



Calorie Control Council

SUITE 500-G • 5775 PEACHTREE-DUNWOODY ROAD • ATLANTA, GA 30342 • (404) 252-3663 • FAX (404) 252-0774
E-MAIL: CCC@ASSNHQ.COM • WWW.CALORIECONTROL.ORG

October 24, 1997

Dr. Larry B. Hart
Executive Secretary
National Toxicology Program
NIEHS
Bldg. 101 South Campus
111 Alexander Drive
Research Triangle Park, NC 27709

Dear Dr. Hart:

Enclosed are the Calorie Control Council's comments on saccharin for the October 30-31 meeting of the National Toxicology Program Board of Scientific Counselor's Report on Carcinogens Subcommittee. A shortened/modified form of these comments will be presented orally by Robert C. Gelardi, President of the Calorie Control Council, on October 31.

Kind regards.

Sincerely,

Lyn O'Brien Nabors
Executive Vice President

LON:jac
Enclosure

**COMMENTS OF THE
CALORIE CONTROL COUNCIL**

SACCHARIN

**FOR THE
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS' MEETING
OCTOBER 30-31, 1997**

The Calorie Control Council is an international association of manufacturers of low-calorie and reduced-fat foods and beverages. Companies that manufacture and use saccharin in their products are among the Council's members. Saccharin has been used to sweeten foods and beverages for nearly a century. It is one of the most studied ingredients in the American food supply.

The Council has petitioned the National Toxicology Program to delist saccharin from its Biennial Report on Carcinogens on the basis of NTP's new criteria incorporating the use of mechanistic data. The extensive data on saccharin clearly demonstrate that the adverse findings in rats are not relevant to humans.

Research on sodium saccharin conducted during the 1970's showed that feeding high dietary levels of sodium saccharin was associated with an increased incidence of rat bladder tumors, predominantly in the male. Studies conducted in mice, hamsters and monkeys, including a recently completed 20-plus year primate study conducted at the National Cancer Institute, have not resulted in any saccharin-related tumor development (JNCI, in press). However, the early rat findings resulted not only in saccharin's listing in NTP's Report on Carcinogens but also the Food and Drug Administration's proposal to ban saccharin and the saccharin warning label requirement.

Research during the past 20 years has focused on the mechanisms underlying the development of bladder tumors in the male rat to provide evidence for or against their relevance for humans. Mechanistic studies of the bladder tumors in male rats fed high dietary levels of sodium saccharin have demonstrated that changes in urine physiology and hyperplastic alterations in the urothelium occur over the same sodium saccharin dose range associated with bladder tumors. Changes observed include increased urinary sodium levels, high pH and low osmolality. Increased urinary crystalluria and a flocculent precipitate also are present. The particulates observed in the urine of male rats fed sodium saccharin were much less marked in female rats and did not occur in mice.

Crystalluria and precipitates do not occur in rats fed high dose levels of sodium saccharin if the pH of the urine is decreased by feeding sodium saccharin in the AIN-76A diet or by adding ammonium chloride to the diet. The overall mechanism involves the formation of an amorphous urinary precipitate, composed primarily of calcium phosphate. When this precipitate and the other urinary physiological changes are present cytotoxic and regenerative changes are observed in the urothelium, leading eventually to the development of bladder tumors. It is a high dose phenomenon and is specific to the rat.

We would like to clarify the following statement from NTP's RC draft summary for saccharin. In the conclusion (page RC-3), the following statement appears: "The mouse data are inconsistent and require verification by additional studies." Of the three studies in question, two are pellet implant studies. There is now general scientific agreement that urinary bladder pellet studies are not useful in determining the human risks of bladder cancer. For example, these, as well as a number of other, direct bladder exposure studies have been assessed by the Mitre Corporation under an FDA contract. The reviewers concluded that "the presence of confounding factors has limited the utility of most direct bladder exposure studies in human carcinogenic risk assessment." At least seven confounding factors were examined (DeSesso, 1989).

The third study in question is a 1986 study by Prasad and Rai. In this study, male and female mice fed 1.5 g/kg saccharin had papillary adenocarcinomas of the thyroid. The tumors were present in 5/10 males and 3/10 females as large protuberant masses beneath the skin. In the absence of confirmatory data it is doubtful that these tumors can be attributed to saccharin. Other authors (Roe et al., 1970; Miyaji, 1977; Homburger, 1978; Frederick et al., 1989) fed saccharin to mice for periods of 18 to 30 months at dietary levels up to 5%. Although thyroids are not mentioned specifically in these publications, it is not credible that the authors would have missed the type of lesions described by Prasad and Rai.

It is further stated on p. 7.1 of the NTP review that "extensive mechanistic studies in mice exposed to high doses of sodium saccharin, with or without previous exposure to a urinary bladder initiator, have not been carried out to definitively rule out the possibility that mice could also develop urinary bladder neoplasia under specific experimental conditions." We draw attention to a paper by Frederick et al. (1989). This study also was reported in the National Center for Toxicological Research Technical Report No. 258 (1989). Weanling Balb/c mice were initiated with 200 ppm dietary 2-acetylaminofluorene for 13 weeks. Following a 2-week period of control diet they were fed sodium saccharin at levels of 0, 0.1, 0.5, 1.0 and 5% in the diet for the remainder of a 132 week study. The resultant elevated incidence of persistent bladder transitional cell hyperplasia and hepatocellular tumors indicated an adequate dose of initiator. Sodium saccharin dosing did not increase the incidence of tumors in either the bladder or the liver and was not considered to be a promoter of carcinogenesis at these sites in the mouse.

We do not believe, therefore, that additional studies in mice would be useful in the evaluation of saccharin.

Also specific to the NTP review, we note that the review (p. 7.7) points out that a dietary level of 7.5% saccharin increases the sodium level in the diet only 3-fold and it is stated that "the sodium ion concentrations in the feed from carcinogenic doses of saccharin are not much higher than in the rat feed itself." In fact, a 3-fold increase in sodium intake is physiologically quite significant. This additional sodium intake is responsible for the increased water consumption and urine volume and the decreased urine osmolality that occur in sodium saccharin-fed rats. These physiological changes in the urine occur at sodium saccharin dietary levels as low as 3% (Schoenig and Anderson, 1985). They are also considered to be important etiological cofactors in the development of bladder changes in rats fed sodium saccharin (Anderson et al., 1987; Anderson, 1988; Renwick and Sims, 1983). The approximately 1% sodium level in the diet of rats fed 7.5% sodium saccharin is within the range of sodium intakes that would cause permanent increases in the systolic blood pressure of Sprague Dawley rats (Dahl, 1961; Dahl and Schackow, 1964).

It is important to note that extensive research in human populations has established no association between saccharin and bladder cancer. More than 30 human studies have been completed indicating saccharin's safety at human levels of consumption. In a 1993 review of the epidemiologic studies on "artificial sweeteners and bladder cancer," Elcock and Morgan concluded "that saccharin is not related to bladder cancer in humans."

In summary, we urge you to carefully review the extensive data on saccharin, and consistent with other national and international scientific organizations' findings, to conclude that the development of tumors in male rats fed high doses of sodium saccharin are not relevant to man and to delist saccharin from NTP's Biennial Report on Carcinogens.

References

- Anderson RL (1988). An hypothesis of the mechanism of urinary bladder tumorigenesis in rats ingesting sodium saccharin. *Fd Chem Toxicol* 26:637-644.
- Anderson RL, Lefever FR, Maurer JK (1987). Effects of inherent urine output on the response of male rats to 7.5% dietary sodium saccharin. *Fd Chem Toxicol* 25:641-645.
- Dahl LK (1961). Effects of chronic excess salt feeding. Induction of self-sustaining hypertension in rats. *J Exp Med* 114:231-236.
- Dahl LK, Schackow E (1964). Effects of chronic excess salt ingestion: Experimental hypertension in the rat. *Can Med Assoc J* 90:153-160.
- DeSesso JM (1989). Confounding factors in direct bladder exposure studies. *Comments Toxicology*, 3:317-334.
- Elcock M, Morgan RW (1993). Update on artificial sweeteners and bladder cancer. *Reg Toxicol Pharmacol* 17:35-43.
- Frederick CB, Dooley KL, Kodell RL, Sheldon WG, Kadlubar FF (1989). The effect of lifetime sodium saccharin dosing on mice initiated with the carcinogen 2-acetylaminofluorene. *Fund Appl Toxicol* 12:346.
- Homburger F (1978). Negative lifetime carcinogenicity studies in rats and mice fed 50,000 ppm saccharin. In: *Chemical Toxicology of Food*. pp. 359-373. North-Holland Biomedical Press.
- Miyaji T (1977). Cited in: Office of Technology Assessment. Cancer Testing Technology and Saccharin. U.S. Government Printing Office. October, p. 46.
- Prasad O, Rai G (1986). Induction of papillary adenocarcinoma of thyroid in albino mice by saccharin feeding. *Ind J Exp Biol* 24:197-199.
- Renwick AG, Sims J (1983). Distension of the urinary bladder in rats fed saccharin-containing diet. *Cancer Lett* 18:63-68.
- Roe FJC, Levy LS, Carter RL (1970). Feeding studies on sodium cyclamate, saccharin and sucrose for carcinogenic and tumour-promoting activity. *Fd Cosmet Toxicol* 8:135-145.
- Schoenig GP, Anderson RL (1985). The effects of high dietary levels of sodium saccharin on mineral and water balance and related parameters in rats. *Fd Chem Toxicol* 23:465-474.
- Takayama S, Sieber SM, Adamson RH et al (1997). Long term feeding of sodium saccharin to non-human primates. *JNCI* in press.