021-7/10/78-10-03

July 18, 1972

Charles C. Edwards, Commissioner
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20852

Dear Commissioner Edwards:

In November, FDA scientists recommended that FD&C Red Dye #2 be taken out of the food supply, since human safety could not be assured when the dye was used. Rather than act on that advice, you referred the question of Red #2 toxicity to a committee of the National Academy of Sciences Eight months and over 400,000 lbs. of red dye later, the NAS has released a report which is a giant whitewash of test data showing adverse effects on reproduction, and an homage to ill-prepared industry summaries showing safety. On the basis of this NAS report, FDA has rejected the position of its own scientists.

In view of the inconsistencies between the data and conclusion of the NAS report, and of FDA's reliance on it for regulatory action, we request your detailed analysis of the report, showing in what respects you agree and disagree with the test summaries and conclusions of the committee.

Our own review of the NAS report follows.

The NAS committee report concluded that Red #2 as normally used constitutes no hazard to human health or reproduction. The report noted that the scientific results of animal tests "have generated concern" but that they are as yet "inconclusive". Included in the report is the recommendation that "high priority be given to a more complete and definitive study of the effects" reported to the committee.

The scientific data on Red #2 reviewed by the NAS committee included reports by scientists from FDA and Industry laboratories. Among these reports were those of FDA scientists which demonstrated that Red #2 causes fetal toxicity (ie. resorption of implanted fetuses) in rats at a dosage level of 30mg/kg/day* and in chickens at even lower dosage levels. Another FDA report of a mutagenesis study by Dr. M. Legator yielded results which led him to conclude that Red #2 was "one of the most potent (mutagenic) compounds found to date in the host-mediated assay".

Other scientific studies, presented to the NAS committee by industry laboratories, purported to find no effects of Red #2 on reproduction and fetal viability in several mammalian species However, a careful reading of these reports reveals that certain pieces of positive data were listed as results but were left unanalyzed

* At present, the no effect level for fetal toxicity is 15mg/kg/day,

and unmentioned in the summaries and conclusions. For example, in a study by Food and Drug Research Laboratories (under contract with FDA) no mention is made of the fact that the investigators found that Red #2 administered to pregnant rats and mice (at levels from 27-100mg/kg/day) resulted in an increased frequency of fetal resorptions compared with untreated rats. These findings of fetal toxicity appear clearly in the tables of the results of the study. This same report also concludes that no fetal skeletal abnormalities were attributable to the use of Red #2. However, the results of this study clearly show that the fetuses of animals given Red #2 at levels from 2-1000mg/kg/day exhibited an increased incidence of incomplete sternbrae (in mice and hamsters), incomplete ribs (in rats), and incomplete vertebral ossification and delayed cranial ossification (in hamsters) compared with fetuses of untreated animals. Surely these findings indicate that use of Red #2 is related to several kinds of fetal abnormalities. The report mentions none of the adverse effects. Apparently, the committee merely reiterated the prepared summary of the study without carefully reviewing the data.

In another report submitted to the NAS committee, scientists at Woodard Laboratories (under the aegis of the inter-industry committee), studied the effects of Red #2 administered by two different methods, on the reproductive functions of rabbits. The results of this study indicate that pregnant rabbits dosed with Red #2 at a level as low as 15mg/kg/day by gavage (through a tube inserted directly into the stomach) suffered significant weight loss and bore 8 times more resorbed fetuses than did the control rabbits no receiving any Red #2. When the dye was administered in the diet at levels up to 450mg/kg/day, no such harmful effects were observed. The NAS committee report contains no mention whatsoever of the harmful effects on reproduction found to result when Red #2 is administered by gavage. These findings were significant, and an objective review would have considered them. The NAS neglected to do so.*

In its evaluation of the scientific data, the NAS committee dismissed as unconvincing and inconclusive, reports that Red #2 is a teratogenic and mutagenic agent. FDA scientists have issued a strong recommendation, in a memorandum dated, November 18, 1971, that in light of their test findings the current widespread use of Red #2 in human food should be drastically curtailed. The NAS report states that such action is "a premature and unnecessary measure at this time although it stated that the subcommittee is sympathetic with the policy

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* It should be noted that the different methods used to administer Red #2 to animals (by gavage and in the diet) have been discussed and reviewed by FDA scientists. Their November 18, 1971 memorandum mentions the fact that gavage treatment of an animal might be similar to the experience of a human drinking a beverage containing the dye.

of the FDA to "err on the side of safety". The report further suggested that the toxic effects already reported should be substantiated by more tests in animals, but that even if they were confirmed in this manner the relationship between these effects in animals and possible effects on human reproduction would be "uncertain".

It is true that the most direct way to establish that a compound has fetal toxicity in humans is to test it on humans. However, well-controlled studies on humans are extremely difficult if not impossible to obtain given the range of chemical substances to which humans are exposed, and given the difficulty in obtaining subjects of identical life-styles and chemical exposure. Further, our society has deemed experimentation on human beings to be unethical once suspicion of hazard has appeared. FDA itself would not condone tests on human reproduction after animal studies have warned of toxicity. Given the widespread use of Red #2 in the food supply and the chronic nature of its suspected toxicity, it is unlikely that <u>without</u> controlled studies, reliable data on human will ever appear. Thus, the NAS was irresponsible in deciding that Red #2 can safely remain in widespread use in human food, drugs and cosmetics simply because toxic effects have been reported only in animals. Carefully planned and performed animal experiments are thus agreed on by all scientists as a proper and sufficient indication of potential harmful effects of a substance on human health. With widespread substances of chronic toxicity, they are likely to be the <u>only</u> indicator available to scientists. The results of such experiments cannot be discounted or discredited merely because they are animal studies.

The oft-invoked but false platitude, "common use in foods show safety," cannot be used, even by a committee of the NAS, to obscure scientific evidence that alerts consumer protectors to danger.

The NAS report admitted that a sufficient amount of scientific evidence has already been accumulated on the toxic and mutagenic effects of Red #2 in animals to warrant concern. However, this same report chose to overlook these findings in recommending that no reduction in the widespread use of this red dye be made at this time. This course of inaction is irresponsible considering the seriousness of the reported effects in animals and the large quantity of Red #2 which is ingested daily by humans. The public interest can not countenance a policy of continued use of a substance which has not yet been definitively tested, but for which there exists a substantial preliminary evidence of potential hazardous effects on human health.

Color additives should be proven safe before they are put in our food. If "further tests are needed," they should be done BEFORE we eat Red #2. A policy of eat now, test later, benefits no one but the food industry.

Sincerely yours,

Helen Robinson, Ph.D.
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Sidney M. Wolfe, M.D.

cc: Philip Handler
Prof. George Kistiakowsky