IRIS Summary

Substance code
Chloroprene; CASRN 126-99-8

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Chloroprene

File First On-Line _/_/_

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfC Assessment (I.B.)	under review	
Carcinogenicity Assessment (II.)	under review	

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Chloroprene
CASRN -- 126-99-8
Last Revised -- 0/00/0000

An oral RfD is not available at this time. There are no subchronic or chronic studies in laboratory animals. The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also 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.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Not Applicable

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

Not Applicable

___I.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

Not Applicable

___I.A.5. CONFIDENCE IN THE ORAL RfD

Not Applicable

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document – U.S. EPA, 2000

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (fax), or RIH.IRIS@EPAMAIL.EPA.GOV (email address)

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Chloroprene
CASRN -- 126-99-8
Last Revised -- 10/17/2000

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 (extrarespiratory effects). It is generally 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 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

An RfC could not be derived for $-chloroprene. The NTP (1998) chronic inhalation study in which the F344/N rat and $B6C3F_1$ mouse were exposed to chloroprene at three concentration levels did report concentration-related adverse effects in the nasal olfactory epithelium of both species. These effects normally would have been chosen as critical effects in a derivation. However, there was treatment-related low survival in all concentration groups of the male rat with statistical significance at the two highest concentrations and a positive trend. Survival of the controls was in line with historical controls. Survival was considered not related to the incidence of neoplasms which occurred at various sites. Treatment-related mortality was also seen in both sexes of mice in all concentration groups. Because of the treatment-related low survival in both species, the lowest experimental concentration (duration-adjusted concentration = 8.2 mg/m^3) was identified as a frank-effect level (FEL).

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Not Applicable

___I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

Not Applicable

___I.B.4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

Not Applicable

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Not Applicable

___I.B.7. EPA CONTACTS (INHALATION RfC)

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___II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- $-Chloroprene
CASRN -- 126-99-8
Last revised -- 00/00/0000

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 ：g/L drinking water or risk per ：g/cu.m air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with 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 -- B1; probable human carcinogen (Risk Assessment Guidelines of 1986)

Basis -- Inadequate human data and sufficient rodent (mouse and rat) studies in which exposure to airborne concentrations of chloroprene caused multi-site multiple neoplasms (NTP, 1998) form the basis for this classification. Although there is only limited evidence that chloroprene is mutagenic (i.e., H-*ras* mutations in the mouse), structural analogues (e.g., 1,3-butadiene, vinyl chloride, isoprene) are carcinogenic and mutagenic.

Under the current guidelines (U.S. EPA, 1986), chloroprene is classified as Group B1, a probable human carcinogen. Under the proposed new guidelines (U.S. EPA, 1996), chloroprene is characterized as an agent that should be treated as if it were “likely to produce cancer in humans due to the production or anticipated production of tumors by modes of action that are relevant or assumed to be relevant to human carcinogenicity.” These characterizations are based on the following summary of the evidence available:

Cancer mortality and incidence studies in humans provide inconclusive evidence that chloroprene has carcinogenic potential. The cohort study of Shouqi et al. (1989) found an increase in the standard mortality ratio (SMR) both for the entire cohort of 1,213 chloroprene/polychloroprene production workers (and most retirees) as well as SMRs for specific

cancer sites. Those workers in "high" exposure jobs had high SMRs whereas workers associated with low-level exposures had low SMRs. However, factors other than exposure to chloroprene (e.g., co-exposure to chloroprene oligomers, smoking, and alcohol consumption) that may have been contributory to the elevated SMRs were not evaluated in this study. In contrast, the cohort studies of Pell (1978) with chloroprene/polychloroprene production workers exposed from 1931-1948 and from 1957-1974 found no exposure-related increase in cancer incidence. The results of the1957-1974 cohort were confirmed by the data re-analysis of Leet and Selevan (1982). However, Leet and Selevan reported that the study had limited statistical power to detect an effect, in part, because all workers with potential for exposure, but who terminated employment before study start, were not included. Nevertheless, the absence of exposure-related cancer incidence in the cohort of the Pell study exposed from 1931-1948, a cohort likely to have been exposed to much higher concentrations than subsequent workers, diminishes the concern by Leet and Selevan.

A chronic inhalation study in both the rat and mouse (NTP, 1998) found that chloroprene produced carcinogenic and benign neoplasms at a variety of sites in both species. The multi-site nature of the neoplasms has also been observed with structural analogues such as 1,3-butadiene and isoprene in chronic inhalation studies with the same species and strains. The mode of action whereby chloroprene is believed to exert its carcinogenic potential is through production of mono- and di-epoxides, metabolites that have been identified from structural analogues. Preliminary results from ongoing in vitro studies indicate that human liver microsomes produce chloroprene mono-epoxide, albeit many-fold less than similar preparations from rat and mouse liver (Himmelstein, 1999). Chloroprene has very limited mutagenic potential as evidenced by divergent results in the Ames assay, no recessive lethal mutations in *D. melanogaster,* an absence of effect on micronuclei formation, and no dominant lethal effects in male mice. However, evidence in the $B6C3F_1$ mouse exposed to chloroprene indicates that *ras* mutations occur (Sills et al., 1999).

___II.A.2. HUMAN CARCINOGENICITY DATA

Limited. A study of lung cancer mortality among workers at two chloroprene/ polychloroprene production plants, where a primary exposure chemical is presumed to be chloroprene, found no significant elevation in lung cancer or overall cancer mortality among two cohorts, one observed for up to 40 years and the other for 17 years (Pell, 1978), despite expected higher concentrations in the earlier years. Extensive efforts were made to ensure that follow-up losses were kept to a minimum. Leet and Selevan (1982) reanalyzed the Pell (1978) results in the cohort followed for 17 years and confirmed the findings, but cautioned that the statistical power of the study was limited because previously terminated workers were not included in the cohort. On the other hand, a case-control study of 54 cancer deaths among workers at a polychloroprene production plant in China found a significantly decreased average age of death from cancer among chloroprene-exposed workers, and a significantly increased risk of cancer death associated with chloroprene exposure (Shouqi et al., 1989). The same study reported significantly increased risks of liver cancer, lung cancer, and malignant lymphoma (only one case) among a cohort of 1,213 workers exposed to chloroprene/ polychloroprene at the plant for over 15 years. Possible

confounding factors, e.g., possible co-exposure to oligomers, smoking and alcohol use, evidently were not controlled for in the analyses. A cohort study that followed 2,314 workers at an Armenian chloroprene production plant for over 40 years found a significant increase in mortality from liver cancer (Bulbulyan et al., 1999), but co-exposure to oligomers and lack of control for smoking and alcohol use were confounding factors limiting interpretation. Given the methodological limitations of the different studies and uncontrolled confounding factors, the epidemiologic evidence relating chloroprene monomer exposure as a causative factor in cancer in humans (e.g., Shoqui et al., 1989) is considered inconclusive.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. A lifetime whole-body inhalation exposure study by the National Toxicology Program reported neoplasms at multiple sites in both the F344/N rat and $B3C6F_1$ mouse (NTP, 1998). The treatment protocol involved 2-year exposures of each species (50/sex/group) to actual concentrations of 0, 12.8, 32, or 80 ppm (0, 46, 116, or 290 mg/m^3) chloroprene for 6 hours/day, 5 days/week. Concentration-related increases in tumor incidence at multiple sites were seen, including bronchiolar and alveolar adenomas/carcinomas (rats and mice), squamous cell papillomas/carcinomas in the oral cavity (rats), renal tubule adenomas (rats and mice), liver adenomas/carcinomas (female mice), hemangiosarcomas (mice), harderian gland neoplasms (mice), and thyroid gland follicular cell adenomas/carcinomas (rats). On the other hand, a lifetime whole-body inhalation exposure of the Wistar rat to actual concentrations of 0, 10, or 50 ppm (0, 36 or 181 mg/m^3) produced few neoplastic responses (Trochimowicz, 1998). The only statistically significant neoplastic finding was an increase in the incidence of mammary fibroadenomas in females in the 50 ppm group. The incidence of thyroid follicular adenomas in females in the 50 ppm group was 3/100 while the incidence of papillary carcinoma was 2/100; no neoplasms were found in the thyroid for female controls. Thyroid tumors were not seen in males. The apparent difference in the extent of response between the F344 and Wistar strains has no obvious explanation. Possibilities include strain differences in metabolism and differences in the exposure concentrations used. A lifetime oral exposure study in BD-IV rats reported statistically nonsignificant increases in thyroid, ovary, pituitary, and soft tissue tumors (Ponomarkov and Tomatis, 1980). However, inconsistencies between text and tabular presentation of data limited interpretation of the study. The treatment protocol involved weekly gavage doses of 50 mg/kg chloroprene to progeny of treated dams beginning at time of weaning and continuing for 120 weeks. The dams had been given a single gavage dose of 100 mg/kg on day 17 of gestation.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Pharmacokinetic data are being developed for chloroprene (Himmelstein, 1999). Preliminary results indicate that human liver microsomes incubated with chloroprene produce the mono-epoxide, although levels appear to be considerably less than that produced by either the F344/N or Wistar rat and the $B6C3F_1$ mouse. Structurally similar compounds, such as vinyl chloride and 1,3-butadiene, are known to be metabolized by the mixed-function oxidase system to produce reactive epoxide intermediates that are considered to initiate carcinogenesis. Chloroprene analogs, such as isoprene and 1,3-butadiene, are genotoxic.

Chloroprene appears to have limited mutagenic potential as measured by the Ames assay. Highly purified chloroprene was slightly mutagenic in *S. typhimurium* TA100 without S9 metabolic activation, and its mutagenicity was increased with S9 metabolic activation (Bartsch et al., 1975); dimers were ruled out as a cause. However, Westphal et al. (1994) found that freshly distilled chloroprene was negative with TA100, with or without S9. Recent studies by Himmelstein et al. (2000) have shown that chloroprene mono-epoxide is mutagenic in TA100, TA1535, TA97a, and TA98. Tests for recessive-lethal mutations in *D. melanogaster* were conflicting. One report (Vogel, 1979) found highly-purified chloroprene dissolved in DMSO to produce recessive-lethal mutations (Berlin-K strain) whereas Foureman et al. (1994) found chloroprene (purity not specified) dissolved in ethanol to have no effects in the Canton S strain. Strain differences and/or interactions with DMSO are suggested as possible explanatory factors in these results. Gahlman et al. (1993) has demonstrated that some chemicals can react with DMSO to form degradation products that are mutagenic. Sills et al. (1999) reported that H- and K-*ras* mutations in neoplasms from mice exposed to chloroprene may be one oncogenic-activating mechanism.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None. No adequate data are available to derive an oral exposure risk estimate for chloroprene. Because it is a highly volatile liquid, long-term exposure to chloroprene through ingestion is unlikely.

___II.B.1. SUMMARY OF RISK ESTIMATES

Not Applicable

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Not Applicable

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

Not Applicable

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

Not Applicable

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___II.C.1. SUMMARY OF RISK ESTIMATES

____II.C.1.1. Inhalation Unit Risk –1.3 x 10^{-4} or 2.6 x 10^{-4} per (：g/cu.m) based on dosimetric and mode of action considerations discussed in Appendix B of the Toxicological Review.

____II.C. 1.2. Extrapolation Method –Time-to-tumor model applied to female mouse transformed data (combined tumor incidence), with Maximum Likelihood Estimates (MLEs) summed across tumor sites (extra risk).

The inhalation unit risk indicated above is greater than that obtained by a quantal linearized multistage (LMS) approach using the GLOBAL86 computer program. In this latter approach, the inhalation unit risk based on lung tumor incidence from female mice ranges from 8.6 x 10^{-5} (if mode of action is systemic) to 2.6 x 10^{-5} (if direct acting). When derived using male mouse circulatory system tumors, the risk was calculated as 3.4 x 10^{-5}. The quantal approach does not fully characterize the cancer potency because, unlike the time-to-tumor method, it does not take into account the multiple tumor sites at higher exposure concentrations nor chloroprene-related decrease in survival. Further details are provided in Appendix B of the Toxicological Review.

Air Concentrations at Specified Risk Levels

Risk level	Concentration
E-4(1 in 10,000)	8E-1 to 4E-1 ：g/m^3
E-5 (1 in 100,000)	8E-2 to 4E-2 ：g/m^3
E-6 (1 in 1,000,000)	8E-3 to 4E-3 ：g/m^3

___II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Species/Strain Tumor Type	Dose Administered in Air (Duration-adjusted)		Tumor Incidence (survival-adjusted)[a]	Reference
female mouse/B6C3F1; alveolar/bronchiolar adenomas and carcinomas	Route: Inhalation			NTP, 1998
	ppm	mg/cu.m		
	0	0	4/49	
	2.3	8.2	28/47	
	5.7	20.6	34/49	
	14.3	51.4	42/48	

[a]adjusted for death before first observed tumor

___II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

HEC concentrations were derived for lung tumors based on either chloroprene acting directly, in which case an RGDR value of 3.3 was applied to the duration-adjusted concentration or that it acted systemically, in which case the RDGR value was not applied. This approach was used both for quantal and time-to-tumor analysis.

___II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 2000

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to _____.

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- 00/00/0000

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (fax), or RIH.IRIS@EPAMAIL.EPA.GOV (email address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Substance Name -- Chloroprene
CASRN -- 126-99-8
Last Revised –10/11/2000

__VI.A. ORAL RfD REFERENCES

None

__VI.B. INHALATION RfC REFERENCES

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__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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_VII. REVISION HISTORY

Substance Name
CASRN -- __-__-__
Last Revised -- 00/00/00

_VIII. SYNONYMS

Substance Name -- Chloroprene
CASRN -- 126-99-8
Last Revised -- _/_/_

126-99-8
chlorobutadiene
2-chlorobuta-1,3-diene
2-chloro-1,3-butadiene

$-chloroprene