

2506 Cliffborne Place
Washington, D.C. 20009
November 12, 1971

Dr. Charles C. Edwards, Commissioner
Food and Drug Administration
5600 Fishers Lane Rm. 1481
Rockville, MD. 20852

Dear Dr. Edwards:

This report calls to your attention evidence already in the possession of the FDA and urges you to terminate the provisional listing of FD & C Red #2 and immediately suspend its use. Any further delay will assure the continued ingestion of and exposure to 1 1/2 million pounds per year of this widely used food, drug and cosmetic dye which has recently been shown to cause cancer, fetal death and birth defects in animals. This action is within your jurisdiction, as stated in a recent Federal Register notice: (F.R. 36 No. 177 Sat., Sept. 11, 1971)

The Commissioner may give consideration to the termination of a provisional listing of the color additives...if any report, be it a progress report or a final report, shows that the color additive is unsafe under its proposed conditions of use.

In 1969, the color additive amendment to the Food, Drug and Cosmetic Act was passed. Along with other food colors, FD & C Red #2 was provisionally listed with the final determinations regarding safety to have been made by December 1962.

Review of Carcinogenicity Studies (Mannel et al (1958)) J. Pharm. Pharmacol. 10 625 and Wilhelm et al (1953) Gastroenterology 23

Although 2 studies in rats using oral feedings of FD&C Red #2 failed to show carcinogenicity, they were both less than two years in duration. An FDA study during the 1950's lasting two years did show a slightly increased incidence of mammary tumors associated with ingestion of FD&C Red #2.

In 1968, a study in Russia using a paste containing FD&C Red #2 caused cancer in rats. (Baygusheva, Vopr. Pitan 27 1968 p. 46) This study was criticized on the basis that since the pure dye was not used, the tumors might have been caused by other ingredients in the paste.

A second Russian Study, begun in 1966, was published one year ago. (Andrianova, Vopr. Pitan (1970), 29 (5). 61) In this study, a variety of tumors were found in animals eating food containing FD&C Red #2 and a statistically different incidence was found between the control group (no tumors in 50 animals) and the experimental group (13 tumors in 48 animals).

This study has been criticized on several grounds and, thus uncertainty exists as to whether or not FD&C Red #2 can cause cancer. Rather than pursue this serious question to its scientifically acceptable resolution, the FDA has chosen to "close" the issue of carcinogenicity by not conducting further studies.

Embryotoxicity Study

In 1966, the FAO/WHO Export Committee on food additives requested that studies be performed to evaluate the effect of FD&C Red #2 and other food dyes on reproduction. Such studies previously had never been done.

In December 1969, a report by the FDA's own advisory committee concerning safety evaluation of food additives recommended that the FDA should obtain information about the effects of food additives, including studies of effects on reproduction. Among the reasons the advisory committee gave for the urgency of these studies are:

- a) Hazards which exist during reproduction will not be manifest in any other type of study;
- b) Other azo dyes are known to cause birth defects;
- c) Since there are no benefits derived from the use of food additives, "...Any interference with the reproductive process is a deleterious effect to which no segment of the human population should be exposed."
[Pef. Toxicol & Appl. Pharmacol. 16 264-96 (1970)]

The report also stated,

Since (1) food additives, color additives, and pesticide residues are subject to continuous ingestion, (2) the consumer being unaware of intake, cannot be segregated from the population at large for observation, and (3) the ratio of benefit to risk is often low and ill-defined, it is important to have as much information as possible to justify a conclusion that conditions of safe use have been established.

This statement suggests that these non-essential products should be considered unsafe until proven otherwise.

More than 1 1/2 years ago the first studies on reproduction were published (Shtenberg & Gavrilenko, Vopr. Pitan (1970) 29 (2), 66) Although the number of animals was small, the study showed increased fetal death in rats fed low levels (1.5 mg/kg per day) of FD&C Red #2.

It is to be noted that this level corresponds to the upper limit set by the FAO/WHO in 1966 as an acceptable daily intake for humans. Thus, amounts of FD&C Red #2 which are consumed by many people were found to cause fetal toxicity in rats. In the spring of 1971, about one year following the publication of the above study and 5 years after the FAO/WHO request, the FDA finally initiated studies to test the effect of FD&C Red #2 on reproduction.

Although these studies on reproduction are not yet completed, there is evidence that the findings thus far give credence to the Russian study and raise serious questions about the safety of FD&C Red #2. Recent statements by FDA and industry officials suggest that this is the case: In a notice in the Federal Register, (Sept. 11, 1971) the FDA requested all manufacturers wishing to continue use of FD&C Red #2, after Dec. 31, 1971 "to present their data (to the FDA) as to all specific uses showing the amounts of this color proposed for continued use in foods, ingested drugs, and ingested cosmetics not later than Oct. 31, 1971."

An accompanying notice requested manufacturers wanting a further extension of provisional listing beyond Dec. 31, 1971 to initiate studies on teratologic potential and multigeneration reproduction and to submit, by Dec. 31, progress reports on these animal studies, estimated data of completion of the studies and current usage data. This was thought by the President of the Pharm. Man. Ass'n., Joseph St tler, to relate to "recent Russian Studies indicating that this color might produce birth defects in rats." (Pharmaceutical Manufacturers Association Bulletin, October 1, 1971)

It is no coincidence that September corresponds to the time, after the initiation of the reproduction studies by the FDA in the spring, when data would have become available on fetal deaths or teratogenicity during the first pregnancy of the rats. (If, as in the Russian study, the first pregnancy occurred at 4-5 months of age.) An industry spokesman, James Noonan of Warner-Jenkinson, stated that "FDA repeated the Russian work in the rat and to some extent corroborated the findings of embryotoxicity." (Food Chemical News, Nov. 1971)

In a seemingly apologetic letter to the Pharm. Man. Ass'n., an FDA official in the Bureau of Foods stated, "The prospects that the FDA will be able to follow the continued use of FD&C Red #2 at any but drastically-reduced levels is far from encouraging." (Food Chemical News, 25 Oct., 1971, p. 4)

It therefore appears that now, 11 years after the original provisional listing of FD&C Red #2, there is un rebutted evidence that this color additive may be unsafe.

Present Usage

A 110 pound pregnant woman who drinks 2 bottles of cherry soda is ingesting .5 mg/kg or one-third of the 1.5 mg/kg per day level of FD&C Red #2 which has caused toxicity in pregnant rats. Add to this innumerable other foods containing the dye, lipstick, red-coated pills she might be taking and it is easily seen how the 1.5 mg/kg limit can be exceeded.

Aside from being the most commonly used color additive in the drug industry, its major use is in foods and it represents about 30% of all provisionally listed color additives consumed in this country. A partial list of products in which FD&C Red #2 is used includes soft drinks, drink

powders, gelatin desserts, breakfast cereals, jellies, gum, syrups, hard candies, coatings of pills and cosmetics and pet foods. This limited information was obtained from scientific bulletins and journals not generally available to the public.

If people in this country wanted to know how much Red #2 was in a specific product so they might avoid ingesting foods or drugs in which it was contained, they would have no recourse. The archaic and grossly inadequate labelling requirements allow the inclusion of "artificial coloring" to describe any amount of any color additive. The FDA has further undermined the ability of consumers to exercise the freedom to choose a safe product by "agreements" made immediately following the notice in the Federal Register of September 11:

Under an arrangement worked out with Food and Drug Administration, trade associations, such as PMA and Proprietary Association, will collect the information from member firms and forward it to the government. The data will go to FDA in category totals only, with individual submissions to PMA kept secret. The urgency arises from the fact FDA might impose use limitations prior to publication in the Federal Register of regulations. (P.M.A. Bulletin, Oct. 1, 1971, p. 1)

A similar arrangement was devised with the Cosmetic, Toiletries and Fragrance Association:

CTF has also reached an agreement with FDA under which the cosmetic trade assn. will serve as the collection agency for all usage data on lipstick color additives. By filing usage data with CTf -- to be incorporated into totals for the entire industry -- individual mfgs. eliminate the possibility that FDA will seek information on their specific formulations. (FDC Reports, Sept. 13, 1971)

Thus, the American people are prevented from knowing which specific products contain large amounts of FD&C Red #2 by agreements which your "regulatory" agency makes with the trade associations. Many scientists, including some in the FDA, believe that substances such as food colorings which serve no useful purpose should not be used until their safety has been established. (c.f. 1969 FDA report on Food Additives)

But certain top-level FDA officials seem to have adopted a different outlook. In response to a letter written by Ralph Nader concerning the lack of safety of another provisionally-listed food coloring (Citrus Red No. 2) last year, you (Dr. Edwards) responded that "...we are not convinced by the data available to us at this time that the color is a carcinogen upon ingestion." (Letter from Comm. Charles C. Edwards to Ralph Nader, February, 1971) Yet among the data available to you was the joint FAO/WHO committee report in which Citrus Red No. 2 was found to have carcinogenic activity; thus the report recommended that Citrus Red No. 2 not be used as a food color.

Rather than suspend the provisional listing of many color additives due to serious doubts about their safety, your letter explained that "The delay in making the listings permanent has been due to our demand that petitioners submit additional information about the conditions and use of the color additive." (Our emphasis)

The amount of time it took for FDA personnel to become aware of the Russian studies of the effects of FD&C Red #2 on reproduction underscores the FDA's lack of aggressiveness. Nearly a year passed before the FDA became aware of the Russian reproductive study published in March-April 1970. Moreover it was the Allied Chemical Corporation -- not the agencies own scientists -- who brought FDA's attention to this article. Allied Chemical Corporation, itself, translated the Russian article into English for the FDA. This act of "public service", however, may not be as selfless as it appears. Allied Chemical Corp. is a major producer of FD&C Red No. 40 and according to Food Chemical News, Nov. 1, 1971, "there has been strong industry sentiment that many of the products can be shifted to FD&C Red 40.

Recommendations

In light of the above, the following recommendations are respectfully submitted regarding FD&C Red #2 and other provisionally-listed color additives.

- 1) Terminate the provisional listing of FD&C Red #2 and suspend any further use.
- 2) As requested by the FAO/WHO expert committee in 1966, initiate research on the combined effects of FD&C Red #2 with Sunset Yellow FCF and Tartrazin (and other combinations of food colors);
- 3) Discontinue the practice of encouraging corporate secrecy by making agreements with trade associations;
- 4) No substitute should be allowed to replace FD&C Red #2 (such as FD&C Red 40 or Violet 1, or any other) unless its safety has been established by tests which rule out carcinogenicity and effects on reproduction. The American people will not suffer from not having artificial red coloring.

In summary, it is a fact that in not initiating tests of the effects of food colors on reproduction until last spring, the FDA chose to violate the 1960 Food and Drug Law amendment, to disregard the FAO/WHO recommendation of 1966, and to pay no heed to the advice of its own committee in 1969.

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At this time, however, FDA scientists now possess sufficient information from current studies to strongly suggest that FD&C Red #2 is unsafe. There is little doubt from remarks by FDA officials that the use of FD&C Red #2 will be virtually eliminated at some time in the future. The decision not to act immediately allows food, drug and cosmetic manufacturers precious time to change from one unlisted and unsafe artificial color to another with a minimal amount of public attention and loss of sales. Any further delay in removing this hazardous substance from the marketplace should incur sanctions as provided by law for the nonfeasance of those officials responsible.

Sincerely,

Sidney M. Wolfe, M.D.

Ralph Nader

Loren Anderson, M.D.
Health Research Group