#234

Public Citizen

October 31, 1974

Associate Commissioner Lloyd Tepper
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Tepper:

November 12, 1971, almost three years ago, the Health Research Group petitioned FDA to ban the use of red dye #2, because of studies which suggested that it was toxic to fetuses and caused cancer. We have repeated our petition periodically, without success. Red #2 is used in $10 billion worth of foods annually, exceeding the sales of the entire prescription drug market. "In the first place, we're stuck with Red 2," FDA Bureau of Foods Director Wodicka has stated* in what he apparently believes to be a justification for disregarding adverse test results.

Since 1971 consumers have eaten over $30 billion of Red #2 food, exposing themselves to alarming and unnecessary risks.

CARCINOGENICITY OF RED #2

In 1971, a Russian study concluded that the dye caused cancer in laboratory animals (Vopr. Pitan. 29,5,61, 1970). When we wrote to FDA Commissioner Edwards urging a ban, he replied Dec. 3, 1971: "FD&C Red No. 2 has been studied for its carcinogenic potential as extensively as any substance of which we know." Referring to FDA studies in the early and late 1950's (all unpublished) Dr. Edwards stated that Red #2 was "without evidence of carcinogenic action." Similarly, Dr. Wodicka stated, "In our own tests, the [cancer] results have been negative."**

We now have the data from the FDA unpublished studies. In fact, in combination with the above-mentioned Russian study, these studies strongly indicate that Red #2 does cause cancer. A review

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* Interview with Dr. Wodicka reported in Medical World News, Sept. 8, 1972

** Ibid.

of the three unpublished FDA studies follows:

1. FDA Study, 1951-1953 -- never published --

This was a 2-year study in rats in which Red 2 was added to the animal feed. In a previously unreleased memo dated July 2, 1954 from Dr. A.A. Nelson, the FDA scientist who conducted the study along with Dr. Fitzhugh, to Dr. A.J. Lehman of the FDA, the following statements were made:

> "the only effect of any consequence attributable to the colors (3 other dyes were studied separately) was the increase, roughly a doubling, in the number of breast tumors with 3 of the 4 colors" (including Red 2) (emphasis and parenthesis added)

An FDA statistician, Mr. Weiss, upon studying the data, is quoted in the same memo as saying this "offers grounds for suspicion that there is an effect of the dye."

Dr. H.L. Stewart, of the National Cancer Institute commented in the memo that "there was a suspicion that the colors fed were increasing the incidence of breast tumors."

The data are as follows:

CONTROL FEMALES 7 out of 36 with breast tumors
RED 2-FED FEMALES 16 out of 48 with breast tumors

Although Red 2 almost doubled the incidence of breast tumors in rats, the number of animals was too small for statistical significance. However, if the same experiment had been performed with larger numbers of animals, e.g. twice as many, and the same percentage had gotten breast tumors, the results would have been highly significant.

(HYPOTHETICAL) CONTROL FEMALES 14 out of 72 with breast tumors
RED 2-FED FEMALES 32 out of 96 with breast tumors
$p < .05$ ($p = .0341$)

The memo also states that

> "Later, on checking Dr. Fitzhugh's original data, a total of 7 additional subcutaneous (in all probability breast) tumors which for one reason or another had not been sent to the pathology laboratory were found. Since 6 of these were in treated rats and 1 in a control the significance of the original findings was not lessened." (emphasis added)

2. FDA Rat Study, 1955-1957

Presumably because of the strong suggestion of carcinogenicity of Red 2 in the earlier study, a slightly larger study was undertaken by the FDA in 1955. The results are as follows:

CONTROL FEMALES 5 out of 100 with breast tumors
RED 2-FED FEMALES 12 out of 100 with breast tumors

Red 2 more than doubled the incidence of breast tumors but, again, the number of animals was too small for statistical significance. If the size of the experiment had been twice what it was, the following results would have been obtained.

(HYPOTHETICAL) CONTROL FEMALES 10 out of 200 with breast tumors
RED 2-FED FEMALES 24 out of 200 with breast tumors

Under these conditions, the results would again have been highly significant. ($p < .01$; $p = .0099$)

(This study was done on Sprague-Dawley rats; a parallel study on Osborne-Mendel rats was negative.)

3. FDA Mouse Study 1957-1959

This study was also undertaken because of the "questionable" previous findings of carcinogenicity. This study again shows an increase in total tumors in animals fed Red 2:

CONTROL MALES 11 out of 100 with tumors
1% RED 2-FED MALES 13 out of 50 with tumors

In an internal FDA memo dated November 9, 1961, from Dr. W.K. Webb to Dr. A.J. Lehman, it states that, "Statistically, the (Red 2-fed) mice had significantly more total tumors than did the control(s)." ($p < .05$; $p = .03$)

We now know, based on the above data, that the FDA has had in its possession for more than 15 years, the results of 3 studies in 2 species of animals supporting the carcinogenicity of Red 2. Although it is reasonable to ask why the FDA didn't ban Red 2 in the late 1950's when the results of these three experiments were obtained, even more disturbing is the failure to act in 1970, when yet another study supporting the carcinogenicity of Red 2 became known.

This Russian study alluded to earlier, was a rat feeding study conducted in males only and it provided the following results:

CONTROL RATS NONE out of 50 with tumors
RED 2-FED RATS 13 out of 50 with tumors

These results are highly statistically significant with $p < .00005$, and in conclusion, the authors stated that;

> "Chemically pure amaranth (Red 2) possesses carcinogenic activity of medium strength and should not be used in (the) food industry."

FDA officials have refused to act on this study, on the basis that the incidence of spontaneous tumors in the control animals was too low (the control animals had no tumors; only the animals given red 2 had tumors). In our opinion, this is a ridiculous reason to discount the study. Recently, an industry-sponsored pathologist told FDA advisers on metronidazole (Flagyl), that even though experimental animals fed metronidazole had a significantly higher incidence of breast tumors, the results should be discounted because the control animals in the study had a high incidence of tumors. High or low -- the importance of a cancer study lies in the differences in the incidence of cancer between the animals exposed to the test substance and the control animals. Attempts to ignore significant findings on the basis of low or high controls, merely reflects a desire to have positive results troublesome to industry go away, as opposed to a desire to protect the public.

Although there are several published studies which do not show Red 2 to be carcinogenic, an analysis of these studies reveals that:

> "either the duration of the study or dosage of amaranth used did not meet the requirements set for carcinogenicity studies with chemical substances." (Vopr. Pitan., ibid.)

These four studies demonstrating the carcinogenicity of Red 2 are reason enough to immediately ban this widely-used food additive on the grounds that its use violates the Delaney Amendment to the Food, Drug and Cosmetic Act.

FETOTOXICITY OF RED NO. 2

1. Pre-1974 tests.

Some of these tests had positive results; some had negative results. The following studies demonstrated adverse reproduction effects:

i. Shtenberg and Gavrilenko noted that Red 2 caused fetal death

in doses of 1.5 mg/kg body weight/per day and 15 mg/kg body weight/per day, when Red 2 was administered to rats by gavage (with water by stomach tube) from day 0. Vopr. Pitan. 29, 66 (1970).

ii. Shtenberg and Gavrilenko noted various adverse effects such as decreased survival of newborns, decreased vitality of sperm; increased fetal death, atrophy of ovaries, etc., at 1.5 mg/kg in food. Vopr. Pitan. 5, 28 (1972).

iii. Collins found statistically significant fetotoxic results at 30 mg/kg, when Red 2 was administered by gavage to rats days 0-19 Fd. Cosmet. Toxic. 10; 619-624, 1972.

iv. Woodward Laboratories found 55% fetal resorption at 15 mg/kg when administered by gavage to rabbits days 6-18. NAS Report on Red 2, Attachment 9. By our calculations, Woodward Laboratories also showed positive results when Red 2 was administered by diet, days 6-19.

v. Food and Drug Research Laboratories tests resulted in increased frequency of fetal resorption and/or birth defects, by our calculations, when Red 2 was administered by gavage, at levels as low as 27 mg/kg, in 3 of 4 species of animals studied.

vi. Biotest Laboratories showed that doses as low as 1.5 mg/kg resulted in increased fetal resorption in rabbits. (Data in FDA files.)

The following tests apparently demonstrated no adverse effects on reproduction:

i. Food and Drug Research Laboratories found no significant results in rabbits by gavage, days 6-15.

ii. Collins et al, found no fetotoxicity and no effect on survival, in 3-generation rat studies, where the rats were fed Red 2 from weaning.

iii. Biotest Laboratories apparently found no adverse effects when Red 2 was administered by gavage 15-150 mg/kg, days 6-15. We do not have the raw data on this study, and have therefore not re-calculated it.

2. 1974 data from the FDA advisory Committee protocol.

In the face of conflicting test results, FDA devised a theory

that the traditional gavage method of administering test substances to animals may have caused the adverse effects noted. FDA formed the "Ad hoc Advisory Committee on Red #2" which constructed a protocol to compare the effects of Red 2 on rats given the dye by gavage and in food. The protocol was run by FDA, the federal National Center for Toxicological Research (NCTR) and an industry-sponsored lab.

FDA results did not, according to FDA calculations, demonstrate any untoward fetotoxicity in either the gavage or diet groups. We did not recalculate FDA's findings because the raw data was not available.

The NCTR concluded that their results were either negative or "accidental." We disagree, on the basis of our own calculations. Using the Gross, Fitzhugh and Mantel method for calculating safety (Biometrics, June 1970), it was concluded that the number of viable fetuses would be reduced by no more than .1 per litter, using a 95% confidence level, at the levels in the chart. The levels in the column labelled mg/kg are comparable to the "no-effect" level in animals.

GROUPS	TREATMENTS	LEVEL	
		Osborne-Mendel Rats mg/kg	Charles River Rats mg/kg
E_1 vs C_1	200 mg/kg Red 2 vs 1.9% NaCl Solution by gavage days 0-19	9.0	14.4
E_1 vs C_4	200 mg/kg Red 2 by gavage vs Control gavage days 0-19	9.0	17.7
E_1 vs C_5	200 mg/kg Red 2 vs water by gavage days 0-19	8.6	11.1
E_4 vs C_6	0.2% Solution drinking ad lib days 0-20 vs no treatment (it is assumed that rats consumed approximately 200 mg/kg/day Red 2)	11.2	7.2
E_2 vs C_2	200 mg/kg Red 2 vs 1.9% NaCl Solution by gavage days 6-15	200.0	20.2
E_3 vs C_3	200 mg/kg Red 2 vs 1.9% NaCl Solution by gavage days 7-9	154.0	5.2

By these calculations, the dye is safe as far as fetotoxicity is concerned, only at extremely low levels. For the rats taking the dye by gavage -- a situation similar to human beverage use -- the "safe" levels in animals were about 9 mg/kg/body weight. As a rule, FDA divides the "no effect" or "safe" dose in animals by a safety margin of 100 (21 C.F.R. 8.34), to prevent damage resulting from human sensitivity greater than animals. This results in a safe level for Red 2 of .09/mg/kg/body weight per day. A 110 lb. (50 kg.) woman could safely ingest only about 1/3 can of soda daily. A child would exceed the safe limit with a couple of gulps of one soda. As far as this fetotoxicity test determines, a "safe" dose is close to no dose.

The "safe" levels of 9 mg/kg from the NCTR study are very close to the safe level as to fetotoxicity determined by the first Collins study (Collins and McLaughlin, "Teratology Studies on Food Colors: Embryotoxicity of Amaranth," Fd. Cosmet. Toxicol. Vol. 10, pp. 619-624, 1972). That study, sponsored by FDA concluded:

> At present 7.5 mg/kg appears to be a no-effect level under the conditions of this study. Although the effect at the 15/mg dose level (P=approximately 0.19, 0.22 and 0.16) did not attain the usual P value of 0.05 for statistical significance, it cannot be ignored. A dose-related fetotoxic response was obtained which was statistically significant at and above the 30 mg/kg dose level.

These findings are consistent with the results of other studies, where test animal exposure from day 0 of pregnancy usually produced adverse reproductive effects, and exposure from day 6 sometimes produced negative results. (In the present NCTR study, Osborne-Mendel rats fed Red 2 days 6-15 only had a high "safe" level of 200 mg/kg; rats fed on days 7-9 had 154 mg/kg, in comparison to the low safety levels by gavage.

We did not analyze the industry-sponsored data.

The differences in the results of the many fetotoxicity tests have not been explained. Faced with conflicting results and unable to explain them, the NAS Food Protection Committee in 1972 renounced the tests showing danger on the basis that they were animal studies rather than human studies and that the dye had been in use for many years without human harm having been

observed before. This basis for rejecting the positive studies was a radical, unwelcome departure from health-conservative principles. The "Food Protection" Committee ignored the fact that thorough toxicity tests cannot be conducted on humans for ethical reasons and that without controlled toxicity tests, chronic adverse effects are unlikely to be observed (unless the effect is bizarre and the suspect chemical is used in a very defined population).

With conflicting results on the fetotoxicity alone, we believe FDA is obligated for the protection of thepublic to severely limit Red 2. As for the cancer effect, scientists are in agreement that no dose of a carcinogen can be determined to be safe. Heretofore, industry has succeeded in convincing a gullible FDA, that FDA has the burden of proof of safety (when in fact industry has the burden of proof) and that FDA had to show that all tests had identical results before it could act.

With strong fears of cancer, added to fetotoxicity, we believe that the risk of this chemical cannot be borne by the public for the sake of cosmetizing synthetic foods, or for any reason. On the basis of the scientific studies available, the Delaney Clause and common sense mandate that Red #2 has no place in the American food supply.

Yours truly,

Anita Johnson

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Sidney M. Wolfe

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