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Provisional Peer Reviewed Toxicity Values for

Epichlorohydrin
(CASRN 106-89-8)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

8-15-2006

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR EPICHLOROHYDRIN (CASRN 106-89-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

The HEAST (U.S. EPA, 1997) lists subchronic and chronic oral reference doses (RfDs) of 0.002 mg/kg-day for epichlorohydrin (1-chloro-2,3-epoxypropane). A comment in the HEAST indicates that the subchronic RfD was adopted from the chronic oral RfD. The RfD of 0.002 mg/kg-day is also included on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). This value was derived by route-to-route extrapolation from a LOAEL for kidney damage observed in an inhalation study conducted by Laskin et al. (1980). A composite (aggregate) uncertainty factor (UF) of 1000 was applied that included factors of 10 each for protection of sensitive individuals, extrapolation from animals to humans, and use of a LOAEL. The source document was a Drinking Water Criteria Document (U.S. EPA, 1984a). The RfD is not listed on IRIS (U.S. EPA, 2006a). A comment in the HEAST indicates that the chronic RfD was withdrawn from IRIS on April 1, 1992.

The HEAST lists a value of 0.01 mg/m^3 for the subchronic inhalation RfC and references IRIS for the chronic inhalation RfC of 1E-3 mg/m^3. The chronic RfC value was derived from a NOAEL of 19 mg/m^3 identified for changes in the nasal turbinates of F344 and Sprague-Dawley rats in a 90-day inhalation study (Quast et al., 1979). The corresponding LOAEL was 95 mg/m^3. The NOAEL was adjusted for intermittent exposure, converted to a human equivalent concentration NOAEL ($NOAEL_{HEC}$) value of 0.36 mg/m^3 and divided by a composite UF of 300. The composite UF included a factor of 10 for protection of sensitive individuals, a factor of 3 for interspecies extrapolation, and an additional factor of 10 to account for extrapolation from a subchronic study and for database deficiencies, including the lack of a two-generation reproductive study. The RfD/RfC Work Group verified the RfC on December 12, 1991. The State of California (OEHHA, 2002a) has derived a chronic inhalation reference exposure level (REL) of 3 µg/m^3 (0.8 ppb) for epichlorohydrin. The REL was derived from the NOAEL identified in the same study by Quast et al. (1979), using a composite UF of 100. The composite UF includes a factor of 3 for use of a subchronic study, a factor of 3 for interspecies uncertainty, and a factor of 10 for intraspecies uncertainty. ACGIH (2001) lists a TLV-TWA of 0.5 ppm (1.9 mg/m^3) with skin and A3 cancer notations. These values are intended to minimize the potential for reproductive effects, reported in male and female rats, and nasal irritation. The A3 notation identifies epichlorohydrin as a confirmed animal carcinogen with unknown relevance to humans. NIOSH (2002) lists a Ca notation for the REL-TWA and recommends that epichlorohydrin be treated as a human carcinogen, that exposure be limited to the lowest level possible, and that skin exposure be avoided. OSHA (2002) lists a value of 5 ppm (19 mg/m^3) with a skin notation for the PEL-TWA.

The HEAST lists an inhalation slope factor of 4.2×10^{-3} per mg/kg-day and references IRIS for the oral slope factor and inhalation unit risk. IRIS lists values of 9.9×10^{-3} per mg/kg-day and 1.2×10^{-6} per mg/m^3 for the oral slope factor and inhalation unit risk, respectively. These values were verified on August 13, 1986. These oral slope factor and unit risk values are included in the Office of Pesticide Programs List of Chemicals Evaluated for Carcinogenic Potential (U.S. EPA, 1999). The State of California (OEHHA, 2002b) lists a slope factor of 0.08 per mg/kg-day and an inhalation unit risk of 2.3×10^{-5} per µg/m^3. U.S. EPA (2006a) has assigned epichlorohydrin to weight of evidence category B2; *probable human carcinogen*. IARC (1999) has assigned epichlorohydrin to Group 2A, *probably carcinogenic to humans*. NTP (2002) has classified epichlorohydrin as *reasonably anticipated to be a human carcinogen*

In addition to the Drinking Water Criteria Document (U.S. EPA 1984a) mentioned above, the CARA list (U.S. EPA,1991, 1994a) includes a Health Assessment Document (U.S. EPA, 1984b) and a Health Effects and Environmental Profile (U.S. EPA, 1985) for epichlorohydrin. Neither a Toxicological Profile (ATSDR, 2002) nor Environmental Health Criteria document (WHO, 2002) has been prepared for epichlorohydrin. Literature searches to identify studies relevant to the derivation of provisional toxicity values for epichlorohydrin were conducted for the period 1988 through October 15, 2002. Databases searched included: TOXLINE,

MEDLINE, TSCATS, RTECS, CCRIS, DART, EMIC/EMICBACK, HSDB, GENETOX and CANCERLIT. Additional literature searches from October 2002 through October 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

No studies of human exposure to epichlorohydrin via the oral route were identified in the literature examined.

Oral and inhalation studies conducted in animals have identified epichlorohydrin as a male reproductive toxicant (see below). The potential reproductive toxicity of epichlorohydrin in humans has been evaluated in studies of workers in chemical production facilities that use or manufacture it. Venable et al. (1980) evaluated reproductive endpoints in workers exposed to epichlorohydrin in the manufacture of glycerin. Reproductive history, hormone levels, and semen and sperm parameters were determined in 64 epichlorohydrin-exposed workers and 63 nonexposed control subjects. No detrimental effects on fertility were identified as a result of occupational exposure to epichlorohydrin.

Interpretation of this study is complicated in that exposure was reported as being to "three-carbon chlorinated compounds." Specifically, the potential exposures were to epichlorohydrin, allyl chloride or 1,3-dichloropropene. The exposure levels to these three compounds combined were reported to have been less than 1 ppm during the five years immediately preceding the study. Epichlorohydrin exposure may have been less than 0.5 ppm (1.9 mg/m^3). Milby and Wharton (1980) and Milby et al. (1981) assessed testicular function in 128 exposed male workers and 90 controls at an epichlorohydrin production plant. Sperm counts and hormone levels (testosterone, FSH, LH) were measured. The results were stratified into four separate exposure categories, ranging from 0.1 ppm to greater than 1 ppm (upper bound not specified). The method by which exposure levels were determined, however was not reported adequately. Most of the individuals fell into the lowest two categories; approximately 75% of the exposures were less than 0.5 ppm (1.9 mg/m^3). There was a higher fraction of lowest sperm counts in the higher three exposure categories (> 0.3 ppm), but the number of individuals was low and the result was not statistically significant. Milby et al. (1981) concluded that occupational exposure to epichlorohydrin was not associated with reduced sperm counts or altered hormone levels. These studies did not include detailed analysis of sperm motility as performed in some animal studies (Toth et al., 1989, 1991).

Other human studies identified in the literature search examined potential associations between exposure to epichlorohydrin in occupational settings and worker mortality from cancer (e.g., Enterline, 1982; Enterline et al., 1990; Tassignon et al., 1983; Bond et al., 1985, 1986; Delzell et al., 1989; Barbone et al., 1992, 1994; Olsen et al., 1994; Tsai et al., 1990, 1996) or heart disease (Tsai et al. 1990, 1996; Olsen et al., 1994). The mortality data from these studies are not suitable for derivation of chronic or subchronic inhalation reference values.

Animal Studies

Konishi et al. (1980) and Kawabata (1981) reported the results of an 81 week drinking water study conducted in male Wistar rats (18 animals/dose). Epichlorohydrin was provided at concentrations of 0, 375, 750, or 1500 ppm in solutions that were renewed daily. Exposure was stopped intermittently between weeks 60 and 81 as a result of the poor condition of the test animals; the schedule of interruptions was depicted graphically and the total duration of dosing interruption was not reported. Endpoints evaluated in the study included water consumption, mortality, body weight, clinical chemistry at study termination, and gross pathology. Multiple tissues were collected and processed for histopathologic examination. The survival rate decreased in all groups starting at week 48 of the study. The cause of death was pneumonia unrelated to treatment with epichlorohydrin and the affected rats were excluded from the results. Drinking water consumption did not differ significantly between groups. The total amounts of epichlorohydrin consumed per rat for the entire treatment period were calculated to be 0, 5.0, 8.9, and 15.1 g for the 0, 375, 750, and 1500 ppm exposure groups, respectively. These amounts were based on daily initial concentrations in the water and will overestimate actual intake, as epichlorohydrin is highly unstable in water (half-life for hydrolysis of 16.7 hours) and the solutions were renewed only daily. With this half life and only once-daily renewal of drinking water preparations, the average daily intakes would be about 83% of the nominal dose. On this basis, the adjusted individual total intakes would be 4.2, 7.4, and 12.5 g for the 375, 750, and 1500 ppm groups, respectively. The approximate time-weighted average body weights for the same treatment groups, estimated from Figure 4 in Kawabata (1981), were 480, 400, and 300 grams, respectively. Based on adjusted total intakes, estimated body weights, and duration of treatment (567 days), these values correspond to average daily intakes of 15, 33, and 73 mg/kg-day for the 375, 750, and 1500 ppm groups, respectively. Dose-dependent decreases in body weight of 7.7, 22.4, and 44.9% were observed in the 375, 750, and 1500 ppm groups, respectively. The response was statistically significant at 750 and 1500 ppm. Serum cholesterol was significantly increased at 750 and 1500 ppm and neutral lipids were significantly increased at all concentrations relative to the controls. No other changes in clinical chemistry were observed. Stomach weight and relative kidney weight were significantly increased in all exposure groups. Changes in the absolute or relative weight of other organs commonly occurred in the 750 and 1500 ppm groups. There appeared to be a general depression of relative organ weights except for kidney and pancreas. Kawabata (1981) reported statistical significance ($p < 0.05$) for many of these effects, but the statistical methods were not described. Liver weights

showed a trend towards lower values with increasing dose, although the reductions were not statistically significant at the lower two treatment levels. The average increase in relative kidney weights at all treatment levels was about 30%, which is considered biologically significant. The occurrence of non-neoplastic or preneoplastic lesions was reported only for the forestomach, but these lesions are considered to be not relevant for extrapolation to humans (see description of Wester et al., 1985 study following). Therefore, the chronic LOAEL for the Kawabata/Konishi study is established at 375 ppm, or approximately 15 mg/kg-day, for increased relative kidney weight. A NOAEL was not defined. Limitations of this study include uncertainty in the administered dose, administration of compound levels that caused frank toxicity, and interruption of dosing to allow recovery of the test animals.

Wester et al. (1985) dosed male and female Wistar rats (50/sex/dose) by gavage with 0, 2, or 10 mg/kg-day, 5 days/week for two years. Endpoints evaluated included health, behavior, mortality, body weight, hematology after 12 months of exposure, gross pathology, and histopathology. Intercurrent mortality occurred after four months of exposure as a result of intestinal obstruction. This condition was not treatment-related and was resolved by a change in the diet. A slight, possibly dose-related increase in mortality was observed between 12 and 24 months of the study. Surviving males showed a significant dose-related reduction in body weight after 100 weeks. A tendency for reduced body weight gain was observed in females but did not reach statistical significance. Hematological data were similar in treated and control animals. Occurrence of non- or preneoplastic lesions was reported only for the stomach. At earlier time points (i.e., when intercurrent deaths occurred) or lower doses, hyperplasia of basal cells was found over large areas of the forestomach. This change was considered to be preneoplastic as focal outgrowths apparently developed from these lesions and displayed invasive growth or marked dysplasia. The rat forestomach lesions are considered to be not relevant as the basis for the epichlorohydrin RfD (see discussion following in the RfD derivation section). Body weight loss, in conjunction with carcinogenicity, is generally not considered a noncancer effect. In this case, the timing of the body weight loss strongly suggests that it is related to the carcinogenic process, and, perhaps, to the development of the forestomach lesions in general. As the forestomach lesions are not relevant for consideration and no other noncancer lesions were found, the NOAEL in this study is 7.1 mg/kg-day (10 mg/kg-day adjusted for 5-day per week exposure regimen). A LOAEL was not identified. A limitation of this study is occurrence of intestinal blockages early in the study which result in premature death of some study animals. The effects on surviving animals in the study are unknown.

Daniel et al. (1996) dosed male and female adult Sprague-Dawley rats (10/sex/dose) with 0, 1, 5, or 25 mg/kg-day by gavage for 90 days. Endpoints evaluated included behavioral changes, appearance, mortality and morbidity, body weight, water and food consumption, ophthalmology, hematology and serum chemistry at study termination, urinalysis near study termination, gross pathology, and histopathology. The adrenal glands, brain with brain stem, gonads, heart, kidneys, liver, lungs, spleen, and thymus were removed and weighed. Thirty-five

additional tissues and any gross lesions were collected and processed for histopathology. During microscopic examination, inflammatory and degenerative lesions were graded according to severity using a scale of one to four. No animals died during the study. Clinical signs were reported to be "essentially normal" with the exception of excessive salivation which was frequently observed in the high dose group starting at week 2 of the study. No significant differences in food or water consumption or total body weight were observed among treated and control groups. Absolute and relative liver and kidney weights were significantly increased in both sexes at 25 mg/kg-day compared to the controls. Relative liver weight was significantly increased in 5 mg/kg-day males. No liver histopathology or changes in liver enzymes were observed. The authors indicated that their results did not "implicate the liver as a target organ." A change in liver weight in the absence of histopathology or some other indicator of hepatic toxicity is not considered adverse in EPA toxicity assessment. No other significant differences between treated and control groups were observed for absolute or relative organ weight (including testes and ovaries). Treatment with epichlorohydrin at 25 mg/kg-day significantly decreased red blood cell count in both sexes. Males at this dose also had significantly decreased hemoglobin and hematocrit levels. Epichlorohydrin treatment produced only minimal changes in serum chemistry parameters. Specifically, creatinine levels were significantly decreased in 25 mg/kg-day females. Also, serum lactate dehydrogenase (LDH) was significantly decreased in all treated females and a dose-related decrease was observed in males, although not statistically significant. An increase in LDH should be indicative of tissue damage (liver, RBC) but a decrease is not considered to be adverse. An increase in severity of urine protein grading was observed in 6/10 high-dose males at the end of the study. At necropsy, the main treatment-related change noted was marked thickening of the mucosal lining of the forestomach in 5/10 males and 3/10 females at the 25 mg/kg-day level. The only treatment-related microscopic changes were hyperkeratosis and hyperplasia (acanthosis) in the forestomach, which are not considered as the basis for the RfD (see discussion following in RfD derivation section). Microscopic lesions observed in other tissues were considered incidental and unrelated to treatment, with the possible exception of chronic inflammation in the kidney of males. As reported by the authors, 50 to 70% of the dosed males (incidence data by dose group not presented) exhibited this lesion as compared to 30% of the controls. The subchronic NOAEL and LOAEL identified in this study are 5 and 25 mg/kg-day, respectively, for hematological effects.

Epichlorohydrin is a male reproductive toxicant. Hahn (1970) administered daily oral doses of 0 or 15 mg/kg to male Sprague-Dawley rats (number not reported) for 12 days. The animals became infertile within one week of the initiation of treatment, as judged by the number of implantations when mated with unexposed females. Histologic examination of the testes, epididymides, prostate, and seminal vesicles on the twelfth day of treatment revealed no differences between dosed animals and controls. The effect was reversible with fertility restored approximately seven days after cessation of treatment. A LOAEL of 15 mg/kg-day was established for male infertility in rats following a 12 day exposure to epichlorohydrin.

Toth et al. (1989) treated male and female Long-Evans rats (20/sex/dose) with gavage doses of 0, 12.5, 25, or 50 mg/kg-day for 21 days (males) or 0, 25, 50, or 100 mg/kg-day for 14 days (females) prior to mating trials with untreated animals. Treated females were dosed with epichlorohydrin until delivery. No differences between control and treated females were evident for the measured reproductive parameters including fertility rate, litter size, pup survival, birth weight, or weaning weight. High dose males were infertile when mated. Treated males showed normal copulatory behavior, sperm morphology, and ejaculate sperm counts. Cauda epididymal sperm count was slightly reduced at the high dose. Significantly reduced linear velocity and curvilinear velocity were observed for cauda epididymal sperm of males treated with 12.5 mg/kg-day and higher doses. Reduced linearity of motion was observed at 50 mg/kg-day. Impairment of energy utilization was proposed as a mode of action for the observed effects of epichlorohydrin on sperm motility. A LOAEL of 12.5 mg/kg-day for sperm velocity in rats was established.

Toth et al. (1991) treated male Long-Evans rats (20/dose) with oral doses of 0, 6.25, 12.5, or 25 mg/kg-day for 23 days. Mating trials with untreated females were conducted at study days 19 and 22 to evaluate fertility. Fertility was assessed by detection of fertilized ova 18 hours after mating and by the number of implants (i.e., implants/corpora lutea) determined on day 14 of gestation. Treatment with epichlorohydrin did not result in reductions in body weight, testis or epididymis weight, testicular spermatid count, or epididymal sperm count. The percentage of fertilized ova was significantly reduced at 6.25 mg/kg-day and above (Table 1). Percent implantation was reduced at 12.5 mg/kg-day and above. These fertility indices were significantly correlated as determined by Spearman's rank correlation test. Motion analysis of cauda epididymal sperm on day 25 of the study indicated that curvilinear velocity, straight-line velocity, linearity and amplitude of lateral head displacement were reduced in a dose-related manner, suggesting a relationship between epichlorohydrin-induced reductions in sperm motility and fertility. The LOAEL in this study was 6.25 mg/kg-day for effects on fertility, as determined by a 14% reduction in the number of fertilized ova in mating trials with untreated females.

Marks et al. (1982) treated pregnant CD rats (14-35 animals/dose) with gavage doses of 0, 40, 80, or 160 mg/kg-day and CD-1 mice (24-49 animals/dose) with gavage doses of 0, 80, 120, or 160 mg/kg-day on gestation days 6-15. The rats and mice were sacrificed on gestation days 20 and 18, respectively, and liver weight, the number of implantations, number of resorptions, and number of live and dead fetuses were recorded. Fetuses were examined for gross, visceral (one third of fetuses), and skeletal malformations. Maternal weight gain was significantly reduced in rats at 80 mg/kg-day and three deaths occurred at 160 mg/kg-day. There was no evidence of teratogenic effects at any tested dose when compared to the control group. In mice, significantly increased maternal liver weight was observed at 120 mg/kg-day and three deaths were observed at 160 mg/kg-day. Average fetal weight was reduced in the 120 and 160 mg/kg-day groups. The maternal NOAEL and LOAEL for rats in this study are 40 and 80 mg/kg-day, respectively, for reduced body weight gain. The developmental NOAEL for rats is

Table 1. Fertility Assay Results for Male Rats Exposed to Epichlorohydrin by Gavage (Toth et al., 1991)

Fertility Index	Dose	n	Mean	Median	SD	Minimum	Maximum
Fertilized Ova (%)	0	20	97.4	100	10.0	55.6	100
	6.25	19	84.1*	92.3	25.5	0	100
	12.5	18	28.1*	25	30.5	0	100
	25	17	1.8*	0	7.3	0	30
Implantation (%)	0	20	85.8	93.8	29.9	0	100
	6.25	19	93.2	100	16.1	33.3	100
	12.5	18	42.6*	51.7	32.9	0	100
	25	16	0*	0	0	0	0

* Wilcoxon P values ≤ 0.001

160 mg/kg-day, the highest dose tested. The maternal NOAEL and LOAEL for mice are 120 and 160 mg/kg-day, respectively, for frank toxicity including death. The developmental NOAEL and LOAEL for mice are 80 and 120 mg/kg-day, respectively, for reduced average fetal weight.

Laskin et al. (1980) exposed male Sprague-Dawley rats (100/concentration) to epichlorohydrin by inhalation at concentrations of 0, 10, or 30 ppm (0, 38, and 114 mg/m^3) 6 hours/day, 5 days/week for their lifetime (136 weeks). An untreated group of rats was maintained for comparison. Body weight gain in the 10 ppm group was similar to the control; however, body weight gain was significantly depressed in the 30 ppm group after approximately 40 weeks of exposure. Significant mortality in the epichlorohydrin exposure groups was not observed before week 16. Early mortality after week 16 was associated with pulmonary congestion and pneumonia in both control and exposed groups. One hundred percent mortality was observed by week 136. Because approximately 90% of the control rats showed severe inflammatory changes in the nasal cavity (no further details provided), specific effects of epichlorohydrin could not be distinguished from background lesions in the target tissue. Animals in the 10 and 30 ppm groups showed pulmonary congestion, bronchiolectasis, and pneumonia. Exposure to epichlorohydrin increased the incidence and severity of kidney lesions (predominately tubular degenerative changes and tubular dilatation) at the end of the study. The observed incidences were 14, 24, 37, and 65% for the 0 ppm, 10 ppm and 30 ppm untreated

groups, respectively. The kidney lesions were qualitatively similar in the exposed and control groups. Lesion severity was reported to be greater in the 30 ppm group than in the 10 ppm or control groups. Based on the reduction in body weight gain and renal effects, the apparent LOAEL in this study is 30 ppm. The apparent NOAEL for kidney effects is 10 ppm (HEC = 1.2 mg/m^3). NOAEL and LOAEL values for respiratory effects cannot be identified. The interpretation and use of the results from this study are limited by lack of detail in the study report and the high background incidence of chronic inflammation of the nasal cavity in control rats.

U.S. EPA (2006a) reviewed an inhalation study of epichlorohydrin conducted by Union Carbide (1983). Groups of Wistar rats (sex unspecified; 23-32 animals/dose) were exposed to 68 or 136 ppm (266 or 515 mg/m^3), 7 hours/day, 5 days/week for 45 exposures. Similar groups of Wistar rats were exposed to 0, 5, 8, 17, 21, or 43 ppm (19, 30, 64, 80, or 163 mg/m^3, respectively) for 90 or 91 exposures. Hybrid Basenji-Cocker dogs and Rhesus macaque monkeys (sex unspecified; 2/dose) were exposed to 0 or 12 ppm (0 or 80 mg/m^3) for 90 exposures. Data collected in this study included weekly body weight, clinical chemistry at six time points, liver and kidney weights, and occurrence of microscopic lesions. Exposure-related deaths occurred in rats exposed to epichlorohydrin concentrations of 68 ppm or higher. These rats displayed lung irritation, reduced body weight gain, and kidney injury. A NOAEL of 43 ppm (HEC = 34 mg/m^3) was identified for these effects. Lung effects (e.g., hemosiderin deposits, bronchial irritation, focal proliferation of alveolar septa) and kidney effects (e.g., focal cloudy swelling of the proximal convoluted tubule) were reported in dogs and monkeys exposed at 21 ppm. U.S. EPA (2006a) reported that no incidence data or statistical analysis were provided for these findings. Other reported limitations of the study included lack of examination of the nasal turbinates and the small number of dogs and monkeys tested.

Quast et al. (1979) exposed $B6C3F_1$ mice, Fischer 344 rats, and Sprague-Dawley rats (10/dose/strain) to epichlorohydrin vapor at target concentrations of 0, 5, 25, or 50 ppm (0, 19, 95, or 185 mg/m^3) 6 hours/day, 5 days/week for 61-62 exposures over 87-88 days. The test animals were whole-body exposed in chambers designed for dynamic airflow. The concentration of epichlorohydrin in individual test chambers was monitored three times per exposure period by gas chromatography. All animals were observed daily. Data were collected on body weight, hematology, clinical chemistry, urinalysis, organ weights, gross, pathology, and histopathology at study termination and at an interim sacrifice conducted at approximately day 30 (10 animals/sex/dose). Histopathological examination at 30 days was conducted on five animals per sex from the control and 50 ppm exposure groups. Histopathologic examination at study termination was conducted on all control and 50 ppm animals, and on the respiratory system, liver, and kidney of animals in the 5 and 25 ppm groups.

In F344 rats, no significant, treatment-related changes were observed for hematology, clinical chemistry, or urinalysis parameters (Quast et al., 1979). Slight decreases were noted in

the body weights of 25 ppm females and 50 ppm males and may have been treatment-related. Minimal treatment-related-effects were noted in the liver and kidneys of males and females as changes in absolute or relative organ weights at either the interim or terminal sacrifice. Minimal changes were seen in kidneys of 50 ppm females and consisted primarily of slightly dilated tubules with minimal epithelial swelling. Epichlorohydrin-related microscopic lesions were observed in the respiratory system of males and females. The nasal turbinates showed the most degenerative lesions of all body tissues examined; there were no treatment-related lesions observed in the trachea or lungs. Lesions of the respiratory epithelium were observed at terminal sacrifice in the 25- and 50-ppm exposure groups (males: 9/10, 10/10; females: 8/10, 10/10, respectively) and included inflammation, focal erosion, hyperplasia, and metaplasia. The nasal turbinates were reported to be more severely involved in males than in females. These effects were not observed in the 5 ppm groups at terminal sacrifice or in the controls at the interim or terminal sacrifices. The NOAEL and LOAEL for F44 rats are 5 and 25 ppm, respectively, for changes in the nasal turbinates. The corresponding $NOAEL_{HEC}$ values for extrathoracic effects are 0.43 and 0.32 mg/m^3 for males and females, respectively.

In Sprague-Dawley rats, no significant, treatment-related changes were observed for hematology, clinical chemistry, or urinalysis parameters (Quast et al., 1979). A slight decrease in the body weight of 50 ppm males during the first month of the study may have been treatment - related. Minimal treatment-related effects were observed in the liver and kidneys of male and female rats from the 25 or 50 ppm group at the interim or terminal sacrifices. These were evident as changes in absolute or relative organ weight or gross pathology. The kidneys of the 50 ppm male rats from the interim sacrifice showed an increased incidence of moderate and severe focal tubular necrosis and an increased number of rats with a moderate degree of nephrosis. The changes in the kidney were less severe at the terminal sacrifice than at the interim sacrifice, suggesting a lack of progression with repeated dosing. In several 50 ppm rats, the epididymides contained not only normal sperm content, but also increased numbers of nucleated cells and/or amorphous eosinophilic staining material. This material was not associated with altered testicular gross pathology, histopathology or changes in testes weight. The nasal turbinates showed the most degenerative lesions of all body tissues examined; there were no treatment-related lesions observed in the trachea or lungs. Lesions of the respiratory epithelium were observed at terminal sacrifice in the 25- and 50-ppm exposure groups (males: 9/10, 10/10; females: 10/10, 10/10, respectively) and included inflammation, focal erosion, hyperplasia, and metaplasia. These effects were not observed in the 5 ppm groups at terminal sacrifice or in the controls at the interim or terminal sacrifices. The inflammatory changes in the nasal turbinates of Sprague-Dawley rats were reported to be more severe than in F344 rats. The NOAEL and LOAEL values for Sprague-Dawley rats in this study are 5 and 25 ppm, respectively. The corresponding $NOAEL_{HEC}$ values for extrathoracic effects are 0.61 and 0.50 mg/m^3 for males and females, respectively.

$B6C3F_1$ mice exposed to 0, 5, 25, or 50 ppm epichlorohydrin for 90 days developed focal erosion, hyperplasia, and metaplasia in the respiratory epithelium of the nasal turbinates (males: 0/10, 0/9, 8/8, 10/10; females: 0/9, 0/9, 10/10, 9/9, respectively) (Quast et al., 1979). This effect was also evident in males (4/5) and females (5/5) in the 50 ppm group at the interim sacrifice, but did not occur in the controls. Suppurative inflammatory exudate or mucus in the lumen of the nasal turbinates was reported in 7/10 males and 7/10 females in the 50 ppm group. Inflammatory reactions in the tracheobronchiolar and pulmonary region were observed in a few 50 ppm mice and may have been treatment-related. The NOAEL and LOAEL values for $B6C3F_1$ mice in this study are 5 and 25 ppm, respectively. The corresponding $NOAEL_{HEC}$ values for extrathoracic effects are 0.60 and 0.45 mg/m^3 for males and females, respectively. These values are comparable to the $NOAEL_{HEC}$ observed in F344 and Sprague-Dawley rats in this study.

A potential confounding factor in the Quast et al. (1979) study is the presence of underlying inflammatory reactions in the respiratory tract of control and exposed animals, as indicated by the presence of mononuclear cell infiltrates or focal pneumonitis in the lung and focal subepithelial mononuclear cell infiltrate in the nasal turbinates. Although no treatment-related lesions were reported in the lungs, it is possible that tissue response to epichlorohydrin was masked by the existing inflammation. Although inflammation was also present in the nasal turbinates, U.S. EPA (2003) suggest that the location of the inflammatory lesion should make it distinguishable from the epithelial response to epichlorohydrin.

In a reproduction study, John et al. (1983a) exposed Sprague-Dawley rats (male and female) and male New Zealand white rabbits to epichlorohydrin concentrations of 0, 5, 25, or 50 ppm (0, 19, 95, or 189 mg/m^3, respectively), 6 hours/day, 5 days per week for 10 weeks. The exposure period was followed by a 10 week recovery period. The duration of exposure was selected to be equivalent to one cycle of spermatogenesis. Twenty-five exposed male rats were mated to unexposed females in exposure weeks 2, 4, 7, and 10. Fecundity was significantly reduced in 50 ppm males at all time points. The average number of implants was significantly reduced in unexposed females mated with 25 or 50 ppm males during the exposure period. These effects were not evident at two weeks post-exposure. No histopathological changes were observed in the testes of five male rats at the end of the exposure period or in the testes of 10 male rats examined at the end of the recovery period. No effects on reproductive parameters were observed in exposed female rats mated to untreated males. The NOAEL for rats in this study was 5 ppm, which corresponds to a HEC of 3.4 mg/m^3, as determined by U.S. EPA (2003). No effects on reproductive parameters were evident in 10 male rabbits mated during the tenth week of exposure to epichlorohydrin.

John et al. (1983b) exposed pregnant Sprague-Dawley rats (33-39 animals/dose) and New Zealand white rabbits (16-23/dose) to epichlorohydrin vapor concentrations of 0, 2.5, or 25 ppm (0, 9.5, and 95 mg/m^3). Exposures were for 7 hours/day on gestation days 6-15 (rats) or 6-18 (rabbits). The animals were sacrificed on the last day of gestation (day 21 for rats and day 29 for

rabbits). Maternal body and liver weight were recorded and the number of corpora lutea and the number and position of live, dead, and resorbed fetuses were recorded. Fetuses were examined for external, soft tissue (one third of fetuses), and skeletal abnormalities. Maternal toxicity was evident in rats exposed to 25 ppm as reduced body weight on days 6, 8, 10, 12, and 16 of gestation and reduced food consumption on days 6-14. Maternal toxicity was not observed in rabbits. Reproductive parameters were not affected in rats or rabbits. There was no evidence of compound-related teratogenic or embryotoxic effects in either species. The maternal NOAEL and LOAEL for rats are 2.5 and 25 ppm, respectively. The maternal NOAEL for rabbits is 25 ppm, the highest dose tested. The developmental NOAEL for both species is 25 ppm, the highest dose tested.

There is limited information of the toxicokinetics of epichlorohydrin, with the primary conclusion being that epichlorohydrin is rapidly eliminated from the body and does not accumulate in tissues. Wiegel et al. (1978) reported rapid elimination of epichlorohydrin in male and female rats. Gingell et al. (1985) estimated a half-life of initial elimination of about 2 hours in Fischer 344 male rats. The primary routes of elimination were expired air (as CO_2) and urine. A few major metabolites were identified, which were consistent with an initial glutathione conjugation metabolic process (Gingell et al., 1985). Rossi et al. (1983) reported similar epichlorohydrin elimination kinetics in mice, with a single dose of 200 mg/kg disappearing from circulation within 20 minutes. The WHO IPCS Environmental Health Criteria document for epichlorohydrin (WHO, 1984) reported a Dow Chemical Company report (Smith et al., 1978) that showed rapid elimination of epichlorohydrin from rats exposed orally or by inhalation; by either exposure route, 90% of the dose was eliminated within 72 hours, with 25-42% exhaled as CO_2, the remainder excreted as other metabolites in the urine. Ginsberg et al. (1996) proposed a dosimetry model for comparison of the carcinogenic potency of epichlorohydrin across routes of exposure (inhalation, drinking water and oral gavage). The model reduced significantly an apparently large (2 O.M.) discrepancy in the carcinogenic potency by these three routes of exposure.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR EPICHLOROHYDRIN

Consistent toxicological observations for epichlorohydrin in the literature for animal studies were forestomach irritation (most studies), increased kidney weight (Konishi et al., 1980; Daniel et al., 1985; Laskin et al., 1980; Quast et al., 1979; the latter two by inhalation) and male infertility (Hahn, 1970; Toth et al., 1989; Toth et al., 1991).

The rat forestomach lesions are discounted as endpoints for derivation of an RfD. Humans have neither an anatomical or physiological equivalent to the forestomach. The rat forestomach has minimal vascularization and is lined by stratified squamous cells, which results

in a longer residence time of food-borne agents than in human organs such as the esophagus and the glandular stomach (Grice, 1988; Poet et al., 2003). For this reason the rat forestomach may be ultra sensitive to irritation by direct-acting agents such as epichlorohydrin, particularly when administered as a bolus dose by gavage. Finally, direct portal-of-entry irritation is generally not considered as the basis for an RfD, as this mode of action is presumed to be primarily a high-dose effect and would not be expected to "scale-down" to adjust for greater human sensitivity. That is, toxicokinetics is not a significant factor given that systemic distribution to the site of action is not involved and metabolism by the liver is not a factor. In addition, because of the direct chemical reactivity of epichlorohydrin, interspecies differences in tissue sensitivity would tend to be minimal.[1] Also note that portal effects are considered for the inhalation RfC, however, as anatomically-based dosimetry models have been developed for specific classes of inhaled toxicants, allowing for adjustment across species. No such dosimetry models have been adopted for RfD derivation. A dosimetry model proposed by Ginsberg et al. (1996) for "normalizing" contact-site carcinogenic potencies across routes of exposure for epichlorohydrin is of interest, but guidance for application of such models remains to be developed.

The kidney effects were observed at higher doses (15-25 mg/kg-day) than those causing male infertility and cannot serve as the basis for the RfD. None of the three male infertility studies established a NOAEL. The LOAELs were 15 mg/kg-day (Hahn, 1970), 12.5 mg/kg-day (Toth et al., 1989) and 6.25 mg/kg-day (Toth et al., 1991). Studies of reproductive function in humans occupationally exposed (by inhalation) 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. However, the occupational studies did not examine sperm morphology or motility, which were the principal findings in Toth et al. (1991). As sperm count also was unaffected in rats exposed to epichlorohydrin (Toth et al. 1989, 1991), the negative evidence for humans is inconclusive.

The male fertility study conducted in Long-Evans rats by Toth et al. (1991) was selected as the principal study for derivation of the provisional subchronic oral RfD. Although this study evaluated specific limited endpoints, other studies have covered general toxicity endpoints adequately. The LOAEL of 6.25 mg/kg-day for reduced male fertility identified in this study was the lowest among the candidate studies for derivation of the provisional RfD values. Although the Daniel et al. (1985) study established a NOAEL of 5 mg/kg-day, it does not provide protection against critical effect (male fertility) at only a slightly higher dose.

The benchmark dose (BMD) modeling approach was used to evaluate the data from Toth et al. (1991). The available continuous models in the BMDS program (U.S. EPA, 2006b) were

[1]The use of portal-of-entry effects in the derivation of RfDs is currently under investigation in the U.S. EPA.

fit to the data for percent fertilized ova, an index of fertility, reported by Toth et al. (1991). A BMR of 1.0 standard deviations was used. The resulting BMDL values were in the range of 2.9 to 5.6. However, none of the available models provided an acceptable fit to the data, with p values less than 0.001. Current guidance recommends that data obtained by benchmark dose modeling be used only if the p value for a particular model is greater than or equal to 0.1. Therefore, the BMDS results are rejected as the basis for the p-RfD.

Therefore, the Toth study LOAEL of 6.25 mg/kg-day for male fertility effects is selected as the "critical dose" on which to base the subchronic p-RfD. As the critical effect was only a 14% reduction in the number of fertilized ova and sperm motility and morphology parameters are minimally affected, the LOAEL is judged to be minimal, and the LOAEL-to-NOAEL uncertainty factor is reduced to 3 ($10^{0.5}$). An aggregate uncertainty factor (UF) of 1000 is applied to account for the lack of a NOAEL ($10^{0.5}$), interspecies extrapolation (10), intra-human variability (10), and an incomplete data base ($10^{0.5}$; for lack of toxicity data in a second species). The resulting provisional **subchronic RfD of 0.006 mg-kg-day** is calculated as follows:

$$\text{p-sRfD} = \frac{\text{LOAEL}}{\text{UF}}$$

$$= \frac{6.25 \text{ mg/kg-day}}{1000}$$

$$= 0.006 \ (6\text{x}10^{-3}) \text{ mg/kg-day}$$

Confidence in the principal study is high. Although a NOAEL was not identified, the LOAEL was minimal and the study was well-conducted. Confidence in the database is medium. The longer-term toxicity of epichlorohydrin has not been investigated in a species other then the rat. The lack of a two-generation reproduction study is not considered a significant data base deficiency, as the Toth et al. (1989, 1991) studies address reproductive effects adequately. Developmental effects have been studied in two species and found not to be a sensitive endpoint for epichlorohydrin. The critical effect is supported by two other rat studies. Human occupational studies were negative but inconclusive. Therefore, no more than medium confidence can be given to the p-sRfD overall.

For the (chronic) p-RfD, the two rat chronic studies (Konishi et al., 1980; Wester, 1985) did not identify noncancer effects below exposure levels of 15 mg/kg-day. The forestomach

hyperplasia observed at lower doses is not relevant for the RfD as discussed previously. The lowest LOAEL of 6.25 mg/kg-day is established in the Toth et al. (1991) fertility study, which precludes using the highest chronic NOAEL as the basis for the p-RfD.

Therefore, the LOAEL for the chronic p-RfD is set to 6.25 mg/kg-day. An aggregate UF of 1000 is applied to account for the lack of a NOAEL ($10^{0.5}$; minimal LOAEL), interspecies extrapolation (10), intra-human variability (10), and an incomplete data base ($10^{0.5}$; multi-generation reproduction study and longer-term toxicity in a second species missing). A subchronic-to-chronic factor is not applied, as the chronic study of Wester et al. (1985) does not indicate that epichlorohydrin becomes more toxic with increased exposure duration. Although the chronic studies did not evaluate male fertility, uncertainty in the longer-term effects of epichlorohydrin on male fertility is covered by the database uncertainty factor. In addition, epichlorohydrin does not accumulate in tissues and is rapidly eliminated. The provisional **chronic RfD of 0.006 mg-kg-day** is calculated as follows:

$$\text{p-RfD} = \frac{\text{NOAEL}}{\text{UF}}$$

$$= \frac{6.25 \text{ mg/kg-day}}{1000}$$

$$= 0.006 \ (6\text{x}10^{-3}) \text{ mg/kg-day}$$

Confidence in the principal study is high for the same reasons as for the p-sRfD. Confidence in the database is medium. Although the long-terms effects of epichlorohydrin have not been evaluated in a second species, one subchronic and two chronic studies in rats have indicated no systemic toxicity below levels much higher than the LOAEL for male fertility. A multi-generation reproductive study has not been conducted. Developmental effects have been studied in two species and found not to be a sensitive endpoint for epichlorohydrin. The critical effect is supported by two other rat studies. Human occupational studies were negative but inconclusive. Therefore, no more than medium confidence can be given to the p-sRfD overall.

DERIVATION OF SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR EPICHLOROHYDRIN

A **chronic RfC of 0.001 mg/m^3** is listed for epichlorohydrin on IRIS (U.S. EPA, 2006a), based a NOAEL of 19 mg/m^3 for nasal lesions in rats exposed to epichlorohydrin vapor intermittently for 90 days (Quast et al., 1979). The presence of a chronic RfC on IRIS precludes derivation of a provisional chronic RfC for this chemical.

The Quast et al. (1979) study, however, can be used to derive the subchronic p-RfC. This study identified a NOAEL of 5 ppm (19 mg/m^3) for changes in the nasal turbinates of male and female F344 and Sprague-Dawley rats and B6C3F$_1$ mice exposed to epichlorohydrin vapor for 6 hours/day, 5 days/week, for 61-62 exposures. Data for female F344 rats were used for the risk assessment because the effects were more severe in rats than mice and the $NOAEL_{HEC}$ was lowest for the female F344 rats. The $NOAEL_{HEC}$ is calculated using the procedure for a respiratory effect in the extrathoracic region (U.S. EPA, 1994b), as follows:

$NOAEL_{ADJ}$ = 19 mg/m^3 x 6 hrs/24 hrs x 5 days/7 days =3.4 mg/m^3

$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x RGDR

$RDGR_{ET}$ = $(V_E / SA_{ET})_A / (V_E / SA_{ET})_H$
= (0.14 m^3/day / 15 cm^2) / (20 m^3/day / 200 cm^2) = 0.093

$NOAEL_{HEC}$ = 3.4 mg/m^3 x 0.093
= 0.317 mg/m^3 ≈ 0.32 mg/m^3

where:

$RDGR_{ET}$ = regional gas deposition ratio in the extrathoracic region
V_E = ventilation rate (m^3/day)
SA_{ET} = surface area of extrathoracic region (cm^2)
A,H = subscripts denoting laboratory animal and human, respectively
$(V_E)_A$ = 0.14 m^3/day (subchronic, female F344 rat; U.S. EPA, 1988)
$(V_E)_H$ = 20 m^3/day (U.S. EPA, 1988)
$(SA_{ET})_A$ = 15 cm^2 (U.S. EPA, 1994b)
$(SA_{ET})_H$ = 200 cm^2 (U.S. EPA, 1994b)

A provisional **subchronic RfC of 0.01 mg/m^3** is derived by applying an aggregate uncertainty factor (UF) of 30 to the $NOAEL_{HEC}$. The UF includes a factor of 10 to protect sensitive individuals and a factor of 3 for interspecies extrapolation using the dosimetric equations. An additional database uncertainty factor was not applied because male reproductive effects, a known target of this chemical, were studied in rats and rabbits and found to be of similar or lower sensitivity than the nasal lesions. In addition, developmental effects were

studied in two species and found not to be a sensitive endpoint for epichlorohydrin. The provisional subchronic RfC is calculated as follows:

$$\text{subchronic p-RfC} = NOAEL_{HEC} / UF$$
$$= 0.32 \text{ mg/m}^3 / 30$$
$$= 0.01 \text{ mg/m}^3$$

The subchronic p-RfC is essentially the same as the chronic RfC on IRIS, without the 10-fold subchronic-to-chronic uncertainty factor. Confidence in the principal study is medium. The study was well-conducted and reported histopathological data for numerous tissues including the respiratory tract. Medium confidence was assigned because an inflammatory reaction was observed in the respiratory tract of control and exposed animals and may have impaired the ability to detect compound-related lesions. Confidence in the database is medium-to-high. The nasal findings in F344 rats were supported by similar findings in Sprague-Dawley rats and $B6C3F_1$ mice. Supporting data were also located in other inhalation studies. Gestational exposure studies in rats and rabbits showed no developmental effects. The male reproductive system is known to be a target of epichlorohydrin, and male reproductive effects were studied in rats and rabbits and found to be less sensitive than nasal tissues to epichlorohydrin. However, confidence in the database is not high because a multigeneration reproduction study is not available. In addition, the occupation studies of reproductive function in humans 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, with approximate 8-hr inhalation exposure levels in the range of 0.1 to greater than 1 ppm (0.4 - 4 mg/m^3). Adjusting for continuous 24 hour/day, 7 day/week continuous exposure, these exposure levels correspond to a range of about 0.1 to 1 mg/m^3. However, the occupational studies did not examine sperm morphology or motility, which were the principal findings in Toth et al. (1991), and exposure quantification was inadequate. As sperm count also was unaffected in rats orally exposed to epichlorohydrin (Toth et al. 1989, 1991), the negative evidence for humans is inconclusive. Medium confidence in the provisional subchronic RfC follows.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR EPICHLOROHYDRIN

A cancer assessment, including derivation of an oral slope factor and inhalation unit risk, is available for epichlorohydrin on IRIS (U.S. EPA, 2006a), precluding derivation of a provisional carcinogenicity assessment for this chemical.

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