

Comments of the
STYRENE INFORMATION RESEARCH CENTER
on the
AMERICAN CONFERENCE OF GOVERNMENTAL
INDUSTRIAL HYGIENISTS (ACGIH[®])
Notice of Intended Change to Establish a
THRESHOLD LIMIT VALUE (TLV[®])
FOR STYRENE OXIDE

May 31, 2017

A. Executive Summary

The ACGIH[®]'s TLV[®] Committee should decline to adopt the draft styrene oxide (C.A.S. 96-09-3, C₈H₈O) TLV[®]. The data relied upon for the assertion that styrene oxide is used commercially are incorrect; except for small quantities used in research, styrene oxide is not synthesized commercially. The liver tumors in low-dose male mice that the draft TLV[®] references in the absence of liver tumors in high-dose male mice or in female mice, are not indicative of a chemically-induced response. The studies cited for forestomach tumors in mice and rats form no basis for concluding that styrene oxide induces tumors by a mechanism similar to ethylene oxide, propylene oxide, or epichlorohydrin. Finally, although the draft TLV[®] cites comparisons with epoxides for establishing a proposed TLV[®] of 0.2 parts per million (ppm), the only data present for potency indicates that styrene is 20-fold *less* potent at producing single-strand DNA breaks than propylene oxide, suggesting that any TLV[®] adopted for styrene oxide should be higher, not lower. The justification for a TLV[®] of 0.2 ppm is lacking, so the draft should be rejected.

In North America, the Styrene Information & Research Center, Inc., (SIRC) serves as a resource for industry, federal and state governments, and international agencies on issues related to the potential impact of exposure to styrene on human health and the environment. Headquartered in Washington, D.C., SIRC was formed in 1987 as the principal focal point for the public information and research on styrene. SIRC is a non-profit organization comprising voting member companies involved in the manufacturing or processing of styrene, and associate member companies that fabricate styrene-based products. Collectively, SIRC's membership represents approximately 95% of the North American styrene industry. SIRC's charter also addresses the interests of ethylbenzene producers.

B. List of Recommendations/Actions

1. The TLV[®] Committee should reject the draft TLV[®] of 0.2 ppm as it relies on incorrect, inadequate, or contradictory data on styrene oxide's use and effects.

C. Rationale

The ACGIH[®] has no TLV[®] for styrene oxide, but they have issued a Notice of Intended Change (NIC) for styrene oxide. They are proposing a TLV[®] of 0.2 ppm, based on forestomach tumors in rats and mice of both sexes and liver tumor in low-dose male mice. "The TLV-TWA of 0.2 ppm for styrene oxide is just below the range of TLVs for other epoxides, including ethylene oxide, epichlorohydrin, and propylene oxide, and should provide adequate protection against potential neoplastic (e.g., nasal tumors, forestomach tumors, brain tumors, leukemia) and non-neoplastic change (e.g., hyperplasia of the nasal epithelium) associated with these structurally similar compounds."

1. The NIC cites decades-old IARC manufacturing information (IARC 1994) that styrene oxide is a starting material for the synthesis of several products. Except for small quantities used for research, styrene oxide is not synthesized commercially. Similarly, the US National Library of Medicine (US NLM) TOXNET reference is based on even older information, such as a 1981–1983 NIOSH NOES Survey and a 1972-1974 NIOSH National Occupational Hazard Survey (1972–1974). Even the cited 1981-1983 NOES survey “statistically estimated that 458 workers are potentially exposed to styrene-7,8-oxide in the US.”
2. Styrene oxide is not used or intentionally generated in reinforced plastics manufacture and boat making. The draft documentation is incorrect in stating: “In operations using styrene oxide, such as in reinforced plastics manufacture and boat making . . . ,” which appears in the Major Sources of Occupational Exposure” section.
3. The NIC cites liver tumors in male mice (Lijinsky, 1986; Maltoni et al., 1979; Conti et al., 1988). The referenced studies, however, show no increase in liver tumors in either males or females at the high dose, nor in females at the low dose. Liver tumors in male mice without liver tumors in female mice is very unusual. This pattern – increased liver tumors only low-dose male mice – is not indicative of a chemically-induced response.
4. The NIC cites increased forestomach tumors in mice and rats (Lijinsky et al., 1986; Conti et al., 1988). Not mentioned in the NIC is a complete description of the histopathologic findings in the forestomach of the rats and mice. These mice and rats had severe ulceration and necrosis in the forestomach. Application of styrene oxide to the skin of mice did not produce skin tumors in studies from two laboratories (Weil et al., 1963; Van Duuren et al., 1963).

The document cites increased DNA adducts in forestomach of rats given 500 mg/kg styrene oxide by gavage (Lutz et al., 1993); the document did not include the authors’ conclusion that the level of DNA adducts was so low that styrene oxide did not induce forestomach tumors solely by a mutagenic mode of action. These authors found increased cell proliferation from exposure to 137, 275, and 550 mg/kg/day styrene oxide 3 times/week for 4 weeks without dose response. Dalbey et al. (1996) looked at lower doses and found dose-response paralleling dose response for tumors.

Taken together, oral administration of styrene oxide results in severe necrosis and ulceration in the forestomach of rodents, followed by tumors at the site of contact, but not at distant sites. There are no studies that evaluate tumor formation absent forestomach necrosis. Application to the skin of mice did not result tumors at the

site of contact or distant sites. There is no basis for concluding that styrene oxide induces tumors by a mechanism similar to ethylene oxide, propylene oxide or epichlorohydrin.

5. Based on the above-mentioned animal studies and “analogy to other epoxides,” the NIC proposes to set the TLV[®] at 0.2 ppm, which is slightly below the range of other epoxides. No basis is provided to conclude that styrene oxide is as potent as the other epoxides listed. Studies of styrene oxide produced none of the tumors cited as prevented by the proposed TLV (nasal tumors, brain tumors, leukemia), except forestomach tumors. At levels of potential human exposure, ulceration and necrosis is unlikely, as is tumor formation.

The NIC justifies the proposed TLV[®] on the need to protect from “non-neoplastic changes (e.g., hyperplasia of the nasal epithelium)” caused by other epoxides. However, there is no evidence that exposure to styrene oxide produces such changes. Gaté et al. (2012).

The only data presented comparing potency of epoxides indicates that styrene oxide is 20-fold less potent at producing single strand DNA breaks than propylene oxide. Sina et al. (1983)

Based on a comparison of epoxides, the TLV for styrene oxide should be 20-fold higher than propylene oxide, not slightly less.

In conclusion, styrene oxide is not a commercial material. The data indicate that styrene oxide induces site of contact tumors in the presence of severe necrosis and ulceration. The data indicate that styrene oxide is 20-fold less potent than propylene oxide. There is no justification for a TLV[®] of 0.2 ppm.

D. Citable Material

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Styrene-7,8-oxide. IARC Monograph on the Evaluation of Carcinogenic Risk to Man (Vol 60), pp 321–346. International Agency for Research on Cancer, Lyon, France, World Health Organization (1994).

Sina JF; Bean CI; Dysart GR; et al.: Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenesis/mutagenic potential. *Mutat Res* 113:357–391 (1983).

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Weil CS; Condra N; Haun C; et al.: Experimental carcinogenicity and acute toxicity of representative epoxides. *Am Ind Hyg Assoc J* 244:305–325 (1963).