March 31, 1987

EPICHLOROHYDRIN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

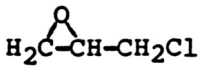
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Epichlorohydrin (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86--118023/AS. The toll-free number is (800) 336--4700; in the Washington, D.C. area: (703) 487--4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 106-89-8

Structural Formula



Synonyms

- 1-Chloro-2, 3-epoxypropane, 3-chloro1 -1, 2-epoxypropane, (chloromethyl) oxirane, 2-(chloromethyl) oxirane and chloropropylene oxide.

Uses

- Used in the manufacture of: epoxide resins, surface active agents, pharmaceuticals, and agricultural chemicals (Verschueren, 1983).

Properties (U.S. EPA, 1985a)

Molecular Formula	C_3H_5ClO
Molecular Weight	92.53
Physical State	Colorless liquid
Boiling Point	116.1ºC
Melting Point	-57.2ºC
Density	--
Vapor Pressure	12 mm at 20ºC
Specific Gravity	1.18 at 20ºC
Water Solubility	66 g/L at 20ºC
Log Octanol/Water Partition Coefficient	0.26
Taste Threshold	--
Odor Threshold	0.5 -- 1.0 mg/L; 3 mg/L (Amoore and Hautala, 1983)
Conversion Factor 1 ppm = 3.78 mg/m^3	1 $mg/_{m3}$ = 0.265 ppm
Irritation Threshold	0.1 mg/L

Occurrence

- Total epichlorohydrin production in 1982 was approximately 350 million pounds. Though epichlorohydrin reportedly hydrolyzes readily in aqueous solution (hydrolysis half-life of 8.2 days at 20ºC and pH 7) to water soluble alcohols, its use in water treatment resins and coatings make exposure possible (Mabey and Mill, 1978).

- No information has been located in either State or Federal surveys to indicate the presence or absence of epichlorohydrin in drinking water.

III. PHARMACOKINETICS

Absorption

- Epichlorohydrin is absorbed readily following either oral, inhalation or dermal exposures (U.S. EPA, 1985a).

- Gingell et al. (1985) assessed the pharmacokinetics and metabolism of epichlorohydrin in male Fischer 344 rats treated (6 mg/kg once by gavage) with [2-^{14}C] epichlorohydrin (98% pure) in water and sacrificed after 3 days. Ready absorption was shown by an initial elimination half-life of 2 hours and total excreta recovery of 91.61% of the radiolabel.

- Smith et al. (1979) have reported the extensive absorption of epichlorohydrin in water by male Fischer 344 rats (190 to 220 g) following a single gavage exposure. Based on excretion data, the extent of absorption, approximately 100% within 72 hours after administration, appeared to be similar following doses of either 1 or 100 mg/kg bw.

- Smith et al. (1979) indicated that epichlorohydrin was absorbed readily by male Fischer 344 rats (190 to 220 g) following a 6-hour exposure to atmospheres containing 1 or 100 ppm epichlorohydrin (approximately 3.78 or 378 mg/m^3). Uptake rates of 15.48 and 1394 ug/hr were calculated for exposures to 1 and 100 ppm, respectively. The investigators stated that these exposures correspond to doses of 0.37 and 33 mg/kg bw.

- The toxicity study of Kremneva and Tolgskaya (1961) indicates that epichlorohydrin also is absorbed following dermal exposure. When the tails of mice were immersed in epichlorohydrin either for a single exposure of 1 hour or for repeated exposures of 20 to 30 minutes/day on 2 to 3 successive days, toxic signs and death were observed within 3 days.

Distribution

- In the study by Gingell et al. (1985), 8--9% of ^{14}C was in tissues, with the highest levels (specific activity, dpm x 10-^{3}/g tissue wet weight) in liver (177.5; 2.82% of dose), kidney (127.1; 0.41% of dose), and forestomach (81.6; 0.03% of dose).

- Smith et al. (1979) compared the distribution of [1, 3-^{14}C]-epichlorohydrin in male Fischer 344 rats following oral (100 mg/kg bw) or inhalation (100 ppm for 6 hours) exposure. At 3 hours post-exposure in the oral study and at the termination of inhalation exposure, the plasma levels of radioactivity were 36.1 and 18.3 mg/g, respectively. Concentrations in tissues were expressed as ug equivalents of epichlorohydrin per g of tissue. After oral treatment, the greatest concentrations were in stomach, followed by intestine, kidney, liver, pancreas and lung. Following inhalation exposure, the highest levels were in nasal turbinates, followed by intestine, liver and kidney.

Metabolism

- Gingell et al. (1985) concluded that the initial elimination half-life of 2 hours indicated rapid metabolism in their study. Main urinary metabolites were N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine and α-chlorohydrin, representing 36 and 4% of the delivered dose, respectively. One major metabolite and 4 minor metabolites were identified in urine. These investigators stated that the presence of the two dominant urinary metabolites is consistent with initial metabolic reactions being conjugation of the epoxide with glutathione and hydration of the epoxide.

- Smith et al. (1979) administered [1, 3-^{14}C]-epichlorohydrin to male Fischer 344 rats as single oral doses of 1 or 100 mg/kg bw or as 6-hour inhalation exposures to 1 or 100 ppm (approximately 3.78 or 378 mg/m^3). Urinary metabolites were separated by ion-exclusion chromatography. Seven radioactive peaks were found in the urine following oral dosing and six radioactive peaks following inhalation exposure, but none corresponded to epichlorohydrin. the authors noted that the patterns of urinary metabolite excretion were similar following oral or inhalational dosing; metabolites were not identified.

- Epichlorohydrin has two electrophilic centers and may bind to cellular nucleophiles. It is also a substrate for epoxide hydratase resulting in the formation of α -chlorohydrin which may be oxidized to oxalic acid, converted to glycidol or phosphorylated to 3-chloroglycero-phosphate (U.S. EPA, 1985a). However, Gingell et al. (1985) did not find oxalic acid as a metabolite in their study.

- Rossi et al. (1983) found that epichlorohydrin rapidly disappeared from the blood of CD1 mice, with a half-life of approximately five minutes, with α -chlorohydrin appearing as epichlorohydrin levels dropped. α-Chlorohydrin, however, had a much longer half-life for disappearance (50--60 minutes).

Excretion

- In the study by Gingell et al. (1985), the half-life of initial elimination of ^{14}C in both urine and exhaled air was about 2 hours. Approximately 38% of the radioactive dose was exhaled as CO_2, 50% was excreted as urinary metabolites, and 39% was eliminated in feces.

- Smith et al. (1979) administered [1, 3-^{14}C]-epichlorohydrin by single gavage doses of 1 or 100 mg/kg to groups of four male Fischer 344 rats. In parallel experiments, four rats were exposed (head only) to atmospheres containing 100 ppm (378 mg/m^3) epichlorohydrin for six hours. An additional three rats were exposed to atmospheres containing 1 ppm (3.78 mg/m^3) for six hours. The rates or routes of excretion essentially were unaffected by either the route of exposure or the dose administered. Urine was the major route of excretion, accounting for 46% to 54% of the dose. An additional 25% to 42% was recovered as $^{14}CO_2$ in the expired air. Only 3% to 6% of the dose was recovered in the feces. Excretion was biphasic, with an initial rapid phase that dominated the first 24 hours post-exposure and a slower second phase that was dominant after 24 hours. The calculated half-lives for elimination from the plasma were 1 to 2 hours and 26 to 27 hours for the fast and slow phases, respectively.

IV. HEALTH EFFECTS

Humans

- In humans, acute effects have been reported following both dermal and inhalation exposures (U.S. EPA, 1985a). Dermal exposure produces predominantly local irritation effects, but inhalation produces significant systemic effects, including hepatic and renal toxicity. In one case report of a worker exposed to epichlorohydrin vapor, systemic effects were evident for at least 2 years after the exposure. (U.S. EPA, 1985a) Chronic exposure to epichlorohydrin has been associated with chromosome and chromatid breaks, decreased hemoglobin concentration, decreased erythrocyte counts and decreased leukocyte counts. Increases (not statistically significant) in the mortality due to lung cancer have been reported in workers sequentially exposed to isopropyl alcohol and epichlorohydrin (U.S. EPA, 1985a). No effects on reproductive function have been detected.

Animals

Short-term Exposure

- Epichlorohydrin is acutely toxic following oral, percutaneous, subcutaneous or respiratory exposure, producing similar symptoms in each case. At the site of application, epichlorohydrin is a strong irritant. The major acute systemic effects occur in the central nervous system, with death being due to depression of the respiratory center. The major internal organs affected are the lungs, liver and kidneys (U.S. EPA, 1985a).

- Oral doses as low as 10 mg/kg for 5 days/week for 2 weeks resulted in decreased ($p < 0.05$) erythrocyte counts in male rats and decreased ($p < 0.01$) kidney/body weight ratios in females (Van Esch, 1981). Similar exposures to 40 or 80 mg/kg resulted in degenerative changes in the kidneys of both male and female rats.

Long-term Exposure

- Epichlorohydrin given in drinking water at levels of 375, 750 and 1,500 ppm (18, 39 and 89 mg/kg/day) to male Wistar rats for 81 weeks induced forestomach hyperplasia and decreased body weights at all doses (Konishi et al., 1980).

- With gavage administration of epichlorohydrin in water at doses of 2 and 10 mg/kg, 5 days/week for 104 weeks, stomach hyperplasia and a dose-related decrease in white blood cells were observed in male and female Wistar rats (Van Esch, 1982).

- Inhalation exposure of Fischer 344 rats, Sprague-Dawley rats, B6C3F1 mice and New Zealand rabbits to epichlorohydrin at 19 mg/m^3 for 90 days was without observable effect. Higher exposure levels induced nasal irritation, eye irritation, kidney lesions and respiratory tract lesions (Quast et al., 1979; John et al., 1983).

- Lifetime inhalation exposure of male Sprague-Dawley rats to 38 and 114 mg/m^3 epichlorohydrin elicited kidney lesions (Laskin et al., 1980).

Reproductive Effects

- Male and female Wistar rats were given epichlorohydrin in water starting 10 days before mating and continuing for three months (Van Esch, 1981). A dose of 2 mg/kg was ineffective. A 10 mg/kg dose reduced fertility and crossmating with untreated rats attributed the antifertility effect to males. Sterility of male rats given epichlorohydrin orally also was observed by Hahn (1970) and Cooper et al. (1974) with gavage doses of 15 mg/kg and higher for 15 and 5 days, respectively; however, these investigators showed the effect to be reversible.

- Exposure of male rats to epichlorohydrin by inhalation at levels above 19 mg/m^3 for 10 weeks resulted in reversible sterility, and the fertility of male rabbits was unaffected by inhalation exposure levels of epichlorohydrin as high as 189 mg/m^3 (John et al., 1983).

Developmental Effects

- Epichlorohydrin was not teratogenic when given by gavage in cottonseed oil to pregnant CD rats and CD-1 mice on days 6 through 15 of gestation (Marks et al., 1982). Doses above 40 mg/kg were maternally toxic (reduced body weight, increased liver weight, death) in rats. Doses above 80 mg/kg were maternally toxic (increased liver weight, death) and fetotoxic (reduced body weight) to mice.

- Inhalation exposures of pregnant Sprague-Dawley rats and New Zealand rabbits to 9.5 and 95 mg/m^3 of epichlorohydrin during gestation days 6 through 15 (rats) and 6 through 18 (rabbits) were neither teratogenic nor fetotoxic. Pregnant rats exposed to 95 mg/m^3 weighed less than controls (Pilny et al., 1979).

Mutagenicity

- Epichlorohydrin is a mutagen in several systems (U.S. EPA, 1985a). It is a potent inducer of base-pair substitution-type mutations in prokaryotic systems. Incubation with mammalian liver homogenates results in a marked reduction in mutation frequency. Epichlorohydrin also induces gene mutations and very likely chromosomal aberrations in mouse lymphoma cell cultures (Moore-Brown and Clive, 1979) and clastogenesis in human lymphocytes in vitro (Norppa et al., 1981) but not in rat liver cell cultures (Dean and Hodson-Walker, 1979). Epichlorohydrin was found to induce sister chromatid exchange in cultured human lymphocytes (Norppa et al., 1981; Carbone et al., 1981; White, 1980). Examination of occupationally exposed workers indicates that chromosomal aberrations also occur in vivo (Picciano, 1979a,b; Kucerova et al., 1977; Sram et al., 1976).

- In in vivo studies, epichlorohydrin treatment results in an increased incidence of sex-linked recessive lethals in Drosophila when administered by injection, but not when incorporated in the

food (Knapp et al., 1982; Wurgler and Graf, 1981). In other in vivo studies, epichlorohydrin has produced negative results in the mouse dominant lethal assay (Epstein et al., 1972; Sram et al., 1976) and the mouse micronucleus assay (Kirkhart, 1981; Tsuchimoto and Matter, 1981). Clastogenic effects of epichlorohydrin in bone marrow cells in vivo were found in mice (Sram et al., 1976) but not in rats (Dabney et al., 1979).

Carcinogenicity

- Epichlorohydrin is carcinogenic at the site of administration.

- Administration of 375, 750 and 1,500 ppm epichlorohydrin in drinking water [equivalent to 18, 39 and 89 mg/kg/day based on data by the authors (total doses of 5.0, 8.9 and 15.1 g/rat during 81 weeks of treatment divided by body weight)] to male Wistar rats for 81 weeks resulted in forestomach hyperplasia at all doses and papillomas and carcinomas of the forestomach at the two highest doses (Konishi et al., 1981).

- Lifetime gavage treatment of male and female Wistar rats with aqueous epichlorohydrin solution at doses of 2 and 10 mg/kg induced papillomas and carcinomas of the forestomach (Wester et al., 1985; Van Esch, 1982).

- Laskin et al. (1980) found nasal carcinomas in male Sprague-Dawley rats exposed to 378 mg/m^3 of epichlorohydrin by inhalation 6 hours/day, 5 days/week for six weeks followed by lifetime observation.

- Subcutaneous injection of epichlorohydrin in ICR/Ha Swiss mice induced local sarcomas; epichlorohydrin was effective as an initiator but not as a complete carcinogen on the skin of ICR/Ha Swiss mice (Van Duuren et al., 1972; 1974).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{\text{(NOAEL or LOAEL)x (BW)}}{\text{(UF) x (\_\_\_L/day)}} = \text{\_\_\_mg/L (\_\_\_ug/L)}$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

Organoleptic Properties

A reported threshold for odor perception of epichlorohydrin is 0.5 to 1.0 mg/L, and 0.1 mg/L was cited as the threshold for its irritant action by the NAS (1980). Amoore and Hautala (1983) reported an odor threshold of 3 mg/L.

One-day Health Advisory

Because appropriate data for calculation of a One-day HA are not available, the Ten-day HA (0.14 mg/L) is recommended for use as the One-day HA.

Ten-day Health Advisory

The reproductive toxicity study by Van Esch (1981) can be used to derive the Ten-day HA. In this study, male and female rats were given epichlorohydrin by gavage 5 days/week at doses of 0, 2 or 10 mg/kg. Exposure was started 10 days prior to mating and continued until the F_{1b} generation was produced. The fertility index at the first mating was reduced in the high-dose group but not in the low-dose group. The study of Hahn (1970) which reported infertility in male rats exposed by gavage to epichlorohydrin at 15 mg/kg/day for 12 days supports an assumption that at least a portion of the reduced fertility index observed by Van Esch (1981) was the result of infertility in the males associated with the ten-day exposure prior to mating. In this study, 2 mg/kg was a NOAEL for reproductive effects and is appropriate for use in deriving the Ten-day HA.

Using the NOAEL of 2 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{2 \text{ mg/kg/day}) (10 \text{ kg}) (5)}{(100) (1 \text{ L/day}) (7)} = 0.14 \text{ mg/L (140 ug/L)}$$

where:

2 mg/kg/day = NOAEL based on absence of reproductive toxicity in rats.

10 kg = assumed body weight of a child.

5/7 = conversion of dose to represent continuous exposure (7 days per week).

1 L/day = assumed daily water consumption of a child.

Although the antifertility effect in male rats in the Van Esch (1981) study relates to men as a specific sensitive subpopulation for this effect, this study is preferred for the calculation of a Ten-day HA for the general population because of its design with oral short-term exposure and its demonstration of no-effect and effect levels. Additionally, the 2 mg/kg NOEL in the Van Esch (1981) study appears consistent with the dose responses in the overall Van Esch (1981) work where both systemic and reproductive effects were found with 10-day oral exposures to 10 mg/kg of epichlorohydrin.

Longer-term Health Advisory

There are insufficient data for calculation of a Longer-term HA. The DWEL (0.07 mg/L), is recommended as a conservative estimate of the Longer-term HA.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL

is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Of the reviewed studies in which the effects of long-term exposure to epichlorohydrin were investigated (Laskin et al., 1980; Konishi et al., 1980, also reported by Kawabata, 1981; Wester et al., 1985, also reported by Van Esch, 1982), the Laskin et al. (1980) study was selected as the most appropriate from which to derive the DWEL. Forestomach hyperplasia in all three treatment groups and papillomas and carcinomas of the forestomach in the two highest dose groups were found in the study by Konishi et al. (1980). Since the hyperplasia could be considered a pre-neoplastic effect and the progression of forestomach lesions beyond the 81-week duration of this study is uncertain, it would be questionable to use this effect in the low-dose group (18 mg/kg/day) for calculating a DWEL for drinking water exposure. Dose-response for toxicity/carcinogenicity in the Konishi et al. (1980) drinking water study is given preference over that in the bolus gavage dosing study by Wester, et al. (1985), and use of the estimated 2.16 mg/kg/day dose in the Laskin, et al. (1980) study is concluded to be consistent with the dose-response indicated by the Konishi et al. (1980) study. The LOAEL based on renal damage of 2.16 mg/kg/day estimated from the data in the Laskin et al. (1980) study was, therefore, used to derive a DWEL. Additionally, carcinogenic effects were not apparent at the LOAEL in the Laskin et al. (1980) study. Using this LOAEL, the DWEL is derived as follows:

Step 1: Conversion of Inhalation Exposure to Oral Exposure

Applying the 38 mg/m^3 inhalation LOAEL in the Laskin et al. (1980) study and the assumptions in U.S. EPA (1985a) for converting inhalation exposure to oral exposure for the rat, the estimated oral dose would be:

$$\frac{(38\ mg/m^3)\ (0.0093\ m^3/hr)\ (6\ hr/day)\ (5)\ (0.5)}{(0.35\ kg)\ (7)} = 2.16\ mg/kg/day$$

where:

38 mg/m^3 = LOAEL based on kidney toxicity in rats.

0.0093 m^3 = amount of air breathed by a rat/hour.

6 hr/day = a 6-hour exposure each day.

5/7 = adjust from a 5 days/week exposure to 7 days/week.

0.5 = the assumed inhalation absorption factor.

0.35 kg = the assumed weight of a rat.

Step 2: Determination of the Reference Dose (RfD)

$$RfD = \frac{(2.16\ mg/kg/day)}{(1{,}000)} = 0.002\ mg/kg/day\ (2\ ug/kg/day)$$

where:

2.16 mg/kg/day = LOAEL based on kidney toxicity in rats.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 3: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.002 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0{,}07 \text{ mg/L } (70 \text{ ug/L})$$

0.002 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Epichlorohydrin may be classified in Group B: Probable human carcinogen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing epichlorohydrin at 70 ug/L is approximately 2×10^{-5}. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), epichlorohydrin may be classified in Group B2: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

- The study of Konishi et al. (1980) provides appropriate data for a quantitative risk assessment based on the relevant route of exposure and the observed dose-response pattern. Using the calculated $q1^*$ of 9.9×10^{-3} $(\text{mg/kg/day})^{-1}$, the 95% upper-limit lifetime dose associated with a 10^{-5} risk level may be calculated to equal 70.7 ug/day. Assuming an average water consumption of 2 L/day, this risk level corresponds to a water concentration of 35.4 ug/L. Corresponding levels for 10^{-6} and 10^{-4} are 3.54 and 354 ug/L, respectively.

- Maximum likelihood estimates as well as 95% upper limits of cancer risks by the multistage model have been calculated (U.S. EPA, 1984). For example, at 10 ug/L cancer risk estimates are 1.4×10^{-17} (MLE) and 2.8×10^{-6} (UL) and at 100 ug/L cancer risk estimates are 2.6×10^{-14} (MLE) and 2.8×10^{-5} (UL).

- The EPA's Carcinogen Assessment Group has estimated cancer risks with other models besides the multistage (U.S. EPA, 1984). As an example, 10 ug/L lifetime exposure was associated with additional risks (95% upper confidence limit) of 2.8×10^{-5} by the multistage, 3.4×10^{-5} by the one-hit, 0 by the Weibull, and 0 by the log-probit. While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the EPA has recommended use of the linearized multistage approach.

- Epichlorohydrin is classified as a 2B carcinogen by IARC (1982) with sufficient animal evidence and inadequate human evidence.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The NAS (1980) SNARLs (Suggested-No-Adverse-Response-Levels) for 1- or 7-day exposures to epichlorohydrin are 0.84 and 0.53 mg/L, respectively. An ADI (Acceptable Daily Intake) or a cancer risk was not calculated by the NAS (1980).

- The ACGIH has recommended a TLV (Threshold Limit Value) of 2 ppm (10 mg/m^3) (ACGIH, 1982). Current OSHA standards allow a TWA occupational exposure of 19 mg/m^3 (29 CFR 1910.1000); however, they are currently considering lowering this value to 0.5 ppm (2 mg/m^3) with a ceiling value of 15 ppm (60 mg/m^3) for 15 minutes. Occupational standards in other countries range from 0.26 ppm in Russia and Czechoslovakia to 3.6 ppm in the Federal Republic of Germany (Sram, et al., 1980).

- Epichlorohydrin has not been regulated under the Safe Drinking Water Act; however, discharge of >1,000 pounds (454 kg) into navigable waters is prohibited under the Clean Water Act (40 CFR 116).

- Epichlorohydrin is also classified as a "hazardous waste" by the U.S. EPA and quantities exceeding 100 kg must be disposed of in a special landfill (40 CFR 261; 40 CFR 122).

- The proposed RMCL by the U.S. EPA Office of Drinking Water is zero (U.S. EPA, 1985b).

VII. ANALYTICAL METHODS

- There is no standardized method for the determination of epichlorohydrin in drinking water samples. However, epichlorohydrin may be determined by a purge-and-trap gas chromatographic/mass spectrometric procedure used for the determination of volatile organic compounds in water (U.S. EPA, 1985c). This method calls for the bubbling of an inert gas through the sample and trapping epichlorohydrin on an adsorbent material. The adsorbant material is heated to drive off epichlorohydrin onto a gas chromatographic column. The gas chromatograph is temperature programmed to separate the method analytes which are then detected by the mass spectrometer.

VIII. TREATMENT TECHNOLOGIES

- No data are available on the removal of epichlorohydrin from potable water by any treatment technique (ESE, 1984; U.S. EPA, 1985d).

- The amenability of epichlorohydrin to removal by conventional treatment or by adsorption is not known. The Henry's Law Constant for epichlorohydrin has been estimated to be 2.44×10^{-5} atm x m^3/mole (ESE, 1984). This value suggests that aeration is unlikely to be a successful removal technique for epichlorohydrin. It also has been concluded that epichlorohydrin would not be removed from water by ozone oxidation (U.S. EPA, 1985d).

IX. REFERENCES

ACGIH, 1982. American Conference of Governmental Industrial Hygienists. Threshold limit values for chemical substances and physical agents in the workroom environment. Cincinnati, Ohio.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor threshold compounds with threshold unit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3:272-290.

Carbone, P., G. Barbata, G. Margiotta, A. Tomasino and G. Granata. 1981. Low epichlorohydrin concentrations induce sister chromatid exchanges in human lymphocytes in vitro. Caryologia. 34(3):261--266.

40 CFR 116. Code of Federal Regulations.

40 CFR 122. Code of Federal Regulations.

40 CFR 261. Code of Federal Regulations.

Cooper, E.R., A.R. Jones and H. Jackson. 1974. Effects of alpha-chlorohydrin and related compounds on the reproductive organs and fertility of the male rat. J. Reprod. Fert. 39(2):379--386.

Dabney, B.J., R.V. Johnston, J.F. Quast and C.N. Park. 1979. Epichlorohydrin --Subchronic studies. III. Cytogenetic evaluation of bone marrow cells from rats exposed by inhalation to epichlorohydrin for four weeks. ICPEM (International Commission for Protection Against Environmental Mutagens and Carcinogens) Document No. 128. 15 pp.

Dean, B.J., and G. Hodson-Walker. 1979. An in vitro chromosome assay using cultured rat-liver cells. Mutat. Res. 64:329--337.

ESE. 1984. Environmental Science and Engineering. Review of treatability data for removal of twenty-five synthetic organic chemicals from drinking water. U.S. EPA. Office of Drinking Water.

Epstein, S.S., E. Arnold, J. Andrea, W. Bass and Y. Bishop. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23:288--325.

Gingell, R., H.R. Mitschke, I. Dzidic, P.W. Beatty, V.L. Sarvin and A.C. Page. 1985. Disposition and metabolism of [2-^{14c}] epichlorohydrin after oral administration to rats. Drug Metab. Dispos. 13:333--341.

Hahn, J.D. 1970. Post-testicular antifertility effects of epichlorohydrin and 2,3-epoxypropanol. Nature (London). 226:87.

IARC 1982. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic ricc of chemicals to humans. Chemical Industrial Processes and Industries Associated with Cancer in Humans. Suppl. 4, pp. 122--123.

John, J.A., J.F. Quast, F.J. Murray, L.S. Calhoun and R.E. Staples. 1983. Inhalation toxicity of epichlorohydrin: Effects on fertility in rats and rabbits. Toxicol. Appl. Pharmacol. 68:415--423.

Kawabata, A. 1981. Studies on the carcinogenic activity of epichlorohydrin by oral administration in male Wistar rats. J. Nara Med. Assoc. 32:270-280.

Kirkhart, B. 1981. Micronucleus test on 21 compounds. In: Evaluation of Short-Term Tests for Carcinogens, F.J. deSerres and J. Ashby, eds. Elsevier/North Holland, Amsterdam. pp. 698--704.

Knapp, A.G.A.C., C.E. Voodg and P.G.N. Kramers. 1982. Comparison of the mutagenic potency of 2-chloroethanol, 2-bromoethanol, 1,2-epoxybutane epichlorohydrin and glycidaldehyde in Klebsiella pneumoniae, Drosophilla melanogaster and L5178Y mouse lymphoma cells. Mutat. Res. 101:199--208.

Konishi, T., A. Kawabata, A. Denda et al. 1980. Forestomach tumors induced by orally administered epichlorohydrin in male Wistar rats. Gann. 71:922--923.

Kremneva, S.N., and M.S. Tolgskaya. 1961. Toxicology of epichlorohydrin. Toksikol. Nov. Prom. Khim. Veschestv. 2:28--41.

Kucerova, M., V.S. Zhurkov, Z. Polwkova and J.E. Ivanova. 1977. Mutagenic effect of epichlorohydrin. II. Analysis of chromosomal aberrations in lymphocytes of persons occupationally exposed to epichlorohydrin. Mutat. Res. 48:355--360.

Laskin, S., A.R. Sellakumar, M. Kuschner et al. 1980. Inhalation carcinogenicity of epichlorohydrin in non-inbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65(4):751--758.

Mabey, W., and T. Mill. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J. Phys. Chem. Ref. Data. 7:385--415.

Marks, T.A., F.S. Gerling and R.E. Staples. 1982. Teratogenic evaluation of epichlorohydrin in the mouse and rat and glycidol in the mouse. J. Toxicol. Environ. Health. 9:87--96.

Moore-Brown, M.M., and D. Clive. 1979. The L5178Y/$TK^{+/-}$ mutagen assay system: In situ results. Banbury Report. 2:71--88.

NAS. 1980. National Academy of Sciences. Drinking Water and Health. Volume 3. National Academy Press. Washington, D.C. pp. 111--124.

Norppa, H., K. Hemminki, M. Sorsa and H. Vainio. 1981. Effect of monosubstituted epoxides on chromosome aberrations and SCE in cultured human lymphocytes. Mutat. Res. 91:423--250.

Picciano, D. 1979a. Cytogenic investigation of occupational exposure to epichlorohydrin. Mutat. Res. 66:169--173.

Picciano, D. 1979b. Faulty experimental design and underutilization of cytogenetic data. Benzene and epichlorohydrin. Ann. NY Acad. Sci. 329:321--327.

Pilny, M.K., T.S. Lederer, J.S. Murray, et al. 1979. Epichlorohydrin subchronic studies. IV. The effects of maternally inhaled epichlorohydrin on rat and rabbit embryonal and fetal development. Unpublished report. Toxicol. Res. Lab., Health Environ. Sci., DOW Chemical U.S.A., Midland, MI.

Quast, J.F., J.W. Henck, B.J. Pastma, D.J. Scheutz and M.J. McKenna. 1979. Epichlorohydrin subchronic studies. I. A 90-day inhalation study in laboratory rodents (Fischer 344 rats, Sprague-Dawley rats, and $B6C3F_1$ mice). Dow Chemical U.S.A., Midland, MI. 166 pp.

Rossi, A.M., D. Migliore, D. Lascialfari, I. Sbrana and N. Loprieno. 1983. Genotoxicity, metabolism, and blood kinetics of epichlorohydrin in mice. Mutat. Res. 118:213--226.

Smith, F.A., P.W. Langvardt and J.D. Young. 1979. Pharmacokinetics of epichlorohydrin (EPI) administered to rats by gavage or inhalation. Dow Chemical U.S.A., Toxicology Research Laboratory, Midland, MI. 52 pp.

Sram, R.J., M. Cerna and M. Kucerova. 1976. The genetic risk of epichlorohydrin as related to the occupational exposure. Biol. Zbl. 95:451--462.

Sram, R.J., Z. Zudova and N.P. Kuleshov. 1980. Cytogenic analysis of peripheral lymphocytes in workers occupationally exposed to epichlorohydrin. Mut. Res. 70:115--120.

Tsuchimoto, T., and B.E. Matter. 1981. Activity of coded compounds in the micronucleus test. In: Evaluation of Short-Term Tests for Carcinogens, F.J. Seeres and J. Ashby, eds. Elsevier/North Holland, Amsterdam. pp. 705--711.

U.S. EPA. 1984. U.S. Environmental Protection Agency. Health assessment document for epichlorohydrin. Final report. Office of Health and Environmental Assessment. Washington, D.C. EPA-600/8-83-032F.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Drinking water criteria document for epichlorohydrin. Final Draft. Office of Drinking Water. Washington, D.C. ECAD-CFN-413.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. National primary drinking water regulations; Synthetic organic chemicals, inorganic chemicals and microorganisms; Proposed rule. Federal Register. 50(219):4693--47002. November 13.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. Technologies and costs for removal of organic chemicals from potable water supplies. Draft. Science and Technology Branch, CSD, ODW, Washington, D.C.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Federal Register 51(185):33992--34003. September 24.

Van Duuren, B.L., C. Katz and B.M. Goldschmidt. 1972. Direct-acting alkylating carcinogenc--Chloro ethers and related compounds. Toxicol. Appl. Pharmacol. 22:279--280.

Van Duuren, B.L., B.M. Goldschmidt, C. Katz, I. Seidman and J.S. Paul. 1974. Carcinogenic activity of alkylating agents. J. Natl. Cancer Inst. 53:695--700.

Van Esch, G.J. 1981. Induction of preneoplastic lesions in the forestomach of rats after oral administration of 1-chloro-2,3-epoxypropane. I. Range finding studies. Prepared by Ryksinstitute Voor De Volksgezondheld Bilthoven Rapport nr. 627805 005.

Van Esch, G.J. 1982. Induction of preneoplastic lesions in the forestomach of rats after oral administration of 1-chloro-2,3-epoxypropane. II. Carcinogenicity study. Prepared by Ryksinstitute Voor De Volksgezondheld Bilthoven Rapport nr. 627805 005.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals. 2nd ed. Van Nostrand Reinhold Co., NY. pp. 611--613.

Wester, P.W., C.A. Van Der Heiden, A. Bisschop, and G.J. Van Esch. 1985. Carcinogenicity study with epichlorohydrin (CEP) by gavage in rats. Toxicol. 36:325--329.

White, A.D. 1980. In vitro induction of sister chromatid exchange in human lymphocytes by epichlorohydrin with and without metabolic activation. Mutat. Res. 78:171--176.

Wurgler, F.E., and U. Graf. 1981. Mutagenic activity of ten coded compounds in the Drosophila sex-linked recessive lethal assay. In: Evaluation of Short-Term Tests for Carcinogens, F.J. de Serres, ed. Elsevier/North Holland, Amsterdam, pp. 666--672.