthetic
	Regulation: • Under Mercosur, GMC 10/06 • Permitted flavouring agents (natural or synthetic), including colourants are listed

(*continued*)

Table 3. Continued.

	• Exclusions from the technical regulations include: o The substances which give only sweet, salty or sour o Substances and food products with odoriferous and/or sapid consumed without processing, with or without reconstitution o Substances of plant or animal origin, having inherent flavours/flavouring properties, where they are used as sources of flavourings
	Guidance document: http://www.anvisa.gov.br/alimentos/guia_pedidos.pdf
	Approval process for a new substances: All flavouring agents that are not listed in GMC10/06 can be submitted for evaluation to ANVISA, who will then submit a request to the Mercosur Sub Work Group #3 to consider the revision of 10/06 and to proceed to its incorporation. Requests must be sent first for evaluation to ANVISA and comply with the guidance document listed on the website (http://www.anvisa.gov.br/alimentos/guia_pedidos.pdf)
Enzymes	*Definition*: Enzymes or enzyme preparations are defined as substances of animal, plant or microbial origin that act by promoting the desirable chemical reactions
	Regulation: Resolução RDC # 26 dated 05/27/2009. Enzymes regulations are not harmonised in Mercosur
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: Submissions dossier should be addressed to ANVISA following the guidance document set forth at: http://www.an visa.gov.br/al imentos/guia_pedidos.pdf
Processing aids	*Definition*: Processing aids are any substances, excluding equipment and utensils, which are not consumed as it is as a food ingredient and which is intentionally used in the processing of raw materials, foods or ingredients, for a technological purpose during treatment or processing. It must be removed from the food or inactivated; the presence of traces of the substances or their derivatives may be admitted in the final product
	Regulation: GMC 18/93 Modificación RES. GMC 31/92 "Definicion y Principios fundamentales referente a empleo de aditivos, ingredientes, coadyuvante de elaboracion, contaminantes". Resolución GMC No. 84/93
	Guidance document: Processing aids are not harmonised in Mercosur, the only harmonised regulation is GMC 84/93 that establishes the definitions of the functions of processing aids (http://www.anvisa.gov.br/alimentos/guia_pedidos.pdf)
	Approval process for a new substances: Submissions dossier should be addressed to ANVISA following the guidance document set forth at: http://www.anvisa.gov.br/alimentos/guia_pedidos.pdf
Nanoscale materials	*Definition*: No authoritative statement found
	Regulation: No authoritative statement found
	Guidance document: No authoritative statement found
	Approval process for a new substances: No authoritative statement found
	Efforts towards developing standards and regulations (Locascio et al. 2011): Committee for the special study of nanotechnology (http://www.abnt.org.br): • Developing practices of health, safety, and environment with a scientific basis

Table 4. Regulatory framework of chemicals added to food in Canada.

Regulatory authority	*Name*: Health Canada (HC) Food Directorate
	Website: http://www.hc-sc.gc.ca/fn-an/index-eng.php (Health Canada 2011)
	Historical overview: • The Food and Drugs Act was introduced in 1920 • http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/info-renseign/hist-eng.php
	Role/responsibility: • Establishing policies, setting standards, and providing advice and information on the safety and nutritional value of food • Promoting the nutritional health and well-being of Canadians by collaboratively defining, promoting and implementing evidence-based nutrition policies and standards • Administering the provisions of the Food and Drugs Act that relate to public health, safety and nutrition
Regulatory enforcement	*Name*: Canadian Food Inspection Agency (CFIA)
	Website: http://www.inspection.gc.ca/english/toce.shtml (CFIA 2011)
	Historical overview: • Established in 1997 by the Canadian Food Inspection Agency Act • Prior to the establishment of the CFIA, inspection and related services for food safety and animal and plant health were provided by Agriculture and Agri-Food Canada, HC, and the Department of Fisheries and Oceans (http://www.oag-bvg.gc.ca/internet/English/parl_oag_199809_12_e_9318.html#mp) (OAG 1998)
	Role/responsibility: • Enforce the food safety and nutritional quality standards established by HC and for animal health and plant protection, to set standards and carry out enforcement and inspection (http://www.inspection.gc.ca/english/util/faqe.shtml) • Plans and priorities link directly to the Government of Canada's priorities for bolstering economic prosperity, strengthening security at the border and the safety of the food supply, protecting the environment and contributing to the health of Canadians (http://www.inspection.gc.ca/english/agen/agene.shtml)
Framework regulations	Food and Drug Regulations: http://laws.justice.gc.ca/PDF/Regulation/C/C.R.C.,_c._870.pdf
Part of an overarching international organisation	• Canada has been a member of the Codex Alimentarius Commission since it was established in 1963 (http://www.hc-sc.gc.ca/fn-an/intactivit/codex/activit/strateg-codex-2008-2012-eng.php) (Health Canada 2009a) • Canada also has been a member of the World Trade Organization since 1995
Recent and/or pending changes	None known
Regulatory overview of specific food chemical groups Food ingredients	Food ingredients are defined as an individual unit of food that is combined as an individual unit of food with one or more other individual units of food to form an integral unit of food that is sold as a pre-packaged product: • The use of a food ingredient does not require pre-market approval unless it meets the definition of a novel food. Novel foods are defined according to Division B.28.001 as: ○ a substance, including a microorganism, that does not have a history of safe use as a food; ○ a food that has been manufactured, prepared, preserved or packaged by a process that: (i) has not been previously applied to that food, and (ii) causes the food to undergo a major change; and ○ a food that is derived from a plant, animal or microorganism that has been genetically modified such that: (i) the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism;

(*continued*)

Table 4. Continued.

	(ii) the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism, or (iii) one or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism
	Regulation: Novel Foods – Division B.28 (http://laws.justice.gc.ca/eng/C.R.C.-C.870/page-1.html#anchorbo-ga:l_B-gb:l_28)
	Guidance document: A guidance document is available on novel foods, whether whole foods, food products or food ingredients, that are derived from plant or microbial sources. The safety assessment criteria for novel foods derived from animals are under development. Manufacturers or importers of novel foods derived from animal sources should consult with the Food Directorate to discuss which type of information is appropriate to the evaluation of the safety of a particular product (http://www.hc-sc.gc.ca/fn-an/index-eng.php)
	Approval process for a new substances: The mechanism by which HC controls the sale of novel foods in Canada is the mandatory pre-market notification requirement as described in Division 28 of Part B of the Food and Drug Regulations. Manufacturers or importers are required under these regulations to submit information to HC regarding the product in question in order to determine the product's safety prior to sale. If the information provided in the notification for a novel food is not considered adequate to determine the novel food's safety, additional data supporting the safety of the food will be required. The type of information required to conduct the safety assessment of a novel food will depend on a number of factors such as the nature of the food, processing methods and the intended use. The approaches used to assess the safety of novel foods are outlined in the guidance document; however, the types of studies considered appropriate to demonstrate the safety of a novel food change with scientific knowledge and development. These guidelines are to be used in conjunction with information available in the scientific literature and from research and development conducted by the manufacturer. Since novel foods represent a diverse range of products, not all types of data outlined in the guidance document will be appropriate for a specific submission. Petitioners should consider the novel characteristics of their particular product when addressing the criteria in the guidance document. Consultation with the Food Directorate is encouraged during the development phase of a product to determine the specific data necessary to demonstrate the safety of the product. Information sufficient to establish that a novel food is safe for consumption may include experimental data as well as sound scientific rationales. To enhance the efficiency of the review process, petitioners should prepare their safety assessment data packages according to the following headings, as applicable: • History of use • Dietary exposure • Detail of novel process • History of organism(s) • Characterisation of derived line/strain • Genetic modification considerations • Nutritional considerations • Toxicology considerations • Allergenicity considerations • Chemical considerations • Microbiological considerations
Direct food additives	*Definition*: According to the Food and Drugs Regulations B.01.001, "a food additive means any substance the use of which results, or may reasonably be expected to result, in it or its by-products becoming a part of or affecting the characteristics of a food, but does not include: • Any nutritive material that is used, recognised or commonly sold as an article or ingredient of food; • Vitamins, mineral nutrients and amino acids, other than those listed in the tables to Division 16 • Spices, seasonings, flavouring preparations, essential oils, oleoresins and natural extractives; • Agricultural chemicals, other than those listed in the tables to Division 16, • Food packaging materials and components thereof; and • Drugs recommended for administration to animals that may be consumed as food".

(*continued*)

Table 4. Continued.

	It should be noted that a substance not present in the final food but which has affected the characteristics of that food would be regulated as a food additive. The official food additive provisions are listed in the tables of B.16.100 of the Food and Drug Regulations (Department of Justice 2011). Listings of permitted food additives include the common name of the food additive, a list of the foods in which the additive may be used, and the maximum level of use. Table III lists food additives that may be used as colouring agents; Table IX lists sweeteners permitted for use as a food additive. In Canada, food contact substances are regulated separately from food additives (see "Food contact substances" section below). Enzymes that are used in food processing are regulated as food additives or may be considered processing aids, depending on their context of use. Flavouring agents and processing aids do not require a submission like a food additive but petitioners can request a letter of opinion from Health Canada (see "Flavouring agents, Enzymes, and Processing Aids" section below)
	Regulation: Division B.16 (http://laws.justice.gc.ca/eng/C.R.C.-C.870/page-1.html)
	Guidance document: http://www.hc-sc.gc.ca/fn-an/index-eng.php
	Approval process for a new substances: A submission for a food additive is required if a petitioner is seeking approval for use in Canada of a new food additive not currently regulated in the Food and Drug Regulations. A petitioner is also required to present a submission for an extension of use of an existing food additive, e.g. the use of an existing food additive in a different food or the use of a food additive at a higher maximum level of use. In these latter cases, there may not be a need to resubmit data already available at HC. The four possible scenarios are summarised as follows: • Requests for the use of a new food additive (which is a food additive that has never before been approved for use in retail foods in Canada) • Requests to extend the use of an already permitted food additive • Requests to change the maximum level of use of an already permitted food additive • Requests to add a new organism to the list of permitted sources of enzymes used as food additives In the case of submissions on new food additives (those which do not appear anywhere in the Food Additives Tables of the Food and Drug Regulations), detailed data and scientific information meeting the requirements of Section B.16.002 of the Food and Drug Regulations are required in order to support the development of specifications and verify conformity of the additive with those specifications, develop and verify analytical methods, establish claims of efficacy, demonstrate residue levels or reaction products, determine human exposure to a food additive in any given application, and demonstrate the absence of any negative health effects of the food additive when used in the prescribed manner. General requirements include: • Identity of the food additive • Method of manufacture • Chemical and physical properties • Specifications • Purpose/function of food additive • Directions for use • Efficacy data demonstrating the technical effect • Residue data • Proposed maximum level of use • Analytical data (for new food additives only, not required for extension of use or changes to maximum levels of use of current food additives listed in Division 16 of the Food and Drug Regulations). • Safety data • Food intake data • Toxicological data • Pharmacokinetic studies • Human clinical studies • Nutritional safety considerations • Microbiological data (if food additive is derived from microbial sources or is genetically modified or in the case of antimicrobials, efficacy of preservatives) • Labelling information • A sample of the food additive

(*continued*)

Table 4. Continued.

	Other non-statutory requirements for submissions on food additives: • Consumer benefits and food quality considerations • Information on evaluations, approvals, and authorisations of other national/international bodies (such as JECFA, USFDA, EU food safety authorities, Australia and New Zealand food standards, and/or Codex Alimentarius Commission) Environmental assessment of new food additives: The Canadian Environmental Protection Act, 1999 (CEPA 1999) is the primary federal legislation respecting the protection of the environment and human health. The goal of CEPA 1999 is to contribute to sustainable development through pollution prevention. In 2001, HC announced its intent to develop environmental assessment regulations for a new substances regulated under the Food and Drugs Act
Food contact substances (e.g. components of packaging materials)	*Definition*: • Food contact or packaging materials have been excluded from the food additive requirements. Food contact or packaging materials are controlled separately under Division 23, Part B of the Food and Drug Regulations (http://laws.justice.gc.ca/eng/C.R.C.-C.870/page-1.html#anchorbo-ga:l_B-gb:l_23) • "No person shall sell any food in a package that may yield to its contents any substance that may be injurious to the health of a consumer of the food" (http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/guide_packaging-emballage01-eng.php). This link also lists the documents that can be submitted voluntarily
	Regulation: Division 23, B.23.001 (http://laws.justice.gc.ca/eng/C.R.C.-C.870/page-1.html#anchorbo-ga:l_B-gb:l_23) *Guidance document*: Packaging materials (on a trade name basis, not by generic name) intended for use with foods in Canada may be submitted voluntarily to the Health Products and Food Branch (HPFB) for a pre-market assessment of their chemical safety and subsequent issuance of an advisory opinion on their acceptability in relation to Section B.23.001 of the Food and Drugs Act and Regulations dealing with the potential transfer of harmful chemicals to foods. Any type of material, whether it is in the form of a finished product such as a laminated film, a container, etc. or a formulated product such as a plastic resin, a colour concentrate, etc. may be submitted to the branch for a pre-market assessment. In addition, suppliers of single additives such as antioxidants, ultra violet absorbers, etc. may also independently request letters of opinion for their own products before selling them to formulators or converters. Thus, in terms of data requirements, food packaging submissions may be divided into two distinct categories namely, those on formulated products and finished articles, which are normally submitted by converters and formulators and those on specific constituents or single additives which usually originate from raw material suppliers
	Approval process for a new substances: The following information is provided as a guide to the food packaging industry to assist in the preparation of submissions to HPFB: 1. Formulated products and finished articles (formulators/converters). Two elements of information are required initially for a formulated product or a finished packaging article namely, the product's identity and its intended food packaging uses. The information to be provided under each element is as follows: Product identity: • Trade name and number (mostly for records purposes) • Structure (e.g. laminate) • Composition (in the form of a quantitative listing of all components in which each one is identified by proper chemical name and/or trade name, grade and supplier) • Specifications • Chemical/physical properties relative to proposed use Proposed usage: • Form of finished package (e.g. bottle, film, casing, etc.) • Dimensions of package (volume, wall thickness, etc.) • Packaging ratio, i.e. weight of food/unit area of packaging material (g/in^2) • Conditions (time, temperature) to which packaging article will be exposed during packaging, distribution and use by consumers • Estimate of projected market penetration 2. Specific constituents/single additives (raw material supplies). Four elements of information are required for a submission on a new additive or a single constituent in a food contact material. They include information on the product's identity, its proposed usage, data on its extractability characteristics, and toxicological data. The information to be included under each of these four elements is as follows:

(*continued*)

Table 4. Continued.

	Product identity: • Chemical name • Chemical formula (empirical and structural) • Molecular weight • Manufacturing process (including a detailed description and a schematic diagram) • Purity specifications (residual reactants, by products, etc.) • Chemical and physical properties Proposed usage: • Intended technical effect or purpose (e.g. antioxidant, stabiliser, ultraviolet absorber, etc.) • Types of substrates or polymers • Maximum use level in each type of polymer • Efficacy data to demonstrate that the additive will do what it is intended to do at the proposed use levels • Types of foods involved • Conditions of use (time, temperature, etc. to which the packaging material will be exposed, whether during processing, transport or handling by consumers) Migration/extraction data: Extraction studies data are required to identity and quantify the potential contaminants in foods. These studies are usually conducted using food simulants under conditions that reflect as close as possible those of the proposed end-use applications Toxicological data: The submitted toxicological data should provide the basis for the petitioner's safety determination for the packaging material constituent under the proposed conditions of use. The toxicological studies recommended by HPFB for its safety assessment are based on levels of concern that are determined by the level of dietary exposure. Dietary exposures that fall below 0.025 μg kg^{-1} bw are considered to be below the threshold of toxicological concern and toxicological data need not be submitted
Flavouring agents	*Definition*: No authoritative statement found
	Regulation: No specific regulations on flavouring agents. Section 4 of the Food and Drug Act applies. No application/submission required for use of flavouring agents in food within Canada. Standards of identity and composition are available in Division B.10 pertaining to specific flavouring preparations (such as essences or extracts obtained from aromatic plants) (http://laws.justice.gc.ca/eng/C.R.C.-C.870/page-1.html#anchorbo-ga:l_B-gb:l_10). Flavours or flavouring preparations not mentioned in Division 10 are considered unstandardised food ingredients. Certain prohibitions exist in Section B.01.046. The definition of food additive excludes flavouring preparations. On request, the Bureau of Chemical Safety evaluates safety of use of these ingredients and issues a letter of opinion
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: Applicants can voluntary request a letter of opinion on a flavouring agent (see "approval process for processing aids")
Enzymes	*Definition*: • Not specifically defined in the Food and Drug Regulations. Enzymes that are used in food processing are regulated as food additives or may be considered processing aids, depending on their context of use. • An enzyme meets the definition of a food additive, as described in Section B.01.001 of the Food and Drug Regulations, when it affects the characteristics of the food and/or it or its by-products become part of the food. It is the physical enzyme residues, not enzyme activity, that are considered in determining if enzyme residues remain in or on a food
	Regulation: Enzymes approved as food additives are listed within Table V of Section B.16.100 Listings of permitted enzymes as food additives include the common name of the enzyme, permitted sources of the enzyme, a list of the foods in which the enzyme may be used, and the maximum level of use
	Guidance document: See "Direct food additives" (above)
	Approval process for a new substances: See "Direct food additives" (above)

(*continued*)

Table 4. Continued.

Processing aids	*Definition*: According to the Food Directorate, "a food processing aid is a substance that is used for a technical effect in food processing or manufacture, the use of which does not affect the intrinsic characteristics of the food and results in no or negligible residues of the substance or its by-products in or on the finished food". This definition implies the absence of residues of any given chemical and its by-product in the final food product, which is different from Australia's definition of a processing aid (in which the absence of by-products is not mentioned). Also, characteristics of the final food must not be affected by the use of any given chemical classified as a processing aid. The definition of processing aid in Canada differs from the definition used by the Codex Alimentarius Commission. The CAC definition does not have a limitation on residue levels and does not refer to affecting the characteristics of the food. These restrictions must be included in the Directorate's definition because a substance is considered to be a food additive, under the Canadian regulatory definition of food additive, if use of the substance results in residues in the food or affects the characteristics of the food
	Regulation: There is no regulatory definition of food processing aid in Canada. Canadian regulators have typically used "processing aid" in an informal manner for substances used as adjuncts in food processing and manufacture. Most processing aids are not mentioned in the Regulations and unlike food additives, there is no regulatory requirement for preclearance of new processing aids by the Minister of Health. Like all substances used with food, the use of a processing aid is ultimately controlled by Section 4, Part I of the Act which states: "No person shall sell an article of food that: • has in or on it any poisonous or harmful substance; • is unfit for human consumption; • consists in whole or in part of any filthy, putrid, disgusting, rotten, decomposed or diseased animal or vegetable substance; • is adulterated; or • was manufactured, prepared, preserved, packaged or stored under unsanitary conditions"
	Guidance document: Not applicable
	Approval process for a new substances: The use of a processing aid does not require a submission like a food additive but a petitioner may seek a so-called "Letter of Opinion" from the Bureau of Chemical Safety of HC's Food Directorate, confirming that, under its conditions of use, the substance in question is considered to be a processing aid and is acceptable for use.
Nanoscale materials	*Definition*: Nanotechnology is described as the application of nanoscience to develop new materials and products, and involves the manipulation of matter at the nanometre scale. In the food sector, nanotechnology could be used to preserve food, improve nutritional values and enhance flavours (http://www.hc-sc.gc.ca/dhp-mps/nano-eng.php) (Health Canada 2009b). Health Canada considers any manufactured product, material, substance, ingredient, device, system or structure to be nanomaterial if: • it is at or within the nanoscale in at least one external dimension, or has internal or surface structure at the nanoscale; or • it is smaller or larger than the nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena. • For the purposes of this definition: • the term "nanoscale" means 1–100 nm, inclusive; • the term "nanoscale properties/phenomena" means properties which are attributable to size and their effects; these properties are distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material; and • the term "manufactured" includes engineering processes and the control of matter (http://www.hc-sc.gc.ca/sr-sr/pubs/nano/pol-eng.php)
	Regulation: No authoritative statement found. No reference to nanomaterials is stated in the acts and regulations; however, HC is using the existing legislative and regulatory framework to regulate applications of nanotechnology, but it is recognised that new approaches may be necessary in future to keep pace with the advances in this area. Within the Health Portfolio, a Nanotechnology Working Group has been established to gather information, identify areas where additional regulations may need to be considered, and to act as a discussion forum for issues related to nanotechnology (http://www.hc-sc.gc.ca/dhp-mps/nano-eng.php)

(*continued*)

Table 4. Continued.

	Guidance document: Only general guidance has been given (http://www.hc-sc.gc.ca/sr-sr/pubs/nano/pol-eng.php). In order to identify and assess potential risks and benefits (where applicable) of nanomaterials, the following types of information may be required, when relevant: • Intended use, function and purpose of the nanomaterial, and information regarding any end product in which it will be used • Manufacturing methods • Characteristics, and physical chemical properties of the nanomaterial such as: o composition, identity, purity o morphology o structural integrity o catalytic or photo-catalytic activity o particle size/size distribution o electrical/mechanical/optical properties o surface-to-volume ratio o chemical reactivity o surface area/chemistry/charge/structure/shape o water solubility/dispersibility o agglomeration/aggregation (or other properties) and o descriptions of the methods used to assign these determinations • Toxicological, eco-toxicological, metabolism and environmental fate data (both generic and specific) to the nanomaterial if applicable • Risk assessment and risk management strategies, if considered or implemented
	Approval process for a new substances: No authoritative statement found
	Efforts towards developing standards and regulations (Locascio et al. 2011): • National Institute for Nanotechnology (Alberta) (http://www.nrc-cnrc.gc.ca/eng/ibp/nint.html) • Developing methods to assess the risk of nanomaterials, such as developing *in vitro* assays, *in vivo* studies and tests for systemic responses

Table 5. Regulatory framework of chemicals added to food in China.

Regulatory authority	*Name*: Ministry of Health (MOH)
	Website: http://www.moh.gov.cn/publicfiles//business/htmlfiles/wsb/index.htm (Ministry of Health of the People's Republic of China 2010)
	Historical overview: Established 21 November 1949
	Role/responsibility: • To draft health laws, regulations and policies; to propose health development programmes and strategic goals; to formulate technical protocols, health standards, and to supervise their enforcement • To propose regional health programmes, to conduct overall planning, and to coordinate the nationwide allocation of health resources • To supervise communicable disease prevention and treatment, food health, occupational, environmental, radiological and school health. To formulate food and cosmetics quality control protocols and be responsible for their accreditation • To organise and guide multilateral and bilateral governmental and non-governmental health and medical cooperation and exchanges and medical aid to other countries, to participate in major health events initiated by international organisations • To coordinate medical and health exchanges and collaborations between China and the World Health Organization and other international organisations • To undertake other work as designated by the State Council
Advisory scientific body	*Name*: Same as Regulatory authority (above)
	Website: Same as Regulatory authority (above)
	Historical overview: Same as Regulatory authority (above)

(*continued*)

Table 5. Continued.

	Role/responsibility: Same as Regulatory authority (above)
Framework regulations	• Food Safety Law of the People's Republic of China (adopted at the 7th Session of the 11th Standing Committee of the National People's Congress of the People's Republic of China on 28 February 2009) • Implementation Rules of Food Safety Law of the People's Republic of China – Order of State Council of the People's Republic of China No. 557 (adopted at the 73rd Standing Committee Meeting of the State Council on 8 July 2009)
Part of an overarching international organisation	• China has been a member of the World Trade Organization since 2001 • China is a member of the Codex Alimentarius Commission
Recent and/or pending changes	None known
Regulatory overview of specific food chemical groups	
Food ingredients	*Definition of food ingredients*: any substance, including a food additive, used in the manufacture or preparation of a food and present in the final product although possibly in a modified form. Novel foods are referred to as new resource foods, which are defined as raw food materials or food ingredients, which do not have a significant history of consumption in China (Roberts & Rogerson 2008). Novel foods are separated into four categories: • Animals, plants and microorganisms that are not traditionally consumed in China • Raw food materials that are derived from animals, plants and microorganisms and are not traditionally consumed in China • New varieties of microorganisms that are used during food processing • Raw food materials the original composition or structures of which are changed by the adoption of new techniques during production
	Regulation: Order No. 56 – Administrative Measures on Novel Food
	Guidance document: English translation of the guidance is available at: http://www.fas.usda.gov/gainfiles/200704/146280956.pdf (USDA 2007)
	Approval process for a new substances: Premarket application demonstrating safety of the novel food. Applications for novel food shall include the following: • Application for hygiene administration permit of novel food (manufacturer must obtain a hygiene license before producing, marketing or using the food additive) • Research and production report • Brief summary and flow chart of processing techniques • Product quality standards • Status on research and production at home and abroad, as well as safety-related documents • Product label and instructions • Other materials helpful to assessment and review • A product sample or 30 g of raw material • For the importation of novel food, it is also required to submit certificates indicating the production (or marketing) of the food products are permitted in the exporting country (region) or documents showing the traditional consumption history of the food in the exporting country (region), which are issued by relevant departments or institutions of the exporting country (region)
Direct food additives	*Definition*: "An artificially chemosynthetic or natural substance to be added to foods in order to improve food quality, colour, fragrance and taste, and for the purpose of preservation and processing technology. Nutrition enhancers, gum-based substances in chewing gum, flavouring agents, and processing aids in the food industry are also included in food additives." Permitted food additives (including colouring agents, sweeteners, and flavour enhancers) are classified according to their function with permitted maximum levels indicated (USDA 2008). A new food additive is a food additive that: • Is not included in the national food safety standards • Is not included in the public announcement of permitted use issued by the Ministry of Health • Whose scope of use or dosage is increased

(*continued*)

Table 5. Continued.

	Regulation: • National Standard GB-2760-2007 – Hygienic Standards for the Use of Food Additives National Food Safety Standard – Standards for uses of food additives GB-2760-xxxx (Draft for comment; Notified to the WTO as G/SPS/N/CHN/308 on 4 August 2010) • Administrative Licensing Regulation for New Varieties of Food Additive (Notified to the WTO as G/SPS/N/CHN/201 on 8 January 2010)
	Guidance document: Order No. 73: Measures for Administration of New Food Additives (as of 10 March 2010) (http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Food%20Additive%20Registration_Beijing_China%20-%20Peoples%20Republic%20of_5-12-2010.pdf) (USDA 2010b)
	Approval process for a new substances: Pre-market application demonstrating technological need and safety of the additive. The application shall include: • Generic name, functions, dosage and scope of use of additives • Documents demonstrating technical necessity and efficiency of additives • Quality requirements, manufacturing process and testing methods of food additives, and testing methods of such additives or relevant explanations • Safety assessment data, including raw materials or sources, chemical constitution and physical properties, manufacturing process, toxicological safety assessment data, or test report and quality test report • Label, specifications, and sample of food additives • Data on permission of manufacture and use granted by other countries or regions or international organisations and other data that may be useful in safety assessment Any application for increase in the scope of use or dosage of food additives may be exempt from provision of materials identified in the fourth point above, unless additional data are required during technical review (http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Food%20Additive%20Registration_Beijing_China%20-%20Peoples%20Republic%20of_5-12-2010.pdf/) Any applicant applying for the initial import of new food additives shall submit the following materials in addition to those specified above: • Supporting documents permitting manufacture or sale of such additives in the exporting country or region that are issued by relevant authority or agency thereof • Supporting documents examining or certifying the manufacturer that are issued by relevant agency or organisation in the country or region where the manufacturer is located
Food contact substances (e.g. components of packaging materials)	*Definition*: All materials in contact with the food including the food containers, packaging materials and the things which contact the food in the course of manufacture, transport, sale and serve. The licensing scope of the food-related new product varieties includes: • Food materials or mouldings without national food safety standards that are used for food packaging or containerisation and machinery that has direct contact with the food during production or packaging • Additives not included in the Hygienic Standards for Additives Used in Food Containers and Packaging Materials (GB 9685) • Food materials or mouldings not included in the list of food packaging materials or containers announced by the Ministry of Health and all operational tools and equipment that have direct contact with food during food production, and their processing additives • Additives which are included in the Hygienic Standards for Additives Used in Food Containers and Packaging Materials (GB 9685) or the list announced by the Ministry of Health but with the scope or dosage expanded upon • New detergent materials which may have food safety risks and are used for food, food production and operational tools and equipment that have direct contact with food during food production and packaging • New disinfectant materials which are not included in the List of Food Disinfectant Materials and are used for food, food production and operational tools and equipment that have direct contact with food during food production and packaging
	Regulation: Hygienic Standards for Additives Used In Food Containers and Packaging Materials (GB 9685)
	Guidance document: Rules on Administrative Licensing of Food-Related New Product Varieties (Notified to the WTO as G/SPS/N/CHN/120 on 13 August 2009)

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Table 5. Continued.

	Approval process for a new substances: Premarket application demonstrating technological need and safety of the additive. If an additive in the food containers or packaging materials meets the following conditions, such additive shall be an exemptible substance and does not need to be reported for examination and approval: • The migration volume of the additive is less than 0.01 mg kg^{-1} (i.e. 10 ppb); the additive is not carcinogenic, mutagenic or a reproductive toxic substance; the additive migrating into food does not cause the food ingredients, structure, colour, smell or taste to change • There is multilayer composite packaging with a functional barrier layer and the migration volume of the substance outside the barrier layer is less than 10 ppb
Flavouring agents	*Definition*: Flavourings (flavour compound): • A concentrated and prepared mixture incorporated by flavourings substances and flavouring adjuncts, and used for producing flavour (excluding preparations only producing salty, sweet or sour taste), which may contain or not contain flavouring adjuncts. Usually, they are not directly used for consumption. The flavourings include food flavourings, feed flavourings, flavourings in contact with mouth cavity and lips and the flavourings for dish washing detergent: o Oil-soluble liquid flavourings o Water-soluble liquid flavourings o Emulsified flavourings o Paste flavourings o Blending powder flavourings o Encapsulated powder flavourings Flavouring (flavour compound) adjunct: • A food additive and food ingredient necessary for producing, preserving and applying the flavourings. The additive added to food (except flavour enhancer) does not play the role for final aromatic products. Process flavourings: • A product or mixture prepared for the purpose of characteristics of odour, which is a kind of product prepared with the ingredients or ingredient mixtures allowed to be used in process flavourings or process flavourings allowably used for food or natural application in food through the preparation process suitable for foods consumed by humans. It can add flavouring substances and flavouring adjuncts to process flavourings. A list of allowable flavourings is available (Annex B, People's Republic of China, 2010)
	Regulation: National Standard of the People's Republic of China – Flavourings (TBT/N/CHN/575)
	Guidance document: See "Direct food additives" (above)
	Approval process for a new substances: See "Direct food additives" (above)
Enzymes	*Definition*: "Biological products directly extracted from edible or non-edible parts of a plant or animal or fermented and extracted from traditional or genetically modified microorganisms (including but not limited to bacteria, actinomycetes, and fungi) that are used in food processing and have a special catalytic function." A list of allowable food enzyme preparations is available (Annex C, People's Republic of China, 2010)
	Regulation: Hygienic Standard for Enzyme Preparations Used in Food Processing (Notified to the WTO as G/SPS/N/CHN/112 on 5 January 2009)
	Guidance document: See "Direct food additives" (above)
	Approval process for a new substances: See "Direct food additives" (above)
Processing aids	*Definition*: A substance or material (not including apparatus or utensils), and not consumed as a food ingredient by itself, and only used to fulfil a certain technological purpose during processing or treatment. Processing aids refers to various kinds of substances to enable food processing to go smoothly, irrelative to food itself, e.g. filtration aids, clarifiers, absorbents, lubricants, mould release agents, decolouring agents, peeling agents, extraction solvents, and nutritional substances for fermentation, etc. Processing aids are regulated under food additives
	Regulation: See "Direct food additives" (above)
	Guidance document: See "Direct food additives" (above)

(*continued*)

Table 5. Continued.

	Approval process for a new substances: See "Direct food additives" (above)
Nanoscale materials	*Definition*: Nanoscience and nanotechnology encompass studying the characteristics (manipulating of atom and molecular) and interactions (primary quantum effect) of the matter on nanometre (1–100 nm) scale, as well as the interdisciplinary science and technology using these characteristics. It extends a human's method and ability on understanding and changing the physical world to atomic and molecular level (http://english.nanoctr.cas.cn) (NCNST 2010)
	Regulation: No regulations pertaining to nanoscale materials are available
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: No authoritative statement found
	Efforts towards developing standards and regulations: Ministry of Science and Technology: • Supports standardisation activities in nanotechnology including health, safety, and environment Bio-Environmental Health Sciences of Nanoscale Materials Laboratory, National Center for Nanoscience and Technology of the Chinese Academy of Sciences: • Studies the nanotoxicology of manufactured nanomaterials • Includes an "Innovative methodology for nanotoxicological studies"

Table 6. Regulatory framework of chemicals added to food in the European Union.

Regulatory authority	*Name*: European Commission (EC) – Directorate General for Health and Consumers
	Website: http://ec.europa.eu/food/food/index_en.htm (EC 2011)
	Historical overview: • The Treaty of Rome, establishing the European Economic Community (EEC), signed on 25 March 1957, and entered into force on 1 January 1958 (Europa 2007a) • The Treaty establishing the European Atomic Energy Community (also known as Euratom) was signed at the same time and the two are jointly known as the Treaties of Rome (Europa 2007b)
	Role/responsibility: • The EC is the European Union's (EU) executive body. Their responsibilities include: • Proposing and enforcing regulation • Representing and upholding the interests of Europe as a whole • Drafting proposals for new European laws • Managing the day-to-day business of implementing EU policies and allocating EU funds • Ensuring that everyone abides by the European treaties and laws The responsibilities of the Directorate General for Health and Consumers is to ensure food and consumer goods sold in Europe are safe, that the EU's internal market works for the benefit of consumers, and that Europe helps protect and improve its citizen's health
Advisory scientific body	*Name*: European Food Safety Authority (EFSA)
	Website: http://www.efsa.europa.eu/
	Historical overview: • The establishment of EFSA (also known as the Authority) was one of the key measures contained in the Commission's White Paper on Food Safety which was published in January 2000 • Regulation 178/2002/EC providing a legal basis for the Authority was formally adopted on 28 January 2002 • Two additional Commission Regulations were adopted: 1304/2003/EC, which set up the procedure applied by EFSA to request for scientific opinions referred to it, and 2230/2004/EC, which established rules with regard to the network of organisations operating in the fields within the EFSA's mission

(*continued*)

Table 6. Continued.

	• EFSA's work covers all stages of food production and supply, from primary production to the safety of animal feed, right through to the supply of food to consumers. It collects information and analyses new scientific developments in order to identify and assess any potential risks to the food chain. It can carry out scientific assessment on any matter that may have a direct or indirect effect on the safety of the food supply, including matters relating to animal health, animal welfare, and plant health. EFSA also gives scientific advice on non-food and feed genetically modified organisms as well as on nutrition in relation to EU legislation. It can communicate directly with the public on any issue within its area of responsibility. The five committees which were transferred to EFSA in May 2003 include: • Scientific Committee on Food (SCF) • Scientific Committee on Animal Nutrition • Scientific Committee on Veterinary Measures relating to Public Health • Scientific Committee on Plants • Scientific Committee on Animal Health and Animal Welfare
	Role/responsibility: The Authority shall provide scientific advice and scientific and technical support for the Community's legislation and policies in all fields which have a direct or indirect impact on food and feed safety. It shall provide independent information on all matters within these fields and communicate on risks (178/2002/EC, article 22)
Framework regulations	178/2002/EC – General principles and requirements of food law, establishing the EFSA and laying down procedures in matters of food safety
Part of an overarching international organisation	• The EU has been a member of the World Trade Organization since 1995 • The EU is a member of the Codex Alimentarius Commission
Recent and/or pending changes	On 16 December 2008, the regulations of the Package on Food Improvement Agents were adopted. This includes regulations on food additives, food enzymes, and flavourings and food ingredients with flavouring properties, and an additional fourth regulation (Regulation (EC) No. 1331/2008, adopted on 16 December 2010) establishing a common authorisation procedure for additives, enzymes, and flavourings
Regulatory overview of specific food chemical groups	
Food ingredients	Food ingredients are defined as: • Any substance, including additives, used in the manufacture or preparation of a foodstuff and still present in the finished product, even if in altered form • Where an ingredient of the foodstuff is itself the product of several ingredients, the latter shall be regarded as ingredients of the foodstuff in question • The following shall not be regarded as ingredients: o the constituents of an ingredient which have been temporarily separated during the manufacturing process and later reintroduced but not in excess of their original proportions; o additives whose presence in a given foodstuff is solely due to the fact that they were contained in one or more ingredients of that foodstuff, provided that they serve no technological function in the finished product, which are used as processing aids; and o substances used in the quantities strictly necessary as solvents or media for additives or flavourings • In certain cases, decisions may be taken in accordance with the procedure laid down in Article 20 (2) in Directive 2000/13/EC as to whether the conditions described above are satisfied. *Novel foods*: Novel foods are foods and food ingredients that have not been used for human consumption to a significant degree within the Community before 15 May 1997
	Regulation: Regulation 258/97/EC for Novel Foods (http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN& numdoc=31997R0258&model=guichett)
	Guidance document: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31997H0618:EN:HTML

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Table 6. Continued.

	Approval process for a new substances: Foods commercialised in at least one member state before the entry into force of the Regulation on Novel Foods on 15 May 1997, are on the EU market under the "principle of mutual recognition". In order to ensure the highest level of protection of human health, novel foods must undergo a safety assessment before being placed on the EU market. Only those products considered to be safe for human consumption are authorised for marketing. Companies who want to place a novel food on the EU market need to submit their application in accordance with Commission Recommendation 97/618/EC, which outlines the scientific information and the safety assessment report required
	Novel foods or novel food ingredients may follow a simplified procedure, only requiring notifications from the company, when they are considered by a national food assessment body as "substantially equivalent" to existing foods or food ingredients (as regards to their composition, nutritional value, metabolism, intended use, and the level of undesirable substances contained therein)
Direct food additives	*Definition*: Food additives are substances that are not normally consumed as food itself but are added to food intentionally for a technological purpose described in Regulation (EC) No. 1333/2008, e.g. such as the preservation of food. All food additives should be covered by this Regulation, and therefore in the light of scientific progress and technological development the list of functional classes should be updated (currently there are 26 functional classes listed in the Annex I to Regulation (EC) No. 1333/2008). However, substances should not be considered as food additives when they are used for the purpose of imparting flavour and/or taste or for nutritional purposes, such as salt replacers, vitamins and minerals. Moreover, substances considered as foods which may be used for a technological function, such as sodium chloride or saffron for colouring, and food enzymes also should not fall within the scope of Regulation (EC) No. 1333/2008. However, preparations obtained from foods and other natural source material that are intended to have a technological effect in the final food and which are obtained by selective extraction of constituents (e.g. pigments) relative to the nutritive or aromatic constituents, should be considered additives within the meaning of Regulation (EC) No. 1333/2008. The new Regulation (EC) No. 1333/2008 does not apply to the following substances unless they are used as food additives: • Processing aids • Substances used for the protection of plants and plant products in conformity with Community rules relating to plant health • Substances added to foods as nutrients • Substances used for the treatment of water for human consumption falling within the scope of Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption • Flavourings, which fall within the scope of Regulation (EC) No. 1334/2008 • Regulation (EC) No. 1333/2008 does not apply to food enzymes falling within the scope of Regulation (EC) No. 1332/2008 with effect from the date of adoption of the Community list of food enzymes in accordance with Article 17 of that Regulation
	Regulation: Regulation (EC) No. 1333/2008 includes the Community list of approved food additives for use in foods and conditions of use (Annex II as amended by Commission Regulation (EU) No. 1129/2011) and the Community list of food additives approved for use in food additives, food enzymes, food flavourings and nutrients and their condition of use (Annex III as amended by Commission Regulation (EU) No. 1130/2011). Food additives in Annex II are listed on the basis of the categories of food to which they may be added. Food additives in Annex III are listed on the basis of the food additives, food enzymes, food flavourings and nutrients or categories thereof to which they may be added. Before these Community lists apply (1 June 2013) the Annexes to Directives 94/35/EC, 94/36/EC and 95/2/EC are still valid. A food additive may be included in the Community lists only if it meets general conditions: no safety concerns at the level of use proposed; there is a technological need; the consumer is not misled; and there are advantages and benefits for the consumer. Other more specific conditions exist for sweeteners and colours. Links to more information on food additives including the legislation are available at: http://ec.europa.eu/food/food/fAEF/additives/framework_reg_fA_en.htm/. All authorised food additives have to fulfil purity criteria which are set out in detail in three Commission Directives (EC) No. 10/2009 (food additives other than sweeteners and colours, amending Directive 2008/84/EC), 2008/60/EC (sweeteners), and 2008/128/EC (colours). It should be

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Table 6. Continued.

	noted that new regulations on purity criteria were adopted on 9 March 2012 (Regulation (EU) No. 231/2012 on specifications for food additives listed in Annexes II and III) which will repeal the mentioned directives as of 1 December 2012. Food additives must be kept under continuous observation and must be re-evaluated whenever necessary in the light of changing conditions of use and new scientific information. Therefore, when the EC is informed about new scientific evidence relating to a permitted food additive, it requests EFSA to assess the new data. In addition to this ongoing observation the EC has also asked the EFSA to undertake a re-evaluation of all currently permitted food additives (Regulation (EU) No. 257/2010). Regulation (EC) No. 1333/2008 on food additives: • The regulation, except transitional provisions, has been in application since 20 January 2010 • The regulation strengthens the principle of food safety and consumer information. It allows a more efficient and simplified procedure for authorisation of food additives by comitology. The consolidation of all food additives legislation in one single legal instrument makes legislation user-friendly for citizens and business operators. Comitology is the procedure by which the Commission prepares the draft legislation and member states vote at the Standing Committee on the Food Chain and Animal Health. If a qualified majority is in favour, it is then passed to the European Parliament and the Council, which have 2 months to object. If they do not object, it is published in the *Official Journal* and then it is EU law • In accordance with Article 30 of Regulation (EC) No. 1333/2008, additives that are permitted in food under Directives 94/35/EC, 94/36/EC, and 95/2/EC and their conditions of use were entered in the Community list of food additives in Annex II to the regulation. To that end the compliance with their general and specific conditions of use was reviewed. The new EU lists amending Annexes II and III to Regulation EC 1333/2008 were adopted on 11 November 2011 • The use of food additives already permitted in Directives 94/35/EC, 94/36/EC, and 95/2/EC will continue to be permitted until the application of Annex II as amended by Regulation (EU) No. 1129/2011 (1 June 2013)
	Guidance document: The Practical Guidance for Applicants was prepared to provide applicants with information that aims at facilitating the preparation and submission of applications for establishing or updating (adding, removing or changing conditions, specifications or restrictions) the Community lists. The links to other relevant documents are made in this guidance (http://ec.europa.eu/food/food/fAEF/authorisation_ application_en.htm) as well as additional guidance documents (EFSA Panel 2012)

	Approval process for a new substances: Applicants who wish to introduce new additives into the EU market, or seeking to revise existing provisions regulating individual additives already authorised within the EU, or seeking confirmation that an already approved additive made from a new source or by a new method of production is acceptable, must submit an application. Beside the Practical Guidance for Applicants there is also the Guidance on Submissions for Food Additive Evaluations by the SCF which provides details on the administrative and technical data required, and the range of toxicological tests generally required for new food additives, and on the format for formal submissions on additives. It must be noted that EFSA is preparing a new guidance document, which will replace the old one. The requirements for the application are also mentioned in Regulation (EU) 234/2011, which implements Regulation (EC) No. 1331/2008. The general requirements consist of:
	• Administrative data
	• Risk assessment data:
	  ○ Identity of the substance
	  ○ Information on particle size
	  ○ Presence of impurities
	  ○ Microbiological characteristics
	  ○ Proposed chemical and microbiological specifications
	  ○ Manufacturing process
	  ○ Methods of analysis in foods
	  ○ Reaction and fate in food
	  ○ Case of need and proposed uses
	  ○ Exposure
	  ○ Additives produced by microbiological processes
	  ○ Additives produced from genetically modified organisms

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Table 6. Continued.

	○ Information on national authorisations ○ Proposed normal and maximum use levels • Toxicological data: ○ General framework for the toxicological evaluation of food additives ○ Study protocols ○ Toxicological section of the dossier (core studies and other studies) ○ Data reporting ○ Review of results and conclusions • Risk management data: ○ Function and technological need ○ Investigations on the efficacy ○ Advantages and benefits for the consumer ○ Information why the use would not mislead the consumer ○ Compliance with specific conditions for sweeteners and colours
Food contact substances (e.g. components of packaging materials)	*Definition*: Food contact materials and articles are those which in their finished state are intended to be brought into contact with food, or are already brought into contact with food and intended for that purpose or can reasonably be expected to be brought into contact with food or to transfer their constituents to food under normal and foreseeable conditions of use. This includes packaging materials but also cutlery, dishes, processing machines, containers etc. The term also includes materials and articles that are in contact with water intended for human consumption but it does not cover fixed public or private water supply equipment
	Regulation: Framework Regulation (EC) No. 1935/2004. Food contact materials should be safe and should not transfer their components into the foodstuff in unacceptable quantities. The transfer of constituents from food contact materials into food is referred to as migration. In the context of the framework Regulation, specific Regulations on plastics (10/2011/EU), Active and intelligent (A&I) FCM substances (450/2009/EC), Recycling of plastics (282/2008/EC), Regenerate cellulose (Directive 2007/42/EC), ceramics (Directive 84/500/EEC) have been published. The specific Regulation on plastic FCM contains a positive list of monomers and additives, which can be used for their manufacture. The EU Food Contact Materials Database lists all approvals and conditions of use from the above Regulations and Directives. It is available at: https://webgate.ec.europa.eu/sanco_foods/main/?event=display/. To ensure the protection of the health of the consumer and to avoid any contamination of the foodstuff, two types of migration limits have been established for plastic materials: • An overall migration limit (OML) of 60 mg (of substances) kg^{-1} (of foodstuff or food simulants) that applies to all substances that can migrate from food contact materials to foodstuffs • A specific migration limit (SML) applies to individual authorised substances and is fixed on the basis of the toxicological evaluation of the substance. The SML is generally established according to the acceptable daily intake (ADI) or the tolerable daily intake (TDI) set by the SCF in the past and by EFSA since 2003. To set the limit, it is assumed that every day throughout his/her lifetime, a person weighing 60 kg eats 1 kg of food packed in plastics containing the relevant substance at the maximum permitted quantity
	Guidance document: The guidance document on the submission of a food contact material for evaluation by EFSA by the Panel on Additives, Flavourings, Processing Aids, and Materials in Contact with Food is available at: http://www.efsa.europa.eu/en/scdocs/scdoc/21r.htm
	Approval process for a new substances: General requirements include: • Identity of the substance • Physical and chemical properties of the substance • Intended use of the substance • Authorisation of the substance (authorisation for use of the substance in EU member states and other countries) • Migration data on the substance • Data on the residual content of the substance in the food contact material • Microbiological properties of the substance • Toxicological data • General requirements • Core tests (not all types of studies may be applicable for the substance of interest – all tests should be carried out according to EU or OECD guidelines, and including good laboratory practice)

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Table 6. Continued.

	• Three mutagenicity studies *in vitro* • 90-day oral toxicity studies, normally in two species • Studies on absorption, distribution, metabolism and excretion • Reproduction studies in one species • Developmental toxicity studies, normally in two species • Long-term toxicity/carcinogenicity, normally in two species • Additional studies/special investigations may be required if prior knowledge, or structural considerations indicate that other biological effects such as peroxisomal proliferation, neurotoxicity, immunotoxicity or endocrinological events may occur • Dermal or inhalation sensitisation studies, if applicable • Depending on the chemical nature of the substance to be used in food contact materials, the list of required tests mentioned above may be modified • Additional details available in the guidance document
Flavouring agents	*Definition*: Flavouring substances are defined chemical substances that include flavouring substances obtained by chemical synthesis or isolated using chemical processes, and natural flavouring substances. Flavourings are used to improve or modify the odour and/or taste of foods for the benefit of the consumer. Flavourings and food ingredients with flavouring properties should only be used if they fulfil the criteria specified in Regulation (EC) No. 1334/2008. They must be safe when used, and certain flavourings should therefore undergo a risk assessment before they can be permitted in food
	Regulation: New Regulation (EC) No. 1334 was adopted on 16 December 2008; however, as of 20 January 2011, this new regulation repeals Directives 88/388/EEC and 91/71/EEC. In order to protect human health, this Regulation should cover flavourings, source materials for flavourings and foods containing flavourings. It should also cover certain food ingredients with flavouring properties which are added to food for the main purpose of adding flavour and which contribute significantly to the presence in food of certain naturally occurring undesirable substances (hereinafter referred to as food ingredients with flavouring properties), their source material and foods containing them. The Regulation sets out flavourings and source materials for which an evaluation and approval is required. The Regulation prohibits the addition of certain substances as such to food and sets maximum levels for certain substances, which are naturally present in flavourings and in food ingredients with flavourings properties, but which may raise concern for human health. As of 20 January 2010, Regulation (EC) No. 1334/2008 on flavouring and certain food ingredients with flavouring properties amended the following: Council Regulation (EEC) No. 1601/91, Regulations (EC) No. 2232/96 and (EC) No. 110/2008, and Directive 2000/13/EC; however, Regulation (EC) No. 2232/96, laying down a Community procedure for flavouring substances, will continue to apply until the date of application of the Union list of flavourings and source materials. Smoke flavourings are regulated under Regulation (EC) No. 2065/2003
	Guidance document: The guidance document is available at: http://ec.europa.eu/food/food/fAEF/authorisation_application_en.htm
	Approval process for a new substances: After the completion of the evaluation programme but at the latest by 31 December 2010, the EU list of flavouring substances for use in or on foods in the EU shall be adopted [Article 5 (1) of Regulation (EC) No. 2232/96]. New substances follow the authorisation procedure laid down in Regulation (EC) No. 1331/2008 on the common authorisation procedure for food additives, food enzymes and food flavourings. Data requirements for flavouring substance application include: • Manufacturing process • Specifications • Data on dietary and non-dietary sources • Assessment of dietary exposure • Assessment of the genotoxic potential of the flavouring substance • Examination for structural/metabolic similarity to flavouring substances in an existing flavouring group evaluation (if applicable) Other requirements are specified for other categories of flavouring substances (see the guidance document for full details)
Enzymes	*Definition*: A food enzyme is defined as a product obtained from plants, animals or microorganisms or products thereof including a product obtained by a fermentation process using microorganism containing one or more enzymes capable of catalysing a specific biochemical reaction and added to food for a technological purpose at any stage of the manufacturing, processing, preparation, treatment, packaging, transport or storage of foods.

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Table 6. Continued.

	A food enzyme preparation is defined as a formulation consisting of one or more food enzymes in which substances such as food additives and/or other food ingredients are incorporated to facilitate their storage, sale, standardisation, dilution or dissolution (see Article 3 of Regulation (EC) No. 1332/2008). Regulation (EC) No. 1332/2008 does not include food enzymes used in the production of food additives falling within the scope of Regulation (EC) No. 1333/2008 or processing aids. The scope of this Regulation does not extend to enzymes that are not added to food to perform a technological function but are intended for human consumption, such as enzymes for nutritional or digestive purposes
	Regulation: Regulation (EC) No. 1332/2008 on food enzymes amends Council Directive 83/417/EEC, Council Regulation (EC) No. 1493/1999, Directive 2000/13/EC, Council Directive 2001/112/EC and Regulation (EC) No. 258/97. This Regulation harmonises for the first time the rules for food enzymes in the EU. It applies from 20 January 2009, except labelling provisions which apply from 20 January 2010. National provisions concerning the placing on the market and the use of food enzymes and food produced with food enzymes continue to apply in the member states until the adoption of the Union list of enzymes applies. According to Regulation (EC) No. 1332/2008, only food enzymes included in the Community list may be placed on the market as such and used in foods, in accordance with the specifications and conditions of use provided for in Article 7
	Commission's website: http://ec.europa.eu/food/food/fAEF/enzymes/index_en.htmEFSA's guidance on food enzymes. Guidance document: • http://www.efsa.europa.eu/en/scdocs/scdoc/1305.htm (EFSA 2009) • http://www.efsa.europa.eu/en/efsajournal/pub/2193.htm
	Approval process for a new substances: Food enzymes shall be subject to safety evaluation by EFSA and approval via an EU list. A 2-year period has been fixed in this Regulation for submission of applications on existing enzymes and new enzymes. This period started on 11 September. The inclusion of a food enzyme in the EU list will be considered by the Commission on the basis of Article 6 of Regulation (EC) No. 1332/2008, namely the opinion from EFSA, and also other general criteria such as technological need and consumer aspects. For every food enzyme included in the positive list, specifications including the purity criteria and the origin of the food enzyme shall be laid down. Data required for risk assessment and for risk management of food enzymes are laid down in Regulation (EC) No. 234/2011
Processing aids	*Definition*: According to Article 3.2(b) of Regulation (EC) No. 1333/2088 a processing aid shall mean any substance which is not consumed as a food by itself; is intentionally used in the processing of raw materials, foods or their ingredients, to fulfil a certain technological purpose during treatment or processing; and may result in the unintentional but technically unavoidable presence in the final product of residues of the substance or its derivatives provided they do not present any health risk and do not have any technological effect on the final product
	Regulation: Processing aids are not harmonised at EU level with the exception of food enzymes used as processing aids (see above "enzymes") and extraction solvents used in the production of foodstuffs and food ingredients (Directive 2009/32/EC). If a processing aid does not meet the criteria outlined in the definition (above), it can be regulated as a food additive, and the applicable Regulation (EC) No. 1333/2008 (regulations for food additive) would be applicable
	Guidance document: Refer to direct food additives
	Approval process for a new substances: There is no approval process for processing aids at the EU level
Nanoscale materials	*Definition*: The Commission has adopted a Recommendation for a definition of "nanomaterial" for regulatory purposes which it intends to integrate progressively and where necessary in the EU food Law (http://europa.eu/rapid/pressReleasesAction.do?reference=IP/11/1202& format=HTML& aged=0& language=EN& guiLanguage=en) (Stamm et al. 2012)
	Regulation: Existing legislation covers in principle the potential health, safety and environmental risks in relation to nanomaterials. Recently, specific provisions on the risk assessment of nanomaterials were introduced in EU legislation on food additives and food contact materials (EC 2009). A definition of "engineered nanomaterial" and a mandatory

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	labelling requirement for all food ingredients containing such nanomaterials were introduced in the Regulation on Food Information to consumers. For example, food additives that are prepared through nanotechnology would be considered as new additives. In Article 12 of 1333/2008/EC, "when a food additive is already included in a Community list and there is a significant change in its production methods or in the starting materials used, or there is a change in particle size, for example through nanotechnology, the food additive prepared by those new methods or materials shall be considered as a different additive and a new entry in the Community lists or a change in the specifications shall be required before it can be placed on the market"
	Guidance document: In November 2009, the EC asked EFSA to prepare a guidance document on how to assess potential risks related to certain food-related uses of nanotechnology. Given the knowledge which is currently available, the guidance to be developed will provide practical recommendations on how to assess applications from industry to use engineered nanomaterials in food additives, enzymes, flavourings, food contact materials, novel foods, food supplements, feed additives, and pesticides. The proposed guidance document was published and comments requested. This guidance document was published in May 2011 (http://www.efsa.europa.eu/en/efsajournal/doc/2140.pdf)
	Approval process for a new substances: No authoritative statement found
	Efforts towards developing standards and regulations: The EC has given the Finnish Institute of Occupational Health (FIOH), and Finland as a country, the opportunity to coordinate the EU-funded NanoSafety Cluster, which is a cluster of projects promoting nanomaterial safety: • This project includes all nanosafety-related areas, such as toxicology, ecotoxicology, exposure assessment, risk management and standardisation • The objective of NanoSafety Cluster is to standardise and harmonise nanotoxicology research and research methods British Standards Institute (BSI): • National committee NTI/1 on Nanotechnologies Safety of the Nano-Materials Interdisciplinary Research Centre (SnIRC) • Develop internationally agreed *in vivo* and *in vitro* protocols and models for investigating the routes of exposure, bioaccumulation and toxicology of nanoparticles in humans and non-human organisms

Table 7. Regulatory framework of chemicals added to food in Japan.

Regulatory authority	*Name*: Ministry of Health, Labour and Welfare (MHLW)
	Website: http://www.mhlw.go.jp/english/index.html (MHLW 2011a)
	Historical overview: • In 1947, then MHLW enacted the Food Sanitation Law as the first comprehensive law for food safety/hygiene and introduced a positive list system for food additives. Under the system, only additives designated as safe by the MHLW may be used in foods • Since 1947, all food additives have been regulated by this law; however, the designation system had been applied only to chemically synthesised additives until 1995 when the Food Sanitation Law was amended • Currently, all types of additives are equally subject to the designation system, synthetic or non-synthetic with minor exceptions
	Role/responsibility: • To protect the health of the public through the strengthening measures for the assurance of food safety • Responsibilities include the regulation of the manufacture, import, and sale of food, food additives, food apparatus, containers/packages, and the provision of related information to consumers and businesses (MHLW 2011c). • The administration is under the jurisdiction of the Department of Food Safety under the Pharmaceutical and Food Safety Bureau

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Table 7. Continued.

Advisory scientific body	*Name*: Food Safety Commission (FSC)
	Website: http://www.fsc.go.jp/english/index.html
	Historical overview: The FSC was established on 1 July 2003, as a part of Japanese Cabinet Office, following the founding regulation of Food Safety Basic Law
	Role/responsibility: The FSC's core role is risk assessment of food-associated hazards that are potentially contained in food including chemical substances (e.g. food additives, pesticides and veterinary medicines), biological (e.g. microorganisms and natural toxins), and novel foods. The FSC also emphasises risk communication on food-related hazards to the general public and also provides emergency response in the case of food poisoning outbreaks
Framework regulations	• The food safety administrative work is based on the Food Safety Basic Law (enacted in May 2003) and related laws including the Food Sanitation Law, the Abattoir Law, and the Poultry Slaughtering Business Control and Poultry Inspection Law • Other related laws include the Law of Temporary Measures for Enhancing the Control Method of the Food Production Process and the Health Promotion Law • The Food Sanitation Law (JETRO 2006) covers various responsibilities, such as the establishment of standards/specifications for food, additives, apparatus, and food containers/packages, and inspection to determine whether these established standards are met
Part of an overarching international organisation	• Japan has been a member of the World Trade Organization since 1995 • Japan is a member of the Codex Alimentarius Commission
Recent and/or pending changes	• The MHLW has deleted 80 substances from the list of existing food additives, as there are currently no uses in the Japanese market (WTO 2010). The list is available at: http://members.wto.org/crnattachments/2010/sps/JPN/10_2581_00_e.pdf (USDA 2010c) • The use of those substances as an additive is prohibited in foods produced in or exported to Japan. It should be noted that although a substance withdrawn from the list is prohibited for use as a food additive, it does not mean that the substance is prohibited for use as a food ingredient, e.g. as a health food
Regulatory overview of specific food chemical groups	
Food ingredients	*Definition*: Foods (including food ingredients) are defined as all foods and drinks; provided, however, this term does not include drugs and quasi-drugs in the Pharmaceutical Affairs Law (Article 4, Food Sanitation Law) (JETRO 2006).
	Novel foods: Novel foods are not defined under Japanese jurisdiction. There are no specific approval procedures for new food or food ingredients. The FSC conducts safety assessment for novel foods that are derived from a genetically modified organism (GMO). The MHLW may prohibit the sale of a food, which could possibly injure human health according to the opinion of the Pharmaceutical Affairs and Food Sanitation Council (Article 7 of the Food Sanitation law). This includes: • food that has never before generally served for human consumption; • any article containing the same is, or is to be newly sold as food; and • any article served for consumption in a different recipe from the ordinary way of consumption
	Regulation: No authoritative statement found
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: No authoritative statement found
Direct food additives	*Definition*: • According to Food Sanitation Law under Article 4 (JETRO 2006), a food additive is defined as a substance used in or on food in the process of manufacturing food or substances used for the purpose of processing or preserving food • Consequently, an "additive" includes both substances remaining in the finished food products, such as food colours and preservatives, and substances not remaining in the finished products, such as infiltration-supporting agents

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Table 7. Continued.

	• Food additives include sweeteners and food colouring agents • For food additives produced by recombinant DNA techniques food, a safety assessment is mandatory according to the Food Sanitation Act as of 2001. The "Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants)" (2004) is available in English from the FSC *Regulation*: • Food Safety Basic Law (the translated document is available at: http://www.fsc.go.jp/sonota/fsb_law1807.pdf) (Food Safety Commission 2006) • Food Sanitation Law (JETRO 2006) (the translated document is available at: http://www.japaneselawtranslation.go.jp/law/detail/?id=12& vm=04& re=02) (Ministry of Justice 2009) There are currently 345 designated food additives approved by the MHLW under Article 10 of the Food Sanitation Law (http://www.mhlw.go.jp/english/topics/foodsafety/foodadditives/index.html) (MHLW 2011b). The MHLW has decided to start evaluating certain food additives with intent to authorise them even when there is no application from a person who wishes to use them. These food additives are those that meet the two standards given below: • for which safety assessments have been conducted by the JECFA and whose safety has been confirmed within a certain level; and • that are widely used in the US and EU countries and whose need is considered to be high This decision was made from the viewpoint of international harmonisation for substances that are internationally proven safe and widely used in the world.
	Establishment of specifications and standards: Usually, people continue to consume food additives throughout their lifetime; thus, food additives must be subjected to stringent regulations. All designated chemicals, with a few exceptions, and some natural additives (existing food additives) are currently regulated by specifications and/or standards. These specifications and standards include specifications concerning chemical and physical characteristics, and standards for manufacturing, storage, and use. These standards, along with labelling and storage standards are published in an official compilation of food additives, entitled "Japan's Specifications and Standards for use of Food Additives" (MHLW 2000)
	Guidance document: A guidance document on food additives is available at: http://www.ffcr.or.jp/zaidan/FFCRHOME.nsf/pages/PDF/$FILE/Guideline.pdf
	Approval process for a new substances: The procedures required to apply for designation of a new substance intended to be used as a food additive pursuant to Article 6 of the Food Sanitation Law or for revision of standards for use of a food additive pursuant to Article 7, paragraph 1 of the Food Sanitation Law are provided within the guidance document. A checklist is provided in the last page of the guidance document, which outlines the requirements. It should be noted that all documents should be completed in Japanese; however, all documents except for the summary may be submitted in English. A brief summary of the general requirements include: • Summary • Chronology on origin or development and overseas use conditions • Physicochemical characteristics and specifications: o Name o Structural formula and rational formula o Molecule formula and formula weight o Assay o Manufacturing methods o Description o Identification tests o Specific properties o Purity tests o Loss on drying, loss on ignition or water o Residues on ignition o Method of assay o Stability o Analytical method for the food additives in foods o Principles to establish proposed specifications • Effectiveness: o Effectiveness and comparison in effect with other similar food additives o Stability in foods o Effects on nutrients of foods

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Table 7. Continued.

	• Safety information:
	  ○ Toxicity studies
	  ○ 28-day toxicity study
	  ○ 90-day toxicity study
	  ○ One-year toxicity study
	  ○ Reproduction study
	  ○ Teratogenicity study
	  ○ Carcinogenicity study
	  ○ Combined chronic toxicity/carcinogenicity study
	  ○ Antigenicity study
	  ○ Mutagenicity study
	  ○ General pharmacological study
	  ○ Metabolism/pharmacokinetic studies
	  ○ Daily intake of food additives
	• Proposed standards for use
	• It should be noted that not all of the above requirements are needed if applying for revision of standards for use of a food additive

Food contact materials (e.g. components of packaging materials)	*Definition*: No authoritative statement found
	Regulation: No regulations are available on food contact materials. In 1973, the Japan Hygienic Olefin and Styrene Plastics Association (JHOSPA) established the industry's voluntary standards composed of a positive list describing raw materials that can be used safely for food utensils, containers, packaging materials, and the Standard Methods of Analysis that defined specifications for each resin. JHOSPA aims to carry out activities to prevent sanitary hazards caused by food utensils, containers, and packaging materials
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: No authoritative statement found
Flavouring agents	*Definition*: Natural flavouring agents are defined as food additives intended for use in flavouring food and are substances obtained from animals or plants, or mixtures thereof (The Food Sanitation Act, Article 4, Paragraph 3) (JETRO 2006). No specifications are established for natural flavouring agents
	Regulation: http://www.fantastic-flavour.com/files-downloads/flavour_agents_japan.pdf
	Guidance document: Refer to direct food additives (above)
	Approval process for a new substances: Refer to direct food additives (above)
Enzymes	*Definition*: No authoritative statement found
	Regulation: Enzymes listed as a permitted food additive can be used in food under the conditions indicated; however, for enzymes produced by genetically modified microorganisms, a safety assessment would be required under Standards for the Safety Assessment of Food (additives) Produced Using Genetically Modified Microorganisms (only available in Japanese)
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: No authoritative statement found
Processing aids	*Definition*: Processing aids defined under labelling standards according to the Food Sanitation Law (JETRO 2006) are substances added to a food in processing the food which are (1) removed from the food before the completion of the food; (2) derived from raw materials of the food and converted into components normally included in the food but do not significantly increase the amounts of the components; or (3) present in the finished food at insignificant levels but do not have any technical or functional effect of these components on the food
	Regulation: Processing aids are regulated under the same process as food additives. Processing aids that are listed on the permitted list of food additives are permitted for use in foods (Government of Japan 2002)
	Guidance document: Refer to direct food additives (above)

(*continued*)

Table 7. Continued.

	Approval process for a new substances: Refer to direct food additives (above)
Nanoscale materials	*Definition*: No authoritative statement found
	Regulation: No authoritative statement found
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: No authoritative statement found
	Efforts towards developing standards and regulations (Locascio et al. 2011): The National Institute of Advanced Industrial Science and Technology (AIST) has sponsored several projects at the Ministry of Economy Trade and Industry (METI) since 2005 (http://www.aist.go.jp/): • Standardisation of Nanoparticle Risk Evaluation Method with the objective to develop methods for the characterisation of nanoparticles, develop methods for assessment of health impact and safety of nanoparticles, and develop systems for data collection and data standardisation • Risk assessment of manufactured nanomaterials

Table 8. Regulatory framework of chemicals added to food in Mexico.

Regulatory authority	*Name*: Ministry of Health (SSA) through the Federal Commission for the Protection against Sanitary Risks (COFEPRIS 2010)
	Website: http://www.cofepris.gob.mx
	Historical overview: COFEPRIS was established 5 July 2001 with the publication of the "Decreto de Creación de la Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS)" in the "Diario Oficial de la Federación". This decree established the structure and organisation of a decentralised administrative office with technical, administrative and operative autonomy responsible for the implementation of its legal attributes as related to sanitary regulation, control and support as stated in the General Health Law and other applicable regulations. This new Commission is composed of different General Directions that include: The General Direction of Drugs and Health Technologies, Sanitary Control of Products and Services, Environmental Health, The National Public Health Laboratory and the Direction of Sanitary Control of Publicity
	Role/responsibility: According to the General Health Law, the Ministry of Health will enforce its legal attributes as related to sanitary regulation, control and support through the Federal Commission for the Protection Against Sanitary Risks as related to (Art. 17 bis): • The control and vigilance of health establishments • The prevention and control of adverse environmental health effects as related to human health • Occupational health and safety • The sanitary control of products and services including importation, exportation and of the establishments that process such products • The sanitary control of the process, use, maintenance, importation, exportation and final disposition of medical instruments, prosthetics, functional aids, diagnostic agents, odontological supplies, surgical materials, hygienic products and the establishments where these are processed • The sanitary control of publicity of activities, products and services • The sanitary control of the disposition of human organs, tissue and their components as well as cell cultures • International sanitary controls • The sanitary control of human organ, tissue and cell donations
Advisory scientific body	*Name*: See "regulatory authority" (above)
	Website: See "regulatory authority" (above)
	Historical overview: See "regulatory authority" (above)
	Role/responsibility: See "regulatory authority" (above)

(*continued*)

Table 8. Continued.

Framework regulations	For foods the following regulations apply: • General Health Law (Ley General de Salud) • The Regulation on Sanitary Control of Products and Services (Reglamento de Control Sanitario de Productos y Servicios) • An agreement that establishes the substances allowed as additives and processing aids in foods, beverages and nutritional supplements (ACUERDO por el que se determinan las sustancias permitidas como aditivos y coadyuvantes en alimentos, bebidas y suplementos alimenticios) (Secretaría de Salud México 1999) • Applicable Official Mexican Norms (Normas Oficiales Mexicanas)
Part of an overarching international organisation	• Mexico has been a member of the World Trade Organization since 1995 • Mexico is a member of the Codex Alimentarius Commission
Recent and/or pending changes	• Pending (since 2007–2008) update and publication of a new Food Additive Positive List • Recently implemented (June 2011) labelling regulation NOM-051-SSA1-2010 mandates nutritional labelling for foods and non-alcoholic beverages as well as quantitative ingredient declaration • Upcoming review and publication of NOM-086-SSA1-1994 Foods with Modified Composition to homologate it with the new labelling regulation • Upcoming publication (2012) of a new food additive and processing aid positive list that will include limits and approved applications for each compound
Regulatory overview of specific food chemical groups	
Food ingredients	*Definition of a food ingredient*: Any substance or product including the additives that is used in the manufacture, elaboration, preparation or treatment of a food or non-alcoholic beverage and that is present in the final product transformed or not. There are no regulations pertaining to new food ingredients or novel foods
	Regulation: No authoritative statement found
	Guidance document: No authoritative guidance document found
	Approval process for new substances: No authoritative statement found
	Definition: Food additives are defined as those substances added directly to food and drinks during its manufacture in order to provide or intensify aroma, colour or flavour, to improve its stability or its preservation. The term does not include contaminants, substances added to foods to maintain or to improve the nutritional quality, or sodium chloride. Additives always perform a technological function in the final product (USDA 2009)
	Regulation: • General Health Law • The Regulation on Sanitary Control of Products and Services (Reglamento de Control Sanitario de Productos y Servicios) contains some specific limits for additives in specific products • An agreement that establishes the substances allowed as additives and processing aids in foods, beverages and nutritional supplements (ACUERDO por el que se determinan las sustancias permitidas como aditivos y coadyuvantes en alimentos, bebidas y suplementos alimenticios). This is only a positive list and does not specify limits or specific applications. However, the new 2012 updated list includes limits and specific applications and will list processing aids separately • Applicable Official Mexican Norms (Normas Oficiales Mexicanas) (NOM) may establish limits and applications • Authorised food additives including colorants and sweeteners provided in English are available in the GAIN report MX6058 (http://www.fas.usda.gov/gainfiles/200607/146208414.pdf) (USDA 2006a) • The authorised additives must follow the established specifications in the provisions included in the Appendix Chapter VIII of the "Regulations for the Sanitary Control of Goods and Services", which are provided on the SSA's website (http://www.ssa.gob.mx) • In addition, the list of authorised purified substances, enzymes, and synthetic flavours provided in English are available in the GAIN report MX6070 (USDA 2006b) • The list of permitted food additives is not available in English • It is important to consider all levels of regulations. The major challenge is that the documents are not all updated so limits and substances listed in specific NOMs may not be updated with the most recently approved additives

(*continued*)

Table 8. Continued.

	Guidance document: Agreement that establishes the substances allowed as additives and processing aids in foods, beverages and nutritional supplements *Approval process for a new substances*: Through technical consultation presenting a technical dossier to request approval and inclusion in the positive list. After an official approval is obtained, it is important to follow up to ensure that the substance is included in the next update of the positive list (agreement) and any updated applicable NOMs
Food contact substances (e.g. components of packaging materials)	*Definition*: No authoritative statement found
	Regulation: The Regulation on Sanitary Control of Products and Services (Reglamento de Control Sanitario de Productos y Servicios – 24th Title)
	Guidance document: No authoritative guidance document found Voluntary Mexican Norms (NMX) may be available for specific products
	Approval process for new substances: No specific process. Any approval should be obtained through technical consultation. Although there is no specific, formal process, most major customers will require legal confirmation that a specific compound is allowed. If a company wants to be sure that the product is allowed, then they should consult with the authorities
Flavouring agents	*Definition*: Substance or blend of substances of natural origin, identical to natural or synthetic with or without solvents and with or without the addition of other additives that are used to give or intensify flavours or aromas to products
	Regulation: Same as food additives
	Guidance document: Same as food additives
	Approval process for new substances: Same as food additives. Usually when the positive list is updated, the FEMA-GRAS lists are reviewed for inclusion
Enzymes	*Definition*: Biological catalyser protein substance produced by live cells that catalyse specific reactions in diverse production processes. Source: The Regulation on Sanitary Control of Products and Services
	Regulation: Same as food additives
	Guidance document: Same as food additives
	Approval process for a new substances: Same as food additives
Processing aids	*Definition*: Substance or material, excluding instruments, utensils and additives that is not consumed as a food ingredient by itself and is used intentionally in the production of raw materials, foods or their ingredients to achieve a technological function during the treatment or processing and that can lead to the unintentional presence of residues or derivatives in the final product. Colour aid is the substance that is used to intensify, retain or develop colour
	Regulation: Same as food additives
	Guidance document: Same as food additives
	Approval process for a new substances: Same as food additives
Nanoscale materials	*Definition*: No authoritative statement found
	Regulation: No authoritative statement found
	Guidance document: No authoritative guidance document found
	Approval process for a new substances: No authoritative statement found Any specific approval should be obtained through technical consultation
	Efforts towards developing standards and regulations: None known

Table 9. Regulatory framework of chemicals added to food in the USA.

Regulatory authority	*Name*: US Food and Drug Administration (USFDA)
	Website: http://www.fda.gov/Food/FoodIngredientsPackaging/default.htm
	Historical overview: • Began as the Bureau of Chemistry, as part of the US Department of Agriculture in 1862 • The Food and Drugs Act was passed in 1906 • Bureau of Chemistry is split into the Food Drug and Insecticide Administration and the Bureau of Chemistry and Soils in 1927 • Food Drug and Insecticide Administration is renamed the Food and Drug Administration in 1930 • The Federal Food Drug and Cosmetic Act was passed in 1938 • The Food Additives Amendment of 1958 was passed in 1958 • http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm081229.htm
	Role/responsibility: • Protect the public health by ensuring that foods are safe, wholesome, sanitary, and properly labelled • Promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner • Participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonise regulatory requirements, and achieve appropriate reciprocal arrangements • Where appropriate, carry out its mission in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products
Advisory Scientific body	*Name*: USFDA Science Board and USFDA Food Advisory Committee
	Website: • Science Board to the US Food and Drug Administration (Science Board): http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/default.htm • Food Advisory Committee: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/default.htm
	Historical overview: Both the Science Board and the Food Advisory Committee were authorised by the Federal Advisory Committee Act (Pub. L. 92-463) passed in 1972. The Science Board was established on 26 June 1992. The Food Advisory Committee was established on 15 December 1991 (21 CFR §14.100)
	Role/responsibility: • Science Board: Provides advice to the Commissioner and other appropriate officials on a wide variety of food and drug related issues including: o specific complex scientific and technical issues important to the agency and its mission o emerging issues within the scientific community o keeping pace with technical and scientific developments, including in regulatory science o agency research o upgrading the agency's scientific and research facilities and training opportunities As of 2012, the Board is made up of a committee with a core of 21 voting members knowledgeable in fields including food science, safety, and nutrition; chemistry; pharmacology; toxicology; public health and epidemiology; international health and regulation; and nanotechnology. • Food Advisory Committee: Provides advice to the Commissioner and other appropriate officials on emerging food safety, food science, nutrition, and other food-related health issues and may be tasked with making recommendations on matters including: o broad scientific and technical food or cosmetic related issues o the safety of new foods and food ingredients o labelling of foods o nutrient needs and nutritional adequacy and o safe exposure limits for food contaminants As of 2012, the Committee consists of 17 standing members knowledgeable in the fields of physical sciences, biological and life sciences, food science, risk assessment, nutrition, food technology, molecular biology, and other relevant scientific and technical disciplines

(*continued*)

Table 9. Continued.

Framework regulations	*Food and Drug Regulations*: 21 CFR, Chapter 1 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm)
Part of an overarching international organisation	• The US has been a member of the Codex Alimentarius Commission since it was established in 1963 (http://www.codexalimentarius.org/members-observers/members/en/?no_cache=1) • The US also has been a member of the World Trade Organization since 1995 (http://www.wto.org/english/thewto_e/whatis_e/tif_e/org6_e.htm) • http://www.fda.gov/InternationalPrograms/HarmonizationInitiatives/default.htm
Recent and/or pending changes	The Food Safety Modernization Act was signed into law on 4 January 2011. Changes include requiring food facilities to document in writing that all substances at the facility that are intended to be added to food are allowed by the food additive regulatory programme (http://www.fda.gov/food/foodsafety/fsma/default.htm)
Regulatory overview of specific food chemical groups	
	The US does not define the term "food ingredient". Instead, it defines food. Food means, "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article" (21 USC §321(f)). Food includes human food, pet food, animal feed and substances migrating to food from food contact articles (21 CFR §170.3(m)). Any substance that is reasonably expected to become a component of food is a food additive that is subject to premarket approval by the USFDA, unless the substance is generally recognised as safe (GRAS) among experts qualified by scientific training and experience to evaluate its safety under the conditions of its intended use, or meets one of the other exclusions from the food additive definition in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FFDCA). *Novel foods*: The US does not define novel foods. New substances are regulated through a variety of mechanisms described below
	Regulation: 21 CFR, Chapter 1 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm)
	Guidance document: USFDA guidance regarding substances allowed in food, including new substances is available at: http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/default.htm
	Approval process for a new substances: There are three ways a food manufacturer can get clearance to add a new substance to its products: • A manufacturer or trade association can decide on its own that a substance's use is "generally recognised as safe", which is commonly known as a "GRAS substance". This determination must be based on the opinion of "experts qualified by scientific training and experience to evaluate the safety …". Notice to the USFDA or the public of the safety decision or its use is not required • The USFDA approves the use of a substance by issuing a new or amended regulation. The USFDA usually makes this safety determination in response to a petition by a manufacturer or its representative. It provides the public with the opportunity to comment before the chemical use is approved and a regulation is issued. Since 2000, use of this method has fallen dramatically • A manufacturer voluntarily asks the USFDA to review its safety assessment of a chemical it wants to use in food by submitting a notification. If the agency's review raises no concerns, the USFDA sends a letter stating that it has "no objections" or "no questions" to the manufacturer's decision A determination that a particular use of a substance is GRAS (unless established by common use prior to 1958) requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted (i.e. general recognition of safety). 21 CFR 170.30. In contrast, a determination that a particular use of a food additive is safe via premarket approval requires only technical evidence of safety

(*continued*)

Table 9. Continued.

	A substance added directly to food can fall into one of several categories: food additive, prior sanctioned substance, colour additive, or the use of the substance is considered GRAS, depending on its intended use and the mechanism through which approval is sought. *Definition*: • A food additive is a substance "the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting or holding food; and including any source of radiation intended for any such use); if such substance is not GRAS or sanctioned prior to 1958[1] or otherwise excluded from the definition of food additives • Direct food additives are a subcategory of this larger category. They are substances intentionally added directly to food whose use has been expressly approved by the USFDA, usually in response to a food additive petition from a manufacturer or manufacturer's representative • Prior-sanctioned substances are chemicals that were government-approved for use in food prior to 1958 • GRAS substances are substances "generally recognized among experts qualified by scientific training and experience to evaluate their safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to 1 January 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use". GRAS substances are distinguished from food additives by the type of information that supports the GRAS determination, that it is publicly available and generally accepted by the scientific community, but should be the same quantity and quality of information that would support the safety of a food additive. USFDA notification of the GRAS determination of a chemical's use is voluntary • Colour additives are substances that are capable (alone or through reaction with other substances) of imparting colour when added or applied to food. Substances intended to be used solely for purposes other than colouring, that may also impart colour, do not fall within this category. The USFDA must approve all colour additives, typically in response to a colour additive petition. Colour additives cannot be GRAS
	Regulation: • 21 CFR §§70–82 and §§170–189 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm) • GRAS Notifications: http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm
	Guidance documents: http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/default.htm#food
	Approval process for new substances: Same as described for food ingredients above. In this case, the petitions submitted would be food or colour additive petitions. Regarding voluntary notifications, the notification submitted by a manufacturer would be known as a GRAS notification and if the agency's review of this notification raises no concerns, the USFDA would send a letter stating that it has "no questions" regarding the manufacturer's decision
Food contact substances (e.g. components of packaging materials)	In the US, substances added to food indirectly may be known as indirect additives, food contact substances (FCS), FCS below the threshold of regulation, or GRAS substances depending on their use and the method of clearance for use in food. Since 2000, FCSs are the most applicable category. Food contact substances are chemicals not intended to be added directly to or have a technical effect on the food, but which may reasonably expected to become a component of food. These include substances used in packaging, transporting or the production of food
	Regulation: • General: 21 CFR §170–171 • Existing indirect additive approvals: 21 CFR §§174–178 and 186 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm) • FCS notification regulation: 21 CFR 170.3(e)(3) • FCS threshold of regulation: 21 CFR 170.39 • See also http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/default.htm

(*continued*)

Table 9. Continued.

	Guidance document: http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/default.htm
	Approval process for a new substances: Same as described for food ingredients above. The petition would be known as a food additive petition. Regarding notifications, although a manufacturer could submit a GRAS notification, most manufacturers of FCS choose to submit FCS Notifications because the approval by the USFDA is applicable only to that manufacturer. If a FCS Notification is submitted, the USFDA must object within 120 days
Flavouring agents	Flavouring agents are regulated as both food additives and GRAS substances (see "Direct food additives" above for a description of both). Most flavouring agents in the US have been found to be GRAS by the Flavor and Extract Manufacturers Association (FEMA) expert panel, which makes safety decisions, publishes them, and submits them to the USFDA for review. http://www.femaflavour.org/gras. USFDA has also approved a number of flavours as food additives and GRAS substances
	Regulation: No specific regulations on flavouring agents. They are regulated as direct food additives or GRAS substances: • Regulations regarding labelling of flavours: 21 CFR §101.22 • Lists of flavours approved in the regulations can be found at: 21 CFR §§172, 182 and 184 • GRAS Notifications: (http://www.fda.gov/FoodFoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm)
	Guidance document: http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/default.htm
	Approval process for a new substances: Same as described for direct food additives above. Manufacturers can also seek a determination by FEMA
Enzymes	*Definition*: There is no specific regulation governing enzymes. They would be regulated as direct or secondary direct additives, or GRAS substances depending on their intended use and the method used to allow the substances in food
	Regulation: See "Direct food additives" (above)
	Guidance document: See "Direct food additives" (above)
	Approval process for new substances: See "Direct food additives" (above)
Processing aids	*Definition*: A subcategory of direct food additives, are what are known as "secondary direct additives". These are food additives that have a technical effect in food during processing but that are not intended to have an ongoing technical effect in the food. These are sometimes more commonly known as processing aids. Direct food additives are described above. The USFDA may also consider processing aids to be food contact substances in some cases. Food contact substances are described above
	Regulation: See "Direct food additives" and "Food contact substances" (above)
	Guidance document: See "Direct food additives" and "Food contact substances" (above)
	Approval process for a new substances: See "Direct food additives" and "Food contact substances" (above)
Nanoscale materials	*Definition*: There is no formal definition for "nanotechnology" or "nanoscale" at this time. However the USFDA has indicated that "In the absence of a formal definition, when considering whether a USFDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, the USFDA will ask: (1) whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1–100 nm); or (2) whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer". This definition is contained in the USFDA's Draft Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food contact substances, Including Food Ingredients that are Colour Additives, which was issued in April 2012 (FDA 2012).

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Table 9. Continued.

	Regulation: There are currently no formal regulations specifically governing nanotechnology or nanoscale materials as applied to food
	Guidance document: The USFDA has issued draft guidance, most recently in April 2012: • http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm300661.htm • http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm
	Approval process for a new substances: New substances, whether direct food additives or food contact substances, cannot be GRAS per the USFDA's recently issued draft guidance. Manufacturers seeking approval for a nano-engineered substance must submit a food additive petition or a food contact substance notification. These are described above
	Efforts towards developing standards and regulations: The USFDA Nanotechnology Task Force, formed in August 2006 to: • Develop regulatory approaches • Identify and recommend ways to address any knowledge or policy gaps that exist so as to better enable the agency to evaluate possible adverse health effects from USFDA-regulated products that use nanotechnology materials • http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm2006658.htm

have their own regulatory systems in place, many of their food standards are gradually being replaced by official Mercosur standards as they are developed.

Regulatory authorities

Table 10 outlines the regulatory authorities and the Advisory Scientific Body/Regulatory Enforcement Agency for each of the target countries. Labelling and compositional standards for both Australia and New Zealand are developed by FSANZ; thus, these regulations discussed within this report will be identical for both countries. The EU regulations apply verbatim in all member states.

Participation in international organisations

All the target countries (Argentina, Australia, Brazil, Canada, China, Japan, Mexico, New Zealand, the EU and US) are members of the WTO and CAC. In addition, Argentina and Brazil follow Mercosur standards. Mercosur was established in 1991 and encompasses Argentina, Brazil, Uruguay, Paraguay and, as of 2006, Venezuela. Mercosur standards are influenced by the EU, CAC and USFDA. For further details, see the individual summary Tables 1–9. A summary of the target countries and their participation in international organisations is presented in Table 11.

Direct food additives

Food additives are defined and regulated among Argentina, Australia/New Zealand, Brazil, Canada, China, the EU, Japan, Mexico and the US. Although, the precise definition of a food additive differs among the target countries, in general a food additive is defined as a substance added to foods intentionally and to achieve a technological function in the final product. In each of these countries a permitted list of food additives is published and available to the public. The permitted list contains food additives, which are deemed safe for human consumption under the specified conditions of use. In all target countries except the US, if a food additive is not on the permitted list or its use is not permitted in a particular food and an applicant wants to use the food additive, the applicant must submit an application to approve its use in the respective country, following the conditions and requirements laid out by the respective authoritative body.

In Argentina and Brazil, food additives are regulated under Mercosur standards (GMC 11/06, 34/10 and 35/10). For new food additives, applicants must submit to the Comisión Nacional de Alimentos (CONAL) or Agência Nacional de Vigilância Sanitária (ANVISA) (for Argentina and Brazil, respectively), which will subsequently forward the application to Mercosur's Sub Work Group #3. In Canada, all new food additives or changes to the permitted uses of already approved food additives under Division 16 of the Food and Drug Regulations must undergo a pre-market assessment focused on safety. Similarly, in Japan and China a safety assessment was conducted on all currently permitted food additives. In all the target countries, a pre-market application is generally required for new food additives and for changes pertaining to an existing permitted food additive (such as changing the maximum permitted level, revision of a standard of use, etc.).

In the EU, on 16 December 2008, new regulations were adopted, which include food additives (1333/2008/

Table 10. Authoritative bodies among the target countries.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Regulatory authority	Ministry of Health (Ministerio de Salud) and The National Administration of Drugs, Foods, and Medical Technology (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica – ANMAT)	Food Standards Australia New Zealand (FSANZ); New Zealand Ministry for Primary Industries (MPI) (formerly Ministry of Agriculture and Forestry – MAF)	Ministry of Health (Ministério da Saude)	Health Canada (HC)	Ministry of Health (MOH)	European Commission (EC) – Directorate General for Health and Consumers	Ministry of Health, Labour and Welfare (MHLW)	Ministry of Health (SSA) through the Federal Commission for the Protection against Sanitary Risks (COFEPRIS)	US Food and Drug Administration (USFDA)
Advisory scientific body	National Committee of Food (CONAL)	FSANZ Board, FSANZ Fellows, and Scientific Advisory Groups	National Health Surveillance Agency; Agencia Nacional de Vigilancia Sanitária (ANVISA)	Same as above	Same as above	European Food Safety Authority (EFSA)	Food Safety Commission	Same as above	USFDA Science Board; USFDA Food Advisory Committee

Table 11. Participation of target countries in international organisations.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Member of CODEX	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Member of the World Trade Organization	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Additional participation in international organisations	Mercosur	–	Mercosur	–	–	–	–	–	–

EC), food enzymes (1332/2008/EC), and flavourings and food ingredients with flavouring properties (1334/2008/EC). The regulation on food additives applies to food additives used for a technological purpose in the manufacture, processing, preparation, treatment, packaging, transport or storage of food, excluding those substances used as processing aids. Under the regulation, food additives shall be subject to safety evaluation by the EFSA and approval via a Community list. The inclusion of a food additive in the Community list is considered by the Commission on the basis of the opinion on its safety from EFSA and a demonstrated case of need. The Commission takes into account other general criteria such as technological need and consumer aspects when considering whether to include the food additive in the Community list. For every food additive included in the positive list, specifications, including the criteria on purity and the origin of the food additive, shall be laid down. In order to increase consistency in common areas of the procedural aspects of food additives' approval, guidelines for evaluation by EFSA and decision-making by the Commission, are provided in Regulation (EC) No. 1331/2008 (adopted 16 December 2010) which establishes a common authorisation procedure for food additives, food enzymes and food flavourings. In June 2012, new guidance for the submission of food additive applications was published outlining a tiered approach, in which the extent of toxicological testing is determined by the results of initial testing, with key issues and triggers described that can result in additional required testing (EFSA Panel 2012).

In the US, substances to be added to food are subject to a premarket approval requirement unless they are exempt as outlined below. Rulis and Levitt (2009) provide an excellent detailed description of the food additive approval process in the US. The 1958 Food Additive Amendments of the Federal Food, Drug and Cosmetic Act (FFDCA) required demonstration of the safety of food additives, but also included two clauses to exempt food additives currently in use from safety assessments by making them "grandfathered" ingredients. This included food additives that had been previously sanctioned for use in foods, and food additives that were "generally recognised as safe" (GRAS) for use as food. These ingredients became known as GRAS substances and were permitted to remain on the market, although in later years subsequent reviews of the safety of many of the grandfathered GRAS substances were undertaken and the USFDA affirmed their GRAS status. In 1997, the USFDA issued a proposed rule to eliminate the GRAS affirmation petition process and replace it with a voluntary notification procedure. Thus, the USFDA no longer accepts GRAS affirmation petitions. Additional details on the history of GRAS is available on the USFDA website.

As a result of these amendments to the FFDCA, a food additive pre-market approval is not required for a new food additive or use if the use is GRAS. The use of the substance can be determined to be GRAS by experts qualified by scientific training and experience to evaluate its safety, and having been adequately shown through scientific procedures (or in the case of a substance used in food prior to 1 January 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of intended use. The requirement for "general recognition" of safety is often satisfied through publication of the pivotal safety data in the peer-reviewed literature, and cited in the GRAS dossier or notification submission. A list of GRAS substance notifications reviewed by the USFDA and the agency response can be found in an online database maintained by the agency. In general, the USFDA's response is one of the following: (1) the USFDA has no questions about the notifier's conclusion of GRAS status; (2) the notice does not provide a basis for a conclusion of GRAS status; or (3) at the notifier's request, the USFDA ceased to evaluate the notice.

Several important points about GRAS substances should be noted. Firstly, the GRAS status of a compound is based on the intended use(s) and levels of use documented in the determination dossier, which will determine the anticipated exposure and thus safety. Thus, it is the specific use, and not the substance in general, that is determined to be GRAS. Other uses of that substance in foods are not GRAS. Secondly, as USFDA notification of the GRAS determination is voluntary, there is no publicly available list of the uses of substances that have been "self-determined" to be GRAS and thus no opportunity for public scrutiny of safety

Table 12. Comparison of the regulations on direct food additives among the target countries.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Definition of a food additive includes:	Any ingredient added to foods intentionally, without intent to nurture, in order to modify the physical, chemical, biological or sensory characteristics of foods, during its manufacture, processing, preparation, processing, packaging, conditioning, storage, transport or during food handling: it will have, or it can be reasonably expected to have (directly or indirectly) as a result, the additive itself or its by-products become part of that food	Any substance not normally consumed as a food in itself and not normally used as an ingredient of food, but which is intentionally added to a food to achieve one or more of the technological functions specified in Schedule 5. It or its by-products may remain in the food	Same as for Argentina[a]	Any substance the use of which results, or may reasonably be expected to result, in it or its by-products becoming a part of or affecting the characteristics of a food. It should be noted that a substance not present in the final food but which has affected the characteristics of that food would be regulated as a food additive	An artificially chemosynthetic or natural substance to be added to foods in order to improve food quality, colour, fragrance and taste, and for the purpose of preservation and processing technology. Nutrition enhancers, gum-based substances in chewing gum, flavouring agents, and processing aids in the food industry are also included in food additives	Substances that are not normally consumed as food itself but are added to food intentionally for a technological purpose. Preparations obtained from foods and other natural source material that are intended to have a technological effect in the final food and which are obtained by selective extraction of constituents relative to the nutritive or aromatic constituents, should be considered additives	Substances used in or on food in the process of manufacturing food, or substances used for the purpose of processing or preserving food. Consequently, an "additive" includes both substances remaining in the finished food products, such as food colours and preservatives, and substances not remaining in the finished products, such as infiltration-supporting agents	Substances added directly to food and non-alcoholic beverages during its manufacture in order to provide or intensify aroma, colour or flavour, to improve its stability or its preservation. Additives always perform a technological function in the final product	Substances that may become a component or otherwise affect the characteristics of food and which do not fit into any other category. Subcategories include direct food additives which are intentionally added directly to food and "Secondary direct additives" which may more commonly be known as processing aids

(*continued*)

Table 12. Continued.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Definition of a food additive does not include:	Contaminants or nutrients that are incorporated into a food in order to maintain or improve its nutritional properties		Same as for Argentina[a]	Any nutritive material used, recognised or commonly sold as an article or ingredient of food; vitamins, mineral nutrients and amino acids, other than those listed in Division 16; spices, seasonings, flavouring preparations, essential oils, oleoresins and natural extractives; agricultural chemicals, other than those listed in Division 16, food packaging materials and components thereof; and drugs for administration to animals that may be food		Substances used for the purpose of imparting flavour and/or taste or for nutritional purposes. Substances considered as foods which may be used for a technological function, such as sodium chloride or saffron for colouring, and food enzymes		Contaminants, substances added to foods to maintain or to improve the nutritional quality, or sodium chloride	Contaminants or substances that are not intended to be added directly to food or have a technical effect, but which may reasonably be expected to become a component of food
Regulation	Mercosur regulations, GMC 11/06, GMC 34/10, and GMC 35/10	Food additives may only be added to food where expressly permitted in Food Standard 1.3.1	Same as for Argentina[a]	Division B.16	Order No. 73: Measures for Administration of New Food Additives	1333/2008/EC	Food Sanitation Law	Regulation on Sanitary Control of Products and Services	21 CFR §§70–82, and §§170–189. Proposed rule published in 1997 (62 FR 18938)

(*continued*)

Table 12. Continued.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Additional regulation details	Permitted list of food additives according to GMC 11/06. Food additives used according to GMP (GMC 34/10). Food additives used according to maximum levels (GMC 35/10)	Additives can only be added to food in order to achieve an identified technological function according to GMP. Some additives have specific permissions and maximum use levels allowed in food and other additives are limited to GMP. Specific flavouring agents, sweeteners, and colouring agents are regulated as food additives	Same as for Argentina[a]	Permitted list of food additives	Permitted list of food additives	Community list of food additives 129/2011 and 1130/2011	Approved food additives list containing 411 additives (under Article 10 of Food Sanitation Law)	Permitted list of food additives	

(*continued*)

Table 12. Continued.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Approval process	Pre-market application is required. Submission to CONAL, who will forward petition to Mercosur's Sub Work Group #3	Pre-market application is required	Pre-market application is required. Submission to ANVISA, which will forward petition to Mercosur's Sub Work Group #3	Pre-market application is required for a new substances, for an extension of the use of a permitted food additive, changing the maximum level of a permitted food additive, or adding a new organism to the list of permitted sources of enzymes used as a food additive	Pre-market application is required for new food additives; a new food additive is an additive that is not included in the national food safety standards, not included in the public announcement of permitted use issued by the MOH, and whose scope of use or dosage is increased	Pre-market application is required (new common authorisation procedure under Regulation (EC) No. 1331/2008. Details found in Regulation (EU) 234/2011 that implements Regulation (EC) No. 1331/2008 and in Practical Guidance for Applicants. New additives, or seeking to revise existing provisions regulating individual additives already authorised, or seeking confirmation that an approved additive made from a new source or method is acceptable, must submit an application	Pre-market application is required for a new substance intended to be used as a food additive and for applying for revision of standards for use of a food additive	Pre-market application is required	Pre-market application in the form of a food or colour additive petition. Exempt from food additive petition if prior sanctioned or use determined to be GRAS

Note: [a]Regulations pertaining to Argentina follow Mercosur Standards. Brazil also follows Mercosur Standards.

Table 13. A comparison of the regulations on novel foods among the target countries.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Definition	No formal definition; however, novel foods are recognised in practice	A non-traditional food with no history of safe use and food requires an assessment of public health and safety considerations. Non-traditional food is defined as a food that does not have a history of human consumption in Australia/New Zealand; a substance derived from a food, where that substance does not have a history of human consumption in Australia/New Zealand other than as a component of that food; or any other substance, where that substance, or the source from which it is derived, does not have a history of human consumption as a food in Australia/New Zealand	Foods with no history of use in the country; foods containing novel ingredients, except those listed in Table 1; foods containing substances already consumed that may be added or used at levels much higher than those currently observed in the foods that constitute part of a regular diet; and food offered in the form of capsules, pills, tablets and the like	(1) Substance, including a microorganism, that does not have a history of safe use as a food; (2) a food that has been manufactured, prepared, preserved or packaged by a process that has not been previously applied to that food, and causes the food to undergo a major change; and (3) a food that is derived from a plant, animal or microorganism that has been genetically modified	Novel foods are referred to as new resource foods, which are defined as raw food materials or food ingredients, which do not have a significant history of consumption in China	Novel foods are foods and food ingredients that have not been used for human consumption to a significant degree within the Community before 15 May 1997	Not defined	Not defined	Not defined

(*continued*)

Table 13. Continued.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Regulation	No authoritative statement found	Food Standard 1.5.1.	Resolution No. 16	Division B.28	Order No. 56 Administrative Measures on Novel Food	258/97/EC	No authoritative statement found	No authoritative statement found	Regulated as direct food additives or food contact substances depending on use
Additional regulation details		This standard prohibits the sale of these foods unless they are listed in Food Standard 1.5.1 and comply with any special conditions of use		This provision prohibits the sale of these foods unless the manufacturer or importer of the novel food (1) has notified the Director in writing of their intention to sell or advertise for sale the novel food (which includes providing data to support the safety of the novel food); and (2) has received a written notice from the Director (called a Letter of No Objection)		Foods commercialised in at least one member state before the entry into force of the Regulation on Novel Foods on 15 May 1997 are on the EU market under the "principle of mutual recognition"			

(*continued*)

Table 13. Continued.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Approval process	Requests for modification to follow guidance document GMC 26/03. If the product requested is considered a novel food in Europe its inclusion will be delayed until the novel foods chapter is written, approved and incorporated to the CAA	Pre-market application is required. FSANZ is reviewing the regulation of novel foods and nutritive substances. Criteria for "eligible foods" (i.e. foods in the wider sense including ingredients, additives and other substances added to food) is proposed. Any non-eligible foods would be prohibited and will require an appropriate safety assessment	Pre-market application is required	Pre-market application is required (safety assessment)	Pre-market application is required	Pre-market application is required (safety assessment)	No authoritative statement found	No authoritative statement found	Regulated as direct food additives or food contact substances depending on use

decisions. A recent review by Neltner et al. (2011) provides further discussion of the US food additive regulatory programme. For a summary of the regulations pertaining to direct food additives, see Table 12.

Novel foods

Novel foods (which usually encompass novel food ingredients) are generally foods or ingredients without a history of human consumption. Novel foods are specifically defined and regulated among Australia/New Zealand, Brazil, Canada, China and the EU. Although among these countries the definition of a novel food may differ (see definitions in Table 13), all novel foods marketed for sale in these countries require premarket approval or notification to their respective authoritative bodies. The safety assessment for novel foods that are whole foods cannot be conducted in the same manner as is used for individual ingredients. Whole foods are complex mixtures, often with considerable variation in composition depending on growing conditions. As they contribute calories, nutrients and bulk to the diet, they cannot be tested at high levels without altering the nutritional composition of the animal diet, and thus is not possible to achieve the same safety margins between animal dose levels and projected human intakes. Critical components include evaluation of the nutritional composition, presence of known toxins or anti-nutrients, and allergenicity of proteins as well as assessment of the potential nutritional impact of introducing the novel food into the human diet.

The majority of these target countries regulate novel foods and novel food ingredients based on a risk or safety assessment model to ensure safety following human consumption as outlined within the applicable regulations. In Argentina, Japan and Mexico, novel foods are neither defined nor regulated. In the US, novel foods are not defined but are regulated as direct food additives or food contact substances depending on their use (see "Direct food additives" above or "Food contact substances" below). For a summary of the regulations pertaining to novel foods, see Table 13.

Food contact substances

Food contact substances are generally any materials or articles intended to come into contact with food, including food containers, packaging, processing, etc. The basic safety principle of food contact materials is that they should generally be inert and not result in addition of compounds to the foods. Thus, the potential for migration of components of food contact materials into foods, and the assessment of exposure and toxicity of any migration is the basis for the safety determinations. In Argentina and Brazil, food contact substances are defined and regulated as food additives as per Mercosur standard GMC 32/07. In Canada and Japan, food contact substances are regulated separately from food additives and approval for use of food contact substances is not required (i.e. only voluntary submission of the food contact substance to the authoritative body).

In Australia/New Zealand, food contact substances are defined as any materials in contact with food and provided that such articles or materials, if taken into the mouth, are not capable of being swallowed or of obstructing any alimentary or respiratory passage and are not otherwise likely to cause bodily harm, distress or discomfort. Plastic materials for food contact use may voluntarily comply with the Australian Standard AS 2070-1999, a positive list of food contact substances. Discussions are in progress to include food packaging in the Food Standard Code, which would require compliance with US or EU regulations. At present, applications for food packaging materials are generally unnecessary provided there is approval in the US or the EU.

In contrast, pre-market notification or approval is required for use of food contact substances in China and the EU to confirm safety. In China, food contact substances are defined as materials in contact with the food, which include the food containers, packaging materials and anything in contact with the food in the course of manufacture, transport, sale and service. The EU has a more extensive definition for food contact substances (i.e. substances used to create all materials and articles intended to come into contact with foodstuffs, including packaging materials but also cutlery, dishes, processing machines, containers, etc.). The term also includes materials and articles that are in contact with water intended for human consumption.

In Mexico, food contact substances are not defined and no specific regulations are available pertaining to their use. The Regulation for the Sanitary Control of Products and Services establishes that packaging materials that contain substances that can migrate to the finished product, without endangering the health of consumers will be considered indirect additives. The classification of packaging materials and the physical, chemical and toxicological characteristic of each type of material will be established in specific norms. In general, the substances that are used to line packages used for foods, non-alcoholic beverages, alcoholic beverages, and health and beauty products will have to: remain perfectly adhered to the surface that is covered and do not crack, flake or become in any way a component of the food; be insoluble or inert in the food matrix, not be toxic; remain totally exempt of the volatile compounds that are used for their dilution and application; be free of heavy metals; avoid metal corrosion and not alter the pH of the product. Most major customers will require legal confirmation that a specific compound is allowed for use and should seek technical consultation. For certain products, a voluntary standard (Mexican Norm – NMX) may be available.

In the US, food contact substances are specifically defined and are also known as indirect additives. They include substances that are not intended to be added directly to food or to have a technical effect, but which

may reasonably be expected to become a component of food. These include substances used in packaging, transporting or the production of food.

Premarket approval is required for all food contact substance uses, unless exempted. A substance used in a food contact article may be exempted if the use in question has been shown to meet the requirements for a Threshold of Regulation exemption. The Threshold of Regulation is an application of the concept of the Threshold of Toxicological Concern (TTC). The TTC will be discussed in greater detail in the section on flavouring agents.

In 1995, the USFDA established a "threshold of regulation" of 0.5 ppb (equivalent to 1.5 μg/person/day) for indirect food additives that are not known to be carcinogens and do not contain structural alerts indicative of carcinogenicity (FDA 1995). A list the exemptions that have been issued under 21 CFR 170.39 *Threshold of regulation for substances used in food-contact articles*, is published on the USFDA website. Food contact substances uses that have been determined to be GRAS as also exempt from premarket approval. Similar to food additives, USFDA notification of the GRAS determination of the use of the food contact substances is voluntary.

In 1997, a food contact notification (FCN) process was established to allows for faster review of food contact substance uses that are not exempt from premarket approval. Unlike food additive regulations and threshold of regulation exemptions, approvals under the FCN process are proprietary and effective only for the manufacturer and substance identified in the notification.

An online inventory of effective premarket notifications for food contact substances that have been demonstrated to be safe for their intended use is maintained by the USFDA.

For a summary of the regulations pertaining to food contact substances, see Table 14.

Flavouring agents

Flavouring agents are substances or mixtures of substances intended for use in flavouring, intensifying or enhancing the aroma or taste of a food. Due to the very large number of flavouring agents and their use at very low levels in foods, regulations pertaining to this category represent a unique approach in many cases. Many flavouring agents have been approved based on long history of safe use (i.e. grandfathered) or through use of the TTC approach. The history, assumptions and databases used to develop the TTC were recently reviewed and evaluated by the EFSA Scientific Committee (2012) for consideration of potential application of the TTC to the safety assessment of other categories substances of present in foods and feed. In brief, the TTC is based on the concept that reasonable assurance of safety can be given, even in the absence of chemical-specific toxicity data, providing that the intake is sufficiently low, i.e. that an exposure level or threshold can be defined below which there is no significant risk to human health. The TTC requires that the chemical structure of the compound is known, and there is adequate information on the likely human exposure. Human threshold values or TTC values have been determined for structural classes of compounds using probabilistic approaches based on databases of toxicological testing for both cancer and non-cancer endpoints on a wide variety of chemical structures (EFSA 2012).

Flavouring agents, similar to food contact substances, do not require pre-market notification prior to use in Canada or the US. In the US, flavouring agents can be approved by the USFDA through a petition or though the GRAS determination process. The Flavor and Extract Manufacturers Association (FEMA) expert panel has served as the primary body for the safety evaluation of food flavourings since 1959, through GRAS assessment of flavouring substances, which often utilises the TTC approach. The panel safety decisions are provided to the USFDA and are published in the peer-reviewed literature (Smith et al. 2011) as well as on the FEMA webpage. As discussed below, the conclusions of the FEMA Expert Panel are often used as the basis for the acceptance of flavouring substances as safe food ingredients in many countries around the world.

In Australia/New Zealand, China, the EU, Japan and Mexico flavouring substances fall under the regulations for food additives. The permitted list of food additives generally includes specific flavouring substances. For a new flavouring substance (substance not listed on the permitted list of food additives for use), the approval process follows the same process as a food additive (see "Direct food additives" above). In Australia/New Zealand, FSANZ does not require a risk assessment to be done if the flavours are already listed in various publications such as the GRAS list published by the FEMA (Smith et al. 2011).

Recently in the EU, a new regulation was issued for flavouring substances under Regulation (EC) No. 1334/2008 and a new authorisation procedure under Regulation (EC) No. 1331/2008 was adopted (as discussed above in "Direct food additives"). EFSA and the JECFA also, when possible and feasible, apply the TTC approach for assessment of flavour substance.

In Argentina and Brazil, flavouring agents are regulated under Mercosur standards GMC 10/06. For new flavouring agents, applicants must submit to CONAL or ANVISA (for Argentina and Brazil, respectively), who will forward the application to Mercosur's Sub Work Group #3. For a summary of the regulations pertaining to flavouring agents, see Table 15.

Table 14. Comparison of the regulations on food contact substances among the target countries.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Definition	Primary container or primary wrapping or container. Container that is in direct contact with food	Any materials in contact with food, including packaging material, which may include materials such as moisture absorbers, mould inhibitors, oxygen absorbers, promotional materials, writing or other graphics	Same as for Argentina[a]	Anything in which any food is wholly or partially contained, placed or packed	All materials in contact with the food including the food containers, packaging materials and the things which contact the food in the course of manufacture, transport, sale and serve	Food contact materials and articles are those which in their finished state are intended to be brought into contact with food, or are already brought into contact with food and intended for that purpose or can reasonably be expected to be brought into contact with food or to transfer their constituents to food under normal and foreseeable conditions of use. Includes packaging materials cutlery, dishes, processing machines, containers, etc. The term also includes materials and articles in contact with water intended for human consumption. Fixed water installations are excluded, however	Not defined	Not defined	Any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting or holding food if such use is not intended to have a technical effect in such food

(*continued*)

Table 14. Continued.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Regulation	Mercosur GMC 32/07	Food Standard 1.4.1 and 1.4.3	Same as for Argentina[a]	Division 23, Part B	Hygienic Standards for Additives Used in Food Containers and Packaging Materials (GB 9685)	1935/2004/EC. This is the framework Regulation with general provisions for all FCM	No authoritative statement found	No authoritative statement found	General: 21 CFR §170–171. Existing indirect additive approvals: 21 CFR §§174–178 and 186. FCS notification regulation: 21 CFR 170.3(e)(3). FCS Threshold of regulation: 21 CFR 170.39. Proposed rule published in 1997 (62 FR 18938) for GRAS determinations
Additional regulation details	There is a positive list of substances that are added to plastics to achieve a technical effect in the final product	Food contact substances may be placed in contact with food, provided such articles or materials, if taken into the mouth, are not capable of being swallowed or of obstructing any alimentary or respiratory passage and are not otherwise likely to cause bodily harm, distress or discomfort	Same as for Argentina[a]			(EU) 10/2011 is the specific Regulation for plastic FCM with a positive list of substances. (EC) 450/2009 is the specific Regulation for A&I FCM. Regulation (EC) 282/2008 is specific for Recycling of plastics. Directive 2007/42/EC is specific for Regenerate cellulose film. Directive 84/500/EEC is specific for ceramics. For all those materials for which no specific measure is adopted at the EU level, national legislation in member states may exist			

(*continued*)

Table 14. Continued.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Approval process	Same process as direct food additives	Applications for food packaging materials are generally unnecessary if there is approval in the EU or US. Plastic materials for food contact use may comply with the voluntary Australian Standard AS 2070-1999	Same as for Argentina[a]	Voluntary submission to the Health Products and Food Branch (HPFB) for a pre-market assessment of their chemical safety	Pre-market application is required	Pre-market application is required only for substances for which a positive listing is not set out specifically. Regulation at the EU includes plastics, A&I FCM and Regenerated cellulose film. For the other materials the general provisions of the framework Regulation 1935/2004 apply and specific measures may exist at the national level	JHOSPA established the industry's voluntary standards composed of a positive list of raw materials that can be used safely for food utensils, containers, packaging materials, and Standard Methods of Analysis with specifications for each resin	Although no specific process, most major customers require legal confirmation that the compound is allowed. Any approval should be obtained through technical consultation	Pre-market request for review in the form of a food contact notification, a threshold of regulation exemption request, or a GRAS determination. Notification to the USFDA of GRAS determinations is voluntary. The USFDA review of GRAS notifications is not considered a formal approval

Notes: [a]Regulations pertaining to Argentina follow Mercosur Standards. Brazil also follows Mercosur Standards.
JHOSOA, Jopan Hygienic Orefin and Styrene Plastics Association.

Table 15. Comparison of the regulations on flavouring agents among the target countries.

Country	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Definition	Substances or mixtures of substances with odoriferous and/or flavour properties that are able to confer or enhance the aroma and/or taste of food	Flavourings are defined as intense preparations that are added to foods to impart taste and/or odour, which are used in small amounts and are not intended to be consumed alone, but do not include herbs, spices and substances which have an exclusively sweet, sour or salt taste	Same as for Argentina[a]	Not defined; however, there are standards of identity and composition for certain flavouring preparations in Division B.10	Food additive and food ingredient necessary for producing, preserving and applying the flavourings. The additive added to food (except flavour enhancer) does not play the role for final aromatic products	Flavourings are products that are not intended to be consumed as such, but which are added to food in order to impart or modify odour and/or taste of food. Flavouring substances are chemically defined substances obtained by chemical synthesis or isolated using chemical processes, and natural flavouring substances	Natural flavouring agents are defined as food additives intended for use in flavouring food and are substances obtained from animals or plants, or mixtures thereof	Substance or blend of substances of natural origin, identical to natural or synthetic with or without solvents and with or without the addition of other additives that are used to give or intensify flavours or aromas to products	Not defined; regulated as substances added directly to food, specifically as direct food additives and GRAS substances
Regulation	Mercosur GMC 10/06	Food Standard 1.3.1 Section 11. FSANZ does not require a risk assessment to be done if the flavours are GRAS by FEMA or others	Same as for Argentina[a]	Division B.10	National Standard of the People's Republic of China Flavourings (TBT/N/CHN/575)	1334/2008/EC (framework Regulation 2065/2003/EC (smoke flavourings)	Food Sanitation Law	Regulated as food additives	Labelling of flavours: 21 CFR §101.22. Lists of flavours approved in the regulations: 21 CFR §§172, 182 and 184. Proposed rule published in 1997 (62 FR 18938)
Additional regulation details	Permitted list of flavouring substances (natural or synthetic)		Same as for Argentina[a]	Certain prohibitions exist in Section B.01.046. Definition of food additive excludes flavouring preparations					

(*continued*)

Table 15. Continued.

Country	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Approval process	Application submission to CONAL and subsequent submission to Mercosur	Flavouring agents are regarded as food additives. An application is generally not required for a flavouring agent	Application submission to ANVISA and subsequent submission to Mercosur	Voluntary request a letter of opinion on a flavouring agent (see "approval process for processing aids")	Same process as direct food additives	New common authorisation procedure under Regulation (EC) No. 1331/2008, data requirements provided in Regulation (EC) No. 234/2011. For smoke flavourings Regulation (EC) 2065/2003 specifies the procedure	Same process as direct food additives	Same process as direct food additives	Same process as substances added directly to food. See "direct food additives" above. Most flavouring agents in the US are reviewed by the Flavor and Extract Manufacturers Association (FEMA) expert panel to determine if their uses are GRAS

Note: [a]Regulations pertaining to Argentina follow Mercosur Standards. Brazil also follows Mercosur Standards.

Enzymes

In general, enzymes are substances or products extracted from animals, plants or microbes that act by either promoting a desirable chemical reaction or are used in processing. The definition of an enzyme according to each target country is presented in Table 17. In Canada, China, the EU, Japan, Mexico and the US enzymes are regulated as food additives. Likewise, the approval process for new enzymes also follows the same approval process for direct food additives (see "Direct food additives" above). However, depending on the context of use, Canada may consider enzymes to be processing aids. In Australia/New Zealand, enzymes as such are not specifically defined in the Food Standards Code; however, specified enzymes are permitted for use as processing aids (see "Processing aids" below). Recently in the EU, a new regulation was issued for enzymes under Regulation (EC) No. 1332/2008 and a new authorisation procedure under Regulation (EC) No. 1331/2008 was adopted (as discussed above). In Argentina and Brazil, enzyme regulations are not harmonised in Mercosur; thus, enzyme regulations are regulated differently for these two countries. In Argentina, enzymes are regulated under the CAA, Chapter XVI (Articles 1261, 1262 and 1263). The approval processes for new enzymes require an application submitted to CONAL. In Brazil, enzymes are regulated under Resolution No. 26 and the use of new enzymes requires an application submitted to ANVISA.

JECFA (2001) has also provided specific comments for consideration of the safety assessment of enzymes derived from recombinant sources. These include: (1) characterisation of genetic materials introduced into the organism producing the enzyme to demonstrate that no unexpected genetic materials are introduced into the host; (2) consideration of potential of proteins from the microorganism leading to antibiotic resistance; and (3) evaluation of the allergenic potential of the gene products.

For a summary of the regulations pertaining to enzymes, see Table 16.

Processing aids

The definition of processing aid varies across the target countries; however, in general, processing aids are substances not consumed as food ingredients by themselves and are used intentionally in processing or in the production of raw materials, ingredients or foods to achieve a technological purpose. As illustrated in Codex inventory of processing aids, with the exception of enzymes and solvents, most processing aids have not been evaluated by JECFA. Furthermore, this inventory is not considered to be complete. Development of a comprehensive Codex database of processing aids is under discussion.

In Canada, similar to flavouring agents and food contact substances, processing aids are permitted for use without pre-market notification providing they meet the specific criteria for the definition of a processing aid (i.e. results in no or negligible residues in the food). If they do not meet these criteria, the processing aid is considered to be a food additive and the approval process for direct food additives would be applicable. Similarly in the EU, no regulations pertain to processing aids specifically; however, if a processing aid does not meet the criteria for the definition of a processing aid, it is classified as a food additive, and Regulation (EC) No. 1333/2008 (regulation for food additives) would be applicable. Processing aids are regulated as food additives for the following countries: China, Japan and Mexico; therefore, all regulations pertaining to direct food additives are applicable (see "Direct food additives" above). In Mexico, publication in 2012 of the new updated food additive positive lists processing aids separate from food additives. In Argentina and Brazil, processing aids are not harmonised in Mercosur. The only harmonised regulation is 84/93, which establishes the definitions of the functions of processing aids. In Argentina, certain processing aids are listed under Chapter XVI of the CAA; however, this list is not comprehensive. In Australia/New Zealand, processing aids are regulated under Food Standard 1.3.3, a general standard for processing aids. New processing aids or existing processing aids with new food uses require an application to modify the Standard Food Code. It should be noted that processing aids are regulated into a specific horizontal standard (i.e. across the whole food supply) in Australia, unlike the systems used by other countries, as well as for standards promulgated by the CAC. In the US, processing aids would be known as "secondary direct food additives" and regulated as direct food additives. In some cases, they may also be regulated as food contact substances (see "Direct food additives" and "Food contact substances" above).

For a summary of the regulations pertaining to processing aids, see Table 17.

Nanoscale materials

The regulation of products of nanotechnology is a dynamic and evolving activity, due largely to the wide spectrum of nanomaterials, nano-enabled products, and applications that are being developed and the uncertainties that are associated with defining, characterising, and appropriately testing them for efficacy and safety (PEN 2011). Nanotechnology is a term that has been defined in a few countries (Australia/New Zealand, Canada, China and the EU), but not all. In Canada, nanotechnology is described as the application of nanoscience to develop new materials and products, and involves the manipulation of matter at the nanometre scale. The development of the definition of nanomaterials has begun in several countries, including Canada, the EU and the US. For example, the European Commission (EC) proposed definition was "a material that

Table 16. Comparison of the regulations on enzymes among the target countries.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Definition	Enzymes or enzyme preparations are substances of animal, plant or microbial origin that act by promoting the desirable chemical reactions	Not specifically defined in the Food Standards Code	Enzymes or enzyme preparations are substances of animal, plant or microbial origin that act by promoting the desirable chemical reactions	Not specifically defined in the Food and Drug Regulations	Biological products directly extracted from edible or non-edible parts of a plant or animal or fermented and extracted from traditional or genetically modified microorganisms (including but not limited to bacteria, actinomycetes, and fungi) that are used in food processing and have a special catalytic function	A food enzyme is defined as a product obtained from plants, animals or microorganisms, or products thereof including a product obtained by a fermentation process using a microorganism containing one or more enzymes capable of catalysing a specific biochemical reaction and added to food for a technological purpose at any stage of the manufacturing, processing, preparation, treatment, packaging, transport or storage of foods	Not defined	Biological catalyser protein substance produced by live cells that catalyse specific reactions in diverse production processes	Not defined

(*continued*)

Table 16. Continued.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Regulation	CAA, Chapter XVI, Articles 1261, 1262 and 1263. Enzymes regulations are not harmonised in Mercosur	Enzymes may be used in the course of manufacture of any food, provided the enzyme is derived from the corresponding source or sources specified in the tables of Sections 15–17 of Food Standard 1.3.3 (standard for processing aids)	Resolução RDC # 26 dated 27 May 2009 (on the ANVISA site). Enzymes regulations are not harmonised in Mercosur	Enzymes are regulated as food additives or may be considered processing aids depending on their context of use	Enzymes are regulated as food additives	Regulation (EC) No. 1332/2008 (Regulation (EC) No. 1332/2008 does not include food enzymes used in the production of food additives within the scope of Regulation (EC) No. 1333/2008 or processing aids). The scope of this regulation does not extend to enzymes that are not added to food to perform a technological function but are intended for human consumption such as enzymes for nutritional or digestive purposes	Enzymes listed as a permitted food additive can be used in food under the conditions indicated	Enzymes are regulated as food additives	Enzymes are regulated as substances added directly to food, specifically as direct food additives, secondary direct food additives, or GRAS substances
Approval process	Application submission to CONAL	Same process as processing aids	Application submission to ANVISA	Same process as direct food additives and processing aids	Same process as direct food additives	New common authorisation procedure under Regulation (EC) No. 1331/2008 and Regulation (EC) No. 234/2011	Same process as direct food additives	Same process as direct food additives	Same process as substances added directly to food. See “direct food additives” above

Table 17. Comparison of the regulations on processing aids among the target countries.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Definition	Any substance, excluding equipment and utensils that is not consumed by itself as a food ingredient and which is intentionally used in the processing of raw materials, foods or ingredients, for a technological purpose during treatment or processing. It must be removed from the food or inactivated; the presence of traces of the substances or their derivatives may be admitted in the final product	Substances used in the processing of raw materials, foods or ingredients to fulfil a technological purpose relating to treatment or processing but does not perform a technological function in the final food; and the substance is used in the course of manufacture of a food at the lowest level necessary to achieve a function in the processing of that food, irrespective of any maximum permitted level specified	Same as for Argentina	Substance used for a technical effect in food processing or manufacture, the use of which does not affect the intrinsic characteristics of the food and results in no or negligible residues of the substance or its by-products in or on the finished food	Substance or material (not including apparatus or utensils), and not consumed as a food ingredient by itself, and only used to fulfil a certain technological purpose during processing or treatment	Any substance that is not consumed as a food by itself; is intentionally used in the processing of raw materials, foods or their ingredients to fulfil a certain technological purpose during treatment or processing; and may result in the unintentional but technically unavoidable presence in the final product of residues of the substance or its derivatives provided they do not present any health risk and do not have any technological effect on the final product	Substances added during processing food which are: (1) removed from food before completion of the food; (2) derived from raw materials of food and converted into components normally included in food but do not significantly increase the amounts of components; or (3) present in the finished food at insignificant levels but do not have any technical or functional effect of these components on the food	Substance or material, excluding instruments, utensils and additives, that is not consumed as a food ingredient by itself and is used intentionally in the production of raw materials, foods or their ingredients to achieve a technological function during the treatment or processing and that can lead to the unintentional presence of residues or derivatives in the final product	Substances that have a technical effect in food during processing but that are not intended to have an ongoing technical effect in the food

(*continued*)

Table 17. Continued.

	Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Regulation	Processing aids are not harmonised in Mercosur, the only harmonised regulation is GMC 84/93 which establishes the definitions of the functions of processing aids. Certain processing aids are listed under Chapter XVI of the CAA, but this list is not comprehensive	Food Standard 1.3.3, a general standard for processing aids	Processing aids are not harmonised in Mercosur, the only harmonised regulation is GMC 84/93 which establishes the definitions of the functions of processing aids	No specific regulations on most processing aids. If a substance does not meet the specific criteria for the definition of a processing aid as outlined above, it may be considered to be a food additive and the regulations pertaining to food additives would be applicable	Processing aids are regulated as food additives	Processing aids are not regulated at the EU level, with the exception of extraction solvents used in the production of foodstuffs and food ingredients (Directive 2009/32/EC). If a substance does not meet the criteria for the definition of a processing aid, as outlined in the definition above, it can be considered as a food additive and Regulation (EC) No. 1333/2008 would be applicable	Processing aids are regulated as food additives	Processing aids are regulated as food additives	Regulated as food additives or in some cases as food contact substances. When approved in the regulations, they are known as "secondary direct additives"
Approval process	Application submission to CONAL	Pre-market application is required	Application submission to ANVISA	May seek a so-called "Letter of Opinion" which confirms that, under its conditions of use, the substance is considered a processing aid and use is acceptable	Same process as direct food additives	As they fall out of the scope of EU legislation, there is no process for their approval. Nevertheless, member states or the COM may address the issue of their safety to EFSA	Same process as direct food additives	Same process as direct food additives	Same process as substances added directly to food except where the USFDA may consider them to be food contact substances. See "direct food additives" and "food contact substances" above

consists of particles with one or more external dimensions in the size range 1–100 nm for more than 1% of their number"; and/or "has internal or surface structures in one or more dimensions in the size range 1 nm–100 nm"; and/or "has a specific surface area by volume greater than 60 m^2 cm^{-3}, excluding materials consisting of particles with a size lower than 1 nm".

The development of engineered nanomaterials with new beneficial properties has potential food applications including improved nutrient and bioactive delivery systems, improved texture and flavour encapsulation; improved microbiological control, food processing, packaging, and package biodegradability; and highly sensitive biosensors for detecting pathogens, allergens, contaminants and degradants (reviewed in Chaudhry et al. 2008; Augustin & Sanguansri 2009; Magnuson et al. 2011). The regulation of use of engineered nanomaterials in food and feed production represents many new challenges. However, it should be noted that nanomaterials and nanostructures also occur naturally in all plant and animal products that are consumed as food. Examples of naturally occurring nanomaterials include DNA molecules and proteins such as casein micelles and whey proteins. Examples of nanostructures include the muscle structure of meats and fish, and pectin nanostructure in fruits.

The challenges regarding safety assessment of engineered nanomaterials that may be present in foods were discussed in a FAO/WHO Expert meeting on the application of nanotechnologies in the food and agriculture sectors (FAO/WHO 2010). As numerous studies have demonstrated that the biological properties of materials can change substantially when reduced to the nano-size range, the toxicological properties of nanomaterials cannot be assumed to be the same as their non-nano counterparts. A critical review of the published literature on the toxicity of nanomaterials with potential use or occurrence in food, food-related materials or dietary supplements demonstrated that there are very few published studies with adequate characterisation and repeated-dose exposures, which are necessary to assess safety of food-related exposures (Card et al. 2011). Thus, considerable additional research is needed to understand the potential effects of oral exposure to engineered nanomaterials. The FAO/WHO Expert meeting report also discussed gaps in knowledge and a need for sharing of existing data on the characterisation, toxicological and exposure data as well as appropriate methodologies to facilitate risk assessment (FAO/WHO 2010).

Currently, none of the listed "target countries" has established specific regulations on nanoscale materials for food-related uses; however, several have issued comments or opinions which are briefly discussed below. Many of the countries are involved in international organisations working toward developing approaches to risk assessment of nanomaterials. For further details, see the summary tables (Tables 1–9) for each target country.

Australia and New Zealand

In Australia and New Zealand, any new substances intended to be added to food that are manufactured using nanotechnologies that may present safety concerns will have to undergo a comprehensive scientific safety assessment under the appropriate standard (e.g. as a novel food or food additive) before they can be legally sold in those countries. FSANZ has developed a factsheet for nanotechnology and foods, outlining the presence of naturally occurring nanomaterials in foods and the environment (FSANZ 2011b).

Canada

Health Canada is using existing legislative and regulatory frameworks to regulate applications of nanotechnology but recognises that new approaches may be necessary in future to keep pace with the advances in this area, particularly given that there currently is inadequate information on risks associated with nanomaterials (Health Canada 2010). Various acts (and regulations contained therein) are envisioned by Health Canada to be relevant to nanomaterials, including the Food and Drugs Act, the Canadian Environmental Protection Act 1999, the Hazardous Products Act, and the Pest Control Products Act.

Health Canada has indicated that in order to identify and assess potential risks and benefits (where applicable) of nanomaterials, the following types of information may be required to be submitted for review:

- Intended use of the nanomaterial, including any end product in which it will be used.
- Characterisation of the nanomaterial, including manufacturing methods, identity and purity.
- Physicochemical properties and toxicological, ecotoxicological, metabolism and environmental fate data that may be both generic and specific to the nanomaterial if applicable.
- Risk assessment and risk management strategies, if considered or implemented.

Health Canada has noted that future guidance specific to different programme areas and legislative and regulatory authorities will be developed in a manner that promotes a consistent set of approaches (Health Canada 2010).

European Union

Although there are no specific provisions in the EU legislation on nanoscale materials, existing legislation covers in principle the potential health, safety and environmental risks in relation to nanomaterials. A close examination of the definition for food additives already incorporates nanoscale materials (i.e. food additives that are prepared

through nanotechnology would be considered under novel foods). In Article 12 of 1333/2008/EC:

> when a food additive is already included in a Community list and there is a significant change in its production methods or in the starting materials used, or there is a change in particle size, for example through nanotechnology, the food additive prepared by those new methods or materials shall be considered as a different additive and a new entry in the Community lists or a change in the specifications shall be required before it can be placed on the market.

EFSA has published guidance for assessing the risks of nanoscience and nanotechnologies in food and feed (EFSA 2011). It stressed the importance of adequate physicochemical characterisation of the forms of engineered nanomaterials in food/feed products and under testing conditions. The physicochemical parameters that should be characterised regardless of the route of exposure include agglomeration and/or aggregation, chemical composition, crystal structure/crystallinity, particle size/size distribution, purity, shape, surface area, surface charge, and surface chemistry including composition and reactivity. The following characteristics are considered to be indicators of increased probability of toxicity: a high level of reactivity (e.g. catalytic, chemical); complex morphology (e.g. long fibre, crystal); interaction with biomolecules (e.g. proteins, DNA); complex transformations (e.g. loss of coating); the presence of antimicrobial activity; and evidence of persistence and/or bioaccumulation (EFSA 2011).

United States of America

The USFDA issued draft guidance in April 2012 regarding nanotechnology. At this time, there is no formal definition for "nanotechnology" or "nanoscale", however the USFDA indicated that, "In the absence of a formal definition, when considering whether a USFDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, the USFDA will ask: (1) whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1–100 nm); or (2) whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to 1 μm". New substances, whether direct food additives or food contact substances, cannot be GRAS per this draft guidance. Manufacturers seeking approval for a nano-engineered substance must submit a food additive petition or a food contact substance notification.

No specific documents on the regulation of nanomaterials for food-related uses were found for Argentina, Brazil, China, Japan and Mexico, although work is in progress. Argentina, Brazil, China and Japan have established or are participating in various groups for the development of nanotechnology standards in the areas of health, safety and environment. A summary of the developing approaches to risk assessment of nanomaterials among the target countries is listed in Table 18.

Conclusions

JECFA, whose genesis occurred at the FAO/WHO Conference on Food Additives in 1955, continues to be of fundamental importance to the activities of the CAC and especially to the Codex Committee on Food Additives and the Codex Committee on Contaminants in Foods. While the outcome of JECFA's evaluations does not have any direct bearing on the regulatory approval of a food additive in any specific country, JECFA's scientific evaluations and reassessments are widely recognised and may affect an application for approval for a new food additive in a particular country. Similar to JECFA, the CAC has no regulatory authority and its standards are not enforceable unless they have been adopted into the regulatory framework for a nation; however, its standards for food additives continue to serve as guidelines to many nations.

In addition to their guiding international influence, the early work of JECFA and CAC and the principles outlined by those committees laid the foundation for how substances added to food are regulated in many individual countries today, including the countries examined: Argentina, Australia, Brazil, Canada, China, the EU, Japan, Mexico, New Zealand, and the US. The regulatory authority for each target jurisdiction/country utilises its own regulatory framework and although the definitions, regulations and approval processes may vary among all target countries, in general there are many similarities across all target countries. In all cases, the main purpose of each regulatory authority is to establish a framework and maintain/enforce regulations to ensure the safety of food consumed and sold within its respective countries. Although the path for approval of different categories of food additives varies from jurisdiction to jurisdiction, there are many commonalities in terms of the data requirements and considerations for assessment of the safety of use of substances added to food, including the use of positive lists of approved substances, pre-market approval, and a separation between science and policy decisions. There is also a move toward harmonisation of food regulations, as illustrated by Australia and New Zealand, by Mercosur and by the EU. International collaboration is occurring to address the challenge of developing regulatory guidance and safety assessment for use of nanomaterials in foods. Harmonisation of global food regulations is envisioned to promote use of all available foods through free trade, to support farmers, and to reduce hunger and poverty globally.

Table 18. Summary of the developing approaches to risk assessment of nanomaterials among the target countries.

Argentina	Australia/New Zealand	Brazil	Canada	China	European Union	Japan	Mexico	USA
Argentina has established or is participating in various groups for the development of standards in the area of nanomaterials (see nanoscale materials under Table 1 for further details)	Any new food substances manufactured using nanotechnologies that may present safety concerns will have to undergo a comprehensive scientific safety assessment under the appropriate standard before they can be legally sold in those countries (see nanoscale materials under Table 2 for further details)	Brazil has established or is participating in groups for the development of standards in the area of nanomaterials (see nanoscale materials under Table 3 for further details)	Health Canada is using existing legislative and regulatory frameworks to regulate applications of nanotechnology, but it recognises that new approaches may be necessary in future to keep pace with the advances in this area, particularly given that there currently is inadequate information on risks associated with nanomaterials. Various acts (and regulations contained therein) are envisioned by Health Canada to be relevant to nanomaterials. Health Canada has indicated that in order to identify and assess potential risks and benefits (where applicable) of nanomaterials, a list of documents is required). For further details, see nanoscale materials under Table 4.	China has established or is participating in various groups for the development of standards in the area of nanomaterials (see nanoscale materials under Table 5 for further details)	EFSA published an opinion on nanotechnologies and a guidance document on risk assessment was published in May 2011. Existing legislation covers in principle the potential health, safety and environmental risks in relation to nanomaterials. Recently, specific provisions on risk assessment of nanomaterials were introduced in EU legislation on food additives and food contact materials. A definition of "engineered nanomaterial" and a mandatory labelling requirement for food ingredients containing such nanomaterials were introduced. Examination of the definition for food additives already incorporates nanoscale materials (i.e. food additives prepared through nanotechnology would be considered new food additives). EFSA considers the risk assessment paradigm applicable to nanomaterials, but suggests that a risk assessment of nanomaterials in food and feed take into consideration specific properties of nanomaterials in addition to those common to the equivalent non-nanoforms. For further details, see nanoscale materials under Table 6.	Japan has established or is participating in groups for the development of standards in the area of nanomaterials (see nanoscale materials under Table 7 for further details)	No specific documents on the regulation of nanomaterials for food-related uses were identified	The USFDA issued draft guidance on nanotechnology and food in April 2012. There is no formal definition for "nanotechnology" or "nanoscale" at this time, however the guidance contains considerations the USFDA takes into account when evaluating nanomaterials. New nano-engineered substances, whether direct food additives or food contact substances, cannot be GRAS per the USFDA's recently issued draft guidance. Manufacturers seeking approval for a nano-engineered substance must submit a food additive petition or a food contact substance notification. See "food contact substances" and "food additives" above. For further details see nanoscale materials under Table 9.

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