UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-DWC-90-016

OFFICE OF
THE ADMINISTRATOR

May 15, 1990

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's re-evaluation of issues concerning the health effects of styrene.

Dear Mr. Reilly,

The Toxicology Subcommittee of the Science Advisory Board's Drinking Water Committee (DWC) met in Washington, D.C. on February 1-2, 1990, to discuss, among other issues, the re-evaluation of the health effects of styrene as requested by the Office of Drinking Water (ODW) and the Office of Research and Development (ORD). The charge to the Committee was to answer two questions:

1. Based on the available data, what is the appropriate weight-of-evidence classification for styrene?
2. What are the appropriate data and procedures to be used for the calculation of the Reference Dose for non-carcinogenic effects?

In the attached report, we reaffirm our previous position that styrene should be classified in weight-of-evidence category C (limited animal evidence; inadequate evidence in humans), not category B2 (sufficient evidence in animals; inadequate evidence in humans). We also find that the study entitled "Chronic Toxicity and Three-Generation Reproduction Study of Styrene Monomer in Drinking Water of Rats" by Beliles et al. (1985), which is in agreement with previous studies, could be used appropriately in establishing a Reference Dose for non-carcinogenic effects.

The Committee continues to maintain that the effects of styrene oxide are not relevant to generating a standard for styrene because of its rapid metabolism.

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

Sincerely,

Raymond C. Loehr
Chairman
Executive Committee

William H. Glaze
Chairman
Drinking Water Committee

EPA U.S. Environmental Protection Agency Washington, DC
EPA-SAB-DWC-90-016

Report of the Drinking Water Committee (DWC) of the Science Advisory Board (SAB)

Science Advisory Board Reevaluation of Issues Concerning the Health Effects of Styrene

A SCIENCE ADVISORY BOARD REPORT MAY 1990

1. EXECUTIVE SUMMARY

The Drinking Water Committee reaffirms its previous position (see Science Advisory Board report SAB-EHC-88-039 dated July 19, 1988) that styrene be classified in EPA's weight-of-evidence category C, rather than B2. It also finds that the study entitled "Chronic Toxicity and Three-Generation Reproduction Study of Styrene Monomer in Drinking Water of Rats" by Beliles et al. (1985) could be used appropriately in establishing a Reference Dose (RfD) for non-carcinogenic effects.

2. INTRODUCTION

The Toxicology Subcommittee of the Science Advisory Board's Drinking Water Committee (DWC) met in Washington, D.C. on February 1-2, 1990, to discuss, among other issues, the re-evaluation of the health effects of styrene as requested by the Office of Drinking Water (ODW) and the Office of Research and Development (ORD). The charge to the Committee was to answer two questions:

a. Based on the available data, what is the appropriate weight-of-evidence classification for styrene?
b. What are the appropriate data and procedures to be used for the calculation of the Reference Dose for non-carcinogenic effects?

Background information on these matters was contained in a briefing paper provided by the ODW.

Both questions in the charge had been previously addressed in a report of the Environmental Health Committee (originating in its Drinking Water Subcommittee) that was issued in July, 1988 (SAB EHC-88-039), following a public meeting held in Washington, D.C. in February, 1988.

3.0 RE-EVALUATION OF THE HEALTH EFFECTS OF STYRENE

The principal items of new information presented at the meeting were two studies: Conti et al. (1988) and Beliles et al. (1985). In addition, written public comments from the Styrene Information and Research Center, the National Resources Defense Council, and the Cincinnati Water Works were supplied.

3.1 Carcinogenic effects

Styrene provides an interesting example of the problems involved in using the EPA guidelines for classifying carcinogens. Technically, when the rules in the guidelines are applied to one study at a time, one may come to the conclusion that styrene should be classified D (inadequate evidence in animals; inadequate evidence in humans) in the weight-of-evidence categorization. However, when all the data are considered together and scientific judgment is applied, some scientists have come to the conclusion that it should be classified as a category C carcinogen (limited evidence in animals; inadequate evidence in humans). The DWC came to this latter conclusion in its 1988 review of the issues relating to the health effects of ingested styrene (SAB-EHC-88-039). ODW and ORD have asked the Committee to review its previous conclusion in light of some newer data.

A recent study by Conti et al. (1988) indicated that styrene administered via inhalation, but not via intraperitoneal injection or orally by gavage, caused an increase in total (benign and malignant) tumors of the mammary gland in female rats. These results are difficult to evaluate for four reasons. First, as noted, tumors did not increase in number for all routes of administration. Second, there are no values given for the number of animals that finished the study since the authors do not indicate the number of animals that died. Third, there is no statistical analysis of the data, and only percentages are given. There does not seem to be a well-defined dose-response effect, and the controls demonstrated an incidence of 56.7 percent. Fourth, the paper was not peer reviewed.

The EPA briefing document again fails to evaluate critically the epidemiology data base and does not discuss the negative studies. While the Drinking Water Committee would tend to agree with EPA that the data do not support the classification as a

human carcinogen, it is important that EPA a) more carefully and formally analyze the positive and negative studies and b) consider the overall data in its totality; i.e., a meta-analysis. EPA's overall assessment of the human data may have been too easily dismissed in favor of the animal studies.

The supporting evidence for styrene as a mutagen is not strong. Styrene itself, according to the results of the majority of the well conducted studies, is neither mutagenic nor clastogenic.

The EPA appeared to misinterpret the DWC's earlier comments on styrene oxide. There is no doubt that this chemical is mutagenic in the Salmonella typhimurium (Ames) assay or that it is capable of causing tumors in the rat forestomach. The real question is whether or not such information is biologically relevant to what would be expected from the ingestion of styrene. The Committee continues to maintain that it is not relevant. Certainly at levels of exposure that would be possible via drinking water and in consideration of the ability of the rat and probably man to rapidly detoxify reasonable levels of the styrene oxide formed in vivo from styrene, the effects of styrene oxide are not particularly germane to the setting of a MCLG for styrene. (See the document entitled "A Review of Styrene Pharmacokinetics and Carcinogenicity" provided to the Committee by CanTox Inc., Oakville, Ontario and prepared for SIRC, Shell Canada Ltd., Calgary, Alberta,Canada for more details.)

Consideration of metabolism of a parent compound which may lead to potentially toxic metabolites is usually a necessary ingredient in hazard assessment. Thus, studies conducted with styrene oxide may be considered in the weight-of-evidence approach. However, these studies are interpreted by this Committee with a great deal of caution. Certain principles pertain. First, the rate of formation and the rate of further metabolism of styrene oxide, itself, must be considered. Secondly, the transport and storage of styrene oxide and its metabolite must be considered. Lastly, the sites of formation and the clearance from the sites of formation are important factors.

There are a number of substances which are known to be metabolized in vivo to reactive metabolites that may be

potentially carcinogenic. In addition, the metabolite may even form DNA abducts in vitro studies, and yet the parent compound administered in drinking water is not carcinogenic. One such compound is methanol, which is metabolized to formaldehyde. Methanol does not produce cancers in acute or long term studies and its initial metabolite, formaldehyde, is rapidly metabolized to formate in all species. However, if formaldehyde is administered at high levels by inhalation, it can produce nasal tumors in rats. Thus, formaldehyde can act locally much the same as styrene oxide does; i.e. produce tumors at the site of administration. But methanol cannot be considered as a carcinogen simply because it is metabolized to formaldehyde. The formaldehyde formed systemically is of little concern because of its rapid rate of metabolism. The same can be said for ethanol which is metabolized to acetaldehyde, another reactive compound that can also produce nasal tumors if administered at high dose by inhalation. Thus, the argument that, because a reactive metabolite or a potentially carcinogenic metabolite is formed, the parent compound should be considered carcinogenic is not necessarily valid. For methanol and ethanol, it is invalid. In the case of styrene, the lack of a strong demonstration of carcinogenicity in the many studies performed thus far may be due to the capacity of the animals to dispose of the metabolite generated in an adequate fashion.

With regard to the animal studies cited by EPA as evidence for the reclassification of styrene from C to B2, the Drinking Water Committee sees no compelling arguments presented to shift from its original position. That is, there were difficulties in the interpretation of the published studies. These have been articulated previously. The use of historical control data [e.g., Jersey et al. (1978) and National Toxicology Program (NCI, 1979)], the expectance of dose-response relationships (NCI,1979), and the requirement of adequate experimental design [which is missing in the Ponomarkov and Tomatis (1978) study, in which the dosing schedule was highly unusual and the doses used were certainly toxic] are entirely reasonable. The criterion necessary for inclusion in class B2, "sufficient evidence in animals", is not met. The data are not clear cut either for rats or for mice. At best, the data are equivocal based on the faulty experimental designs and/or interpretation of the results. They do, however, support a class C designation, "limited animal evidence". (According to the EPA cancer risk assessment

guidelines, Class C evidence includes "tumor responses of marginal statistical significance in studies having inadequate design or reporting"; cf., the Conti et al study in which the number of deaths is not given.) This recommendation is made with the knowledge that the International Agency for Research on Cancer (IARC) has classified styrene as 2B in its scheme. Note that the IARC 2B category is defined differently from the B2 category of EPA. Also, the procedures for using the data in reaching classification decisions are different in the two organizations; cf., IARC's strength-of-evidence judgment vs. EPA's weight-of-evidence judgment.

3.2 Non-carcinogenic effects

In the study of Beliles et al. (1985) the styrene was administered in the drinking water for two years, and the results are negative in regard to tumorigenicity, although this has less weight since the study was not designed as a carcinogenicity study. The highest level of styrene administered, 250 ppm, was close to the level of saturation of styrene in water.

The study of Beliles et al. (1985) for rats is suitable for the establishment of a Reference Dose (RfD) for non-cancer endpoints. It is especially relevant because of the oral route of administration. An RfD of 1.6 mg/L is consistent with the data for chronic toxicity. The RfD of 0.14 mg/L which was derived from the study of Quast et al. (1979) in dogs has been adjusted downward by EPA by an additional factor of ten because of styrene's being in class C weight-of-evidence category. This is over and above the 1000 uncertainty factor which was appropriately used. It is interesting to note that if the additional factor of ten is not included, the value would be 1.4 mg/L, very close to the 1.6 mg/L value from the rat study by Beliles et al. (1985). Conversely, if the additional uncertainty factor of ten were used with the Beliles study (assuming a classification as a C carcinogen), an RfD of 0.16 mg/L would result.

3.3 Conclusion

In summary, the Drinking Water Committee reaffirms its previous position and recommends that styrene retain its classification in category C and not be reclassified B2. This conclusion is based on scientific judgment after looking at all the evidence relating to this decision together. The Committee also finds that the study of Beliles et al. (1985) could be used appropriately in establishing an RfD for chronic toxicity.

REFERENCES

Beliles, R.P., J.H. Butala, C.R. Stack and S. Makris. 1985. "Chronic Toxicity and Three-Generation Reproduction Study of Styrene Monomer in Drinking Water of Rats", Fundamental and Applied Toxicology, 5:855-868. (1985).

Conti, B., C. Maltoni, G. Perino and A. Ciliberti. June, 1988. "Long-Term Carcinogenicity Bioassays on Styrene Administered by Ingestion in Sprague-Dawley Rats, and para-Methylstyrene Administered by Ingestion in Sprague-Dawley Rats and Swiss Mice", Annals of the New York Academy of Sciences, pp. 203-234.

Jersey, G.C., M.F. Balmer, J.F. Quast, C.N. Park, D.J. Schuetz, J.E. Beyer, J.K. Olson, S.B. McCollister and L.W. Rampy. 1978. "Two-year Chronic Inhalation Toxicity and Carcinogenicity Study of Monomeric Styrene in Rats", Final Report, Dow Chemical Company, Midland, Michigan.

National Cancer Institute. 1979. "Bioassay of Styrene for Possible Carcinogenicity", Department of Health, Education and Welfare, Publication No. NIH 79-1741, Tech. Rep. Sec. No. 185:42, Washington, D.C.

Ponomarkov, V. and L. Tomatis. 1978. "Effects of Long-term Oral Administration of Styrene to Mice and Rats", Scand. J. Work Environ. Hlth. 4(Suppl. 2):127-135.

Quast, J.F., C.G. Humiston, R.V. Kalnins, K.J. Olson, S.B. McCollister, C.E. Wade, J.E. Beyer and B.A. Schwetz. (July 31, 1979). "Results of a Toxicity Study of Monomeric Styrene Administered to Beagle Dogs by Oral Intubation for 19 Months", MCA No. STY 1.2-Tox-Gav-Dow, Dow Chemical Company, Midland, Michigan.

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