UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

July 19, 1988

OFFICE OF
THE ADMINISTRATOR

SAB-EHC-039

Honorable Lee M. Thomas
Administrator
U. S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of STYRENE health criteria document

Dear Mr. Thomas:

The Drinking Water Subcommittee of the Science Advisory Board's Environmental Health Committee has completed its review of the Drinking Water Health Criteria Document for Styrene dated January 1988. The review was conducted February 4-5, 1988, at the Washington Circle Hotel in Washington, D.C.

The Subcommittee made the following conclusions and recommendations concerning this document on styrene:

- there is insufficient evidence to justify the reclassification of styrene to EPA's category B2 and recommended continuation of the category C classification;

- the study by Quast et al should be discounted because it was less than a lifetime study and the metabolism in the dogs is poorly understood and may not be applicable to humans;

- the rationale for choosing the study used to quantify the risk was unclear and needs to be more clearly articulated;

- all of the epidemiology findings should be included in the analysis; and

- the exposure section needs to be changed to more realistically reflect the existing situation.

A more detailed discussion of these points is attached. Additional chapter-specific comments have already been forwarded from individual members to the Office of Drinking Water.

We appreciate the opportunity to conduct this particular scientific review. We request that the Agency formally respond to the scientific advice provided here.

Sincerely,

Norton Nelson, Chairman
Executive Committee

Richard A Griesemer

Richard A. Griesemer, Chairman
Environmental Health Committee

Gary P. Carlson, Chairman
Drinking Water Subcommittee

SUBJECT: SCIENCE ADVISORY BOARD'S REVIEW OF THE STYRENE HEALTH CRITERIA DOCUMENT

SCIENCE ADVISORY BOARD COMMITTEE: DRINKING WATER SUBCOMMITTEE OF THE ENVIRONMENTAL HEALTH COMMITTEE

DATE OF REVIEW: FEBRUARY 4-5, 1988

PLACE OF REVIEW: WASHINGTON CIRCLE HOTEL, WASHINGTON, D.C.

1. The subcommittee concludes that there is insufficient evidence to justify the reclassification of styrene to EPA's category B2, "probable human carcinogen." The subcommittee recommends continuation of the category C classification.

Those conclusions are based on the subcommittee's being less convinced than the EPA staff of the weight of evidence for styrene carcinogenesis. EPA's evaluation of individual studies properly acknowledged the studies' limitations such as peculiarities of control animals, failure to demonstrate dose-response in some cases, and the presence of tumors having a high spontaneous incidence leading to marginal statistical significance. Further, the data for styrene oxide, while demonstrating cancer causation, are not clearly relevant to the estimation of the human cancer risk for styrene, because the tumors at the site of application were most likely due to the high dose of this most highly alkylating substance (i.e., styrene oxide). This effect is unlikely to be seen with the low doses of the parent compound styrene which might be found in drinking water. Also the data for styrene oxide in humans is for the inhalation route which is not appropriate for ingestion analysis and there is no information whether or not styrene oxide is the direct carcinogenic metabolite of styrene.

The Subcommittee recognized that the EPA placed considerable emphasis on supporting data (e.g., chromosome aberrations) in workers; alkylation of DNA by styrene oxide) in its weight of evidence analysis; however, the subcommittee was less convinced of the value of these data for suggesting carcinogenic potential, because of the confounding factors in studies of styrene and because of the unclear relevance of the styrene oxide data to human risk. The subcommittee recognized that styrene oxide is quite reactive with biological tissue; however, the subcommittee believes that such reactivity may be much less likely to lead to pathology when styrene is administered at doses at which the human body possesses adequate means of detoxification.

The subcommittee noted a difference in interpretation of the Jersey study by EPA and the principal author of the study. We found more persuasive the arguments of Dr. Jersey than those of EPA. The EPA analysis relied on the published interpretation of lymphosarcoma and leukemia in female animals by Dr. Jersey; whereas, Dr. Jersey had discounted his earlier conclusions on the

basis of more recent observations of much higher background tumor rates.

2. The data from paper by Quast et al (1979) used to calculate the 10-day and longer-term health advisories and the lifetime DWEL caused the subcommittee concern for two major reasons. First the duration of the Quast study, conducted in dogs, was less than 600 days, which is a relatively small percent of the lifetime for this species and, consequently, does not approximate lifetime exposure. Second, the metabolism of styrene in this species is known only poorly. It is unclear, for example, whether styrene's metabolism in the dog more closely approximates that of the rodent or that of humans, both of which differ considerably. Rats conjugate styrene to form glucuronides and mercapturic acids whereas, humans form mandelic acid or phenylglyoxylic acid. Consequently, the subcommmittee recommends that EPA discount this study in the formulation of health advisories.

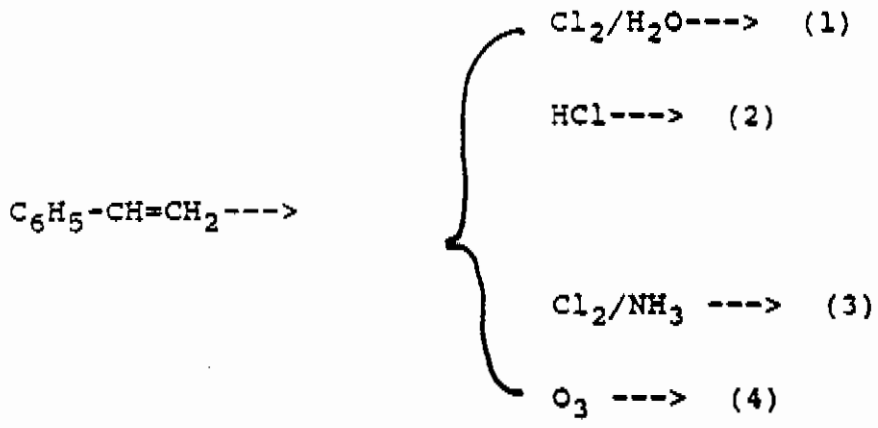
3. EPA properly summarized the toxicity data from which to derive health advisories of varying durations; however, a critical examination of those data to demonstrate convincingly the selection and use of particular data sets was absent. The strength of the health advisories rests in part on the ability to extract salient and relevant knowledge and understanding from diverse studies. If only one study of many is selected as a basis for a health advisory, the relative value of that particular data set must be clearly articulated by EPA. Considerations of major interest in drawing on relevant -- albeit incomplete -- studies include examination of (a) sensitive measures of toxicity, (b) routes and durations of exposure comparable to those of the governing health advisory, (c) dosage regimens, and (d) species of interest.

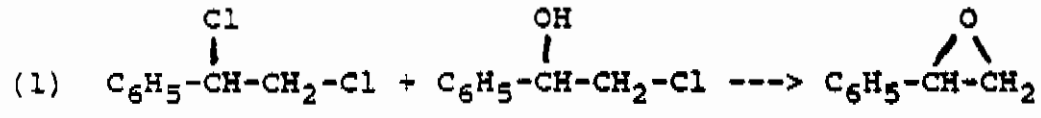
4. EPA concluded that the epidemiologic findings were inconclusive. The subcommittee notes that not all epidemiologic findings were included in its analysis and recommends that its data set be supplemented with the additional information. Further the subcommittee recommends that EPA use the upper confidence limits on those studies to estimate the upper estimate of risk at the lower doses possible via tap water and to compare this estimate with that derived by EPA from the laboratory animal studies. Such a comparison would assist in defining some of the degree of uncertainty incorporated in the EPA's current risk estimates.

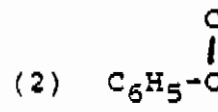
5. The section on human exposure to styrene creates an erroneous impression of high exposure from ambient and indoor air (as high as 70,000 ug/day). In fact, Table IV-1 indicates levels between 0.00 and 3300 ug/m^3. However, the text (page IV-4) indicates that mean levels ranged up to only 16 ug/m3 in the Bayonne/Elizabeth, NJ study. That table and accompanying text should be modified to provide a more representative description of actual exposures.

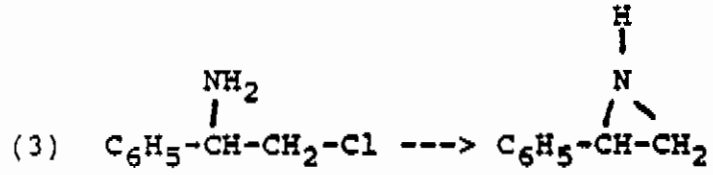
6. As a source of drinking water contaminants and possible health implications, little consideration has been given to reactions of styrene with high concentrations of chlorine, hydrogen chloride, chloramine, or ozone during disinfection. Such probable reactions are presented below. The products (as illustrated in Figure 1), although possibly produced in low concentrations, are prime alkylating agents capable of combining with genetic and other essential biological materials to produce cellular injury of varied physiological consequence. The subcommittee thus recommends a vigorous research endeavor to determine the existence of such byproducts and, if so, the conditions and magnitude of occurrence.

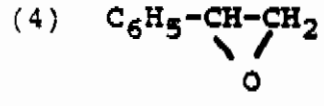
Figure 1.


$C_6H_5-CH=CH_2$ --->
Cl_2/H_2O ---> (1)
HCl ---> (2)
Cl_2/NH_3 ---> (3)
O_3 ---> (4)


(1) $C_6H_5-CH(Cl)-CH_2-Cl + C_6H_5-CH(OH)-CH_2-Cl$ ---> $C_6H_5-CH(O)-CH_2$


(2) $C_6H_5-CH(Cl)-CH_3$


(3) $C_6H_5-CH(NH_2)-CH_2-Cl$ ---> $C_6H_5-CH(NH)-CH_2$


(4) $C_6H_5-CH(O)-CH_2$