

Epichlorohydrin; CASRN 106-89-8

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Epichlorohydrin

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	withdrawn	04/01/1992
Inhalation RfC (I.B.)	yes	04/01/1992
Carcinogenicity Assessment (II.)	yes	03/01/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Epichlorohydrin
CASRN — 106-89-8

The Oral RfD for this substance has been withdrawn pending further review by the RfD/RfC Work Group.

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Epichlorohydrin conducted in September 2002 identified one or more significant new studies. IRIS users may

request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

EPA Contacts:

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Epichlorohydrin

CASRN — 106-89-8

Last Revised — 04/01/1992

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarspiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Changes in the nasal turbinates	NOAEL: 19 mg/cu.m (5 ppm)	300	1	1E-3 mg/cu.m
	NOAEL(ADJ): 3.4 mg/cu.m			
	NOAEL(HEC): 0.36 mg/cu.m			
Rat and Mouse				

Critical Effect	Exposures*	UF	MF	RfC
90-Day Inhalation Study Quast et al., 1979a	LOAEL: 95 mg/cu.m (25 ppm) LOAEL(ADJ): 17 mg/cu.m LOAEL(HEC): 1.82 mg/cu.m			

*Conversion Factors: MW = 92.53. Assuming 25 degrees C and 760 mmHg, NOAEL (mg/cu.m) = 5 ppm x 92.53/24.45 = 19 mg/cu.m. NOAEL(ADJ) = NOAEL (mg/cu.m) x 6 hours/24 hours x 5 days/7 days = 3.4 mg/cu.m. The NOAEL(HEC) was calculated for a gas:respiratory effect in the extrathoracic region. MVa (subchronic, female F344 rat) = 0.14 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq.cm, Sh(ET) = 177 sq.cm. RGDR = (MVa/Sa)/(MVh/Sh) = 0.107. NOAEL(HEC) = 3.4 x RGDR = 0.36 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Quast, J.F., J.W. Henck, B.J. Postma, D.J. Schuetz and M.J. McKenna. 1979a. Epichlorohydrin - subchronic studies I. A 90-Day Inhalation Study in Laboratory Rodents. 8D Submission. Microfiche No. 206200.

In a 3-month study, groups of B6C3F1 mice, Fischer 344 rats, and Sprague- Dawley rats (10/sex/concentration/strain) were exposed to 0, 5, 25, or 50 ppm (0, 19, 95, or 189 mg/cu.m) epichlorohydrin (99.8% purity), 6 hours/day, 5 days/week (duration-adjusted to 3.4, 17, and 34 mg/cu.m, respectively), for 61-62 exposures. Epichlorohydrin vapor was generated by metering the liquid into a warmed vaporization flask then passed through the chamber airflow with compressed air. The dynamic airflow conditions were maintained at 70-75 degrees F and relative humidity at 40-60%. Animals were observed for clinical signs of toxicity and measured biweekly for body weight changes. Clinical chemistry, hematology, and urinalysis were conducted; organ weights were obtained; and gross and histological examination of all tissues, including lungs, nasal turbinates (3-4 sections), liver, kidney, and male reproductive organs was conducted. Animals were sacrificed at 1 month and 3 months (10/concentration) and all parameters were evaluated except that histological observations were made on only five animals per concentration in the control and 50-ppm animals at the interim sacrifice. At the 3-month terminal sacrifice, animals in all groups were evaluated for histopathological effects of the respiratory system, liver, and kidney; other tissues were examined only in the control and 50-ppm groups.

In rats, epichlorohydrin-related effects in the respiratory epithelium of the nasal turbinates (i.e., inflammation, focal erosions, hyperplasia, and metaplasia), were reported in 25- and 50-ppm

F344 rats (males, 9/10, 10/10; females, 8/10, 10/10, respectively) and Sprague-Dawley rats (males, 9/10, 10/10; females, 10/10, 10/10, respectively). This effect was observed in all exposed rats in the 50-ppm group examined at the 1-month interim sacrifice and in none of the controls at 1 or 3 months or in the 5-ppm group at 3 months. Focal effects in the olfactory epithelium and suppurative inflammatory exudate were also observed in male and female rats of both strains after exposure to 50 ppm. Inflammation of the pulmonary region described as mononuclear cell infiltrates or focal pneumonitis was observed in most of the control and exposed rats of both strains, making conclusions about possible effects in the pulmonary region impossible. Inflammation of the nasal turbinates (described as focal subepithelial mononuclear cell infiltrate) was observed in most rats of both strains in the control and 5 ppm groups but not in the 25- and 50-ppm groups. This lesion indicates an underlying inflammatory reaction in these tissues which is not exposure-related. However, the location of this lesion makes it distinct from the epithelial effects observed in the rats exposed to higher concentrations. At the 1- and 3-month sacrifices, the 50-ppm groups in both rat strains (except for the Sprague-Dawley males killed at 3 months) exhibited significant increases ($p < 0.05$) in the relative kidney weight compared with controls. Slight increased kidney effects (e.g., dilated tubules, swollen appearance) were also exhibited in female rats exposed to 50 ppm. No other treatment-related effects were observed. The NOAEL of 5 ppm epichlorohydrin was determined for nasal turbinate injury [rat NOAEL(HEC) values range from 0.36 for female F344 to 0.70 for male Sprague-Dawley (SD), due to differences in ventilation volume; RGDR = 0.107 - 0.206 based on respiratory effects in the extrathoracic region]. A NOAEL for kidney effects is identified at 25 ppm [NOAEL(HEC) = 17 mg/cu.m]. The respiratory effects in rats are used for derivation of the RfC because of the greater severity of the lesion in rats, the involvement of respiratory and olfactory epithelium, and the lower calculated NOAEL(HEC).

Results in mice after 3 months showed focal erosion, hyperplasia, and metaplasia in the respiratory epithelium of the nasal turbinates in 0/10, 0/9, 8/8, and 10/10 males and in 0/9, 0/9, 10/10, and 9/9 females of the 0, 5-, 25-, and 50-ppm groups, respectively. This finding was also reported in 4/5 males and 5/5 females in the 50-ppm group compared with 0/10 in the controls at the 30-day sacrifice. Suppurative inflammatory exudate or mucus in the lumen of the nasal turbinates were reported in 7 males and 7 females in the high- concentration group. Focal effects in the olfactory epithelium were reported in only one female in the 50-ppm group. There were no other clearly exposure- related effects observed. However, 2, 1, 0, and 0 males and 9, 9, 0, and 0 females in the control, 5-, 25-, and 50-ppm groups, respectively, exhibited focal subepithelial mononuclear cell infiltrate in the nasal turbinates. This lesion indicates an underlying inflammatory reaction in these tissues that is not exposure-related. However, the location of this lesion makes it distinct from the epithelial effects in the groups exposed to higher concentrations. Inflammatory reactions in the tracheobronchiolar and pulmonary region, which may have been treatment related, were observed in a few animals in the high- concentration groups. All other microscopic findings were interpreted to be spontaneous. There was no indication that the

investigators tested for viral infection. A NOAEL of 5 ppm was established for changes in the nasal turbinates of mice (HEC = 0.41 mg/cu.m, based on respiratory tract effects in the extrathoracic region in females). The HEC for nasal effects is essentially identical in rats and mice. The lesser severity of the lesion in mice may be due to their ability to reduce their ventilation in response to an irritant to a greater extent than rats (see discussion of Kane et al., 1979). Mice have previously shown an ability to decrease their minute volume by up to 75% as compared with a maximal 45% reduction in rats when exposed to formaldehyde (Barrow et al., 1983; Chang et al., 1983). This study supports the finding of nasal effects at 25 and 50 ppm in rats.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 300 reflects a factor of 10 to account for sensitive human subpopulations and 3 to account for interspecies extrapolation. An additional factor of 10 was applied to account for extrapolation from a subchronic study and for data deficiencies, including the lack of a 2-generation reproduction study.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Quast et al. (1979b) conducted a short-term study in Fischer 344 rats, Sprague-Dawley rats, and B6C3F1 mice (5/species/sex/ concentration). There were nine exposures of 0 or 100 ppm (378 mg/cu.m) to epichlorohydrin 7 hours/day, 5 days/week for 12 days. Significant decreased body weight gain, thymic atrophy, increased relative kidney weights (rats only), and leukocytosis were reported in the 100-ppm exposed animals for both rat strains. Degeneration, discoloration, inflammation, and hyperplasia of the nasal turbinates were consistently observed to some degree in all exposed animals. These effects were located in the respiratory epithelium of mice and in the respiratory and olfactory epithelium of rats. Changes in the kidney (e.g., discoloration, tubular nephrosis, dilated tubules, edema), were also evident in most of the exposed rats, but were not found in the mice. Like the Quast et al. (1979a) study, mononuclear cell infiltrate was evident in the nasal turbinates of the control groups of rats and mice. Mononuclear cell infiltrate in the tracheobronchial and pulmonary region was observed in most rats (control and exposed) and in slightly more exposed mice than controls.

Union Carbide (1983) studied groups of 23-32 Wistar rats (sex unspecified) exposed to 68 or 136 ppm epichlorohydrin (266 or 515 mg/cu.m), 7 hours/day, 5 days/week (duration-adjusted to 55 and 107 mg/cu.m), for 45 exposures. Similar groups of rats were exposed to 0, 5, 8, 17, 21 or 43 ppm epichlorohydrin (19, 30, 64, 80, or 163 mg/cu.m) for 90 or 91 exposures (duration-adjusted to 4, 6.3, 13, 17, and 34 mg/cu.m). Groups of two hybrid Basanji-Cocker dogs and two Rhesus

macaque monkeys (sex unspecified) were also exposed to epichlorohydrin at 0 or 21 ppm (80 mg/cu.m) for 90 exposures (duration-adjusted to 17 mg/cu.m). Body weights were measured weekly and clinical chemistry was conducted six times during the study. Animals were sacrificed after the last exposure. The kidneys and liver were weighed and the tissues examined for histopathological changes. Exposure-related deaths occurred in rats exposed at 68 ppm or greater. These animals exhibited lung irritation, kidney injury, and weight gain depression. In the rat, a NOAEL of 43 ppm (HEC = 34 mg/cu.m) was determined for these extrarespiratory effects. In the 21-ppm exposed monkeys and dogs, lung effects (e.g., hemosiderin deposits, bronchial irritation, and focal proliferation of alveolar septa), and kidney damage (e.g., focal cloudy swelling of the proximal convoluted tubules) were described in the study. However, no incidence data or statistical significance was provided for these findings. The study was also limited because the nasal turbinates were not examined and too few dogs and monkeys were tested.

In a chronic bioassay, groups of 100 male Sprague-Dawley rats were exposed to 10 or 30 ppm epichlorohydrin (38 and 114 mg/cu.m, respectively) 6 hours/day, 5 days/week (duration-adjusted to 7 and 20 mg/cu.m) for their lifetime (136 weeks) (Laskin et al., 1980). The control animals were sham exposed or untreated. Beginning at 40 weeks of exposure, significantly decreased body weight was observed in the high-concentration rats. The incidences of kidney lesions (e.g., tubular degenerative changes, tubular dilation) at the end of the exposure were 14-24, 37, and 65% in animals exposed to 0, 10, and 30 ppm, respectively. The authors reported that, qualitatively, the lesions in exposed animals were similar to those observed in the controls. The severity of the lesion was stated to be greater in the 30-ppm group than in the controls or 10-ppm group. Kidney damage was also observed in rats exposed to 100 ppm 6 hours/day for 30 days. No other nonneoplastic effects were evident. Severe nasal inflammatory changes (not further specified) were exhibited in 90% of the control animals and inflammation of the tracheobronchial and pulmonary regions of the respiratory tract were also reported, making conclusions about the respiratory effects difficult. Details about incidence and severity of lesions were not provided. Because chronic inflammation in the bronchial tree and upper respiratory region were reported in the controls and exposed animals, exposure-related effects on the respiratory tract could not be assessed. Because of the lack of detail in the reporting of the kidney lesion and the high control incidence, the 30-ppm group is considered a LOAEL. The NOAEL for kidney effects is 10 ppm [NOAEL(HEC) = 38 mg/cu.m].

Gage (1959) exposed groups of 8 Wistar rats to 9, 17, 27, 56, or 120 ppm epichlorohydrin (34, 64, 102, 212, or 454 mg/cu.m) 6 hours/day, 5 days/week for a total of 11-19 exposures. No controls are reported. No effects were noted at 9 and 17 ppm. Exposure to 27 ppm resulted in respiratory irritation, but criteria for this judgment were not discussed. Lethargy, weight loss, respiratory distress and nasal discharge were observed at 56 ppm, but no histological effects were noted in the lungs. Exposure to 120 ppm resulted in congestion and edema in the lungs, liver congestion and necrosis, and tubular atrophy in the kidneys. Urinary protein excretion was

significantly increased. Although inadequately reported, this study suggests that high concentration of epichlorohydrin causes peripheral lung effects and extrarespiratory effects.

Acute exposures (6 hours) to 283-445 ppm epichlorohydrin resulted in severe pulmonary edema, hemorrhage, and increased lung-to-body weight ratio (Laskin et al., 1980).

Kane et al. (1979) exposed male Swiss-Webster mice to a range of epichlorohydrin concentrations for 15 minutes and measured the decrease in respiratory frequency. The data were plotted as percent decrease in respiratory rate versus the logarithm of the exposure concentration, to determine the RD50, the concentration predicted to cause a 50% decline in respiratory frequency. The RD50 for epichlorohydrin in this model was 687 ppm. These authors suggested that a minimal irritation level for humans is 0.01 times the RD50-6.87 ppm. In a study designed to evaluate the respiratory lesions resulting from exposure to the RD50, Buckley et al. (1984) exposed 20 male Swiss-Webster mice to 697 ppm for 6 hours. All exposed mice were found dead or in a moribund condition at the end of the exposure. Histopathology of the respiratory tract showed ulceration and necrosis in the respiratory and olfactory epithelium of the nose as well as tracheal epithelial exfoliation and hyperplasia and slight bronchiolar exfoliation.

Thirty Sprague-Dawley rats/sex/concentration and 10 male New Zealand white rabbits/concentration were exposed to 0, 5, 25, or 50 ppm (19, 95, or 189 mg/cu.m, respectively) epichlorohydrin (98.8% purity), 6 hours/day, 5 days/week (duration-adjusted to 3.4, 17, and 34 mg/cu.m), for 10 weeks, followed by a 10-week postexposure period (John et al., 1979, 1983a). The exposure duration was considered equivalent to one spermatogenesis cycle. At the end of the 10-week exposure, 5 rats/sex/concentration and 3-4 rabbits/concentration were sacrificed. At the end of the postexposure period, 10 rats/sex/concentration and the remaining rabbits were killed and examined for histopathologic changes. Histopathology was performed on an extensive list of tissues including kidney, liver, lung, trachea, and four sections of the nose.

Twenty-five exposed male rats were mated to unexposed females on exposure weeks 2, 4, 7, and 10 and postexposure weeks 2, 5, and 10. During mating, exposed males were housed with 2 females during the 18 nonexposure hours per day for 7 days. The 25 exposed female rats were mated with unexposed males after the 10-week exposure. There was a significant reduction in the fertility of the 50-ppm exposed male rats (16, 8, 8, and 12% fertile for exposure weeks 2, 4, 7, and 10, respectively). A slight reduction in fertility in the 25-ppm exposed male rats was not statistically significant. The average number of implants in unexposed females that mated with exposed males was significantly ($p < 0.005$) lower in the 25- and 50-ppm males during the exposure period. These effects were no longer seen at 2 weeks post-exposure. No histological changes were seen in the testes in 5 males at the end of the exposure or in 10 males at the end of the recovery period. Exposed female rats mated at the end of the exposure period showed no effect on estrous pattern, percent pregnant, gestation length, litter size, or pup survival at two

days. Therefore, a NOAEL of 5 ppm (HEC = 3.4 mg/cu.m) was calculated for reproductive toxicity in male rats.

The high-concentration group showed significantly increased relative kidney weight and focal tubular changes in the kidneys. No degeneration or necrosis was observed in the kidney and clinical chemistry parameters reflective of kidney function were normal. Degenerative changes in the nasal turbinates (e.g., inflammation, focal lesions, and changes in the respiratory epithelial region), were seen in the 25- and 50-ppm females and in the 50-ppm males after the exposure period. The NOAEL for these respiratory effects is 5 ppm [NOAEL(HEC) = 0.7 mg/cu.m]. The effects ranged from moderate to severe in the high-concentration group and were similar to the effects described in the principal study. Since these findings were not exhibited in animals at the final sacrifice (10 weeks post exposure), the changes in the nasal turbinates were considered reversible.

In the rabbits, 10 animals per concentration were mated during week 10 of exposure. No reproductive effects were noted in rabbits exposed to epichlorohydrin including percent fertile; number of implantations; and based on weekly examination, no effect on sperm viability, motility, or number. In the 25- and 50-ppm groups, exposed rabbits had bilateral suppurative rhinitis or sinusitis and pneumonia compared with controls. The changes in the nasal turbinates were not observed at the end of the 10-week recovery period. A NOAEL of 5 ppm was determined based on inflammation and erosion of the nasal turbinates in the male rabbits. Lack of data on the surface area of the respiratory tract in rabbits precludes calculation of the HEC.

The male reproductive effects of epichlorohydrin have been studied in short-term inhalation exposures and by other routes of administration. Hahn (1970) reported that male SD rats dosed orally with 15 mg/kg/day for 12 days showed loss of fertility within the first week of exposure; this effect was reversible within 1 week of the end of exposure. No effects were seen on copulatory behavior or on the histopathology of the reproductive organs. Toth et al., 1989, treated male and female rats orally with 12.5, 25, or 50 mg/kg/day epichlorohydrin for 21 days (males) or 25, 50, or 100 mg/kg/day (females) for 14 days prior to mating and during gestation. Both males and females were mated to unexposed animals and no effects were seen on reproduction in exposed females. Male fertility was examined in high-dose males only and they were found to be infertile. No effect was observed on copulatory behavior, sperm counts, or sperm morphology. Significantly reduced linear velocity and curvilinear velocity was observed in exposed animals at 12.5 mg/kg/day and higher, and reduced linearity of motion was observed at 50 mg/kg/day. The percent motile sperm was reported to be unaffected in this study, but a later reanalysis (Toth et al., 1991) reported this parameter to be significantly affected at 25 and 50 mg/kg/day. In a further examination of reproductive effects by the inhalation route, Slott et al. (1990) exposed rats to 100 ppm for a single 4-hour exposure. No effect was seen on percent

motile sperm or sperm counts at 1-14 days post exposure. Significant decreases were reported in curvilinear and linear velocity at 1 day post exposure but not at 2-14 days post exposure.

These studies show a specific effect on sperm motion in rats exposed to epichlorohydrin. This effect has been postulated to be mediated through alpha-chlorohydrin, a metabolite of epichlorohydrin, which also causes reduced sperm motility through a mechanism thought to involve inhibition of sperm glycolytic enzymes. The effects on sperm velocity measured by Toth et al. (1989) and Slott et al. (1990) are considered to reflect sperm energy utilization. In a study designed to evaluate the correlation between sperm motion parameters and fertility measures, Toth et al. (1991) dosed male rats orally with 6.25, 12.5, and 25 mg/kg/day epichlorohydrin for 23 days. Exposed males were mated with unexposed females on days 19 and 22. Fertility was measured as the presence of fertilized ova 18 hours after mating, and the number of implants on day 14 of gestation. Both measures of fertility were decreased in a dose-dependent fashion by epichlorohydrin exposure, as were several measures of sperm motion. A significant correlation was reported between fertility parameters and sperm motion parameters.

Studies of reproductive function in humans occupationally exposed to epichlorohydrin (Milby et al., 1981; Milby and Whorton, 1980; Venable et al., 1980) have shown no evidence of reduced sperm count in the exposed groups. Detailed measurement of sperm motion has not been applied to an occupationally exposed population.

These reproductive studies indicate that the reproductive toxicity of epichlorohydrin is probably mediated by an effect on mature sperm, and that fertility effects are observed at lower epichlorohydrin doses than effects on sperm morphology, production, or testicular histology. Histopathology of the reproductive organs has been observed at much higher doses by oral and injection routes than doses shown to affect fertility (Cooper et al., 1974; Kluwe et al., 1983). The effects show a rapid onset and a rapid and complete reversal after exposure ends.

In a developmental toxicity study by Pilny et al. (1979, also John et al., 1983b), pregnant Sprague-Dawley rats (43-46/group) and New Zealand white rabbits (20-25/group) were exposed to 0, 2.5, or 25 ppm (0, 9.5, and 95 mg/cu.m) epichlorohydrin, 7 hours/day, on gestational days 6-15 or 6-18 for rats and rabbits, respectively. Animals were sacrificed on the last day of gestation (day 21 for rats and day 29 for rabbits). Maternal body weight and liver weight were recorded and fetuses were examined for external, soft tissue (one-third fetuses), and skeletal abnormalities. In the high-concentration rats, maternal weight was significantly decreased on days 6, 8, 10, 12, and 16 of gestation. However, maternal weights were reported to be significantly less prior to exposure (data not provided in report) so this is not a reliable indication of maternal toxicity. In addition, maternal weight gain was not significantly reduced except on day 6. Food consumption was significantly lowered on gestational days 6-14 while water consumption was increased on gestational days 9-20 in the rats. In the 32-36 litters per group

examined, there were no significant effects on fetal body weight, number of corpora lutea, live fetuses, implantations, resorptions, or malformations. In the 16- 23 litters per group of rabbits examined, no effects on maternal toxicity or developmental effects were observed. Although the nose, trachea, and lungs were preserved at necropsy, no histological observations are reported. This study demonstrates a free-standing NOAEL of 25 ppm (HEC = 95 mg/cu.m) for maternal and developmental toxicity.

A pharmacokinetic study (Smith et al. 1979) found that 1 and 100 ppm [14C]-epichlorohydrin inhaled for 6 hours in rats resulted in a 5-fold greater amount of radioactivity per tissue mass in the nasal turbinates than the lungs.

In humans, epichlorohydrin is known to cause respiratory irritation. However, occupational studies other than those focused on reproductive effects discussed above have only evaluated mortality in workers (Enterline et al., 1990; Tsai et al., 1990).

I.B.5. Confidence in the Inhalation RfC

Study — Medium

Database — Medium

RfC — Medium

The subchronic inhalation study in rats and mice (Quast et al., 1979a) was well conducted and contained detailed histopathological examinations of numerous tissues including the respiratory tract. However, it was given a medium confidence because of the inflammation in the respiratory tract of control and exposed animals. The database is given a medium confidence because chronic studies which adequately address the respiratory system and a two-generation reproductive study are lacking. The only chronic inhalation study (Laskin et al., 1980) is confounded by severe nasal inflammation in the controls. Medium confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1985a,b, 1984

Agency Work Group Review — 09/19/1989, 12/12/1991

Verification Date — 12/12/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Epichlorohydrin conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Epichlorohydrin

CASRN — 106-89-8

Last Revised — 03/01/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Human data are inadequate. Multiple studies in rats and mice administered epichlorohydrin by various routes were positive. As epichlorohydrin is a strong alkylating agent, tumors are produced at the site of application.

II.A.2. Human Carcinogenicity Data

Inadequate. A retrospective cohort mortality study has been conducted on 864 workers from epichlorohydrin-producing plants in Louisiana and Texas (Enterline, 1981). Deaths were compared by cause with those expected for the states of Louisiana and Texas. An interim report showed workers to have less than expected overall mortality, but an increase (not significant) in both respiratory cancer and leukemia mortality. An update on the exposed cohort, however, indicated a reversal of this trend. The study is complicated by the fact that of those 10 workers diagnosed with lung cancer, seven were smokers, one was a nonsmoker, and the smoking history of two was not known. Furthermore, there is no apparent dose-response trend, and there is the confounding exposure to the isopropyl alcohol manufacturing process concomitant with epichlorohydrin.

A retrospective cohort mortality study of 533 chemical workers (Shellenberger et al., 1979) and an historic prospective study of European workers (Tassignon et al., 1983) failed to demonstrate a connection between epichlorohydrin and increased cancer mortality. The first study is inadequate for valid carcinogenicity assessment because of low exposure, short exposure duration, short study period, and the young age of the cohort. The second study suffers from some of the same limitations, as well as that of a small cohort size with at least 10 years exposure (274 individuals).

II.A.3. Animal Carcinogenicity Data

Sufficient. Epichlorohydrin has produced cancers of various types at the site of application when administered by several routes. While ineffective as a complete skin carcinogen, epichlorohydrin produced papillomas in mice when used as an initiator followed by phorbol myristate acetate promotion (Van Duuren et al., 1974). Local sarcomas developed in mice at the site of single subcutaneous injections of epichlorohydrin (Kotin and Falk, 1963).

Wester et al. (1985) administered 0, 2 or 10 mg/kg/day epichlorohydrin by gavage to groups of 50 each male and female Wistar rats. Mortality was high in all female rats during the first 12 months because of a high-fiber diet. The incidence of forestomach carcinomas was significantly increased in the high-dose rats. Konishi et al. (1980) reported similar results in male Wistar rats given epichlorohydrin in the drinking water. Drinking water was administered to 18 animals each with 0, 375, 750, or 1500 ppm epichlorohydrin. Poor health of treated animals necessitated that untreated water be given intermittently during weeks 60-81. All surviving high-dose rats

developed forestomach hyperplasia; forestomach papillomas were significantly increased and two squamous cell carcinomas were also noted, as well as squamous cell carcinomas of the oral cavity.

Inhalation exposure of male Sprague-Dawley rats was undertaken by Laskin et al. (1980). Animals (140) were exposed to 100 ppm, 6 hours/day for 30 days and observed for their lifetime. Nasal cavity tumors, including squamous cell carcinomas, developed in 15/140 rats compared to none in either 150 concurrent or in 1920 historical controls. Groups of 100 animals were exposed to 10 or 30 ppm, 6 hours/day, 5 days/week for their lifetime. By 136 weeks, 100% mortality was noted. One nasal cavity tumor and two respiratory tract tumors were observed among the high-dose rats.

II.A.4. Supporting Data for Carcinogenicity

Epichlorohydrin is a direct-acting mutagen by virtue of its activity as an alkylating agent. Positive results have been obtained in mutagenicity tests in several bacterial species, *Neurospora*, *Saccharomyces*, *Drosophila* (including recessive lethal), and cultured mammalian cells (reviewed in Sram et al., 1981). Epichlorohydrin causes mitotic recombination in yeast and sister-chromatid-exchange and chromosomal aberrations in mammalian cells. The latter were observed in lymphocytes obtained from exposed workers (Sram et al., 1981; Kucerova et al., 1977; Picciano, 1979).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — $9.9E-3$ per (mg/kg)/day

Drinking Water Unit Risk — $2.8E-7$ per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	3E+2 ug/L
E-5 (1 in 100,000)	3E+1 ug/L
E-6 (1 in 1,000,000)	3E+0 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type — papillomas and carcinomas of the forestomach

Test Animals — rat/Wistar, male

Route — drinking water

Reference — Konishi et al., 1980

Administered Dose (ppm in d.w.)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0	0/10
375	27.1	0/9
750	55.7	2/10
1500	108.6	9/12

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Doses are equivalent human doses assuming 70 kg bw, and 2 L water consumption using the formula:

$f_{\text{water}}(\text{rat}) \times \text{water concentration}(\text{rat}) =$

$f_{\text{water}}(\text{human}) \times \text{water concentration}(\text{human});$

where:

$f_{\text{water}}(\text{rat}) = 0.078$ (fraction of body weight consumed as water) and

$f_{\text{water}}(\text{human}) = 0.029$.

Since epichlorohydrin is an alkylating agent, its effect in the forestomach is considered to be a local reaction. The unit risk value should not be used if the water concentration exceeds $3E+4$ ug/L, since above this concentration the unit risk may not be appropriate.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

The above study provides the only drinking water data available. Limitations include the following: the study was terminated at 81 weeks; epichlorohydrin concentration in the water was likely to be overestimated because of its short half-life; dose levels administered were toxic to the animals; pathology data obtained on animals dying during the course of the study were not considered reliable by the authors; and few animals were used.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — $1.2E-6$ per (ug/cu.m)

Extrapolation Method — Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	$8E+1$ ug/cu.m
E-5 (1 in 100,000)	$8E+0$ ug/cu.m
E-6 (1 in 1,000,000)	$8E-1$ ug/cu.m

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type — nasal cavity tumors
Test Animals — Rat/Sprague-Dawley, male
Route — inhalation
Reference —

Admin. Dose (ppm in air)	Tumor Incidence
0	0/150
10	0/100
30	1/100

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Historical control incidence for these tumors is 0/1920.

Since epichlorohydrin was administered as a partially soluble vapor, the concentrations in ppm administered to the experimental animals are considered equivalent to the same concentrations in humans. The unit risk value should not be used if the air concentration exceeds $8E+3$ ug/cu.m, since above this concentration the unit risk may not be appropriate.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Analysis was based on nonsignificant increases in incidence. The Laskin et al. (1980) study did show a strong dose rate effect, as evidenced by the tumor response with the high-exposure, short-duration group. A risk estimate including the time-to-tumor, dosing regimen, and lung cancer incidence data from 30 days exposure to 100 ppm gives a unit risk of $1.2E-6$ per (ug/cu.m). Data from the epidemiologic study by Enterline (1981) were used to calculate the risk estimate of 0.15 per (ppm) or $3.9E-5$ per (ug/cu.m) assuming an average exposure of 5 ppm and exposure duration of 13.4 years. Risk estimates based on the Laskin (1980) and Enterline (1981) studies, thus, varied by at least 1 order of magnitude.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1984, 1985

The values in the 1984 Health Assessment Document for Epichlorohydrin have received both Agency and outside review. Those in the 1985 Health and Environmental Effects Profile for Epichlorohydrin have been reviewed by Agency groups.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 08/13/1986, 10/29/1986

Verification Date — 10/29/1986

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Epichlorohydrin conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Epichlorohydrin
CASRN — 106-89-8

VI.A. Oral RfD References

Not available at this time.

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VII. Revision History

Substance Name — Epichlorohydrin

CASRN — 106-89-8

Date	Section	Description
03/01/1988	II.C.	Slope factor changed
04/01/1992	I.A.	Oral RfD summary withdrawn pending further review
04/01/1992	I.B.	Inhalation RfC summary on-line
12/03/2002	I.A., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Epichlorohydrin

CASRN — 106-89-8

Last Revised — 01/31/1987

- 106-89-8
- 1-chlor-2,3-epoxypropane
- chloromethyloxirane
- 2-chloropropylene oxide
- γ-chloropropyleneoxide
- epichlorhydrin