U.S. Food and Drug Administration

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Red No. 3 and Other Colorful Controversies

by Dale Blumenthal

The lure of red cherries in canned fruit cocktail is legendary in many American families. Siblings fight over them, parents use them to bribe or treat their children, and even adults count the cherries spooned into their dessert. But, the days of the fruit cocktail cherry colored by FD&C Red No. 3 may be numbered. Because large amounts of the color have been shown to cause cancer in rats, FDA recently ended certain uses of FD&C Red No. 3 and plans to end the remaining uses. The cherries in 21st century fruit cocktail could well be light brown.

Color has long been recognized as important in consumer acceptance of nearly every food, medication and cosmetic product. Even the hue of the containers can make the difference between a best seller and a "no-sale-er."

A research project in the 1970s, reported in the October 1973 issue of Marketing, illustrated just how big the impact of color can be on the acceptance of food items in particular. Research volunteers were served a meal of steak, peas and French fries. They ate part of the meal under special lighting that concealed the fact that the colors of the food had been altered. When, under normal lighting, the test group discovered that their steaks were blue, peas red, and french fries green, some participants became ill at the sight of the unnaturally colored food they had been eating.

Color Safety

Food once was colored only with natural dyes. Beets, peppers, grape skins, saffron, and even brilliantly scarlet extracts prepared from dried bodies of cochineal insects lent their distinctive colors to the cook's creativity.

By the 19th century, colors derived from other chemicals came into use--with sometimes serious health consequences (see "Additives for Eye Appeal" in the July-August 1973 issue of FDA Consumer). Lead chromate and copper sulfate began to be used to tint candy and pickles. Arsenic and other poisonous impurities were added when mixing up new color additives. Dyes made from coal-tar and petroleum derivatives also appeared in foods, drugs and cosmetics.

How, then, can a consumer be sure that the bright primary colors and the subtle shadings that color many consumer products today are safe to eat, use in drugs, put on skin or hair, or--as with colored contact lenses--stick in the eyes? A monitoring process--directed by FDA and refined over several decades--ensures that this is so.

FDA began a comprehensive assessment of the safety of color additives with the passage of the Pure Food and Drugs Act of 1906. The country had changed from an agricultural to an industrial nation. No longer did most Americans live on farms and produce their own food. Instead, much of the food a nation of city dwellers ate was processed, chemically preserved, and marketed by large firms competing for consumers' attention.

It was a time of triumph for synthetic dyes, followed by concern on the part of public health officials about the safety of these dyes. Harvey Wiley, chief of USDA's Bureau of Chemistry, challenged the ease with which manufacturers added chemicals to food. Food safety became Wiley's special

otherwise result in misbranding and adulteration. However, Wiley believed that the use of color additives in food required further investigation. He hired an outside consultant, dye expert Bernard Hesse, Ph.D., to study the problem.

After reviewing 80 of the most commonly used colors, many of which had never been tested before, Hesse recommended only seven color additives as safe for use in food. His recommendation was announced in a 1907 regulation, Food Inspection Decision 76, which also introduced a system for voluntary certification of synthetic food colors.

Pre-Market Approval

The Federal Food, Drug, and Cosmetic Act of 1938 elaborated on the earlier regulations by providing for the listing and mandatory certification of synthetic color additives used in foods, drugs and cosmetics. During the 1950s, a safety concern associated with the improper use of FD&C Orange No. 1 prompted additional safety studies on color additives used in food, including FD&C Red No. 3.

Then, in 1960, Congress amended the Food, Drug, and Cosmetic Act of 1938 to set up a pre-market approval system for new color additives and to require demonstration of the safety of color additives already in use.

Approved color additives were divided into two groups: those requiring FDA's certification (synthetic dyes made mostly from coal tar and petroleum derivatives) and those exempt from FDA's certification (substances derived from vegetable, animal or mineral products). Each batch of a synthetic color is tested by the manufacturer and a sample submitted to FDA for certification according to specifications in the Code of Federal Regulations. Colors exempt from batch certification must also meet specifications in the CFR.

The 1960 amendments placed the color additives already in use on a provisional list to permit their continued use while the manufacturers developed the necessary data for a petition to support the listing of the color additive.

Many of the color additives requiring certification come in two forms: straight colors and lakes. Straight colors in many cases are water-soluble dyes. Certain straight colors are used to make "lakes" or water-insoluble forms of the color additive. Lakes are used in products in which leaching or "bleeding" of color would pose problems, such as in cookie fillings, coated tablets, candies, chewing gum, and lipsticks. The agency is currently planning a proposal regarding the regulation of lakes.

Manufacturers seeking approval for new color additives or for those on the provisional list were required to submit a petition to FDA with scientific data demonstrating that a specific color was safe for its intended uses. If the agency approved the petition, the color was placed on a "permanent" listing. Colors can be approved for use in food, drugs, and cosmetics (FD&C), in drugs and cosmetics only (D&C), or specifically for external drug and cosmetic use (Ext. D&C).

To date, of the original 200 provisionally listed color additives, 90 have been listed as safe and the rest have either been withdrawn by industry or delisted by FDA.

FD&C Red No. 3

FDA terminated the provisional listings for FD&C Red No. 3 on Jan. 29, 1990, at the conclusion of its review of the 200 straight colors on the 1960 provisional list. Commonly called erythrosine, FD&C Red No. 3 is a tint that imparts a watermelon-red color and was one of the original seven colors on Hesse's list.

The provisionally listed uses that were recently terminated include use of the straight color in cosmetics and externally applied drugs and all uses of the lakes of FD&C Red No. 3.

goods, cherries, dairy products, desserts, dietary supplements, food seasonings, jellies, jams, and vegetable products.

This paradox came about because of improvements in scientific methods and the timing of the petitioner's submission for permanently listing the food and ingested drug uses. After the 1960 provisional listings, studies were performed on FD&C Red No. 3. Results did not show any safety concerns, and in response to a petition by the Certified Color Manufacturers Association (CCMA), FD&C Red No. 3 was permanently listed for use in ingested drugs and foods in June 1969.

Cosmetic and externally applied drug uses of the color remained provisionally listed while studies on skin exposure were conducted. Meanwhile, FDA expanded its safety requirements in 1977 to include more extensive studies on provisionally listed color additives. Based upon the results of new studies on FD&C Red No. 3, conducted by the International Research Development Corporation and completed in 1982, the agency concluded that FD&C Red No. 3 causes thyroid cancer in male rats.

The Cosmetic, Toiletry and Fragrance Association and CCMA argued that no direct cancer-causing effect was seen in animals given the color in the low levels used in consumer goods. FDA, however, decided that the evidence of thyroid tumors in rats was clear, and that the additional research cited by industry did not establish that an indirect mechanism--such as a hormonal effect triggered by the dye--caused the tumors, rather than the dye itself. Thus, FDA denied the manufacturers' petition for further permanent listings of the color. Based on data from the studies, the agency estimated that the lifetime risk of thyroid tumors in humans was at most 1 in 100,000.

Like FD&C Red No. 3, FD&C Blue No. 1 and FD&C Yellow No. 5 were also permanently listed for food and ingested drug uses in 1969. When FDA reviewed new, more extensive studies on FD&C Blue No. 1 and FD&C Yellow No. 5, the agency found that these two color additives did not cause cancer in animal studies. (But, since FD&C Yellow No. 5 causes allergic reactions in some people, FDA requires its listing on food labels.)

As experts note, while the provisional listings for straight colors have ended, advances in science will require continual monitoring of the safety of color additives.

Delaney Dilemma

The decision to ban the provisional uses of FD&C Red No. 3 is based on the Delaney Clause of the 1960 Color Additive Amendments. Under that clause, FDA cannot approve color additives shown to induce cancer in humans or animals in any amount.

Many government officials, however, believe that the inflexibility of the Delaney Clause should be replaced by a standard that allows for what may be an insignificant cancer risk. Advances in technology and the ability to detect minute quantities of cancer-causing chemicals in foods may make the risk standard of the Delaney Clause unnecessarily stringent in some cases. In announcing the decision to terminate the provisional uses of FD&C Red No. 3, Health and Human Services Secretary Louis W. Sullivan, M.D., said that the decision to ban the uses of Red No. 3 was not based on risk but on the legal mandate of the Delaney Clause.

In 1986, FDA took a different approach in approving four cosmetic dyes for which cancer risk was trivial. The agency based its approval of D&C Orange No. 17, D&C Red No. 19, and D&C Red Nos. 8 and 9 on the legal maxim "de minimis non curat lex," meaning that the law does not concern itself with trifles. A government review panel had assessed the worst-case risks for externally applied drug and cosmetic uses for D&C Orange No. 17 as 1 in 19 billion (that is, exposure to external cosmetics containing D&C Orange No. 17 may cause at most one additional case of cancer in 19 billion people over a 70-year lifetime of exposure) and for D&C Red No. 19 as 1 in 9 million. The maximum possible cancer risk for D&C Red Nos. 8 and 9 was evaluated as 1 in 60

the colors listed under the de minimis principle.

In the past two Congresses, Senator Edward Kennedy of Massachusetts and Congressman Henry Waxman of California have introduced legislation concerning pesticides that others in government would extend to other additives--including colors--as well. The proposed legislation would substitute a "negligible risk" standard for the "zero-risk" standard (such as described in the Delaney Clause) to the regulation of pesticides. The bills define "negligible risk" as causing at most one additional case of cancer in 1 million people over a 70-year lifetime of exposure to the compound.

President Bush endorsed the negligible risk standard for pesticides in his October 1989 Food Safety Plan. A joint press statement issued that same day by HHS Secretary Sullivan, USDA Secretary Yeutter, and EPA Administrator Reilly noted that while the president's plan specifically addresses pesticide residues, the principle of negligible risk is one that naturally applies to other additives to the food supply.

Small Risks

The ban of the provisionally listed uses of FD&C Red No. 3 applies to new manufacture and production of affected products. Because any health risks posed by Red No. 3 are extremely small, FDA concluded that consumers may continue to use existing supplies of products that already contain that color.

Following the mandate of the Delaney Clause, FDA will now reconsider the permanently listed uses of the straight form of FD&C Red No. 3. The procedure for banning a permanently listed dye, however, is more complex than that for terminating the provisional uses and requires time for public comment.

Though in the future, new definitions of acceptable risk spawned by new technologies may replace the Delaney definition, for now FDA must operate under this meaning and say to consumers that because of the risks, certain uses of FD&C Red No. 3 can no longer be allowed.

Dale Blumenthal is a staff writer for FDA Consumer.

Lists Available

For complete lists of color additives approved for use in food, drugs and cosmetics--including the year approved, uses and restrictions--write to:
Division of Colors and Cosmetics
FDA (HFF-442)
200 C Street, S.W.
Washington, D.C. 20204
