Re: Long-Term Feeding of Sodium Saccharin to Nonhuman Primates: Implications for Urinary Tract Cancer

The assertion by Takayama et al. (1) that their study “strongly supports” saccharin’s lack of carcinogenicity in nonhuman primates is incorrect.

The study actually presents results from four small groups of rhesus, cynomolgus, African green, and rhesus-cynomolgus hybrid monkeys (total, n = 20 animals), the latter two groups having no controls. Study insensitivity from small numbers of animals (at a minimum, six of the 20 animals would have had to have been positive for the results to be significant) is compounded by the low dose of saccharin that was employed—17.9 mg/kg body weight per day, averaged over 1 week. That level of saccharin approximates what many Americans consumed. For instance, the 1977–78 90th-percentiles of saccharin consumption in adults and 3- to 5-year-old children were 10.5 mg/kg body weight per day and 19.7 mg/kg body weight per day, respectively (2). Per capita consumption has increased slightly since then (3). Thus, the study’s results provide no assurance of safety.

While Takayama et al. assert their study indicates that saccharin is not carcinogenic, we note that three of the treated monkeys, but none of the controls, had tumors. Only better-designed studies could determine if saccharin can cause tumors in primates.

Takayama et al., and the accompanying editorial by Zurlo and Squire (4), present as established fact a theory as to how saccharin might cause bladder tumors in male rats, but not in humans. The theory proposes a concatenation of events triggered by high doses of sodium saccharin that lead to amorphous precipitates that irritate epithelial cells and cause tumors. That mechanism is far from proven. Furthermore, saccharin causes bladder tumors not only in male rats but also in females, albeit less frequently, but the mechanism by which saccharin causes tumors in females has been poorly investigated. The mechanism also does not explain saccharin’s promoter activity.

Even if that theory were proven for bladder tumors in male rats, saccharin may cause tumors by more than one mechanism. Moreover, it has caused tumors in other organs and in other species [reviewed in (5)]. In rats, saccharin has caused tumors of the ovaries, uterus, forestomach, skin, and at all sites (other than bladder). In mice, saccharin has caused tumors of the vascular system, lung, uterus, and other sites.

The authors fail to report that saccharin causes dominant-lethal mutations in mice, strongly suggesting potential carcinogenicity (6).

Takayama et al. state that epidemiologic studies “‘failed to show any effect’” on bladder tumor incidences, and Zurlo and Squire note the “‘absence of any conclusive epidemiologic data’” that saccharin is associated with bladder tumors. Those statements ignore findings from the most sensitive studies. By far the largest study (7), conducted by the National Cancer Institute, found associations between consumption of artificial sweetener and bladder cancer in high-risk males, low-risk females, and males and females combined (heavier consumers of artificial sweeteners). While epidemiology can never provide “‘conclusive’” proof of cause and effect, the best studies are consistent with animal studies demonstrating saccharin’s carcinogenicity.

Lastly, we are troubled by the lack of full disclosure of potential conflicts of interest of several authors. Cohen and his colleagues (1) acknowledge funding from the International Life Sciences Institute (ILSI), but readers may not know that the ILSI is funded by food manufacturers, including Cumberland Packing Corp., a marketer of saccharin. Squire has been affiliated with the ILSI and served as a paid consultant to the Calorie Control Council, the trade association of makers and users of artificial sweeteners.

It is unfortunate that the Journal published a study having little scientific merit and lacking full disclosure of affiliations of the authors and invited an editorial to be coauthored by someone who has the same potential conflicts as the authors of the study.

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References


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Responses

Jacobson, Farber, and Clapp raise several questions that we could have responded to in greater detail if they had contacted us, but we can only reply in general here given the restrictions on length imposed by the Journal.

Extrapolation of rodent bioassay data on carcinogens to humans has been and continues to be debated. Nonhuman primates are phylogenetically closer to humans, and their anatomy, physiology, biochemistry, and organ systems are also more similar to humans than to rodents. The longer life span and the low incidence of spontaneous tumors in nonhuman primates and other advantages in...
comparison with rodents have been summarized (1). One obvious disadvantage is the cost associated with using nonhuman primates. Nevertheless, the advantages and the lack of information on the susceptibility of nonhuman primates to compounds known to produce tumors in rodents and to potential human carcinogens prompted studies that were initiated in 1961 (1). The saccharin study began in 1970, utilizing three species of nonhuman primates because little was yet known regarding the effects of chemicals on these species. Subsequently, it has been shown that the two closely related macaque species—rhesus and cynomolgus—react very similarly to numerous compounds investigated. Although fewer data are available on African Green monkeys, these animals respond similarly to the macaques for the compounds that have been studied. Thus, the 20 nonhuman primates in this study can be viewed as a group. Use of nonhuman primates in studies of similar design to that with sodium saccharin has allowed detection of numerous chemicals with carcinogenic activity, including potential human carcinogens (1).

If this study were being designed today instead of 1970, with the vast amount of knowledge now available, we would have used two or more doses of saccharin in one species, i.e., cynomolgus monkeys, with 20 animals/dose. Cynomolgus monkeys would be selected due to their smaller size, ease of handling, and specific caging requirements. Also, more mechanistic studies would be conducted on the monkeys. Nevertheless, the saccharin study as reported is valid today.

Our conclusion, which we reiterate, is that “the results provide additional evidence that sodium saccharin is without a carcinogenic effect on the (nonhuman) primate urinary tract.” There is a wealth of animal, human, and mechanistic research that strongly suggests that saccharin is not a carcinogen to humans. Jacobson et al. have provided a superficial and skewed interpretation of the vast literature on saccharin, much of which has been reviewed in detail by various panels of experts including the International Agency for Research on Cancer and the Congressional Office of Technology Assessment (4).

In contrast to the statements made by Jacobson et al., there has been considerable research in female as well as male rats, although substantially more research has been done in males since they are more susceptible. Tumors at sites other than the urinary tract have been reviewed in detail elsewhere (2,4), and, for a variety of reasons, were not thought to be significant. Similarly, mice are considered resistant to the carcinogenic effects of saccharin (5). The mutagenicity of saccharin has also been reported extensively [e.g., (6)], and, although it is positive in chromosomal aberration studies, other sodium and potassium salts (e.g., NaCl and KCl) are also positive in those studies at similarly high doses, possibly due to an osmotic effect. In addition, saccharin, which is anionic and not cationic, does not react with DNA, and it does not increase unscheduled DNA synthesis in the target tissue, i.e., the rat urothelium.

Also, other sodium salts, such as ascorbate, glutamate, aspartate, citrate, erythorbate, succinate, bicarbonate, and chloride, produce similar urinary and urothelial effects in rats as sodium saccharin when administered at correspondingly high levels (5,7). Mechanistically these salts behave the same in the rat as saccharin, and, like saccharin, they are unlikely to pose a carcinogenic hazard to humans.

Epidemiology has clearly shown that saccharin is not a moderate or a strong carcinogen in humans. Given the limitations of epidemiologic studies, a weak effect cannot be proven or excluded. Mechanistic research is performed to resolve the matter. Dr. Farber has had a long, distinguished career investigating mechanisms of carcinogenesis in animal models. Is he now suggesting that mechanistic research in animals does not have relevance to humans?

Finally, some of us received grants not only from the National Institutes of Health (NIH) but also from the International Life Sciences Institute (ISLI), and this was properly disclosed. Like NIH grants, the ISLI grants to Cohen et al. have been investigator-initiated, and the investigators have the same rights of data interpretation and ownership. More importantly than the source of funds is the validity of the research. Much of the research by Cohen and his colleagues has been corroborated by other scientists from around the world.

References


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Jacobson et al. appeared to have either ignored or mislabeled the salient points of our editorial (1) on the study published by Takayama et al. (2). First of all, we did not state as fact the present theory of why saccharin is a bladder carcinogen in male rats, as Jacobson et al.
assert but, rather, we referred to the substantial evidence supporting that theory [reviewed in (3,4)]. Secondly, while the specific epidemiologic study (5) that Jacobson et al. cited did identify some positive associations between some use of artificial sweeteners (AS) and bladder cancer in several subgroups, the authors concluded “. . . that past AS use has had a minimal effect, if any, on bladder cancer rates. We also conclude that the positive associations in this study do not by themselves establish a causal link between AS use and bladder cancer.” Moreover, it should be noted that the authors did not distinguish between saccharin and cyclamates in the study (5) when recording their data on exposure of subjects to artificial sweeteners. Thus, the study that Jacobson et al. cite as being consistent with animal studies demonstrating the carcinogenicity of saccharin in fact supports our statement in the editorial that there is no conclusive epidemiologic data on the effect of saccharin on human bladder cancer incidence.

In addition to these points of disagreement with the comments of Jacobson et al., I would also bring to their attention that the point of the editorial was to criticize current dependence on animal models and/or invalid experimental designs in animal studies to identify potential hazards in humans, not to pass judgment on the role of saccharin as a human carcinogen. In view of the flaws in the experimental design of the study reported by Takayama et al. (2), we were simply using the case of saccharin to reinforce the validity of our argument. To date, animal models have not provided substantially useful information on the mechanisms of action of saccharin in humans, and they have not been successful in proving definitively whether saccharin is indeed a cancer risk for humans.

It appears that Jacobson et al. have missed our point about the need for better risk assessment models that rely more on human data. Rather, they seem to have misinterpreted the editorial as a declaration that saccharin is not a carcinogen in humans. Furthermore, given the points of the editorial, it is unclear how Dr. Squire’s past affiliation with the International Life Sciences Institute or his independent consulting activities with the Calorie Control Council bear any relevance upon its content. If the intent of Jacobson et al. is to protect the health of the public, their efforts would be better spent on encouraging the Food and Drug Administration and the National Toxicology Program to expand their attempts to develop and implement more reliable testing strategies.

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Blood Supply of Metastatic Hepatic Tumors: Suggestions for Improved Delivery of Chemotherapeutic Agents

On the basis of the results of various multicenter trials, we have learned that the regional chemotherapy of liver metastases of colon cancer is much superior to the systemic chemotherapy (1) and is currently accepted as an alternative strategy to control tumor progression. However, only a limited improvement is observed so far in hepatic arterial infusion technique to make this route of chemotherapeutic agent(s) (mostly 5-fluorouracil [5-FU] and its derivatives) are administered continuously into the hepatic artery (1). This mode of delivery is based upon early reports suggesting that liver tumors primarily receive blood supply via hepatic artery (3). This theory is now held as a dogma and perhaps, as we believe, is limiting the efforts to improve the efficiency of the regional chemotherapy for the treatment of liver metastases.

Extensive experimental evidence is now available which enables us to re-evaluate the idea of arterial blood supply to hepatic metastases. Several groups in the past two decades, e.g., in Sweden (4), Germany (5), Hungary (6) and Japan (7), have provided experimental evidence to suggest that primary as well as metastatic tumors in the liver receive blood supply from both the hepatic artery and the portal vein. The mixed blood is delivered by deeply invading vessels originating from hepatic sinusoids (6,7). In fact, in certain tumor types, the portal vein is the predominant supplier of the blood to the tumor nodule (6). Experimental studies have also indicated that, after the occlusion of the hepatic artery, the therapy of recurring tumor metastases can be developed from unaffected peripheral area(s) including the neighboring sinusoids, which predominantly receive their blood supply (at least 75%) from the portal vein. Such results can be expected because it is now well understood that new vessels can originate from venules during angiogenesis.

We believe that the time has come for scientists and clinicians to reconsider the old dogma and redesign the methodology of regional chemotherapy of liver metastases. The new approach must be based on a strategy that allows delivery of the therapeutic agent(s) via both the hepatic artery and portal vein. The improved design can permit the accumulation of the drug in the tumor irrespective of the actual route of the blood supply available to the individual tumor nodule. The devices and methodology for arterial delivery are already available in the form of totally implantable pumps, hepatic arterial catheters, or implantable percutaneous subclavian arterial catheters.