

October 17, 1997

Dr. Larry Hart  
P.O. Box 12233  
Research Triangle Park, NC. 27709

Dear Doctor Hart:

I am writing in response to the public announcement regarding the potential delisting of sodium saccharin from the NTP list of carcinogens. I have read the background document for saccharin, and find that it summarizes in a reasonable fashion much of the research that has occurred on saccharin. I am enclosing some additional publications and information which may not have been available to your committee, summarizing some of the more recent research. This includes the manuscript describing the monkey study (there has actually only been one, with interim reports). This is in press for the Journal of the National Cancer Institute and reflects a long term study in monkeys performed by the National Cancer Institute. I am also including a copy of a recent manuscript that I have submitted to IARC on species specificity and carcinogenesis for a meeting that is to take place November 3-8, 1997 in Lyon, France. This document summarizes the various issues regarding sodium salts, some of which remain as questions in your document.

I have also enclosed a copy of an abstract summarizing the results of a recent two generation bioassay that we have completed on sodium ascorbate showing that under this type of protocol, similar to the results with sodium saccharin, that this sodium salt is also tumorigenic for the male rat urinary bladder. All of the features associated with high doses of sodium saccharin in the rat have now been similarly demonstrated for other sodium salts in male rats.

One of the issues in your document that appears to be unresolved is the relationship between male and female rats and the role that  $\alpha_{2u}$ -globulin plays in the process, particularly prior to sexual maturity in the male. As indicated in your document, the saccharin anion, like the other anions of various sodium salts that have demonstrated activity in male rats, associates with  $\alpha_{2u}$ -globulin, but also associate with other urinary proteins, such as albumin, but to a much lesser extent. Nevertheless, because albumin is present in extremely large amounts in the normal rat urine, both in the male prior to sexual maturity and in females throughout their life, this provides adequate levels for the formation of the calcium phosphate-containing precipitate in the urine when the other essential parameters of the urine are at appropriate levels. All of the features of the effects of the sodium salts, whether sodium saccharin, sodium ascorbate, or others, occur in female rats as well as in male rats, but to a much lesser extent. This includes the formation of the precipitate, focal mild superficial cytotoxicity of the urothelium, regeneration, but rarely tumors. The extent of the cytotoxicity and regeneration even in the male rat is extremely mild, probably the basis for the usual

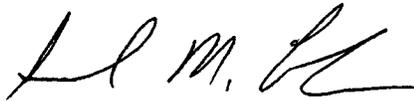
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lack of tumorigenicity when these sodium salts are administered in the standard two year bioassay beginning at 6-8 weeks of age. With an even milder reaction in females, the chances for tumorigenicity are reduced even that much further.

As indicated in the manuscript for the IARC meeting, there appears to be reasonable explanations for the lack of activity for these sodium salts in mice and monkeys, and a plausible explanation as to why there should be no carcinogenic activity in humans. Based on the extraordinary amount of research that has been performed on saccharin and related sodium salts, both in animal models, human studies, and in mechanistic evaluations, I believe that there is a wealth of evidence to support the conclusion that saccharin does not pose a carcinogenic hazard to humans.

If I can provide any additional information regarding our research on saccharin, I would be happy to do so.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'S.M.C.', written in a cursive style.

Samuel M. Cohen, M.D., Ph.D.  
Professor and Chairman

SMC/dm

Enclosures

## Long Term Feeding of Sodium Saccharin to Non-human Primates

S.Takayama<sup>+1</sup>, S.M. Sieber<sup>+</sup>, R.H. Adamson<sup>+2</sup>, U.P. Thorgeirsson<sup>+3</sup>, D.W. Dalgard<sup>§</sup>, L.L. Arnold<sup>♦</sup>, M. Cano<sup>♦</sup>, S. Eklund<sup>♦</sup>, and S.M. Cohen<sup>♦</sup>.

<sup>+</sup>Division of Basic Sciences, National Cancer Institute, Building 37, Room 2DO2, Bethesda, MD 20892, <sup>§</sup>Corning Hazleton Laboratories America, Inc., Vienna, VA 22182, and <sup>♦</sup>Department of Pathology and Microbiology and the Eppley Institute, University of Nebraska Medical Center, 600 So. 42nd Street, Omaha, NE 68198-3135.

Preliminary Results were presented at the 87th Annual Meeting of the American Association for Cancer Research in Washington, DC, April 20, 1996 and in Thorgeirsson, et al. (1994).

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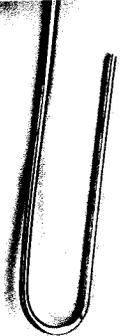
***Tumorigenicity of Sodium Ascorbate in  
Male Rats***

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Keywords: bladder carcinogenesis, saccharin, urinary precipitate, urine, calcium  
phosphate, sodium



**Calcium Phosphate-Containing Urinary**

**Rat Bladder Carcinogenesis**

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**For Meeting on Mechanisms of Carcinogenesis Thought to be  
Species - Specific, International Agency for Research on  
Cancer, (IARC)**

**Rat Urinary Bladder Carcinogenesis**

**by**

**Organic Sodium Salts**

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**For Meeting on Mechanisms of Carcinogenesis Thought to be Species - Specific**

**International Agency for Research on Cancer**

**Lyon, FRANCE - 3-8 November, 1997**