NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for CHLOROPRENE

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NTP Report on Carcinogens Listing for Chloroprene

Carcinogenicity

Chloroprene is *reasonably anticipated to be a human carcinogen* based on evidence of benign and malignant tumor formation at multiple tissue sites in multiple species of experimental animals (NTP, 1998). Inhalation exposure of rats to chloroprene vapors induced increased incidences of neoplasms of the oral cavity, thyroid gland, and kidney in males and females, neoplasms of the lung in males, and neoplasms of the mammary gland in females. Inhalation exposure of mice to chloroprene vapors induced increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), forestomach, and harderian gland in males and females, kidney neoplasms in males, and neoplasms of the mammary gland, liver, Zymbal's gland, skin, and mesentery in females.

There is limited evidence for the carcinogenicity of chloroprene in humans. Data from two studies suggest that occupational exposure to chloroprene may increase cancer risk for digestive and lymphatic/hematopoietic tumors (Pell, 1978) and for liver, lung, and lymphatic tumors (Li et al., 1989).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Recent studies on the genotoxicity of chloroprene have been uniformly negative; conflicting results with earlier studies have been attributed to differences in the age and purity of the test samples. Positive mutagenicity results of chloroprene in bacteria (Bartsch et al., 1975; 1979) were considered to be due to cyclic dimers that accumulate in aged samples (Westphal et al., 1994). At the exposure concentrations used in the cancer inhalation studies, chloroprene did not induce sister chromatid exchanges or chromosomal aberrations in mouse bone marrow cells nor did it increase the frequency of micronucleated erythrocytes in peripheral blood (Tice et al., 1988). Oxidation of chloroprene to epoxide intermediates has been postulated to occur based on the detection of alkylated derivatives of the trapping agent 4-(4-nitrobenzyl)pyridine in incubations of chloroprene and mouse liver microsomes (Bartsch et al., 1979). Chloroprene-induced lung and harderian gland neoplasms in mice had a high frequency of unique K-*ras* mutations (NTP, 1998). Chloroprene (chemical name: 2-chloro-1,3-butadiene) induced all of the types of tumors that were induced by 1,3-butadiene in mice except for lymphomas and ovarian neoplasms.

No data are available that would suggest that the mechanisms thought to account for tumor induction by chloroprene in experimental animals would not also operate in humans.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded, or

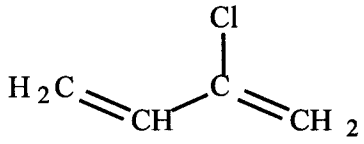
There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 CHEMICAL PROPERTIES

Chloroprene
[126-99-8]



1.1 Chemical Identification

Chloroprene (C_4H_5Cl, mol. wt. = 88.54) is also called:
1,3-Butadiene, 2-chloro- (8CI9CI)
Chlorobutadiene
2-Chlorobutadiene
2-Chlorobutadiene-1,3
β-Chlorobutadiene
2-Chlorobuta-1,3-diene
2-Chloro-1,3-butadiene
Chloroerythrene
2-Chloroprene
β-Chloroprene
Chloroprene, inhibited
Chloroprene, uninhibited

Chloroprene has a UN shipping number of UN1991. Polychloroprene is also called neoprene.

1.2 Physical-Chemical Properties

Property	Information	Reference
Color	Colorless	Lewis (1992)
Physical State	Liquid	Lewis (1992)
Melting Point, °C	-130 ± 2	Johnson (1979a)
Boiling Point, °C	59.4	Lewis (1992)
Specific Gravity at 20 °C	0.9585	Johnson (1979a)
Odor	Pungent, ethereal odor	HSDB (1997)
Solubility:		
Water	Slightly soluble in water	Lewis (1992)
Organic Solvents	Miscible in ethyl alcohol and ethyl ether	Lewis (1992)
Partition Coefficients:		
Log octanol/water	2.06 (est)	HSDB (1997)
Vapor pressure, mm Hg at 20 °C	174	HSDB (1997)
Henry's Law Constant	3.2 x 10^{-2} atm-m^3/mole at 25 °C	HSDB (1997)

Chloroprene is a highly dangerous fire hazard. When exposed to heat or flame, it is explosive in vapor form. Explosive limits in air are commonly given as 4.0% to 20.0%. However, a DuPont Dow Elastomers spokesman (Lynch, 1997 personal communication) states the actual values are 1.9% to 10% in air.

Chloroprene will rapidly auto-oxidize in air to form acidic materials and unstable peroxides, which catalyze exothermic polymerization of the monomer. It will also polymerize at room temperature to produce cyclic dimers or open-chain, high-molecular-weight products. When heated to decomposition, it emits hydrogen chloride (HSDB, 1997).

One part-per-million (1 ppm) chloroprene in air is equivalent to 3.68 mg/m^3 (Ludwig, 1994).

2.0 HUMAN EXPOSURE

2.1 Use

Chloroprene is primarily used as a monomer in the production of the elastomer polychloroprene (neoprene), a synthetic rubber used in the production of automotive and mechanical rubber goods, adhesives, caulks, flame-resistant cushioning, construction goods, fabric coatings, sealants for dams or locks in waterways, roof coatings, fiber binding, footwear, and other applications requiring chemical, oil, or weather resistance, or high gum strength (IARC, 1979a; Johnson, 1979a; Johnson 1979b; Budavari, 1996; NTP, 1998).

2.2 Production Processes and Volume

Chloroprene is produced by the chlorination of 1,3-butadiene or by the addition of hydrochloric acid to dimerized acetylene (Johnson, 1979a; IARC, 1979a; NTP, 1998). 1,3-Butadiene chlorination became more economical about 1965 as the price of acetylene increased and that of 1,3-butadiene decreased. 1,3-Butadiene chlorination in the liquid or vapor phase is the current method of choice for the production of chloroprene in the United States (Lynch, 1997 personal communication). Chloroprene production from 1,3-butadiene involves three essential steps: chlorination, isomerization, and caustic dehydrochlorination (Johnson, 1979a). Vapor-phase chlorination of 1,3-butadiene gives a mixture of 3,4-dichloro-1-butene and 1,4-dichloro-2-butene. Liquid-phase catalytic rearrangement of 1,4-dichloro-2-butene gives 3,4-dichloro-1-butene, which is subsequently dehydrohalogenated by heating with aqueous sodium hydroxide in the absence of oxygen. Chloroprene is separated by distillation (Fishbein, 1976; Kirshenbaum, 1978).

E.I. DuPont de Nemours and Company at the DuPont Pontchartrain Works, in La Place, LA, is listed as the only producer of chloroprene for sale and distribution during 1995 (SRI International, 1996). Other plants as reported in the 1995 Toxic Chemicals Release Inventory (TRI95, 1997) produced chloroprene for on-site use and processing, as a by-product of vinyl chloride production, or as a manufacturing impurity.

Chloroprene is used almost exclusively to produce polychloroprene. Chloroprene is sold to only three U.S. companies for polychloroprene manufacture; less than 20 lb/yr is sold for research applications (Lynch, 1997 personal communication). The total estimated production of polychloroprene in 1986-1988 was approximately 250-300 million pounds (113,000 to 136,000 Mg [metric tons]), and the volume in 1995-1996 was approximately 200-250 million pounds (90,700 to 113,000 Mg) (Lynch, 1997 personal communication). These production numbers are higher than those given for U.S. polychloroprene shipments, which represent only off-site

transfers, based on information from the International Institute of Synthetic Rubber Producers (e.g., 10,000 Mg in 1995-1996) (Chem. Eng. News, 1997).

2.3 Environmental Exposure

Chloroprene is not known to occur naturally in the environment (HSDB, 1997). The effluent and emissions from facilities that use chloroprene to produce polychloroprene elastomers are the main sources of environmental releases of chloroprene. Of 14 facilities reporting atmospheric releases of chloroprene for 1995 (TRI95, 1997), 8 plants reported individual atmospheric releases from 2 to 481,871 lb (0.0009 to 218.6 Mg), for a total release of 983,888 lb (446.3 Mg). Three plants in Kentucky, Texas, and Louisiana each reported atmospheric releases of >100,000 lb, which accounted for most of the reported chloroprene releases. One of the sites is the producer, the other two sites convert chloroprene to polychloroprene. One of the 14 facilities also reported a chloroprene release consisting of 60,000 lb (27.2 Mg) by injection in deep wells, while another facility released 5,104 lb (2.315 Mg) to land.

Volatilization is the primary mechanism of removal of chloroprene from water; chemical hydrolysis, adsorption to suspended solids or sediments, or bioaccumulation (bioconcentration factor = 22) in aquatic animals is not expected to occur. In the atmosphere, the primary mechanism of chloroprene removal is reaction with photochemically generated hydroxyl radicals with smaller amounts removed by reaction with ozone. Formaldehyde, 1-chloroacrolein, glyoxal, chloroglyoxal, and chlorohydroxy acids or aldehydes are expected products of these reactions. If released to soil, chloroprene should be susceptible to removal by rapid volatilization and transport by leaching into groundwater (HSDB, 1997).

The Urban Air Toxics Monitoring Program (UATMP) was developed in 1987 by the United States Environmental Protection Agency. The 1990 program, covering March 1990 through February 1991, collected 349 samples from 12 sites every 12 days for 24-hour periods. Chloroprene was identified in 88 of 349 samples, (25.2%). The range of concentrations was 0.01-1.78 ppbv for samples in which chloroprene was identified with a mean of 0.26 ppbv (0.94 $\mu g/m^3$). The mean concentration based on all samples was 0.06 ppbv, where zero was used for samples not containing chloroprene (McAllister et al., 1991).

2.4 Occupational Exposure

Upon contact with the skin and eyes, chloroprene may cause burns, and it can be fatal if inhaled, ingested, or absorbed through the skin (HSDB, 1997). The most probable route of human exposure to this compound is inhalation by workers employed in the manufacture of chloroprene or polychloroprene (NTP, 1998). Infante (1977) reported that an estimated 2,500 to 3,000 workers were exposed to chloroprene during its manufacture and polymerization. NIOSH (1990) conducted a National Occupational Exposure Survey (NOES) on chloroprene during 1980 through 1983 and reported that an estimated 17,700 workers, including 650 females, were potentially exposed occupationally to chloroprene or polychloroprene (**Table 2-1**). A large number of the workers were employed in auto repair services; their inclusion is probably attributable to their use of polychloroprene in belts, hoses, gaskets, and adhesives. Since residual monomer is appreciable only in polychloroprene latex (≤0.5% monomer), their inclusion may overestimate the actual number of workers exposed to chloroprene. DuPont Dow Elastomers

(Lynch, 1997 personal communication) estimated that fewer than 500 workers are exposed to chloroprene during manufacture. The company currently meets its internal control limit of 10 ppm, with the majority (>95%) of the time-weighted exposures <2 ppm (Lynch, 1997 personal communication).

Table 2-1. NIOSH National Occupational Exposure Survey (NOES 1980-1983)[a]: By Industry

Industry	Number of Plants	Number of Employees	Number of Female Employees
Special Trade Contractors	198	396	
Food and Kindred Products	112	335	
Apparel and Other Textile Products	59	353	353
Lumber and Wood Products	12	1168	
Paper and Allied Products	22	216	
Printing and Publishing	11	387	
Chemicals and Allied Products	47	659	15
Rubber and Miscellaneous Plastics and Products	163	6055	286
Stone, Clay, and Glass Products	109	264	
Miscellaneous Manufacturing Industries	30	268	
Electric, Gas, and Sanitary Services	79	236	
Wholesale Trade - Durable Foods	171	1199	
Auto Repair, Services, and Garages	844	6175	
Health Services	8	41	
Total	1865	17752	654

[a] NIOSH (1990)

2.5 Regulations and Criteria

Chloroprene is regulated by the U.S. Environmental Protection Agency (EPA) under the Clean Air Act (CAA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and Superfund Amendments and Reauthorization Act (SARA Title III, Section 313). As regulated by the U.S. Food and Drug Administration (U.S. FDA, 21 CFR 175.105, 175.300, 177.2600), chloroprene may be used in adhesives assuming that there is a functional barrier between the adhesive and food or the exposure is the minimum acceptable under good manufacturing practice; chloroprene polymers may be safely used in rubber products intended for repeated use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food. The Occupational Safety and Health Administration (OSHA, 29 CFR 1910.1000) set an 8-hour time-weighted average (TWA) permissible exposure limit (PEL) of 25 ppm (90 mg/m^3) for employee exposure to chloroprene during any 8-hour work shift of a 40-hour work week.

The American Conference of Governmental Industrial Hygienists (ACGIH, 1996) recommends a threshold limit value of 10 ppm (36 mg/m^3) for chloroprene in the work environment. NIOSH recommends a 15-minute ceiling value of 1 ppm (3.6 mg/m^3) for chloroprene (Ludwig, 1994).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 60—PART 60—STANDARDS OF PERFORMANCE FOR NEW STATIONARY SOURCES. Promulgated: 36 FR 24877, 12/23/71.	The provisions of this part apply to the owner/operator of any stationary source which contains an affected facility (a stationary source with an apparatus to which a standard is applicable).
	40 CFR 60.740—Subpart VVV—Standards of Performance for Polymeric Coating of Supporting Substrates Facilities.	
	40 CFR 61—PART 61—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS. Promulgated: 38 FR 8826, 04/06/73. U.S. Code: 7401, 7412, 7414, 7416, 7601.	This part lists substances that, pursuant to section 112 of the CAA, have been designated as hazardous air pollutants (HAPs), and applies to the owner or operator of any stationary source for which a standard is prescribed under this part.
	40 CFR 61.01 ff.—Subpart A—Lists of pollutants and applicability of part 61. Promulgated: 59 FR 12429, 03/16/94. U.S. Code: 42 U.S.C. 7661.	Substances that, pursuant to section 112 of the CAA, have been designated as hazardous air pollutants. Substances for which a Federal Register notice has been published that included consideration of the serious health effects from ambient air exposure.
	40 CFR 63—PART 63—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Code: 7401 et seq.	Standards that regulate specific categories of stationary sources that emit (or have potential to emit) one or more hazardous air pollutants are listed in this part pursuant to section 112(b) of the CAA.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 63.100 ff.—Subpart F—National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry. Promulgated: 59 FR 19454, 04/22/94. Owners and operators of sources subject to this subpart shall comply with the requirements of subparts G and H of this part.	This subpart applies to chemical manufacturing process units that manufacture one or more of the chemicals listed in Table 1 and Table 2 of this subpart and are located at a plant site that is a major source as defined in section 112(a) of CAA.
	40 CFR 63.110 ff.—Subpart G—National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry for Process Vents. Promulgated: 59 FR 04/22/94. Emission standard: Emissions of organic HAPs shall be controlled to the level represented by a given equation (see 40 CFR 63.112[a]). Specific process vent and methods and procedures provisions apply.	The provisions of this subpart apply to all process vents, storage vessels, transfer racks, and wastewater streams within a source subject to subpart F of this part.
	40 CFR 63.680 ff.—Subpart DD—Applicability and designation of affected sources. Promulgated: 61 FR 34158, 07/01/96.	The provisions of this subpart apply to plant sites at which a major source of HAP Emissions occurs as defined in 40 CFR 63.2, or at which is located one or more operations that receives offsite materials as specified in 40 CFR 63.680(b).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 63.800 ff.—Subpart JJ—National Emission Standards for Wood Furniture Manufacturing Operations. Promulgated: 60 FR 62936, 12/07/95. Emission limitations for existing sources presented in Table 3 of this subpart shall be met using any of the compliance methods in 40 CFR 63.804. Specific limitations apply to limiting VHAP emissions from contact adhesives. Specific work and compliance requirements apply.	The provisions of this subpart apply to each facility that is engaged in the manufacture of wood furniture or wood furniture components and that is a major source as defined in 40 CFR 63.2.
	40 CFR 258—PART 258—CRITERIA FOR MUNICIPAL SOLID WASTE LANDFILLS. Promulgated: 56 FR 51016, 10/09/91. U.S. Code: 33 U.S.C. 1345(d) and (e); 42 U.S.C. 6907(a)(3), 6912(a), 6944(a) and 6949a(c).	
	40 CFR 261—PART 261—IDENTIFICATION AND LISTING OF HAZARDOUS WASTE, Appendix VIII—Hazardous Constituents. Promulgated: 45 FR 33119, 05/19/80; 53 FR 13388, 04/22/88. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, 6922, and 6938. Although listed in Appendix VIII, an associated hazardous waste number is not given for chloroprene.	Appendix VIII is a consolidated list of hazardous constituents identified in this part. Solid wastes containing these constituents are subject to notification requirements of RCRA section 3010 and must be disposed of in RCRA-permitted facilities.
	40 CFR 261.30 ff.—Subpart D—Lists of Hazardous Wastes.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 264—PART 264—STANDARDS FOR OWNERS AND OPERATORS OF HAZARDOUS WASTE TREATMENT, STORAGE, AND DISPOSAL FACILITIES, Appendix IX—List (Phase 1) of Hazardous Constituents for Ground-Water Monitoring. Promulgated: 45 FR 33221, 05/19/80. U.S. Code: 42 U.S.C. 6905, 6912(a), 6924, and 6925.	The provisions of this part establish minimum national standards which define the acceptable management of hazardous waste, and apply to owners and operators of all facilities which treat, store, or dispose of hazardous waste; exceptions do exist. This specifically is a subset of RCRA Appendix VIII compounds that had suitable analytical methods for monitoring groundwater.
	40 CFR 266—PART 266—STANDARDS FOR THE MANAGEMENT OF SPECIFIC HAZARDOUS WASTES AND SPECIFIC TYPES OF HAZARDOUS WASTE MANAGEMENT FACILITIES. Promulgated: 50 FR 666, 01/04/85. U.S. Code: 42 U.S.C. 6905, 6912(a), 6924, and 6934.	Standards to control emissions are promulgated for generators, transporters, and users of materials used in a manner that constitutes disposal. Affected compounds are listed in 40 CFR 266.40.
	40 CFR 266—Subpart H—Hazardous Waste Burned in Boilers and Industrial Furnaces.	
	40 CFR 268.40 ff.—Subpart D—Treatment Standards. Promulgated: 56 FR 3879, 01/31/91.	Restricted wastes identified in sec. 268.41 may be land disposed only if an extract of the waste or of the treatment residue of the waste developed using the test method in Appendix II of part 261 does not exceed the value shown in Table CCWE of sec. 268.41 for any hazardous constituent listed in CCWE for that waste. Exceptions do apply.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 302—PART 302—DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Code: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.	This part designates under section 102(a) of CERCLA 1980 those substances in the statutes referred to in section 101(14) of CERCLA, identifies reportable quantities for these substances, and sets forth the notification requirements for releases of these substances. This part also sets forth reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the CWA.
	40 CFR 372—PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88. U.S. Code: 42 U.S.C. 11013, 11028.	This part sets forth requirements for the submission of information relating to the release of toxic chemicals under section 313 of Title III of SARA (1986). Information collected under this part is intended to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, and to aid in the development of regulations, guidelines, and standards. See section 372.65 for chemicals and chemical categories to which this part applies.
	40 CFR 414—PART 414—ORGANIC CHEMICALS, PLASTICS, AND SYNTHETIC FIBERS. Promulgated: 52 FR 42568, 11/05/87. U.S. Code: 33 U.S.C. 1311, 1314, 1316, 1317, and 1361.	Limitations representing the degree of effluent reduction attainable by application of best available technology (BAT). EPA gives pretreatment standards for existing sources (PSES) for metals and organics in effluents from several manufacturing categories.
	40 CFR 712—PART 712—CHEMICAL INFORMATION RULES.	
	40 CFR 716—PART 716—HEALTH AND SAFETY DATA REPORTING. Promulgated: 51 FR 32726, 09/15/86. U.S. Code: 15 U.S.C. 2607(d).	The provisions of this part require the submission of lists and copies of health and safety studies on chemical substances and mixtures selected for priority consideration for testing rules under section 4(a) of TSCA and on other chemicals for which EPA requires health and safety information in fulfilling the purposes of TSCA.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
FDA	21 CFR 175—PART 175—INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS. Promulgated: 42 FR 14534 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 348, 379e.	The subparts A through C deal with components of adhesives and of coatings that may migrate into food from packaging.
	21 CFR 175.105 ff.—Subpart B—Substances for Use Only as Components of Adhesives.	Chloroprene may be used in adhesives assuming that there is a functional barrier between the adhesive and food or the exposure is the minimum acceptable under good manufacturing practice.
	21 CFR 177—PART 177—INDIRECT FOOD ADDITIVES: POLYMERS. Promulgated: 42 FR 14572 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 348, 379e.	Subparts A through C govern polymers used as components of single- and repeated-use food-contact surfaces and components of articles for repeated use.
	21 CFR 177.2600—Sec. 177.2600 Rubber articles intended for repeated use.	Chloroprene polymers may be safely used in rubber products intended for repeated use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.
NIOSH	8/77. Criteria for a Recommended Standard: Occupational Exposure to Chloroprene. Pub. No. 77-210, NTIS No. PB274-777.	
	1/20/75. Current Intelligence Bulletin #1—Chloroprene. Pub. No. 78-127, NTIS No. PB83-105080.	
	8/1/88. NIOSH testimony on the OSHA Proposed Rule on Air Contaminants, Docket No. H-020, NTIS No. PB91-115337.	NIOSH concurred that the proposed OSHA PEL, an 8-hr TWA of 10 ppm was appropriate (OSHA, 1988). However, the OSHA rule was remanded by the U.S. Circuit Court of Appeals and the limits are not currently in force.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
NIOSH	Recommended workplace short-term exposure limit to reduce or eliminate adverse health effects and accidental injuries.	NIOSH recommended that chloroprene be treated as a potential occupational carcinogen. Summary of NIOSH recommendation: recommended exposure limit (REL) 1 ppm (3.6 mg/m^3) as a 15-minute ceiling limit.
OSHA	29 CFR 1910.1000—Sec. 1910.1000 Air Contaminants.	8-hr TWA: 25 ppm (90 mg/m^3). An employee's exposure to chloroprene shall not exceed the 8-hour time weighted average (TWA; specified in Table Z-1) in any 8-hour work shift of a 40-hour work week.
	29 CFR 1915—Subpart Z—Toxic and Hazardous Substances. Promulgated: 58 FR 35514, 07/01/93.	8-hr TWA: 25 ppm (90 mg/m^3).
	29 CFR 1926—Subpart D—Occupational Health and Environmental Controls.	
	29 CFR 1926.55—Sec. 1926.55 Gases, vapors, fumes, dusts, and mists.	Exposure of employees via inhalation, ingestion, skin absorption, or contact with any material or substance at a concentration above those specified in the "Threshold Limit Values of Airborne Contaminants for 1970" of the American Conference of Governmental Industrial Hygienists, shall be avoided. See Criteria section of this table.

[a] The regulations in this table have been updated through the 62 Federal Register 23394, April 30, 1997.

3.0 HUMAN STUDIES

Human carcinogenicity studies reported prior to 1987 were reviewed by IARC (IARC, 1979a, pp. 140-141, see Appendix A; IARC, 1982, pp. 89-91, see Appendix B; IARC, 1987a, p. 160, see Appendix C). An additional study, reported by Li et al. (1989), is reviewed below and in **Table 3-1**. More recent studies were not identified as of August 1997.

The conclusion of IARC (1979a, 1982, 1987a) was that the three epidemiological studies reviewed, although suggestive of an increased incidence of lung tumors (Khachatryan, 1972a, cited in IARC, 1979a), skin tumors (Khachatryan, 1972b, cited in IARC, 1979a), and digestive and lymphatic/hematopoietic tumors in one of two cohorts (not statistically significant) (Pell, 1978, cited in IARC, 1979a), were inadequate to demonstrate the carcinogenicity of chloroprene in humans because of numerous methodological deficiencies. The IARC review also noted a case report of an angiosarcoma of the liver in a worker exposed to chloroprene and possibly thermal degradation products of neoprene while vulcanizing and sawing neoprene objects as reported by Infante (1977) (See also Infante et al., 1977.). Average chloroprene concentrations at the plant were 0.14 ppm (area sampling) and 0.2 ppm (personal sampling) (Infante, 1977).

The more recent study conducted by Li et al. (1989) reported a significant association between cancer deaths and exposure to chloroprene in a case-control and cohort study of workers in a Chinese chloroprene and neoprene production plant. Chloroprene was manufactured by the acetylene process. In the nested case-control analysis, workers who died from cancer were pair matched with noncancer worker deaths, according to sex, age at death ± 2 years, and date of death ± 2 years. Chloroprene exposure status (yes/no and low and high) was determined based upon specific job and plant location. The prevalence of presumed chloroprene exposure among the 54 eligible cancer deaths was 29.6%, compared to 7.4% among noncancer (control) deaths (odds ratio = 13). Overall, the average age at death of chloroprene-exposed workers was 41.95 ± 5.5 years, compared to that of unexposed workers at 54.6 ± 9.5 years. In the cohort study, of the 1,213 workers followed (of 1,258 workers originally selected [the original plant worker size was not specified] all had been potentially exposed to chloroprene for at least a year before June 30, 1980. Of these, 852 (70.2%) had exposure histories >15 years; 381 (31.5%), >20 years; and 149 (11.6%), >25 years. The total cohort SMR for all cancers was 2.38 ($p < 0.01$). For low-exposure groups, the SMRs were either 0 (no cases observed) or around 1.00. Among the potentially high-exposed occupations, maintenance workers had the highest risk for cancers, including for liver (SMR = 16.7; 2 observed/0.12 expected), lung (50.0; 1 observed/0.02 expected), and lymphoma (100.0; 1 observed/0.01 expected). Other occupations such as monomer operators and polymer mechanics also had elevated SMRs for these and other tumor sites (nasopharynx, stomach, brain). This study provides suggestive evidence for an association between occupational exposure to chloroprene and an increased risk of several specific cancers. However, a number of study limitations should be noted, including the relatively small cohort size, potential exposure to other carcinogens (intermediates in the acetylene process used to produce chloroprene), uncontrolled lifestyle factors, limited exposure assessment, and lack of analyses stratifying by factors such as latency periods. [It should be noted that most of the world's production of chloroprene does not use acetylene as a starting material (Lynch, 1997 personal communication).]

Table 3-1. Post IARC (1987) Human Studies for Chloroprene

Design	Population Group	Exposure	Effects	Potential Confounders/Effects	Comments	Reference
case-control	**Cases:** 55 former employees of a chloroprene and neoprene production plant in China **Controls:** 54 former employees of the production plant, matched to cases by sex, age at death (± 2 yr), and date of death (± 2 yr) cause of death (cancer or noncancer) from registries in plant and police substation; verification from hospital medical records	**Categories:** expected exposure (high or low) in three plant areas (monomer workshop, neoprene workshop, lab); opinions of workers and administrators **Duration:** 16 of 55 workers exposed from 3-23 yr (median = 11 yr)	**Evaluation:** 1) compared percentage cancer deaths and average age at death from cancer of exposed and unexposed workers 2) calculated odds ratio (OR) from paired data on cancer mortality 1) cancer deaths in exposed workers = 29.6% of total matched pairs; noncancer deaths in exposed workers = 7.4% of total matched pairs (χ^2 = 8.8, p<0.005); average age at death in exposed workers was 12.7 years younger than that of unexposed workers (t = 2.98; p<0.001) 2) OR = 13 (χ^2 = 8.62; p <0.005)	Exposure to other carcinogens (tobacco, alcohol, etc.).	none	Li et al. (1989)
cohort	1213 former employees of chloroprene and neoprene production plant in China; response rate = 96.4%; all potentially exposed to chloroprene for ≥ 1 yr before 6/30/80	**Categories:** expected exposure (high or low) of workers in three plant areas (monomer workshop, neoprene workshop, lab); opinions of workers and administrators **Duration:** 852 workers had exposure history of >15 yr; 381 workers had exposure history of > 20 yr; 149 workers had exposure history of > 25 yr	**Evaluation:** Calculated standardized mortality ratios (SMRs) observed/expected) for total cohort, occupation-specific subgroups, cancer sites; based on sex- and age-specific cancer mortality in the local region SMR=2.38 (p <0.01; 16/6.72) for total cohort SMR=16.7 (p <0.05; 2/0.12) for liver cancer in maintenance workers SMR=50.0 (p <0.05; 1/0.02) for lung cancer in maintenance workers SMR=100.0 (p <0.05; 1/0.01) for lymphoma in maintenance workers all SMRs for high-exposure occupations were significant (p <0.05 or p <0.01) all SMRs for low-exposure occupations were 0 or ~1	Exposures to other carcinogens (tobacco, alcohol, etc.).	Study limitations include small cohort size, limited exposure assessment, no stratifying by factors such as latency periods	Li et al. (1989)

Abbreviations: OR = odds ratio; SMR = standardized mortality ratio

4.0 EXPERIMENTAL CARCINOGENESIS

Experimental carcinogenicity studies reported prior to 1987 were reviewed by IARC (IARC, 1979a, pp. 135-136, see Appendix A; IARC, 1982, pp. 89-91, see Appendix B; IARC, 1987a, p. 160, see Appendix C). These studies, any additional tumor studies reported prior to 1996, and the NTP inhalation bioassay are summarized by NTP (1998; see Appendix D). Another experimental inhalation carcinogenicity study is also described.

The negative tumor studies (one oral gavage, one skin paint, one intratracheal instillation, one subcutaneous injection) were considered inadequate by IARC (1979a; 1982, 1987a).

The more recent Dong et al. (1989) inhalation study reported a significant dose-dependent increase in lung tumors in chloroprene-exposed Kunming albino mice. In this study, mice (sex not provided) were exposed to 0, 2.9, 19.2, or 189.0 mg/m^3 (0, 0.8, 5.3, or 52 ppm) in static inhalation chambers, 4 hr/day, 6 days/week for 7 mo. The incidence of lung tumors was significantly increased at all dose levels, from 1.3% (1/77 mice) in the control group to 8.1% (9/111 mice; $p < 0.05$), 9.4% (10/106 mice; $p < 0.05$), and 19.7% (26/132 mice; $p < 0.01$) at the low-, mid-, and high-dose levels, respectively. The multiplicity of tumors also showed a dose-response relationship, with the increase at the high-dose group being significantly increased over that in the control group (0.273/mouse versus 0.013/mouse in the control group; $p < 0.001$). The majority of lung tumors were papilloadenomas (50/57), with a few adenomas (7/57). No information on the purity of the chloroprene or the presence of degradation products was provided.

In the NTP bioassay (NTP, 1998), there was clear evidence of carcinogenic activity in male and female F344 rats based on an increased incidence of neoplasms of the oral cavity, thyroid gland, kidney, lung (males), and mammary gland (females). There was also clear evidence of carcinogenic activity in male B6C3F$_1$ mice based on an increased incidence of neoplasms of the lung, circulatory system (hemangiomas, hemangiosarcomas), harderian gland, forestomach, and kidney; and clear evidence of carcinogenic activity in female B6C3F$_1$ mice based on an increased incidence of neoplasms of the lung, circulatory system (hemangiomas, hemangiosarcomas), harderian gland, mammary gland, liver, skin, mesentery, forestomach, and Zymbal's gland. The induced carcinogenic response in mice and rats occurred under exposure conditions where the concentration of chloroprene cyclic decomposition products in the distribution line and the exposure chambers, as determined by gas chromatography, was ≤0.1% of the chloroprene concentration (NTP, 1998).

One chronic inhalation study conducted in the late 1970s (Trochimowicz et al., 1998) with rats and hamsters did not find evidence for the carcinogenicity of chloroprene. [This study was not made available to NTP until after the decision to list chloroprene as reasonably anticipated to be a human carcinogen. However, the hamster study (Reuzel and Bosland, 1980 draft) and the rat study (Reuzel et al., 1980) were available as part of an extensive TSCA test submission to the U.S. EPA by DuPont in 1985. These experiments were not discussed in NTP (1998) or its 1996 draft or in IARC (1987b).] In this study, conducted at the TNO-CIVO Toxicology and Nutrition Institute during 1976-78, groups of 100 male and female Wistar rats and Syrian golden hamsters were exposed to 0, 10, or 50 ppm chloroprene for 6 hr/day, 5 days/wk for 24 mo (rats) or 18 mo (hamsters). Chloroprene vapor for the exposure chambers was generated daily by passing nitrogen through liquid chloroprene at 0 °C (99.6% β-

chloroprene, 0.3% α-chloroprene, <50 ppm chloroprene dimers), and the vapor was directed into chambers through Teflon® and stainless steel transport tubes. After 72 wk there were accidental deaths of 87 male and 73 female rats in groups exposed to 10 ppm; consequently, tumor incidence in these groups was not statistically evaluated. In rats exposed to 50 ppm and sacrificed at two years, no difference in tumor incidence was observed between control and test groups. Hamsters exposed to 10 or 50 ppm for 18 mo also showed no increase in tumor incidence at any site.

5.0 GENOTOXICITY

Genotoxicity studies were reviewed by IARC (IARC, 1979a, pp. 137-138, see Appendix A; IARC, 1982, pp. 89-91, see Appendix B; IARC, 1987a, p. 160, see Appendix C). These studies, and additional studies reported prior to 1996, are reviewed in NTP (1998; see Appendix D). More recent studies were not located.

Chloroprene was most often reported as negative for genotoxic activity in prokaryotic, lower eukaryotic, and *in vitro* and *in vivo* mammalian assays. Pure chloroprene was nonmutagenic in *Salmonella typhimurium*, with and without metabolic activation, while other studies reported a significant increase in mutations, with or without metabolic activation, in the same assay. The importance of the age of the chloroprene sample in these studies was demonstrated by Westphal et al. (1994). Freshly distilled, highly pure chloroprene was not mutagenic in *Salmonella typhimurium* strain TA100; however, older aliquots exhibited an age-dependent increase in mutagenic activity in both the presence and absence of metabolic activation. The increase in mutagenic activity was attributed to the presence of decomposition products, notably cyclic chloroprene dimers, in the chloroprene distillate.

Similar conflicting data have been reported for the induction of sex-linked recessive lethals in *Drosophila melanogaster*. *In vitro*, chloroprene was not mutagenic in Chinese hamster V79 lung fibroblasts. *In vivo*, chloroprene was negative for the induction of sister chromatid exchanges (SCE), chromosomal aberrations, and micronuclei in bone marrow of male mice exposed by inhalation for 12 days within a 16-day period, and for micronuclei in male mice exposed by inhalation for 13 weeks. These negative findings occurred at doses (12, 32, and 80 ppm) that were carcinogenic in these mice and where concentrations of cyclic decomposition products greater than 0.1% were avoided (NTP, 1998). However, inhalation exposure to chloroprene for two months at concentrations of <1 ppm (up to 3.5 mg/m^3) was reported by Sanotski (1976) to be positive for the induction of dominant lethal mutations in mice and rats, and chromosomal aberrations in bone marrow cells of mice.

The conflicting positive and negative results in some assays may be due to differences in the age and purity of the chloroprene samples used, strain-related differences in tissue distribution and detoxification, and different experimental protocols (NTP, 1998).

In addition to the experimental studies, several occupational exposure studies (conducted prior to 1977) report an increase in chromosomal aberrations in mitogen-stimulated blood lymphocytes from workers exposed to chloroprene (reviewed in IARC, 1979a, p. 139).

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, Metabolism, and Excretion

The absorption, distribution, metabolism, and excretion of chloroprene have been reviewed by NTP (1998; see Appendix D). In this review, NTP noted that there have been no conclusive studies on the metabolic fate of chloroprene and discussed the hypothesis that the metabolism of chloroprene could follow a pathway similar to that of vinyl chloride, resulting in the formation of two epoxide intermediates: 2-chloro-1,2-epoxy-3-butene and/or 2-chloro-3,4-epoxy-1-butene.

6.2 Pharmacokinetics

No data were located.

6.3 Structure-Activity Relationships

Chloroprene is the 2-chloro analogue of 1,3-butadiene, while isoprene is the 2-methyl analog of 1,3-butadiene. Chloroprene is also an analogue of vinyl chloride. All three structural analogues are animal carcinogens and known (1,3-butadiene, vinyl chloride) or reasonably anticipated to be (isoprene) human carcinogens.

6.3.1 1,3-Butadiene

Based on the human epidemiological and rodent carcinogenicity data published prior to 1992, IARC (1992) concluded that there was sufficient evidence for the carcinogenicity of 1,3-butadiene in experimental animals and limited evidence for its carcinogenicity in humans. The results of more recent mechanistic and epidemiological studies strengthened the link between occupational exposure to 1,3-butadiene and cancer, with the result that NTP has classified 1,3-butadiene as *known to be a human carcinogen* (NTP, 1999a [Report on Carcinogens, 9th ed.]). The increased mortality risk in humans occupationally exposed to 1,3-butadiene is largely for leukemia and other lymphatic cancers (IARC, 1992; West et al., 1995; Ward et al., 1996; Divine and Hartman, 1996; Macaluso et al., 1996; Delzell et al., 1996).

1,3-Butadiene is a multi-species, multi-organ rodent carcinogen (IARC, 1992; NTP, 1993; Melnick et al., 1994). In the NTP inhalation bioassay (NTP, 1993), 1,3-butadiene induced significant increases in the incidence of hemangiosarcomas of the heart, malignant lymphomas, alveolar/bronchiolar adenomas and carcinomas, squamous cell papillomas or carcinomas of the stomach, hepatocellular adenomas or carcinomas, mammary-gland carcinomas and granulosa-cell tumors of the ovary in mice. In a rat inhalation study, 1,3-butadiene induced an increased incidence of pancreatic exocrine neoplasms and Leydig cell tumors of the testis in males, and uterine stromal sarcomas, Zymbal's gland carcinomas, thyroid follicular-cell neoplasms, and mammary gland neoplasms in females (Owen et al., 1987).

Based on generally positive results in a variety of short-term *in vitro* and *in vivo* genotoxicity studies, 1,3-butadiene would be classified as a genotoxic carcinogen (IARC, 1992; NTP, 1993). 1,3-Butadiene was positive for the induction of gene mutations in *S. typhimurium* but not in mouse lymphoma cells, in both the presence and absence of metabolic activation. It was negative for the induction of both wing spot and sex-linked recessive lethal mutations in *D. melanogaster*. In mammalian systems *in vitro*, 1,3-butadiene was weakly positive for the induction of SCE in Chinese hamster ovary cells with metabolic activation, while reported as

negative and positive for SCE induction in human lymphocytes (conflicting studies) with and without metabolic activation. Of most relevance, 1,3-butadiene was positive *in vivo* for the induction of DNA-DNA and DNA-protein crosslinks in liver and lung of mice but not of rats, and in mice for the induction of dominant lethal mutations and sperm abnormalities, SCE and chromosomal damage in bone marrow cells, and micronucleated erythrocytes measured in peripheral blood. In occupationally exposed humans, 1,3-butadiene was positive for the induction of hemoglobin adducts, negative for SCE in lymphocytes, and reported as both positive and negative (conflicting studies) for *hprt* mutations and chromosomal aberrations in lymphocytes.

6.3.2 Isoprene

Based on NTP rodent carcinogenicity data, IARC (1994) concluded that there was sufficient evidence for the carcinogenicity of isoprene in experimental animals and that isoprene was possibly carcinogenic to humans. Additional human studies have not been conducted, and potential human cancer sites have not been identified.

Isoprene is a multi-organ carcinogen in mice (NTP, 1995 draft; Melnick et al., 1996). Male and female mice exposed by inhalation to isoprene vapor for six months showed increases in the incidence of squamous cell papillomas and carcinomas of the forestomach, alveolar/bronchiolar adenomas and carcinomas, hepatocellular adenomas and carcinomas, and harderian gland adenomas and carcinomas (NTP, 1995 draft; Melnick et al., 1996).

Male rats exposed by inhalation to isoprene vapor for six months showed an increase in the incidence and severity of interstitial cell hyperplasia of the testes and a slight increase in the incidence of interstitial cell adenoma (NTP, 1995 draft; Melnick et al., 1996).

Only limited data on the genotoxicity of isoprene are available (IARC, 1994; NTP, 1995 draft). As reviewed by NTP (1995 draft), mutagenicity tests in *S. typhimurium* were negative, while in Chinese hamster ovary cells, no induction of SCE or chromosomal aberrations was observed. In contrast to the negative *in vitro* results, isoprene induced significant increases in the frequency of SCE in bone marrow cells and of micronucleated normochromatic and polychromatic erythrocytes in peripheral blood of mice exposed by inhalation for 12 days over a 16-day period. Also, exposure of mice and rats by i.p. injection and mice by inhalation resulted in isoprene-hemoglobin protein adducts.

6.3.3 Vinyl Chloride

Based on human epidemiological studies and case reports and rodent carcinogenicity data, IARC concluded that there was sufficient evidence for the carcinogenicity of vinyl chloride to humans and experimental animals, respectively. IARC (1987b) reaffirmed vinyl chloride's evaluation as a human carcinogen, citing several additional epidemiological studies and case reports. IARC (1987b) and Green (1990) confirmed a causal association between occupational exposure to vinyl chloride and angiosarcoma of the liver, hepatocellular carcinoma, brain and lung tumors, and malignancy of the hematopoietic and lymphatic system. Some studies (IARC, 1987b) indicated a possibility of increased risk of gastric, liver, and gastrointestinal cancer. Green (1990) noted that workers in vinyl chloride manufacturing also experienced increases in tumors of the skin and thyroid, although a causal relationship was not established. One epidemiological study indicated excessive fetal mortality among wives of workers exposed to vinyl chloride, and several others reported increased rates of birth defects in children whose

parents lived in communities with vinyl chloride-poly(vinyl chloride) or other chemical processing facilities (IARC, 1979b). Two proportionate mortality studies of deceased workers who had been involved in plastics fabrication suggested increases in cancer of the digestive system (both sexes) and increases in cancer of the urinary system and breast in women (IARC, 1979b).

Vinyl chloride has been extensively tested in rats, hamsters, and mice via inhalation exposure and oral, subcutaneous, and intraperitoneal administration. Oral administration or inhalation of vinyl chloride induced Zymbal gland tumors in rats and hamsters, nephroblastomas in rats, forestomach papillomas and melanomas in hamsters, and pulmonary and mammary gland tumors in mice (IARC, 1979b, 1987b). In all three species, exposure to vinyl chloride induced hemangiosarcoma of the liver (IARC, 1979b, 1987b; Green, 1990). Vinyl chloride was carcinogenic in rats exposed prenatally (IARC, 1979b).

Green (1990) observed that vinyl chloride's wide range of effects in many species was characteristic of a genotoxic carcinogen. Workers exposed to vinyl chloride vapor showed induction of chromosomal aberrations in peripheral blood lymphocytes (IARC, 1987b). Two additional studies of exposed workers indicated negative results for SCE, while one study indicated a weakly positive response (IARC, 1987b). In rodents exposed *in vivo*, vinyl chloride induced chromosomal aberrations, SCE, and micronuclei in bone marrow cells, and alkylated DNA in tissues of mice and rats (IARC, 1987b). *In vitro*, vinyl chloride induced unscheduled DNA synthesis in rat hepatocytes, gene mutation in Chinese hamster cells, gene conversion in yeast, and DNA damage and mutation in bacteria. It also induced sex-linked recessive lethals in *Drosophila* and was mutagenic in plants and *Schizosaccharomyces pombe* (but not other fungi) (IARC, 1987b). Green (1990) suggested that vinyl chloride's carcinogenic activity results from its metabolism by microsomal mixed-function oxidases to choro-oxirane (chloroethylene oxide) and chloroacetaldehyde, two mutagenic metabolites, and concluded that vinyl chloride is a classical genotoxin causing cancer by somatic mutation.

7.0 MECHANISMS OF CARCINOGENESIS

No data were found that would suggest that the mechanisms postulated to account for tumor induction by chloroprene in experimental animals would not also operate in humans.

7.1 Metabolic Activation

Neither the metabolic fate nor the biological reactivity of the metabolites of chloroprene has been extensively studied. Chloroprene oxidation to epoxide intermediates has been postulated to occur based on the detection of alkylated derivatives of the trapping agent 4-(4-nitrobenzyl)pyridine in incubations of chloroprene and mouse liver microsomes (Bartsch et al., 1979). NTP (1998) has postulated that 2-chloro-1,2-epoxy-3-butene could undergo rearrangement to form an unsaturated chloroketone, a reaction similar to chloroacetaldehyde formation subsequent to the oxidation of vinyl chloride to chloroethylene oxide [vinyl chloride is classified by IARC (1979b) as a human carcinogen, see section 6.3.3]. It is the oxidative intermediates of chloroprene metabolism that are thought to be protein- and/or DNA-reactive and account for the carcinogenic effects of this compound. The stability, distribution, and reactivity of these various intermediates may impact on the dose-response carcinogenic effects of chloroprene (NTP, 1998).

7.2 Genetic Toxicity

Despite the hypothesis that the *in vivo* metabolism of chloroprene may lead to reactive metabolites, chloroprene has most frequently been reported as negative for genotoxic activity in a variety of *in vitro* and *in vivo* assays (IARC, 1979a; 1982; 1987a; NTP, 1998) (see section 5.0). The infrequent positive studies (including some in the absence of metabolic activation) have been attributed, at least in some cases, to the formation of decomposition products, notably cyclic chloroprene dimers, during sample aging (Westphal et al., 1994). The negative genetic toxicity reports include an inhalation study in which chromosomal damage was not induced in bone marrow cells of mice exposed to chloroprene at carcinogenic concentrations and using exposure conditions where cyclic decomposition products, if present, were at levels less than 0.1% of chloroprene. However, despite the lack of overt genotoxicity, chloroprene-induced lung and harderian gland tumors in chloroprene-exposed mice exhibited a high frequency of unique *-ras* mutations (predominantly A to T transversions at codon 61). The presence of these mutations, uncommon in the corresponding spontaneous tumors, suggests the involvement of a mutagenic mechanism in chloroprene-induced tumor induction (NTP, 1998).

7.3 Structure-Activity Relationships

As described in section 6.3, chloroprene is structurally related to 1,3-butadiene, isoprene, and vinyl chloride. 1,3-Butadiene is a multi-species, multi-organ rodent carcinogen and workplace exposure has been associated with increased risk of lymphatic and hematopoietic cancers (IARC, 1992; NTP, 1993; Melnick and Kohn, 1995; see NTP Report on Carcinogens Background Document for 1,3-Butadiene [NTP, 1999b]). Isoprene is a multi-organ rodent carcinogen and a possible human carcinogen (NTP, 1993; IARC, 1994). For these chemicals, the commonality of metabolic pathways, the similar tumor sites in mice exposed by inhalation, and the mutational events involved in the K-*ras* gene in induced lung and harderian gland tumors (i.e., with isoprene) support a common mechanism of action among these chemicals.

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APPENDIX A

Excerpts from the IARC Monograph on the
Evaluation of the Carcinogenic Risk of Chemicals to Humans
Volume 19 (Some Monomers, Plastics and Synthetic Elastomers, and Acrolein)
Chloroprene and Polychloroprene
pp. 131-156, 1979

CHLOROPRENE and POLYCHLOROPRENE

Chloroprene

1. Chemical and Physical Data

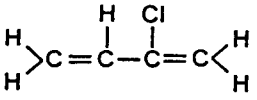
1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 126-99-8

Chem. Abstr. Name: 2-Chloro-1,3-butadiene

2-Chlorobutadiene; β-chloroprene

1.2 Structural and molecular formulae and molecular weight



C_4H_5Cl Mol. wt: 88.5

1.3 Chemical and physical properties of the pure substance

From Weast (1976), unless otherwise specified

(a) Description: Colourless, inflammable liquid (Hawley, 1971)

(b) Boiling-point: 59.4°C

(c) Density: d_4^{20} 0.9583; vapour density, 3 (air = 1) (Anon., 1972)

(d) Refractive index: n_D^{20} 1.4583

(e) Spectroscopy data: λ_{max} 223 nm (E_1^1 = 1595); mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(f) Solubility: Partially soluble in water; soluble in ether, acetone, benzene and most organic solvents

(g) Volatility: Vapour pressure is 300 mm at 32.8°C (Anon., 1975a).

(h) Stability: Flash-point, -20°C (Hawley, 1971); polymerizes on standing (Pollock & Stevens, 1965)

(i) Conversion factor: 1 ppm in air = 3.6 mg/m^3 (Irish, 1963)

1.4 Technical products and impurities

Chloroprene available in the US has a minimum purity of 95% (Hawley, 1971). Inhibitors such as hydroquinone (see IARC, 1977) or phenothiazine are generally added when it is to be stored (Bauchwitz, 1964).

2. Production, Use, Occurrence and Analysis

Two review articles have been published on chloroprene (Bauchwitz, 1964; National Institute for Occupational Safety and Health, 1977).

2.1 Production and use

(a) Production

Chloroprene was first prepared in 1930 by the reaction of monovinylacetylene with hydrochloric acid in the presence of a metal halide (Bauchwitz, 1964; Carothers *et al.*, 1931).

Until 1970, all chloroprene production in the US was based on dimerization of acetylene to monovinylacetylene and addition of hydrogen chloride. However, by 1972, all production was based on butadiene. Chloroprene is produced from butadiene in a two-step process: butadiene is first reacted with chlorine to form a mixture of dichlorobutene isomers, from which the 3,4-dichloro-1-butene isomer is isolated and then reacted with caustic soda to form chloroprene. The other isomer (1,4-dichloro-2-butene) formed during the first reaction step can either be isomerized to 3,4-dichloro-1-butene for additional chloroprene production or be used in the manufacture of adiponitrile. In Japan, 70% of chloroprene is based on acetylene, and 30% is based on butadiene.

Although the date of first US production of chloroprene itself is not known, its polymer (polychloroprene) was first introduced commercially in the US in 1932 (Hargreaves & Thompson, 1965), and separate commercial production of the polymer was first reported in 1943 (US Tariff Commission, 1945). In 1976, two US companies produced an estimated 164 million kg chloroprene.

Data on US imports and exports of chloroprene are not available, presumably because only its sole derivative, polychloroprene, is traded.

In 1977, 100 million kg chloroprene were made in western Europe in the following countries (1 producer each): the Federal Republic of Germany, France, The Netherlands and the UK (Ruebensaal, 1977).

Chloroprene has been produced commercially in Japan since 1962. In 1976, three companies produced a total of 80 million kg.

In 1975, chloroprene was also produced in the USSR and in the People's Republic of China (Ruebensaal, 1975).

Total world production of chloroprene in 1977 is estimated to have been 300 million kg.

(b) Use

Chloroprene is used almost exclusively, without isolation, in the production of polychloroprene elastomers. For a detailed description of the uses of the polymer, see p. 143.

The US Food and Drug Administration permits the use of chloroprene as a component of adhesives that are intended for use in food packaging (US Food & Drug Administration, 1977).

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employee's exposure to chloroprene not exceed an eight-hour time-weighted average of 90 mg/m^3 (25 ppm) in the workplace air in any eight-hour work shift of a forty-hour work week (US Occupational Safety and Health Administration, 1976). In August 1977, the National Institute for Occupational Safety and Health recommended that occupational exposure to chloroprene be limited to a maximum concentration of 3.6 mg/m^3 (1 ppm) in air, determined as a ceiling concentration for a 15-minute period during a forty-hour work week (Anon., 1977; National Institute for Occupational Safety and Health, 1977).

Work environment hygiene standards (all in terms of eight-hour time-weighted averages) for chloroprene in air, as reported by Wincll (1975), are as follows: Czechoslovakia, 50 mg/m^3 (14 ppm); the Federal Republic of Germany, 90 mg/m^3 (25 ppm); the German Democratic Republic, 10 mg/m^3 (2.7 ppm); and Sweden, 90 mg/m^3 (25 ppm). The maximum acceptable ceiling concentration of chloroprene in the USSR is 2 mg/m^3 (0.54 ppm).

2.2 Occurrence

Chloroprene is not known to occur as a natural product.

Chloroprene has been detected as an impurity at levels of several ppm in commercial vinyl chloride in Italy (Sassu *et al.*, 1968) and in Japan (Kurosaki *et al.*, 1968), and in acrylonitrile in the USSR (Panina & Fain, 1968).

During 1973, at a US chloroprene polymerization plant, airborne concentrations of chloroprene were found to range from 50-5000 mg/m^3 (14-1420 ppm) in the make-up area, from 440-24 300 mg/m^3 (130-6760 ppm) in the reactor area, from 10-1500 mg/m^3 (6-440 ppm) in the monomer recovery area and from 400-900 mg/m^3 (113-252 ppm) in the latex area (Infante *et al.*, 1977). In 1977, mean

airborne concentrations of chloroprene of up to 0.72 mg/m^3 (0.2 ppm) were reported in a roll building area in a metal fabricating plant where polychloroprene was applied extensively to metal cylinders prior to vulcanization; an individual who developed an angiosarcoma of the liver with no prior history of vinyl chloride exposure or thorotrast usage had worked in this area (Infante, 1977).

It has been estimated that approximately 2500-3000 workers in the US are currently exposed to chloroprene during its manufacture and polymerization (Infante *et al.*, 1977).

Workers in a Russian shoe factory were reportedly often exposed to chloroprene concentrations of 20-25 mg/m^3 (5.5-7 ppm) (Buyanov & Svishchev, 1973). Concentrations in the air inside a Russian polychloroprene rubber plant were found to be 14.5-53.4 mg/m^3 (4-14.8 ppm); 500 meters from the plant, the concentration was 0.2-1.57 mg/m^3 (0.05-0.43 ppm); and 7000 meters from the plant, the concentration was 0.12-0.38 mg/m^3 (0.03-0.1 ppm) (Mnatsakanyan *et al.*, 1972). Near another Russian polychloroprene rubber plant, the chloroprene concentration in air in the immediate vicinity was 28.45 mg/m^3 (7.9 ppm); 500 meters away, it was 0.727 mg/m^3 (0.2 ppm); and 7000 meters away, it was 0.199 mg/m^3 (0.05 ppm) (Apoyan *et al.*, 1970).

Polychloroprene may contain 0.01-0.5% free chloroprene (National Institute for Occupational Safety and Health, 1977).

2.3 Analysis

A colorimetric method for determining chloroprene in the workplace air has been described in which the coloured complex of chloroprene with the *para*-nitrophenyldiazonium ion is determined spectrophotometrically (Babina, 1969).

Ultra-violet spectrophotometry at 222.6 nm after trapping in ethanol has been used to determine chloroprene in the air around a polychloroprene rubber plant (Apoyan *et al.*, 1970).

Chloroprene and other unsaturated monomers have been removed from air by ethanolic mercuric acetate and analysed by paper chromatography; the sensitivity of the method for chloroprene was 3.0 µg (Kaznina, 1972).

Gas chromatography can be used to determine chloroprene: (1) in air in the presence of other monomers (Gizhlaryan *et al.*, 1976; Sharpanova *et al.*, 1972; Turusova & Khanina, 1975); (2) in air, with a sensitivity of 0.005 mg/m^3 (0.0014 ppm) (Sukiasyan *et al.*, 1976); (3) as an impurity in acrylonitrile (Panina & Fain, 1968); (4) as an impurity in vinyl chloride at several mg/kg (ppm) (Sassu *et al.*, 1968); and (5) as a residual monomer in polychloroprene latexes, with a sensitivity of less than 0.002 wt % and a coefficient of variation of 3-10% (Bunyatyants *et al.*, 1976).

Preparative gas chromatography was also used to separate impurities, including chloroprene, in vinyl chloride, which were then identified using infra-red spectrometry, mass spectrometry, elemental analyses and measurement of physical properties (Kurosaki *et al.*, 1968).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(a) Oral administration

Rat: A group of 100 random-bred albino rats received twice-weekly doses of 200 mg/kg bw chloroprene in sunflower oil by gavage for 25 weeks; 40 rats survived for 2 years. No tumours were observed (Zil'fyan *et al.*, 1975, 1977) [The Working Group noted the incomplete reporting of the experiment].

(b) Skin application

Mouse: Three groups of random-bred albino mice received either (a) 50 twice-weekly skin applications of a 50% solution of chloroprene in benzene for 25 weeks, or (b) 50 twice-weekly skin applications of 0.1% 9,10-dimethyl-1,2-benzanthracene (DMBA) in benzene, or (c) 50 skin applications of the 50% chloroprene solution in benzene and 5 skin applications of a 0.01% DMBA solution in benzene. Of 100 mice treated with 50% chloroprene, 58 survived 6 months, and 37 survivors were killed after 18 months; no tumours of the skin or other organs were reported. Of 80 mice treated with 0.1% DMBA, 60 were still alive at the appearance of the first skin tumour (time unspecified), and 92% of these developed skin carcinomas. Of 80 mice treated with chloroprene and 0.01% DMBA, 42 survived for 6 months; no skin or other tumours were reported (Zil'fyan *et al.*, 1975, 1977) [The Working Group noted the incomplete reporting of the experiment].

(c) Inhalation and/or intratracheal administration

Rat: Chloroprene was administered intratracheally to 100 random-bred albino rats in doses of 200 mg/kg bw five times at 20-day intervals. Gross and microscopic pathological examination revealed no tumours in the lungs of animals that died or were killed 6 or 14 months after chloroprene administration (Zil'fyan *et al.*, 1977) [The Working Group noted the insufficient duration of the experiment].

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[1]The Working Group was aware of studies in progress to investigate the carcinogenicity of chloroprene by oral administration to rats and by inhalation exposure in rats and hamsters (IARC, 1978; Toxicology Information Program, 1976, 1977).

(d) Subcutaneous and/or intramuscular administration

Rat: A group of 110 random-bred albino rats received 10 s.c. injections of 400 mg/kg bw chloroprene in sunflower oil; 88 rats survived 6 or more months. Another group of 100 rats received 50 injections of 200 mg/kg bw, and 46 survived 6 months or more. No local sarcomas were observed in either group within 2 years. Among 60 rats injected with single doses of 0.5 mg/animal DMBA, 50 survived to the appearance of the first tumour (3.5 months), and 32 (64%) developed local sarcomas. Following a single injection of 0.5 mg/animal DMBA in the left flank and 50 s.c. injections of 200 mg/kg bw chloroprene in the right flank, 42 rats were still alive at the appearance of the first tumour (4 months), and 24 (57%) developed local sarcomas (side not specified) (Zil'fyan *et al.*, 1975, 1977) [The Working Group noted the incomplete reporting of the experiment].

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The oral LD_{50} of chloroprene in rats is 251 mg/kg bw and in mice 260 mg/kg bw (Asmangulyan & Badalyan, 1971). In Charles River male rats the LC_{50} for a 4-hour exposure was 8.2 g/m^3 (2280 ppm) (Clary *et al.*, 1978).

The dose that killed about 100% of animals after an 8-hour inhalation exposure was approximately 7.5 g/m^3 (2000 ppm) in rabbits and from 15-20 g/m^3 (4000-5500 ppm) in rats. Symptoms included inflammation of the mucous membranes of the eyes and nose, followed by depression of the central nervous system. Death resulted from respiratory failure. In mice, toxic effects have been reported after 8 hours' exposure to levels of chloroprene as low as 40-500 mg/m^3 (12-130 ppm); and 600 mg/m^3 (170 ppm) killed 100% of animals (von Oettingen *et al.*, 1936).

Repeated inhalation exposure of experimental animals to chloroprene resulted in central nervous system depression (Asmangulyan & Badalyan, 1971; Davtyan, 1972; Nyström, 1948; von Oettingen *et al.*, 1936), delayed reversal of conditioned reflexes (Airapetyan & Matevonyan, 1973) and histological changes in brain tissue (Movsesyan *et al.*, 1964).

Chloroprene induces a number of biochemical alterations in various species, including inhibition of liver detoxification mechanisms (Davtyan, 1972), decreased activity of hepatic enzymes and glycogen content in liver (Gizhlaryan *et al.*, 1972; Martinyan, 1966; Mkhitaryan, 1959, 1960c; Mkhitaryan & Astvatsatryan, 1959; Nikogosyan, 1959) and renal and splenic damage (Asmangulyan & Badalyan, 1971; von Oettingen *et al.*, 1936). Hypertropy and hyperfunction of the adrenals (Allaverdyan, 1970; Mkhitaryan *et al.*, 1971) have also been observed.

In rats, repeated exposure to chloroprene by inhalation for 6 hours/day on 5 days/week for 4 weeks resulted in slight growth depression and behavioural effects with 1.4 g/m^3 (39 ppm) and loss of hair, growth retardation and morphological liver damage with 5.8 g/m^3 (160 ppm) and 22.5 g/m^3 (625 ppm). In hamsters, this exposure resulted in slight irritation and restlessness with 1.4 g/m^3 (39 ppm), growth retardation, irritation and liver damage with 5.8 g/m^3 (160 ppm) and death with 22.5 g/m^3 (625 ppm) (Clary, 1977).

Repeated oral administration of 15 mg/kg bw chloroprene to rats daily for 5 months produced no lethal effects (Asmangulyan & Badalyan, 1971). Acute and chronic effects have been noted following administration of chloroprene to the skin of rats (von Oettingen *et al.*, 1936).

Chloroprene is more toxic to fasted rats with decreased hepatic glutathione content than to fed rats (Jaeger *et al.*, 1975a,b).

A variety of immunological effects have resulted from chloroprene exposure, including a decrease in the number of antibody-forming cells in the spleen (Agakhanyan *et al.*, 1973) and enhancement of transplanted tumour growth (Zil'fyan & Fichidzhyan, 1972).

Embryotoxicity and teratogenicity

An embryotoxic effect was seen in pregnant rats that inhaled concentrations of chloroprene ranging from 0.13-53.4 mg/m^3 (0.035-15 ppm) (Melik-Alaverdyan *et al.*, 1976; Mnatsakayan *et al.*, 1972; Salnikova & Fomenko, 1973, 1975). The highest embryotoxic effect was observed when 4 mg/m^3 (1.1 ppm) chloroprene were inhaled during the entire pregnancy, or intermittently on days 1-2, 3-4 or 11-12, or given orally at a dose of 0.5 mg/kg bw/day for 14 days or on days 3-4 or 11-12. A teratogenic effect (meningoencephaloceles) was seen when chloroprene was administered on days 5-6, 9-10, 11-12, 13-14 and 15-16 of gestation (Salnikova & Fomenko, 1975).

Neither embryotoxic nor teratological effects were reported by Culik *et al.* (1976) after exposing pregnant rats to 90.5 mg/m^3 (25 ppm) chloroprene for 4 hours daily from day 1 to day 12 or from day 3 to day 20 of gestation.

Metabolism

When a mixture of chloroprene in air was passed through a mouse-liver microsomal preparation, a volatile alkylating metabolite was formed, as demonstrated by trapping with 4-(4-nitrobenzyl)pyridine (Barbin *et al.*, 1977; Bartsch *et al.*, 1978).

Mutagenicity and other short-term tests

Chloroprene vapours induced reverse mutations in *Salmonella typhimurium* TA100 and TA1530. Addition of a 9000 x *g* supernatant of liver from mice or

one human surgical specimen enhanced mutagenicity (Bartsch, 1976; Bartsch *et al.*, 1975, 1976, 1979).

In *Drosophila melanogaster*, recessive lethal mutations were induced by feeding male flies 5.7 and 11.4 mM chloroprene for 3 days (Vogel, 1976).

As early as 1936, von Oettingen *et al.* (1936) observed that the reproduction of male mice and rats was affected after inhalation of chloroprene at concentrations of 42-540 mg/m^3 (12-150 ppm) for mice and 430-22,400 mg/m^3 (120-6000 ppm) for rats. Testicular atrophy, or reduction in the numbers and motility of sperm in rats with non-atrophied testes, occurred at an exposure level of 0.15 mg/m^3 (0.04 ppm) (Davtyan, 1972; Sanotskii, 1976). Spermatogenesis in C57BL/6 mice was affected after 2 months' exposure to 0.32 mg/m^3 (0.09 ppm) chloroprene (Sanotskii, 1976). A significant increase in embryotoxicity was observed in female rats fertilized by males exposed to 3.8 mg/m^3 (1 ppm) 4 hours daily for 48 days (Davtyan *et al.*, 1973).

Chloroprene induced dominant lethal mutations and chromosome aberrations in bone-marrow cells of rats exposed to 0.14-3.6 mg/m^3 in air (0.04-1.0 ppm) (Davtyan, 1972; Davtyan *et al.*, 1973; Sanotskii, 1976) and dominant lethal mutations in mice exposed to 1.85-3.5 mg/m^3 in air (0.5-1 ppm) (Sanotskii, 1976). Mixtures of chloroprene plus dodecylmercaptan plus ammonia (Bagramjan & Babajan, 1974), and chloroprene plus methyl methacrylate (Bagramjan & Babajan, 1974; Bagramjan *et al.*, 1976) also induced chromosome aberrations in bone-marrow cells of rats.

(b) Humans

The primary effects of acute exposure to high concentrations of chloroprene in air are central nervous system depression, injury to the lungs, liver and kidneys, irritation of skin and mucous membranes and respiratory difficulties (Irish, 1963; Nyström, 1948). Dermatitis and hair loss due to contact with chloroprene and its polymers have also been reported (Nyström, 1948; Ritter & Carter, 1948; Schwartz, 1945; Volkov, 1971).

Symptoms of chronic chloroprene exposure include headache, irritability, dizziness, insomnia, fatigue, respiratory irritation, cardiac palpitations, chest pain, gastrointestinal disorders, dermatitis, temporary loss of hair, conjunctivitis and corneal necrosis (Barskii *et al.*, 1972; Lloyd *et al.*, 1975; Nyström, 1948; Sax, 1975; Schwartz, 1945). Hepatomegaly, with a decrease in liver function tests, toxic hepatitis, dystrophy of the myocardium and changes in the nervous system (Orlova & Solov'eva, 1962), circulatory changes (Khachatryan & Oganesyan, 1974; Mirzabekyan & Nikogosyan, 1959), anaemia (Nyström, 1948), hypoglycaemia (Mkhitaryan, 1960a; Nikogosyan, 1958), altered enzyme activities (Mkhitaryan, 1960b; Mnatsakanyan & Mushegyan, 1964) and dysfunction of both the central and peripheral nervous systems, particularly the cholinergic branch (Gasparyan,

1965), have also been reported. A decrease in blood cholinesterase activity has also been seen in exposed workers (Gasparyan, 1965). Pathological changes in the cardiovascular and nervous systems were observed in 44% of patients with chronic chloroprene poisoning (Khachatryan & Oganesyan, 1974).

Inhalation of chloroprene causes pathomorphological changes in the periodontium: periodontitis (49%), gingivitis (22%), erosion of teeth (17%) and caries (5%) (Arevshatyan, 1972).

Low immunological reactivity was observed in 208 chloroprene workers immunized with typhoid vaccine (Mikaelyan & Frangulyan, 1965).

Davtyan *et al.* (1973) cited cases of children born with physical and mental defects to female workers in a polymerization area of a chloroprene rubber factory.

A significant rise in the number of chromosome aberrations was observed in blood cells from 18 workers exposed to an average chloroprene concentration of 18 mg/m^3 (5 ppm) for from 2 to more than 10 years. A frequency of 4.7% chromosome aberrations and 3.7% gaps was found in the treated group, as compared with 0.65 and 1.14%, respectively, in a control group of 9 workers from a motor car plant. However, there was no relationship in the exposed group between exposure time and aberration frequency, neither was there any evidence of numerical chromosome changes (Katosova, 1973).

Among 56 workers exposed to chloroprene, chloroprene latex or chloroprene rubber [the concentration of chloroprene in the air being about 6 mg/m^3 (1.6 ppm)] the incidence of chromosomal aberrations (mainly single breaks and double fragments) in cultured peripheral blood lymphocytes was 2.78%, compared with 0.53 and 1.14% chromosome aberrations in two groups of controls (Zhurkov *et al.*, 1977).

Fomenko & Katosova (1973) (reviewed by Sanotskii, 1976) reported an increased frequency of chromosome aberrations in lymphocyte cultures from 28 female workers who were exposed for 1 to 20 years to 1-7 mg/m^3 (0.3-2 ppm) chloroprene.

A statistically significant increase in chromosome aberrations was found in the lymphocytes of 5 workers in contact with 2-2.2 mg/m^3 (0.55-0.6 ppm) chloroprene and 0.5-2 mg/m^3 (0.1-0.5 ppm) methyl methacrylate in air. The incidences of chromatid breaks (single fragments) and chromosome breaks (fragment pairs) were found to be 16.8% and 16.9%, respectively (Bagramjan *et al.*, 1976).

Functional disturbances in spermatogenesis and morphological abnormalities of sperm were observed among workers occupationally exposed to chloroprene (Sanotskii, 1976).

A three-fold excess of spontaneous abortions has been reported in the wives of chloroprene workers (Sanotskii, 1976).

3.3 Case reports and epidemiological studies[1]

Khachatryan (1972a) reported a study of lung cancer risk in relation to industrial exposure to chloroprene based on 87 cases of lung cancer diagnosed in the oncology department of the greater industrial Yerevan region during the period 1956-1970. The frequency ratio of primary lung cancer among the 'control' groups compared with that of the chloroprene groups was reported to be: 2.67 times lower in persons working with chemicals unrelated to chloroprene, 6.3 times lower in workers in non-chemical industries and 17.5 times lower in workers in cultural and civic institutions [The limitations of this study include failure to distinguish prevalent from incident cases, failure to document completeness of case ascertainment among the exposure group, failure to adjust for effects of age and sex, failure to measure the extent of exposure and failure to control for the potential confounding effect of smoking or other non-chloroprene-related exposures].

Simultaneously with the lung cancer study, Khachatryan (1972b) investigated the risk of skin cancer in relation to industrial chloroprene exposure. The percentage of diagnosed skin cancers by exposure group was reported as follows: Group 1 - never worked in industry, 0.12% (11 cases/8520 examined); Group 2 - lengthy experience in non-chemical industries, 0.40% (35/8755); Group 3 - lengthy exposure to chemicals unrelated to chloroprene, 0.66% (32/4780); Group 4 - worked only in plants utilizing chloroprene derivatives, 1.6% (33/2250); and Group 5 - extended work experience in chloroprene production only, 3.07% (21/684) [The limitations of the study are the same as those described above for the lung cancer study; in addition, the absence of histological information on cell type is particularly important in this study of reported skin cancer].

Pell (1978) reported a study of cancer mortality among two cohorts of males engaged in the production and/or polymerization of chloroprene, one cohort consisting of 234 men first exposed between 1931-1948 and the other of 1576 men first exposed between 1942-1957. Both cohorts were followed until the end of 1974. Whereas the numbers of lung cancer deaths in each cohort (3 in the first and 16 in the second) were about those expected on the basis of US or company-wide rates, the risks of digestive cancer (19 *versus* 13.3) and of lymphatic and hematopoietic cancer (7 *versus* 4.5) were

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[1]Khairullina (1973) (quoted by Sanotskii, 1976) referred to the appearance of tumours in female workers, but no anatomical or pathological information was given which would allow an epidemiological evaluation to be made.

slightly elevated in the second cohort when contrasted with company-wide experience (in the first cohort, 3 digestive cancers were observed, which differed very little from the number expected). There were 8 lung cancer cases (4 living and 4 deceased) among maintenance mechanics in the second cohort (1576 men), accounting for 40% of the lung cancers in the total study cohort, although only 17% of the total cohort was composed of maintenance mechanics. Infante *et al.* (1977) have commented on the significance of these observations in mechanics, since their tasks include replacement of leaking pipefittings, installation of equipment and general maintenance in the reactor areas - tasks which have a potentially high exposure to chloroprene. These authors also commented on the methodological shortcoming in the Pell (1978) study inherent in combining chloroprene monomer production workers and polymerization workers in the second cohort [The Pell (1978) study has the following limitations: (1) a possibility of ascertainment bias in the cohort restricted to active employees at inception of the study, since retired workers, disabled workers and former chloroprene workers were not uniformly included in the initial cohort; (2) no data on potential confounding variables such as smoking history and other occupational exposures; (3) no exposure information based on measurements of chemical concentration; (4) no data on cell types of the malignancies; (5) still incomplete follow-up of the second cohort for an adequate latent period; and (6) small number of person-years of exposure].

One case of liver angiosarcoma (pathologically confirmed) has been reported in a worker exposed to chloroprene who had no known occupational exposure to vinyl chloride or medical exposure to thorotrast (Infante, 1977).

Polychloroprene

1. Chemical and Physical Data

1.1 Synonyms and trade names

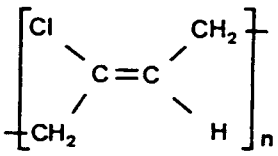
Chem. Abstr. Services Reg. No.: 9010-98-4

Chem. Abstr. Name: 2-Chloro-1,3-butadiene homopolymer

Chlorobutadiene polymer; 2-chloro-1,3-butadiene polymer; chloroprene polymer; poly(2-chlorobutadiene); poly(2-chloro-1,3-butadiene); 1,4-*cis*-poly(chloroprene); polychloroprene; *trans*-1,4-polychloroprene

Duprene; GR-M; Nairit; Neoprene; Perbunan C; Plastifix PC; Sovprene; Svitpren

1.2 Structural and molecular formulae and molecular weight



$(C_4H_5Cl)_n$ Mol. wt: 80 000–200 000

1.3 Chemical and physical properties of the rubber

From Windholz (1976), unless otherwise specified

(a) Description: White-to-amber, rubbery solid (Anon., 1975b)

(b) Melting-point: Softens at about 80°C

(c) Refractive index: n_D 1.55–1.56

(d) Spectroscopy data: Infra-red spectral data have been tabulated for the latex form (Grasselli & Ritchey, 1975).

(e) Solubility: Insoluble in water; swells in kerosene, benzene and acetone (Dean, 1973)

(f) Stability: Combustion of polychloroprene cables has been reported to produce hydrogen chloride and chlorine (Csonev, 1969).

1.4 Technical products and impurities

Over 35 commercial grades of polychloroprene elastomers are available in the US. The two major categories are the solid and latex forms. The solid form has a specific gravity of 1.23 and is generally available in white-to-amber chips. Polychloroprene latex (an aqueous dispersion) is a milky-white liquid with a specific gravity of 1.08–1.15 and contains 41–60% solids, depending on the type (Anon., 1975b). Polychloroprene elastomers are usually vulcanized with metallic oxides (a combination of magnesium and zinc oxide) and must contain antioxidants. The different grades vary with the processing aids used; these may include accelerators (dithiocarbamates and guanidines), lubricants (stearic acid, microcrystalline waxes and low-molecular-weight polyethylenes), tackifiers (hydrogenated rosin esters and coumarone-indene resins), fillers (clay and carbon black), plasticizers (petroleum oils), stabilizers (anionic, nonionic and amphoteric surfactants) and thickeners (natural and synthetic gums). Various grades are blended to obtain specific properties (Hargreaves & Thompson, 1965).

No detailed information on the possible presence of unreacted monomer in the polymers was available to the Working Group.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Polychloroprene was first introduced in the US in 1932 (Hargreaves & Thompson, 1965), although commercial production was not reported separately until 1943 (US Tariff Commission, 1945). Polychloroprene is produced commercially by the emulsion polymerization of chloroprene using free radical initiators. The details of the polymerization vary, depending on the type of polychloroprene produced. The process used to make general-purpose polychloroprene is representative of that used for producing both solid and latex forms: chloroprene is emulsified in water with the sodium soap of rosin acids at 38°C and then polymerized at 40°C by the addition of potassium peroxydisulphate. Sulphur may also be added. The polychloroprene is then vulcanized with a metallic oxide and processed with various other aids, depending on its end use.

2-Mercaptoimidazoline (ethylene thiourea) is used in the production of vulcanized natural or synthetic (including polychloroprene) gaskets or other components (see IARC, 1974).

Two US companies produced about 165 million kg polychloroprene in 1976; imports were 3.1 million kg and were from the following countries: the Federal Republic of Germany (60.7%), France (29.4%), Japan (2.7%), Romania (2.2%) and the UK (5.0%) (US Department of Commerce, 1977); exports were 46.2 million kg.

Production in western Europe in 1976 amounted to 85 million kg. The major producers were the following (in millions of kg): the Federal Republic of Germany (40), France (3) and the UK (20). Exports from western Europe in 1976 were 25 million kg and imports 40 million kg. Total production in 1977 was 100 million kg.

Polychloroprene has been produced commercially in Japan since 1962. In 1976, three companies produced a total of 77 million kg; imports were 1 million kg, and 41 million kg were exported.

Total world production of polychloroprene in 1977 is estimated to have been 300 million kg.

(b) Use

In 1976, about 110 million kg polychloroprene were used in the US, as follows: production of industrial and automotive rubber goods (63%), wire

and cable applications (13%), construction applications (10%), adhesive applications (8%) and miscellaneous uses (6%).

Polychloroprene is used in a wide variety of industrial and automotive goods, including hose, tubing, belting, diaphragms, weather stripping, seals, gaskets and moulded and extruded goods. They are used in wire and cable jackets. Construction applications include highway joint seals, pipe gaskets, bridge mounts and expansion joints. They are also used in adhesive cements and coatings, mastics, caulks and sealants. Miscellaneous applications include: tire sidewalls; chemically blown cellular products; consumer products (shoes, sporting goods and house and garden products); coatings for fabrics, sheet goods and thread; binder or impregnant for fibres, nonwoven fabrics and cellulose or asbestos paper; and as an additive for the elasticization of concrete.

In Japan, polychloroprene is used for the manufacture of industrial goods (60%) and other applications, primarily adhesives (40%).

The US Food and Drug Administration permits the use of polychloroprene as a component of resinous and polymeric coatings and in rubber articles intended for use in contact with food (US Food and Drug Administration, 1977).

2.2 Occurrence

Polychloroprene is not known to occur as a natural product. No data on possible environmental exposure to the compound were available to the Working Group.

2.3 Analysis

Plastics and rubbers, including polychloroprene, have been identified using pyrolysis-gas chromatography (Braun & Canji, 1974; Feuerberg, 1967; Fischer, 1967; Okumoto & Takeuchi, 1972; Sugiki & Yamamoto, 1972; Ural'skii *et al.*, 1976) and differential scanning calorimetry (Sircar & Lamond, 1972).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Chloroprene was tested in rats by oral, subcutaneous and intratracheal administration and in mice by skin application. Although no carcinogenic

effects were found, these studies were considered by the Working Group to be inadequate to allow an evaluation of the carcinogenicity of chloroprene in experimental animals.

Chloroprene is embryotoxic, teratogenic and mutagenic.

No data on the carcinogenicity of polychloroprene were available to the Working Group.

4.2 Human data

Production of chloroprene and polychloroprene is extensive and use of the polymer diffuse. Occupational exposures during the polymerization process have been reported to be associated with a wide variety of organ and systemic toxicological effects. In one study, an excess of lung and skin cancers was related to occupational exposure to chloroprene; in another investigation, no excess of lung cancer or other types of cancer was reported among chloroprene workers.

One case report was available describing the occurrence of an angiosarcoma of the liver in a worker exposed to chloroprene.

Data on cytogenetic effects and reproductive disturbances in workers exposed to chloroprene and in their wives suggest that chloroprene is mutagenic to humans.

No information on possible carcinogenic effects in persons exposed only to the polymer was available to the Working Group.

4.3 Evaluation

Reports of increased frequencies of lung and skin cancer in workers exposed to chloroprene raise the possibility that chloroprene is carcinogenic to humans. These studies, however, have methodological deficiencies: in particular, failure to define epidemiological measures of cancer frequency. The one negative epidemiological study available does not rule out the possibility that chloroprene is carcinogenic, since the period of follow-up of the cohort is still relatively short, because the significance of the study is limited by the low number of person-years of experience, and information is lacking on the extent of exposure.

Despite the obvious limitations inherent in a single case report, attention is called to the reported association of liver angiosarcoma with chloroprene.

The epidemiological reports regarding cytogenetic effects and reproductive disturbances in workers exposed to chloroprene and in their wives are consistent with experimental evidence that chloroprene is mutagenic.

The inconclusive nature of both the epidemiological studies (and the single case report) and the available carcinogenicity studies in experimental animals preclude an evaluation of the potential carcinogenicity of chloroprene to humans. Intensified efforts should be made to obtain further experimental and epidemiological evidence with regard to chloroprene and cancer (see also 'General Remarks on the Substances Considered', p. 35).

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APPENDIX B

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Supplement 4 (Chemicals, Industrial Processes and Industries Associated with Cancer in Humans, Volumes 1-29) Chloroprene, pp. 89-91, 1982

have also been reported in cohorts of men involved in the manufacture of trichlorophenols (mainly, if not entirely, 2,4,5-trichlorophenol)[5-8]. Cases of leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma have also been reported in individuals exposed to pentachlorophenol[9-11]. In all of these studies, exposure to chlorophenols probably involved exposure also to dioxins, as well as to other chemicals. (See also the summaries of data on 2,4,5- and 2,4,6-trichlorophenols and pentachlorophenol.)

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CHLOROPRENE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

In one study, an excess of lung and skin cancers was related to occupational exposure to chloroprene. [The results were inconclusive, since epidemiological measures of cancer frequency were not defined.] In another investigation, no excess of lung or other type of

cancer was reported among chloroprene workers. There is one case report of an angiosarcoma of the liver in a worker exposed to chloroprene[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

A number of experimental studies were considered to be inadequate for an evaluation of the carcinogenicity of chloroprene[1]. In a further study[2], chloroprene was given orally to pregnant rats on the 17th day of gestation, and their offspring were treated weekly from weaning for life with 50 mg/kg bw by stomach tube. The total incidence of tumours was similar in treated and untreated animals.

C. Evidence for activity in short-term tests (*sufficient*)

Chloroprene vapours were weakly mutagenic to *Salmonella typhimurium* TA100 in the presence of an exogenous metabolic activation system[1] and produced a low but statistically significant increase in X-linked recessive lethals in *Drosophila melanogaster*[1,3]. It was not mutagenic to mammalian cells in culture[4]. It has been claimed that chloroprene induced chromosomal aberrations and dominant lethal mutations in rat bone-marrow cells *in vivo*[1]. It induced cell transformation in normal hamster lung cells *in vitro*[5]. Workers exposed to chloroprene exhibited increases in chromosomal aberrations in peripheral lymphocytes. These data and reports of reproductive disturbances in such workers and in their wives suggest that chloroprene is mutagenic to humans[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects		+		
Mammalian cells *(in vitro)*		-		T(+)
Mammals *(in vivo)*			?	DL(?)
Humans *(in vivo)*			+	

T = cell transformation ; DL = dominant lethal mutations

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CHROMIUM AND CERTAIN CHROMIUM COMPOUNDS (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

An increased incidence of lung cancer has been observed among workers in the chromate-producing industry and possibly also among chromium platers and chromium alloy workers. There is a suggestion that cancers at other sites are also increased in such populations. The chromium compound(s) responsible has not been specified[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

Calcium chromate is carcinogenic to rats after its administration by several routes, including intrabronchial implantation. Chromium chromate, strontium chromate and zinc chromate produce local sarcomas in rats at the sites of their application. Inadequate evidence was available for the carcinogenicity in mice and rats of barium chromate, lead chromate, chromic acetate, sodium dichromate and chromium carbonyl[1].

C. Evidence for activity in short-term tests (*sufficient* for Cr VI, *inadequate* for Cr III)

Hexavalent chromium caused DNA damage[2-5] and misincorporation of nucleotides in an in-vitro DNA transcription assay[2]. It was mutagenic in bacteria in the absence of an exogenous metabolic activation system[2,5,6] and mutagenic in fungi[2,5] and in mammalian cells *in vitro*[2,5] and *in vivo*[2]. Potassium dichromate induced dominant lethal mutations in mice treated *in vivo*[7]. Hexavalent chromium caused chromosomal aberrations in mammalian cells *in vitro*[2,5,8] and micronuclei in mice *in vivo*[2]. It produced cell transformation in a number of systems[2,5]. Micronuclei were formed in peripheral lymphocytes from exposed workers[2].

There is no good evidence that *trivalent chromium* causes mutations in bacteria, fungi or mammalian cells in culture or that it transforms mammalian cells *in vitro*[2]. The few positive results in assays for chromosomal aberrations were obtained only with very high doses and could be explained by non-specific toxic effects[9,10]. No data on humans were available.

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* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

APPENDIX C

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Supplement 7 (Overall Evaluation of Carcinogenicity: An Update of IARC Monographs, Volumes 1-42) Chloroprene, p. 160, 1987

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[16]*IARC Monographs, Suppl. 6*, 161-163, 233-236, 538-540, 1987

CHLOROPRENE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

In one study, an excess of lung and skin cancers was related to occupational exposure to chloroprene. In another investigation, no excess of lung or other type of cancer was reported among chloroprene workers. There is one case report of an angiosarcoma of the liver in a worker exposed to chloroprene[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

A number of experimental studies were considered to be inadequate for an evaluation of the carcinogenicity of chloroprene[1]. In a further study[2] in which chloroprene was given orally to pregnant rats and their offspring were treated for life by stomach tube, the total incidence of tumours was similar in treated and untreated animals.

C. Other relevant data

An increased incidence of chromosomal aberrations was found in the lymphocytes of workers exposed to chloroprene[3].

Chloroprene induced dominant lethal mutations in rats and chromosomal aberrations in bone-marrow cells of mice treated *in vivo*. It induced transformation in one hamster cell line but did not induce mutation in Chinese hamster cells. It induced sex-linked recessive lethal mutations in *Drosophila* and was mutagenic to bacteria[3].

References

[1]*IARC Monographs, 19*, 131-156, 1979

[2]Ponomarkov, V. & Tomatis, L. (1980) Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats. *Oncology, 37*, 136-141

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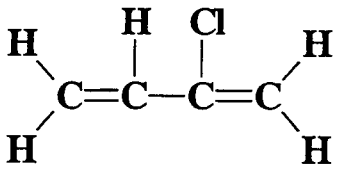
APPENDIX D

Excerpts from the NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chloroprene in F344/N Rats and B6C3F1 Mice (Inhalation Studies) 1998

ABSTRACT



CHLOROPRENE

CAS No. 126-99-8

Chemical Formula: C_4H_5Cl Molecular Weight: 88.54

Synonyms: Chlorobutadiene; 2-chlorobuta-1,3-diene; 2-chloro-1,3-butadiene; β-chloroprene

Chloroprene is used almost exclusively in the manufacture of neoprene (polychloroprene). Chloroprene was chosen for study because it is a high-volume production chemical with limited information on its carcinogenic potential and because it is the 2-chloro analogue of 1,3-butadiene, a potent, multi-species, multi-organ carcinogen. Male and female F344/N rats and B6C3F$_1$ mice were exposed to chloroprene (greater than 96% pure) by inhalation for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, *Drosophila melanogaster*, and B6C3F$_1$ mice (bone marrow cells and peripheral blood erythrocytes).

16-Day Study in Rats

Groups of 10 male and 10 female F344/N rats were exposed to 0, 32, 80, 200, or 500 ppm chloroprene by inhalation, 6 hours per day, 5 days per week, for 16 days. Three 500 ppm males died on day 2 or 3 of the study. Mean body weight gains of 200 ppm males and females and 500 ppm females were significantly less than those of the chamber control groups. On the first day of exposure, rats exposed to 500 ppm were hypoactive and unsteady and had rapid shallow breathing. These effects were also observed to some degree in animals exposed to 200 ppm. After the second day of exposure, the effects in these groups worsened, and hemorrhage from the nose was observed.

A normocytic, normochromic, responsive anemia; thrombocytopenia; and increases in serum activities of alanine aminotransferase, glutamate dehydrogenase, and sorbitol dehydrogenase occurred on day 4 in 200 ppm females and 500 ppm males. Kidney weights of 80 and 500 ppm females were significantly greater than those of the chamber control group, as were the liver weights of 200 and 500 ppm females.

The incidences of minimal to mild olfactory epithelial degeneration of the nose in all exposed groups of males and females were significantly greater than those in the chamber control groups. The incidence of squamous metaplasia of the respiratory epithelium was significantly increased in 500 ppm males. The incidences of centrilobular to random hepatocellular necrosis in 500 ppm males and 200 ppm females were significantly greater than those in the chamber control groups.

16-Day Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 12, 32, 80, or 200 ppm chloroprene by inhalation, 6 hours per day, 5 days per week, for 16 days. All males and females exposed to 200 ppm died on day 2 or day 3 of the study. Mean body weight gains of males exposed to 32 or 80 ppm were significantly less than that of the chamber control group. Mice exposed to 200 ppm exhibited narcosis during exposure and were hypoactive with reduced body tone after the first day of exposure. In general, hematology and clinical chemistry parameters measured for exposed males and females were similar to those of the chamber control groups. Thymus weights of 80 ppm males and females were significantly less than those of the chamber control groups. Liver weights of 80 ppm females were significantly greater than those of the chamber control groups.

Increased incidences of multifocal random hepatocellular necrosis occurred in males and females exposed to 200 ppm. Hypertrophy of the myocardium, foci of hemorrhage, and mucosal erosion were observed in three males and three females exposed to 200 ppm. Squamous epithelial hyperplasia of the forestomach was observed in two males and two females exposed to 80 ppm. Thymic necrosis, characterized by karyorrhexis of thymic lymphocytes, was observed in all males and females in the 200 ppm groups.

13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were exposed to chloroprene at concentrations of 0, 5, 12, 32, 80, or 200 ppm by inhalation, 6 hours per day, 5 days per week, for 13 weeks. One male exposed to 200 ppm died during the study. The final mean body weights and body weight gains of all exposed groups of males and females were similar to those of the chamber control groups. Clinical findings in 200 ppm males included red or clear discharge around the nose and eye region.

At week 13, a normocytic, normochromic, and nonresponsive anemia occurred in 200 ppm males and females. A thrombocytopenia occurred in 200 ppm males and females on day 2 and in 80 and 200 ppm females on day 22. However, at week 13, platelet counts rebounded and were minimally increased in 200 ppm males and females. On day 2, a minimal to mild increase in activated partial thromboplastin time and prothrombin time occurred in 200 ppm males and females. The 200 ppm males and females also had increased activities of serum alanine aminotransferase, glutamate dehydrogenase, and sorbitol dehydrogenase on day 22; these increases were transient, and by week 13 the serum activities of these enzymes were similar to those of the chamber controls. An alkaline phosphatase enzymeuria occurred in 200 ppm females on day 22; at week 13, an alkaline phosphatase enzymeuria oc-curred in 32, 80, and 200 ppm males and 200 ppm females. At week 13, a proteinuria occurred in 200 ppm males. Liver nonprotein sulfhydryl concentrations in male rats immediately following 1 day or 12 weeks of exposure to 200 ppm and in females exposed to 200 ppm for 12 weeks were significantly less than those of the chamber control groups.

Kidney weights of 200 ppm males and females and 80 ppm females were significantly greater than those of the chamber control groups. Sperm motility of 200 ppm males was significantly less than that of the controls. In neurobehavioral assessments, horizontal activity was increased in male rats exposed to 32 ppm or greater and total activity was increased in 32 and 200 ppm males.

Increased incidences of minimal to mild olfactory epithelial degeneration and respiratory metaplasia occurred in males and females exposed to 80 or 200 ppm. The incidence of olfactory epithelial degeneration in 32 ppm females was also significantly greater than that in the chamber control group. The incidence of hepatocellular necrosis in 200 ppm females was significantly greater than that in the chamber control group. Scattered chronic inflammation also occurred in the liver of male and female rats in the 200 ppm groups; the incidence in 200 ppm females was significantly greater than that in the chamber control group. The incidences of hemosiderin pigmentation were significantly increased in males and females exposed to 200 ppm.

13-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to chloroprene at concentrations of 0, 5, 12, 32, or 80 ppm by inhalation, 6 hours per day, 5 days

per week, for 13 weeks. All male and female mice survived to the end of the study. The final mean body weight and body weight gain of males exposed to 80 ppm were significantly less than those of the chamber control group.

Hematocrit concentrations of females exposed to 32 or 80 ppm and erythrocyte counts of 80 ppm females were significantly less than those of the chamber control group. Platelet counts of 32 and 80 ppm females were also greater than that of the chamber control group. Increased incidences of squamous epithelial hyperplasia of the forestomach occurred in males and females exposed to 80 ppm.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female F344/N rats were exposed to chloroprene at concentrations of 0, 12.8, 32, or 80 ppm by inhalation, 6 hours per day, 5 days per week, for 2 years.

Survival, Body Weights, and Clinical Findings

Survival of males exposed to 32 or 80 ppm was significantly less than that of the chamber control group. Mean body weights of males exposed to 80 ppm were less than those of the chamber controls after week 93. Masses of the torso were observed during the study in exposed female groups, and these clinical findings correlated with mammary gland fibroadenomas observed at necropsy.

Pathology Findings

The incidences of squamous cell papilloma and squamous cell papilloma or squamous cell carcinoma (combined) of the oral cavity in male rats exposed to 32 ppm and male and female rats exposed to 80 ppm were significantly greater than those in the chamber controls and exceeded the historical control ranges.

The incidences of thyroid gland follicular cell adenoma or carcinoma (combined) in males exposed to 32 or 80 ppm were significantly greater than that in the chamber control group and exceeded the historical control range. Although the incidences of follicular cell adenoma and follicular cell adenoma or carcinoma (combined) in 80 ppm females were not significantly greater than those in the chamber controls, they did exceed the historical control range for these neoplasms.

The incidences of alveolar epithelial hyperplasia of the lung were significantly greater in all exposed groups of males and females than in the chamber control groups. The incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) in 80 ppm males were slightly greater than those in the chamber control group. Although these neoplasm incidences were not significant, they exceeded the historical control range. The incidence of alveolar/bronchiolar adenoma, although not significant, was greater in 80 ppm females than in the chamber control group.

The incidences of multiple fibroadenoma of the mammary gland in all exposed groups of females were greater than that in the chamber control group. The incidences of fibroadenoma (including multiple fibroadenoma) in 32 and 80 ppm females were significantly greater than that in the chamber controls. The incidences of fibroadenoma in the chamber control group and in all exposed groups of females exceeded the historical control range.

The severity of nephropathy in exposed groups of male and female rats was slightly greater than in the chamber controls. Renal tubule adenoma and hyperplasia were observed in males and females. Additional kidney sections from male and female control and exposed rats were examined to provide a clearer indication of the potential effects of chloroprene on the kidney. The combined single- and step-section incidences of renal tubule hyperplasia in 32 and 80 ppm males and 80 ppm females and the incidences of adenoma and adenoma or carcinoma (combined) in all exposed males were significantly greater than those in the chamber controls.

A slight increase in the incidence of transitional epithelium carcinoma of the urinary bladder was observed in 80 ppm females. In addition, one 32 ppm male had a transitional epithelium carcinoma and one 80 ppm male had a transitional cell papilloma. These findings are noteworthy because no urinary bladder neoplasms have been observed in chamber control male or female F344/N rats.

In the nose, the incidences of atrophy, basal cell hyperplasia, metaplasia, and necrosis of the olfactory epithelium in 32 and 80 ppm males and females and of atrophy and necrosis in 12.8 ppm males were

significantly greater than those in the chamber control groups. The incidences of chronic inflammation were significantly increased in males exposed to 12.8 or 32 ppm and in males and females exposed to 80 ppm. The incidences of fibrosis and adenomatous hyperplasia in 80 ppm males and females were significantly greater than those in the chamber controls. Generally, lesions in the nasal cavity were mild to moderate in severity.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed to chloroprene at concentrations of 0, 12.8, 32, or 80 ppm by inhalation, 6 hours per day, 5 days per week, for 2 years.

Survival, Body Weights, and Clinical Findings

Survival of males exposed to 32 or 80 ppm and of all exposed female groups was significantly less than that of the chamber controls. The mean body weights of 80 ppm females were significantly less than those of the chamber control group after week 75. Clinical findings included masses of the head, which correlated with harderian gland adenoma and/or carcinoma in 32 ppm males and 80 ppm males and females. Dorsal and lateral torso masses of female mice correlated with mammary gland neoplasms in 32 and 80 ppm females and subcutaneous sarcomas in 12.8, 32, and 80 ppm females.

Pathology Findings

The incidences of alveolar/bronchiolar neoplasms in the lungs of all groups of exposed males and females were significantly greater than those in the chamber control groups and generally exceeded the historical control ranges. The incidences of multiple alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma were increased in all exposed groups of males and females. The incidences of bronchiolar hyperplasia in all exposed groups of males and females were significantly greater than those in the chamber control groups.

Male mice had a pattern of nonneoplastic liver lesions along with silver-staining helical organisms within the liver consistent with infection with *Helicobacter hepaticus*. An organism compatible with *H. hepaticus* was confirmed with a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)-based assay. In NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of hemangiosarcoma have been seen in the livers of male mice. Therefore, hemangiosarcomas of the liver were excluded from the analyses of circulatory (endothelial) neoplasms in males in this study. Even with this exclusion, the combined occurrence of hemangioma or hemangiosarcoma at other sites was significantly increased at all chloroprene exposure concentrations in males and in 32 ppm females. Incidences of neoplasms at other sites in this study of chloroprene were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis.

The incidences of harderian gland adenoma and harderian gland adenoma or carcinoma (combined) in males exposed to 32 or 80 ppm and females exposed to 80 ppm were significantly greater than those in the chamber controls. The incidences of harderian gland adenoma or carcinoma (combined) in 32 ppm males and 80 ppm males and females exceeded the historical control ranges.

The incidences of mammary gland carcinoma and adenoacanthoma or carcinoma (combined) in 80 ppm females were significantly greater than those in the chamber control group. The incidences of mammary gland carcinoma and of adenoacanthoma in 32 and 80 ppm females exceeded the historical control ranges. Multiple mammary gland carcinomas occurred in exposed females.

The incidences of hepatocellular carcinoma in all exposed female groups and hepatocellular adenoma or carcinoma (combined) in 32 and 80 ppm females were significantly greater than those in the chamber controls; in the 80 ppm group, the incidence exceeded the historical control ranges for carcinoma and adenoma or carcinoma (combined). The incidence of eosinophilic foci in 80 ppm females was also significantly greater than that in the chamber controls.

The incidences of sarcoma of the skin were significantly greater in all exposed groups of females than in the chamber controls. The incidences of sarcoma of the mesentery were also increased in all exposed groups of females.

The incidence of squamous cell papilloma in 80 ppm females was greater than that in the chamber controls; the difference was not significant, but the incidence exceeded the historical control range. Males also showed a positive trend in the incidence of squamous cell papilloma of the forestomach. In males and females exposed to 80 ppm, the incidences of hyperplasia of the forestomach epithelium were significantly greater than those in the chamber controls.

Carcinomas of the Zymbal's gland were seen in three 80 ppm females, and two carcinomas metastasized to the lung. Zymbal's gland carcinomas have not been reported in control female mice in the NTP historical database.

The incidence of renal tubule adenoma in 80 ppm males was greater than that in the chamber controls. Though this difference was not significant, the incidence of this rare neoplasm exceeded the historical control range. The incidences of renal tubule hyperplasia in males exposed to 32 or 80 ppm were significantly greater than that in the chamber controls. Additional sections of kidney were examined from control and exposed males to verify these findings. The combined single- and step-section incidence of renal tubule adenoma in 80 ppm males and the combined incidences of renal tubule hyperplasia in all groups of exposed male mice were greater than those in the chamber controls.

The incidences of olfactory epithelial atrophy, adenomatous hyperplasia, and metaplasia in 80 ppm males and females were significantly greater than those in the chamber controls. The incidences of hematopoietic proliferation of the spleen in 32 and 80 ppm males and in all groups of exposed females were significantly greater than those in the chamber controls.

GENETIC TOXICOLOGY

Chloroprene was not mutagenic in any of the tests performed by the NTP. No induction of mutations was noted in any of four strains of *S. typhimurium* in the presence or the absence of S9 metabolic activation enzymes, and no induction of sex-linked recessive lethal mutations was observed in germ cells of male *D. melanogaster* treated with chloroprene via feeding or injection. In male mice exposed to chloroprene by inhalation for 12 days over a 16-day period, no induction of chromosomal aberrations, sister chromatid exchanges, or micronucleated erythrocytes in bone marrow or peripheral blood occurred. Results of a second micronucleus assay in male and female mice after 13 weeks of exposure to chloroprene via inhalation were also negative.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of chloroprene in male F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, lung, and kidney were also attributed to chloroprene exposure. There was *clear evidence of carcinogenic activity* of chloroprene in female F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, mammary gland, and kidney were also attributed to exposure to chloroprene. Low incidences of urinary bladder neoplasms in male and female rats and lung neoplasms in female rats may also have been related to exposure to chloroprene.

There was *clear evidence of carcinogenic activity* of chloroprene in male B6C3F$_1$ mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), and harderian gland; increased incidences of neoplasms of the forestomach and kidney were also attributed to exposure to chloroprene. There was *clear evidence of carcinogenic activity* of chloroprene in female B6C3F$_1$ mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), harderian gland, mammary gland, liver, skin, and mesentery; increased incidences of neoplasms of the forestomach and Zymbal's gland were also attributed to exposure to chloroprene.

Exposure of male and female rats to chloroprene was associated with increased incidences of alveolar epithelial hyperplasia in the lung; nephropathy; and several nonneoplastic effects in the nose including olfactory epithelial atrophy, fibrosis, adenomatous hyperplasia, basal cell hyperplasia, chronic inflammation, respiratory metaplasia, and necrosis. Exposure of male and female mice to chloroprene was

associated with increased incidences of bronchiolar hyperplasia and histiocytic cell infiltration in the lung; epithelial hyperplasia in the forestomach; renal tubule hyperplasia (males only); several effects in the nose including olfactory epithelial atrophy, respiratory metaplasia, and adenomatous hyperplasia; and hematopoietic cell proliferation in the spleen.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 14. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 16.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Chloroprene

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure concentrations	0, 12.8, 32, or 80 ppm by inhalation	0, 12.8, 32, or 80 ppm by inhalation	0, 12.8, 32, or 80 ppm by inhalation	0, 12.8, 32, or 80 ppm by inhalation
Body weights	80 ppm group less than chamber control group	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group	80 ppm group less than chamber control group
Survival rates	13/50, 9/50, 5/50, 4/50	29/49, 28/50, 26/50, 21/50	27/50, 27/50, 14/50, 13/50	35/50, 16/50, 1/50, 3/50
Nonneoplastic effects	Lung: alveolar epthelial hyperplasia (5/50, 16/50, 14/49, 25/50) Kidney: severity of nephropathy (2.8, 3.0, 3.1, 3.5) Nose (olfactory epithelium): atrophy (3/50, 12/50, 46/49, 48/49); fibrosis (0/50, 0/50, 0/49, 47/49); adenomatous hyperplasia (2/50, 0/50, 1/49, 42/49); basal cell hyperplasia (0/50, 0/50, 38/49, 46/49); chronic inflammation (0/50, 5/50, 9/49, 49/49); metaplasia (6/50, 5/50, 45/49, 48/49); necrosis (0/50, 11/50, 26/49, 19/49)	Lung: alveolar epithelial hyperplasia (6/49, 22/50, 22/50, 34/50) Kidney: severity of nephropathy (1.9, 2.0, 2.0, 2.2) Nose (olfactory epithelium): atrophy (0/49, 1/50, 40/50, 50/50); fibrosis (0/49, 0/50, 0/50, 49/50); adenomatous hyperplasia (0/49, 0/50, 0/50, 27/50); basal cell hyperplasia (0/49, 0/50, 17/50, 49/50); chronic inflammation (0/49, 0/50, 2/50, 33/50); metaplasia (0/49, 1/50, 35/50, 50/50); necrosis (0/49, 0/50, 8/50, 12/50)	Lung: bronchiolar hyperplasia (0/50, 10/50, 18/50, 23/50); histiocytic cell infiltration (7/50, 8/50, 11/50, 22/50) Forestomach: epithelial hyperplasia (4/50, 6/48, 7/49, 29/50) Kidney: renal tubule hyperplasia (0/50, 4/49, 5/50, 5/50) Nose (olfactory epithelium): atrophy (7/50, 8/48, 7/50, 49/50); metaplasia (6/50, 5/48, 5/50, 49/50); adenomatous hyperplasia (3/50, 2/48, 2/50, 48/50) Spleen: hematopoietic cell proliferation (26/50, 22/49, 35/50, 31/50)	Lung: bronchiolar hyperplasia (0/50, 15/49, 12/50, 30/50); histiocytic cell infiltration (1/50, 14/49, 18/50, 23/50) Forestomach: epithelial hyperplasia (4/50, 3/49, 8/49, 27/50) Nose (olfactory epithelium): atrophy (6/50, 5/49, 4/49, 47/50); metaplasia (2/50, 3/49, 1/49, 44/50); adenomatous hyperplasia (2/50, 3/49, 0/49, 44/50) Spleen: hematopoietic cell proliferation (13/50, 25/49, 42/49, 39/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Chloroprene

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic effects	Oral cavity: squamous cell papilloma (0/50, 2/50, 4/50, 10/50); squamous cell papilloma or squamous cell carcinoma (0/50, 2/50, 5/50, 12/50) Thyroid gland: follicular cell adenoma or carcinoma (0/50, 2/50, 4/49, 5/50) Lung: alveolar/ bronchiolar carcinoma (0/50, 2/50, 1/49, 4/50); alveolar/bronchiolar adenoma or carcinoma (2/50, 2/50, 4/49, 6/50) Kidney: renal tubule adenoma (extended evaluation - 1/50, 6/50, 6/50, 7/50; standard and extended evaluations combined - 1/50, 7/50, 6/50, 8/50); renal tubule adenoma or carcinoma (extended evaluation - 1/50, 7/50, 6/50, 7/50; standard and extended evaluations combined - 1/50, 8/50, 6/50, 8/50)	Oral cavity: squamous cell papilloma (1/49, 2/50, 2/50, 7/50); squamous cell papilloma or squamous cell carcinoma (1/49, 3/50, 5/50, 11/50) Thyroid gland: follicular cell adenoma or carcinoma (1/49, 1/50, 1/50, 5/50) Mammary gland: fibroadenoma (24/49, 32/50, 36/50, 36/50) Kidney: renal tubule adenoma or carcinoma (standard and extended evaluations combined - 0/49, 0/50, 0/50, 4/50)	Lung: alveolar/ bronchiolar adenoma (8/50, 18/50, 22/50, 28/50); alveolar/ bronchiolar carcinoma (6/50, 12/50, 23/50, 28/50); alveolar/ bronchiolar adenoma or carcinoma (13/50, 28/50, 36/50, 43/50) Circulatory system: hemangiosarcoma (3/50, 13/50, 22/50, 19/50); hemangiosarcoma (excludes liver) (1/50, 11/50, 16/50, 15/50); hemangioma or hemangiosarcoma (3/50, 14/50, 23/50, 21/50); hemangioma or hemangiosarcoma (excludes liver) (1/50, 12/50, 18/50, 17/50) Harderian gland: adenoma (2/50, 5/50, 8/50, 10/50); adenoma or carcinoma (2/50, 5/50, 10/50, 12/50) Forestomach: squamous cell papilloma (1/50, 0/50, 2/50, 4/50) Kidney: renal tubule adenoma (extended evaluation 0/50, 1/49, 2/50, 6/50); standard and extended evaluations combined - 0/50, 2/49, 3/50, 9/50)	Lung: alveolar/ bronchiolar adenoma (2/50, 16/49, 29/50, 26/50) alveolar/ bronchiolar carcinoma (2/50, 14/49, 16/50, 28/50); alveolar/ bronchiolar adenoma or carcinoma (4/50, 28/49, 34/50, 42/50) Circulatory system: hemangioma (0/50, 0/50, 2/50, 3/50); hemangiosarcoma (4/50, 6/50, 17/50, 5/50); hemangioma or hemangiosarcoma (4/50, 6/50, 18/50, 8/50) Harderian gland: adenoma (1/50, 3/50, 3/50, 8/50); adenoma or carcinoma (2/50, 5/50, 3/50, 9/50) Mammary gland: carcinoma (3/50, 4/50, 7/50, 12/50) Liver: hepatocellular carcinoma (4/50, 11/49, 14/50, 19/50); hepatocellular adenoma or carcinoma (20/50, 26/49, 20/50, 30/50) Skin: sarcoma (0/50, 11/50, 11/50, 18/50) Mesentery: sarcoma (0/50, 4/50, 8/50, 3/50) Forestomach: squamous cell papilloma or squamous cell carcinoma (1/50, 0/50, 0/50, 4/50) Zymbal's gland: carcinoma (0/50, 0/50, 0/50, 3/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Chloroprene

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Uncertain findings	Urinary bladder: transitional epithelium carcinoma (0/50, 0/50, 1/50, 0/49); transitional epithelium papilloma (0/50, 0/50, 0/50, 1/49)	Urinary bladder: transitional epithelium carcinoma (0/49, 0/50, 0/50, 2/50) Lung: alveolar/ bronchiolar adenoma (1/49, 0/50, 0/50, 3/50)	None	None
Levels of evidence of carcinogenic activity	Clear evidence	Clear evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:			Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537	
Sex-linked recessive lethal mutations *Drosophila melanogaster*:			Negative	
Sister chromatid exchanges Mouse bone marrow cells *in vivo*:			Negative in male mice	
Chromosomal aberrations Mouse bone marrow cells *in vivo*:			Negative in male mice	
Micronucleated erythrocytes Mouse peripheral blood *in vivo* (12 exposures):			Negative in male mice	
Mouse peripheral blood *in vivo* (13-week exposure):			Negative in male and female mice	

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on chloroprene on 11 December 1996 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 11 December 1996, the draft Technical Report on the toxicity and carcinogenesis studies of chloroprene received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.L. Melnick, NIEHS, introduced the toxicology and carcinogenesis studies of chloroprene by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and reporting on compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions for the 2-year studies were *clear evidence of carcinogenic activity* in male and female F344/N rats and B6C3F$_1$ mice.

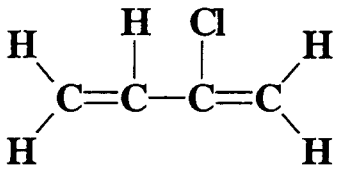
Dr. Ward, a principal reviewer, agreed with the proposed conclusions. He commented that there were many nonneoplastic lesions in the nasal cavity of rats and mice but no nasal neoplasms. He stated that the Discussion section should indicate that many toxic and reparative nasal lesions did not lead to neoplasms, in regard to a current theory/hypothesis that chronic lesions may lead to cancer. Dr. Ward said it was important to know whether the hyperplasias in many organs were focal or diffuse. Dr. Melnick said most of the hyperplasias were focal and this would be emphasized in the text. Because so many tissues were involved, Dr. Ward suggested an additional summary table for comparison to 1,3-butadiene, which might list target organs of toxicity and carcinogenesis. Dr. Melnick agreed.

Dr. Goldsworthy, the second principal reviewer, agreed with the proposed conclusions. He noted the significant changes in survival and body weights that occurred during the study. Dr. Goldsworthy thought the differing decreases in body weights between exposure concentrations might call into question the numbers derived from the dose-response curves. Additionally, he asked for clarification of the impact of *Helicobacter* infection on the interpretation of hepatocellular neoplasms and liver hemangiomas in male mice (see Appendix O).

Dr. Russo, the third principal reviewer, agreed with the proposed conclusions.

Dr. Goldsworthy moved that the Technical Report on chloroprene be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *clear evidence of carcinogenic activity*. Dr. Russo seconded the motion, which was accepted unanimously with nine votes.

INTRODUCTION



CHLOROPRENE

CAS No. 126-99-8

Chemical Formula: C_4H_5Cl Molecular Weight: 88.54

Synonyms: Chlorobutadiene; 2-chlorobuta-1,3-diene; 2-chloro-1,3-butadiene; β-chloroprene

CHEMICAL AND PHYSICAL PROPERTIES

Chloroprene is a pungent-smelling, ether-like, colorless, flammable liquid with a boiling point of 59.4° C, a specific gravity of 0.9583 at 20° C, and a vapor pressure of 188 mm Hg at 20° C. It is soluble in ether, acetone, benzene, and most organic solvents and is slightly soluble in water. Chloroprene has a flash point of -20° C and an explosive limit of 4% to 20% in air and is therefore highly flammable (IARC, 1979; *Patty's*, 1981; *Hawley's*, 1987). Chloroprene is highly reactive, forming peroxides and spontaneously polymerizing at room temperature and in the presence of oxygen (Stewart, 1971).

PRODUCTION, USE, AND HUMAN EXPOSURE

Chloroprene is produced by the addition of hydrochloric acid to dimerized acetylene or by the chlorination of 1,3-butadiene (IARC, 1979; *Hawley's*, 1987). Large volumes of chloroprene are produced for industrial use; cumulative annual production in Japan, Western Europe, and the United States in 1989 was approximately 880 million pounds (Weissermel and Arpe, 1990).

Chloroprene is used almost exclusively as an intermediate in the production of polychloroprene elastomer (neoprene). Polychloroprene is used in automotive rubber goods, wire and cable coatings, construction applications, fabric coatings, cements, sealants, and adhesives (IARC, 1979; ACGIH, 1985; *Hawley's*, 1987). The United States Food and Drug Administration permits the use of polychloroprene as a component of coatings and in rubber articles intended for use in contact with food (CFR 21 §§ 175.105, 175.300, 177.2600). Polychloroprene may contain up to 0.5% free chloroprene (ACGIH, 1986).

The main sources of environmental releases of chloroprene are probably the effluent and emmissions from facilities that produce chloroprene or polychloroprene elastomers. Volatilization is the predominant mechanism of removal of chloroprene from water. Chloroprene's fate in the atmosphere may follow one of two paths: reaction with photochemically generated hydroxyl radicals or reaction with ozone (ACGIH, 1985). Reaction of chloroprene with hydroxyl radicals or ozone may form formaldehyde, 1-chloroacrolein, glyoxal, chloroglyoxal, and chlorohydroxy acids or other aldehydes.

The most probable route of human exposure to chloroprene is inhalation by workers employed in the manufacture of chloroprene or polychloroprene. Human exposure may also occur through ingestion or by contact with the skin or eye (IARC, 1979). In 1977 an estimated 2,500 to 3,000 workers were exposed to chloroprene during its manufacture and polymerization; potential concentrations were as high as 6,760 ppm in some polymerization areas (Infante *et al.*, 1977). The National Occupational Exposure Survey estimated that from 1981 through 1983, approximately 17,700 workers were occupationally exposed to chloroprene (NIOSH, 1990a). Chloroprene is an irritant to the eyes, skin, and mucous membranes of the respiratory tract and may also cause temporary hair loss. Chloroprene may also affect the central nervous system, liver, kidneys, myocardium, and digestive system (*Patty's*, 1981; Sittig, 1985; ACGIH, 1986). In 1980, based on results from rodent studies, the American Conference of Governmental Industrial Hygienists lowered the recommended threshold limit value for chloroprene in the work environment from 25 ppm to 10 ppm (36 mg/m^3) (ACGIH, 1996). The Occupational Safety and Health Administration has set the occupational exposure standard for chloroprene at 25 ppm, based largely on results of 4-week inhalation toxicity studies in rats and hamsters (Clary *et al.*, 1978). NIOSH recommends a 15-minute ceiling value of 1 ppm (3.6 mg/m^3) (NIOSH, 1990b).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Chloroprene may be absorbed from the skin, lungs, and gastrointestinal tract (ACGIH, 1985). The wide distribution of chloroprene or its metabolites in the body is evidenced by the numerous target sites of acute or subchronic exposure: liver, lungs, spleen, central nervous system, kidneys, epicardium, testes, and bone marrow (ACGIH, 1985).

There have been no conclusive studies on the metabolic fate of chloroprene. It has been suggested that chloroprene metabolism may follow a pathway similar to that of vinyl chloride, with 2-chloro-1,2-epoxybutene-3 and 2-chloro-3,4-epoxybutene-1 formed as intermediates. These epoxide intermediates may then be detoxified by glutathione conjugation (Haley, 1978). This hypothesis is supported by the work of Summer and Greim (1980), who observed rapid depletion of hepatic glutathione and elevated excretion of urinary thioethers in rats administered 200 mg/kg chloroprene in olive oil by gavage. The epoxide intermediate may also be detoxified by epoxide hydrolase (Plugge and Jaeger, 1979).

TOXICITY

Experimental Animals

The oral LD_{50} for chloroprene is 251 mg/kg body weight in rats and 260 mg/kg in mice (Asmagulian and Badalian, 1971). In rats, the approximate LC_{50} of chloroprene for a 4-hour inhalation exposure is 2,280 ppm (Clary *et al.*, 1978). A study by von Oettingen *et al.* (1936) reported a minimum lethal dose of 2.5 mg/L (700 ppm) in cats administered chloroprene by inhalation for 8 hours; death occurred 1 to 3 hours after exposure ended. The International Technical Information Institute (1981) lists 8-hour inhalation LC_{100} values of 165 ppm for rats, 825 ppm for mice, 355 ppm for cats, and 1,064 ppm for rabbits and a subcutaneous injection LC_{LO} value of 1,450 mg chloroprene/kg body weight for mice.

The brain, kidney, liver, lung, heart, and testis have been identified as target organs of chloroprene toxicity. Plugge and Jaeger (1979) observed liver injury, evidenced by increased serum sorbitol dehydrogenase activity, in male Sprague-Dawley rats exposed to 225 or 300 ppm chloroprene by inhalation for 4 hours and necropsied 24 hours after exposure ended. Liver nonprotein sulfhydryl concentrations were increased in fasted rats exposed to 100, 150, 225, or 300 ppm, and serum lactate dehydrogenase activity was increased in rats exposed to 300 ppm. Lung nonprotein sulfhydryl concentrations were decreased in the 100 and 300 ppm groups; no other evidence of lung injury was observed.

In 4-week inhalation studies (6 hours per day, 5 days per week) conducted by Clary *et al.* (1978), signs of toxicity were observed in male and female Wistar rats and Syrian golden hamsters exposed to 40, 160, or 625 ppm chloroprene, and chemical-related deaths occurred in both species in the 160 and 625 ppm groups. In the 625 ppm groups of each species, signs of toxicity included eye irritation, restlessness,

lethargy, nasal discharge, orange urine, hair loss, and reduced body weight gains. Body weights of rats were less in all exposed groups than in the controls. Hematology and urinalysis parameters were not affected significantly by exposure to chloroprene. Chloroprene exposure produced significant changes in kidney, liver, and lung weights of male and female rats and hamsters. Gross examination of animals that died during exposure revealed that livers were dark and swollen and lungs were grayish with hemorrhagic areas; livers of several rats and hamsters in the 625 ppm groups that survived until the end of the studies were also dark and swollen. Microscopic examination revealed slight to severe centrilobular degeneration and necrosis in the livers in 10 of 10 male rats and 8 of 10 female rats exposed to 625 ppm and in two of the three male rats exposed to 160 ppm that died before the end of the study. The mucous membrane of the nasal cavity of exposed hamsters was irritated, and the lungs of rats that died early exhibited small hemorrhages and perivascular edema. Renal tubule epithelial degeneration was also observed in exposed rats.

Nyström (1948) tested the effect of inhalation of 1,400 ppm chloroprene (5 mg/L air) for 6 hours on renal function in a group of five milk-fed rats. By the fourth day after exposure, urea nitrogen clearance was reduced, with values returning to normal by the fourteenth day of exposure. Jaeger *et al.* (1975a,b) found that fasted adult male Holtzman rats were markedly more sensitive to chloroprene hepatotoxicity than were exposed rats fed *ad libitum*. Additionally, rats were more sensitive to chloroprene exposure at night, when glutathione concentrations were low (Jaeger *et al.*, 1975a).

Inhalation of 0.56 or 3 mg chloroprene/m^3 (0.16 or 0.8 ppm chloroprene) by rats for 6 months was reported to result in damage to the cerebral cortex, Ammon's horn, corpora quadrigemina, optic thalamus, and pons and to produce hyperemia of the brain, cell shriveling, pyknotic nuclei, karyolysis, and decomposition of cytoplasm (Mnatsakanyan, 1965).

In toxicity studies reviewed by Haley (1978), dogs exposed to 8 to 20 mL/L (7.7 to 19.2 mg/m^3) chloroprene by inhalation developed jaundice. Chronic inhalation of chloroprene by dogs produced decreased blood glucose concentration, increased blood pyruvate concentration, excitation, mydriasis, convulsions, muscle atonia, hemoptysis, and narcosis and death from pulmonary edema. Changes in higher nervous activity, the cells of the cerebral cortex, and brain vasculature, as well as decreases in serum cholinesterase activity, have been observed following chronic inhalation exposure of dogs to chloroprene.

Thirteen-week inhalation toxicology studies were conducted in male and female F344/N rats and B6C3F_1 mice at exposure concentrations of 0, 5, 12, 32, and 80 ppm (6 hours per day, 5 days per week; Melnick *et al.*, 1996a). A 200 ppm exposure group was also included for rats only. In rats, exposure to 80 or 200 ppm chloroprene caused degeneration and metaplasia of the olfactory epithelium, while anemia, hepatocellular necrosis, and reduced sperm motility were seen only in the 200 ppm group. In mice, exposure to 80 ppm chloroprene caused a marginal decrease in body weight gain in males and epithelial hyperplasia of the forestomach in males and females. The complete results of these studies are presented in this Technical Report.

Humans

Symptoms of acute exposure to high concentrations of chloroprene in air include central nervous system depression; injury to the lung, liver, and kidney; skin and mucous membrane irritation; and respiratory difficulties (Nyström, 1948; Irish, 1963). Contact with chloroprene and its polymers may also produce hair loss and dermatitis (Schwartz, 1945; Nyström, 1948; Ritter and Carter, 1948; Volkova, 1971). Chloroprene exposure (0.3 to 0.48 mg/L; 83 to 133 ppm) was reported to induce diuresis and increased 17-ketosteroid concentrations in Soviet children (Mnatsakanyan, 1966). Arevshatyan (1972) also reported periodontal changes in workers exposed to chloroprene.

Reports of chronic exposure to chloroprene cite effects on blood morphology and the cardiovascular system and on liver, lung, kidney, and nervous function, as well as corneal conjunctivitis and focal necrosis, nausea, indigestion, and loss of appetite (ITII, 1981). Studies by Volkova (1976) and Bagdinov (1973) cited in Sanotskii (1976) reported decreased erythrocyte, leukocyte, and thrombocyte counts in workers at a chloroprene production facility. There was a particularly sharp decrease in

thrombocyte counts of women who had worked at the facility from 1 to 5 years. In addition, hemoglobin concentrations were often reduced below the normal range. Cardiovascular effects included tachycardia, reduced arterial pressure, and muffled heart sounds. Liver effects include hepatomegaly, toxic hepatitis, and decreased liver function (Orlova and Solovyova, 1962; Bagdinov, 1973; Volkova, 1976; NIOSH, unpublished). Gooch and Hawn (1981) found no clinically significant hematologic or biochemical alterations in workers exposed to chloroprene at a DuPont chemical facility.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

Soviet researchers have reported that chloroprene is embryotoxic and teratogenic at concentrations below 1 ppm (IARC, 1979). Sal'nikova (1968) and Sal'nikova and Fomenko (1973) exposed pregnant rats and mice to chloroprene concentrations between 15 ppb and 4.1 ppm by inhalation; concentrations of 36 ppb and greater were reported to be embryotoxic. Maternal exposure to chloroprene was also linked to decreased pup survival prior to weaning and low pup body weights at weaning. In a review of the Soviet literature, Sanotskii (1976) reported that male white rats exposed to 1.7 mg/m^3 (0.5 ppm) chloroprene for 4.5 months had decreased numbers of normal sperm, decreased sperm motility, and increased numbers of dead sperm. Sanotskii (1976) also reported an increase in the number of seminiferous tubules with desquamating epithelium in male C57BL/6 mice exposed to 0.32 mg/m^3 (0.09 ppm) for 2 months and increased dominant lethal mutations in germ cells of male and female C57BL/6 mice exposed to 3.5 mg/m^3 (1 ppm) for 2 months. Exposure of pregnant white rats to 4 mg/m^3 (1.1 ppm) produced decreased fetal body weights and increased fetal death.

Other reports do not support or agree with the Soviet findings. Culik *et al.* (1978) observed slight increases in resorptions and fetal body lengths in litters of ChR-CD rats exposed to 10 ppm and in fetal body weights and lengths in litters of dams exposed to 25 ppm chloroprene by inhalation, 4 hours per day, from gestation days 3 to 20; however, these authors observed no other reproductive or developmental effects in a series of teratology, embryotoxicity, and reproductive toxicity studies at exposures up to 25 ppm chloroprene. Exposure of pregnant New Zealand white rabbits to 10, 40, or 175 ppm chloroprene vapor, 6 hours per day, 7 days per week, on gestation days 6 through 28 produced no observable toxic effects to the dam or the offspring (Mast *et al.*, 1994).

Humans

Chloroprene exposure has been reported to affect male reproductive function; however, many of these reports cite the same Russian study, Fomenko (1974). Sanotskii's (1976) review of this study stated that examination of chloroprene workers revealed functional disturbances in spermatogenesis after 6 to 10 years of work in chloroprene production and morphological abnormalities of sperm after 11 or more years. Cases of spontaneous abortion in the wives of chloroprene workers occurred more than three times as often as in the control group. Sanotskii (1976) also cited reports of congenital abnormalities in the children of women working in a chloroprene factory and cases of pregnancies "taking an unfavorable course" in women working with chloroprene latex. However, the methods used to gather data in these studies have been questioned (ACGIH, 1985).

CARCINOGENICITY

Experimental Animals

Chloroprene is the 2-chloro analogue of 1,3-butadiene, a chemical which was shown by NTP to be a potent multi-organ carcinogen in mice exposed by inhalation (Huff *et al.*, 1985; Melnick *et al.*, 1990a; NTP, 1993). Qinan *et al.* (1989) exposed Kunming albino mice to 0, 2.9, 19, or 189 mg chloroprene/m^3 by inhalation (0, 0.8, 5.3, or 53 ppm, respectively), 4 hours per day, 6 days per week, for 7 months. All surviving mice were killed at the end of the eighth month of the study. Compared to controls, exposed mice developed a significantly greater number of lung tumors (1.3%, 8.1%, 9.4%, and 19.7% in the respective groups). Tumor multiplicity was significantly increased in the 189 mg/m^3 group. Most of these tumors were papilloadenomas, although a few were adenomas.

The USEPA summarized a study by Zil'fian and Fichidzhyan (1972), who investigated the effect of chloroprene administration in 60 mixed-breed white mice. Groups of 30 mice received either 0.1 mg/g peach oil subcutaneously or transplanted Crocker murine sarcoma cells in suspension in 0.1 mg/g peach oil. In the latter group, chloroprene administration was found to increase neoplasm growth. This effect was attributed to an immunosuppressive activity of chloroprene.

Menezes *et al.* (1979) transplanted chloroprene-treated (1, 10, or 100 mg/mL for 42 days) and untreated cultured hamster lung cells subcutaneously into newly born hamsters and intraocularly into adult hamsters. Untreated cells did not produce neoplasms; however, cells treated with 1 mg chloroprene/mL produced fibrosarcomas within 14 weeks. Sills *et al.* (1993) found that several types of neoplasms from chloroprene-treated B6C3F$_1$ mice were positive for the protein product of the mutated p53 tumor suppressor gene.

Zil'fian *et al.* (1975) found no induction of neoplasms in mice receiving skin applications of chloroprene or in rats dosed subcutaneously or by intragastric gavage. Ponomarkov and Tomatis (1980) dosed female DB IV rats with 100 mg chloroprene/kg in olive oil by gavage on gestation day 17 and dosed their offspring with 50 mg/kg by stomach tube for their life span after weaning. Although exposed rats had higher incidences of subcutaneous fibroma, chloroprene administration did not affect overall neoplasm incidences.

Humans

In a study of the relationship between industrial chemical exposure and lung cancer risk, Khachatrian (1972a) found that workers were 2.67 times less likely to develop lung cancer if they had not worked with chloroprene-related chemicals. Khachatrian (1972b) also found a correlation between the incidence of skin cancer and degree of exposure to chloroprene; an inverse relationship was found between degree of exposure and age at diagnosis of skin cancer. Khachatrian's (1972a,b) methodology has been criticized (IARC, 1979). Pell (1978) reported increased incidences of digestive, lymphatic, and hematopoietic cancer in chloroprene workers at two DuPont plants. Pell (1978) did not distinguish between chloroprene manufacturing and polychloroprene manufacturing or attempt to control for confounding variables such as prior occupational exposure to other chemicals.

Herbert (1976) reported a case of liver angiosarcoma in a man who had worked for 15 years with liquid polychloroprene (which may contain up to 5,000 ppm chloroprene) or with finished polychloroprene. Concentrations between 0.14 and 0.2 ppm were measured in the air at the man's place of work. The individual had no prior exposure to any chemicals linked to this particular neoplasm (e.g., vinyl chloride). Although information on the carcinogenicity of chloroprene is limited, this singular occurrence was considered a potential health concern due to the rarity of liver angiosarcoma in the general population and the structural similarity between chloroprene and vinyl chloride (Infante *et al.*, 1977). In both case control and cohort studies in China of workers exposed to chloroprene, Shouqi *et al.* (1989) found a significant correlation between cancer deaths and exposure to chloroprene. Maintenance mechanics had the highest risk of cancer. Standardized mortality ratios for liver, lung, and lymphatic cancers were significantly elevated in this group.

GENETIC TOXICITY

Results of mutagenicity tests with chloroprene appear to indicate little mutagenic activity, but the inconsistency among laboratories in the weakly positive responses noted in some tests complicate an assessment of the overall genetic toxicity profile of chloroprene. Chloroprene was reported to be mutagenic, with and without metabolic activation with induced liver S9 enzymes, to *Salmonella typhimurium* strains TA100 (Bartsch *et al.*, 1975) and TA1530 (Bartsch *et al.*, 1979); in these investigations, the level of mutagenic activity was enhanced by the addition of S9. In contrast, Zeiger *et al.* (1987) found no evidence of mutagenic activity for chloroprene in four strains of *S. typhimurium*, including strain TA100. More recently, Westphal *et al.* (1994), using a modified preincubation protocol to control for the volatility of chloroprene, reported no mutagenic activity for freshly distilled chloroprene (highly pure) in strain TA100; however, an S9-independent mutagenic response that correlated directly with the age of older aliquots of chloroprene was observed with and without volatility

control. Westphal *et al.* (1994) attributed the increasing mutagenicity of aged chloroprene samples to the accumulation of several decomposition products in the chloroprene distillate, notably cyclic chloroprene dimers, which were identified by gas chromatography/mass spectrometry. Like Bartsch *et al.* (1975, 1979), Westphal *et al.* (1994) found that S9 enhanced the mutagenic response of *S. typhimurium* strain TA100 to aged chloroprene. In eukaryotic test systems, chloroprene was not mutagenic in cultured V79 Chinese hamster cells (Drevon and Kuroki, 1979). It gave conflicting responses in *Drosophila* sex-linked recessive lethal assays; Vogel (1979) reported weakly positive results in a feeding study conducted within a sealed desiccator, and, more recently, Foureman *et al.* (1994) reported no significant increase in sex-linked recessive lethal mutations in germ cells of male flies exposed to chloroprene through feeding or injection. Foureman *et al.* (1994) also provided a thorough discussion of the possible reasons for the discordant results obtained between the two laboratories in this assay, including differences in chloroprene purity, *Drosophila* strain tested, statistical methods of data analysis, and sample size.

In mammalian systems *in vivo*, chloroprene, administered by inhalation at concentrations from 0.036 to 0.97 ppm for 2 months, was reported to induce dominant lethal mutations in germ cells of male rats and mice and chromosomal aberrations in bone marrow cells of C57BL/6 mice (Sanotskii, 1976). A more recent study of the *in vivo* mutagenic activity of chloroprene showed no effects on the frequencies of sister chromatid exchanges, chromosomal aberrations, or micronucleated erythrocytes in bone marrow or peripheral blood of $B6C3F_1$ mice exposed for 12 days to chloroprene at concentrations of 12, 32, or 80 ppm (Tice *et al.*, 1988). Results of a second micronucleus assay in male and female mice after 90 days of exposure to chloroprene (5 to 80 ppm) by inhalation were also negative. The differences in bone marrow chromosomal effects between these studies and those of Sanotskii (1976) may have been the result of strain-related differences in chloroprene tissue distribution and detoxification processes or of variations in experimental protocols, including the age of the chloroprene.

STUDY RATIONALE

Chloroprene was chosen for study by the National Toxicology Program because it is a high-volume production chemical and because information on its carcinogenic potential in experimental animals and humans was limited. In addition, chloroprene is the 2-chloro analogue of 1,3-butadiene, a potent multi-organ carcinogen in rats and mice, which has consistently been associated with increased risk of lymphatic and hematopoietic cancers in occupationally exposed workers. Thus, the results of the current studies allow assessment of the effects of the chlorine substitution on the carcinogenicity of 1,3-butadiene. Inhalation was chosen as the route of exposure because it is the most likely route of human exposure.

DISCUSSION AND CONCLUSIONS

Chloroprene was selected for study by the National Toxicology Program (NTP) because it is an important high-volume production chemical with a potential for human exposure, there is limited information available on its carcinogenic potential in experimental animals and humans, and it is the 2-chloro analogue of 1,3-butadiene. Chloroprene is also structurally similar to vinyl chloride, a human carcinogen known to induce hemangiosarcomas in the liver of laboratory animals and exposed workers. Based on results of a previous NTP study of 1,3-butadiene in mice in which neoplasms were induced at multiple organ sites (NTP, 1984; Huff *et al.*, 1985), NTP examined chloroprene and isoprene (2-methyl-1,3-butadiene) to see if either of these structural analogues of 1,3-butadiene produces effects similar to those of 1,3-butadiene. A second study of 1,3-butadiene was also conducted over an expanded exposure range to provide a better characterization of dose-response effects.

1,3-Butadiene has been studied intensely over the past 12 years, and results from those studies have raised the level of concern for humans exposed to this chemical and heightened the importance of understanding the toxicologic and carcinogenic potential of chloroprene and isoprene. This report presents the findings of 16-day, 13-week, and 2-year chloroprene inhalation studies in F344/N rats and B6C3F$_1$ mice and makes comparisons to the toxicologic effects of 1,3-butadiene.

In the two NTP long-term inhalation toxicology/carcinogenicity studies of 1,3-butadiene in B6C3F$_1$ mice, exposure concentrations ranged from 6.25 to 1,250 ppm (Huff *et al.*, 1985; Melnick *et al.*, 1990a; NTP, 1984, 1993). Particularly noteworthy in these studies were the induction of malignant lymphomas as early as 20 weeks after the start of exposure and uncommon hemangiosarcomas of the heart. Furthermore, malignant lung neoplasms were induced in female mice at all exposure concentrations. Other sites of neoplasm induction in mice included the liver, forestomach, harderian gland, ovary, mammary gland, and preputial gland. A 2-year inhalation study of 1,3-butadiene in Sprague-Dawley rats, sponsored by the International Institute of Synthetic Rubber Producers, used exposure concentrations of 1,000 and 8,000 ppm. In rats, 1,3-butadiene was carcinogenic to the mammary gland, brain, Zymbal's gland, uterus, pancreas, testis, and thyroid gland (Owen *et al.*, 1987). These studies established 1,3-butadiene as a multiple-species, multiple-organ carcinogen, with mice eliciting the more striking response. Because of differences in sites of tumor induction and in the effective exposure-related responses between rats and mice, recent research has focused on trying to understand the basis for this species difference, especially as it may relate to assessment of human risk. Based on available epidemiological and mechanistic data on 1,3-butadiene as well as the similarities in response between 1,3-butadiene and ethylene oxide, Melnick and Kohn (1995) concluded that butadiene should be considered a human carcinogen and that the mouse is an appropriate model for assessing human cancer risk.

Epidemiologic studies have consistently associated excess mortality from lymphatic and hematopoietic cancers with occupational exposure to 1,3-butadiene. Significant increases in incidences of lymphosarcoma have been observed in individuals who work in the 1,3-butadiene production industry (Divine, 1990; Ward *et al.*, 1995), whereas increases in the incidence of leukemia have been found in individuals who work in the styrene-butadiene rubber manufacturing industry (Matanoski *et al.*, 1990; Santos-Burgoa *et al.*, 1992). Recent follow-up studies of synthetic-rubber producers have confirmed the association between exposure to 1,3-butadiene and chronic leukemia (Delzell *et al.*, 1996). The finding that the risk of chronic leukemia in humans exposed to 1,3-butadiene was similar to risk estimates that were based on the induction of lymphocytic lymphoma in exposed mice supports the use of mice in studies for human risk assessment.

Based on data available on 1,3-butadiene, the Occupational Safety and Health Administration (OSHA) has recently lowered the occupational exposure standard for 1,3-butadiene from 1,000 to 1 ppm, expressed as an 8-hour, time-weighted, average workplace exposure limit, and set a 15-minute short-term exposure limit of 5 ppm (29 CFR, Parts 1910, 1915, and 1926). The current OSHA standard for chloroprene is 25 ppm, based largely on results of 4-week inhalation toxicity studies in rats and hamsters (Clary *et al.*, 1978).

16-Day and 13-Week Studies in Rats and Mice

Exposure of F344/N rats to chloroprene for 16 days at chamber concentrations ranging from 32 to 500 ppm produced several toxic effects: 1) mortality at 500 ppm and reductions in body weight gain in males exposed to 200 or 500 ppm; 2) regenerative, normocytic, normochromic anemia in males exposed to 500 ppm and in females exposed to 200 or 500 ppm; 3) centrilobular hepatocellular necrosis in the 200 and 500 ppm groups and increases in alanine aminotransferase (ALT), glutamate dehydrogenase (GDH), and sorbitol dehydrogenase (SDH) activities in 200 ppm females and 500 ppm males and females; 4) olfactory epithelial degeneration in all exposed groups and respiratory metaplasia in the 500 ppm groups; and 5) thymic atrophy. Similar effects in the liver were reported in a 4-week inhalation study of chloroprene in Wistar rats (Clary *et al.*, 1978).

The hemorrhage observed clinically (epistaxis) in this study suggests that the rapidly developing normocytic, normochromic, responsive anemia that occurred on day 4 in the 500 ppm groups may have been related to acute blood loss. The thrombocytopenia seen in this study is also consistent with the clinically observed hemorrhage. 1,3-Butadiene has also been shown to cause an anemia in mice (Irons *et al.*, 1986; Melnick *et al.*, 1990b); however, in this species the anemia was macrocytic, normochromic, and nonresponsive and was suggested to involve altered bone marrow production of erythrocytes. No hematologic effects were observed in rats exposed to 1,3-butadiene or isoprene at concentrations as high as 8,000 ppm and 7,000 ppm, respectively (Crouch *et al.*, 1979; Melnick *et al.*, 1994).

Findings from the 13-week inhalation toxicity studies of chloroprene in F344/N rats and B6C3F$_1$ mice have been reported by Melnick *et al.* (1996a). Exposure of rats to 32 ppm chloroprene or greater concentrations caused olfactory epithelial degeneration, and 80 ppm or greater caused respiratory metaplasia; exposure to 200 ppm caused anemia (characterized as normocytic, normochromic, and nonresponsive), minimal to mild hepatocellular necrosis, and reduced sperm motility. These lesions had not been observed in rats exposed to 1,3-butadiene or isoprene even at exposure concentrations as high as 8,000 and 7,000 ppm, respectively (Crouch *et al.*, 1979; Melnick *et al.*, 1994). Neurobehavioral assessments showed an increase in motor activity in exposed males but not females with no effects on grip strength or startle response in either male or female rats (Tilson, 1990).

As in the 16-day rat study, rats in the 200 ppm groups demonstrated evidence of hemorrhage, which may, in part, explain the minimal normocytic, normochromic, and nonresponsive anemia that was observed at week 13. The increase in activated partial thromboplastin time and prothrombin time on day 2 of the 13-week study suggests that coagulopathy may have contributed to the hemorrhage and subsequent anemia. The lack of a bone marrow response at the end of the 13-week study may be because the changes in erythroid parameters were not severe enough to stimulate a demonstrable erythropoietic response.

Increases in serum ALT, GDH, and SDH activities indicative of hepatocellular pathology resulting in a loss of cell membrane integrity, or cellular necrosis with subsequent enzyme release, were observed in both the 16-day and 13-week studies. These changes were transient, however, and by week 13 the activities of these serum enzymes had returned to chamber control levels. Centrilobular necrosis was also observed in the liver of rats exposed to 200 ppm or greater concentrations of chloroprene, and this would account for the increases in the serum activities of these enzymes. However, while the biochemical effects appeared to be transient, liver injury (hepatocellular necrosis) was still evident at study termination.

In the 13-week study, proteinuria and alkaline phosphatase enzymeuria occurred in the 200 ppm animals as early as day 22; these findings suggest a renal

tubule effect. There were no microscopic lesions to support these biochemical alterations, suggesting that the renal injury was too mild to result in structural damage or that the biochemical effects may precede the eventual development of microscopic lesions. Exposure-related increases in kidney weights also suggest a renal effect and support the biochemical findings. These findings suggest that the kidney is a target tissue for the inhalation toxicity of chloroprene and that the renal effects would not have been identified by microscopic evaluation alone.

In the 16-day inhalation study of chloroprene in $B6C3F_1$ mice, exposure concentrations were slightly less than those in the rat study (from 12 to 200 ppm in mice versus 32 to 500 ppm in rats). In spite of the lower exposure concentration, all mice exposed to 200 ppm died during the first 3 days of the study. Chloroprene at exposure concentrations up to 80 ppm had no effect on survival, body weight gain, hematology, or clinical chemistry parameters. Histopathologic findings in the 200 ppm group included multifocal hepatic necrosis, thymic necrosis, and focal hemorrhage, erosions, or necrosis of the glandular stomach mucosa. Squamous epithelial hyperplasia of the forestomach was observed in a small number of mice exposed to 80 ppm.

In the 13-week inhalation study in $B6C3F_1$ mice, exposure to 80 ppm caused a marginal decrease in body weight gain in males and epithelial hyperplasia of the forestomach in males and females. This lesion had also been observed in mice exposed to isoprene or 1,3-butadiene. A mild, normocytic, normochromic, nonresponsive anemia was also detected in exposed female mice. Decreases in hepatic nonprotein sulfhydryl concentrations in mice exposed to 80 ppm were not associated with any histopathologic changes in the liver.

In conjunction with these toxicity studies on chloroprene, additional groups of mice were included for evaluations of cytogenetic effects after 12 exposures over a 16-day period. Unlike the effects seen in mice exposed to 1,3-butadiene or isoprene, chloroprene did not induce cytogenetic damage in bone marrow cells of mice exposed to concentrations up to 80 ppm (Tice *et al.*, 1988). For 1,3-butadiene, this exposure concentration produced increases in sister chromatid exchanges and in the frequency of micronuclei in peripheral blood. Isoprene also produced cytogenetic effects in mice but at exposure concentrations greater than those that could be achieved with chloroprene.

The 16-day and 13-week studies indicate that chloroprene is substantially more toxic to rats and mice than either 1,3-butadiene or isoprene. This difference is reflected in the maximum tolerated exposures that were selected for long-term studies of these chemicals: 1,3-butadiene, 8,000 ppm for rats (Owen *et al.*, 1987) and 1,250 ppm for mice (NTP, 1993; Huff *et al.*, 1985); isoprene, 7,000 ppm for rats and mice (Melnick *et al.*, 1994); and chloroprene, 200 ppm for rats and 80 ppm for mice. Table 31 shows that the profile of toxicologic effects of chloroprene, in terms of target sites and effective exposures, differs considerably from that of isoprene or 1,3-butadiene; this may be due in part to differences in exposure concentrations that were used in the toxicology studies of these compounds but is also likely due to the influence of the chlorine substitution on the toxicokinetics and biotransformation of this chemical and the reactivity of metabolic intermediates with tissue macromolecules.

TABLE 31
Toxicologic Effects (Lowest-Observable-Adverse-Effect Level in ppm) of Chloroprene, 1,3-Butadiene, and Isoprene in Rats and Mice[a]

	Rats			Mice		
Toxic Effect	**Chloroprene**	**Butadiene**	**Isoprene**	**Chloroprene**	**Butadiene**	**Isoprene**
Anemia	200[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	62.5[e]	220[d]
Liver, necrosis	200[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	625[f]	neg(7,000)[d]
Nose, olfactory epithelium degeneration	32[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	625[g]	220[d]
Forestomach, squamous epithelial hyperplasia	neg(200)[b]	neg(8,000)[c]	neg(7,000)[d]	80[b]	200[e]	438[h]
Testes, atrophy	neg(200)[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	625[e]	7,000[h]
Cytogenetic damage						
Chromosomal aberrations	NS	NS	NS	neg(80)[i]	625[j]	neg (7,000)[i]
Sister chromatid exchange	NS	neg(10,000)[k]	NS	neg(80)[i]	6.25[j]	220[l]
Micronuclei	NS	neg(10,000)[k]	NS	neg(80)[i]	6.25[l]	438[i]

[a] Taken from Melnick *et al.*, 1996a. Neg = no effect. NS = not studied. The highest concentration studied is given in parentheses.
[b] The current study
[c] Crouch *et al.*, 1979
[d] Melnick *et al.*, 1994
[e] Melnick *et al.*, 1990b
[f] NTP, 1984
[g] NTP, 1993
[h] Melnick *et al.*, 1990c
[i] Tice *et al.*, 1988
[j] Tice *et al.*, 1987
[k] Cunningham *et al.*, 1986
[l] Shelby, 1990

2-Year Study in Rats

In the 2-year study of chloroprene in rats, survival rates were less in all exposed groups of males and significantly reduced in 32 and 80 ppm males relative to the chamber controls. Males exposed to 80 ppm had decreased body weights compared to the chamber controls; a large part of this difference occurred during the last month of the study. There were no differences in survival or body weights among the female exposed and chamber control rats.

Exposure of rats to chloroprene produced a multiple-organ carcinogenic response. Some sites affected by chloroprene were not affected by 1,3-butadiene, whereas other sites were affected similarly even though the exposure concentrations used in the studies of these two chemicals differed substantially (Table 32). Exposure-related carcinogenic effects of chloroprene were seen in the lung, oral cavity, thyroid gland, mammary gland, and kidney. In addition, low incidences of rare neoplasms in the urinary bladder in males and females may have been exposure related.

TABLE 32
Sites of Increased Incidences of Neoplasms in the 2-Year Inhalation Studies of Chloroprene and 1,3-Butadiene in Rats and Mice

	Chloroprene[a]		1,3-Butadiene[b]	
	Male	Female	Male	Female
Rats				
			Pancreas	
				Uterus
	Oral Cavity	Oral Cavity		
	Thyroid gland	Thyroid gland		Thyroid gland
	Lung			
		Mammary gland		Mammary gland
	Kidney	Kidney		
			Testis	
				Zymbal's gland
			Brain	
Mice				
			Hematopoietic system	Hematopoietic system
	Lung	Lung	Lung	Lung
	Circulatory system	Circulatory system		
			Heart (hemangiosarcoma)	Heart (hemangiosarcoma)
	Harderian gland	Harderian gland	Harderian gland	Harderian gland
	Forestomach	Forestomach	Forestomach	Forestomach
	Kidney		Kidney	
		Mammary gland		Mammary gland
		Liver	Liver	Liver
		Skin		
		Mesentery		
		Zymbal's gland		
			Preputial gland	
				Ovary

[a] Current study in F344/N rats and B6C3F$_1$ mice
[b] Studies in Sprague-Dawley rats at exposure concentrations of 1,000 or 8,000 ppm (Owen *et al.*, 1987) and B6C3F$_1$ mice at exposure concentrations of 6.25, 20, 62.5, 200, or 625 ppm (Melnick *et al.*, 1990a; NTP, 1993)

In rats exposed to chloroprene, increased incidences of proliferative lesions of the oral cavity included squamous cell hyperplasia, squamous cell papilloma, and squamous cell carcinoma and involved the palate, pharynx, gingiva, cheek, and tongue. In addition to the positive exposure-related trends, the incidences of squamous cell papilloma and squamous cell carcinoma (combined) increased significantly in males and females and far exceeded the NTP historical control incidence. Oral cavity neoplasms have not been reported in rats or mice exposed to 1,3-butadiene or isoprene (NTP, 1993, 1995).

Exposure-related positive trends and increased incidences of follicular cell adenoma or carcinoma (combined) in rats were indicative of a carcinogenic effect of chloroprene in the thyroid gland. Thyroid gland follicular cell neoplasms have been reported to be induced in female Sprague-Dawley rats exposed to 1,000 or 8,000 ppm 1,3-butadiene (Owen *et al.*, 1987).

The incidences of alveolar epithelial hyperplasia were increased in all exposed groups of male and female rats relative to their respective chamber control groups, and there was also a slight increase in the incidence of alveolar/bronchiolar carcinomas (4 of 50) in 80 ppm males. The NTP historical control database recorded only 6 of 654 (0.9%) chamber control male rats with alveolar/bronchiolar carcinoma. Although exposure to 1,3-butadiene or isoprene induced lung neoplasms in mice, neither of these chemicals has been reported to cause lung neoplasms in rats (NTP, 1993, 1995).

The incidences of mammary gland fibroadenoma were increased in female rats exposed to 32 or 80 ppm; however, the incidence of mammary gland carcinoma was not increased. Increases in the incidences of multiple fibroadenoma of the mammary gland in female rats support the conclusion that this effect is exposure related. Exposure of female rats to 1,3-butadiene also caused increases in the incidence and multiplicity of mammary gland fibroadenoma (Owen *et al.*, 1987; Melnick and Huff, 1992).

Slight increases in the incidences of renal tubule adenoma and renal tubule hyperplasia were observed in male and female rats exposed to chloroprene compared to the chamber controls. Renal tubule hyperplasias are thought to represent an early stage in the morphologic continuum of proliferative kidney lesions leading to renal tubule adenoma and carcinoma. Even though the severity of nephropathy was increased slightly in exposed rats compared to the chamber controls, the renal tubule hyperplasias observed in this study were distinguishable from regenerative epithelial changes associated with renal nephropathy in this strain of rat. Because renal tubule neoplasms are uncommon in chamber control F344/N rats, additional kidney sections were examined from chamber control and exposed male and female rats to provide a clearer indication of the potential effects of chloroprene in this organ. Analyses of the step-section data indicated that the incidences of renal tubule hyperplasia were increased significantly in 32 and 80 ppm males and 80 ppm females. The incidences of renal tubule adenoma or carcinoma (combined) were increased in all exposed groups of males compared to the chamber controls. Particularly unusual was the finding of renal tubule adenomas in four 80 ppm females and a renal tubule carcinoma in one 12.8 ppm male. Thus, the results from the additional kidney step sections support the evidence from the original pathology review, which indicated that chloroprene induces proliferative renal tubule lesions, including neoplasms, in male and female rats.

A variety of exposure-related nasal lesions were induced in male and female rats including necrosis, chronic active inflammation, atrophy, respiratory metaplasia, adenomatous hyperplasia, basal cell hyperplasia, and fibrosis of the olfactory epithelium. Although the incidences of many of these lesions approached or reached 100% in the 80 ppm groups, there was no evidence of progression of these lesions to neoplasms. Similar nasal lesions without neoplastic effects were seen in several other NTP 2-year studies, including 2-chloroacetophenone, *o*-chlorobenzalmalononitrile, *l*-epinephrine hydrochloride, vinyl toluene, and tetranitromethane (NTP, 1990a,b,c,d,e). Although increased cell turnover may contribute to multistage carcinogenesis, a review of 19 NTP inhalation bioassays found that chronic toxicity and cell proliferation frequently were not associated with nasal carcinogenesis (Ward *et al.*, 1993). Olfactory epithelial degeneration and respiratory metaplasia in rats had been identified as a toxic effect of chloroprene in the 13-week studies; however, nasal lesions were not observed in rats exposed to 8,000 ppm 1,3-butadiene

for 2 years (Owen *et al.*, 1987) or to 7,000 ppm isoprene for 26 weeks (Melnick *et al.*, 1994).

2-Year Study in Mice

In the 2-year study of chloroprene in mice, survival rates were less in 32 and 80 ppm males and in all exposed groups of females than in the chamber controls. Many early deaths and moribund kills were associated with chloroprene-induced neoplasms. Mean body weights of 80 ppm female mice were less than those of chamber controls after week 75.

Exposure of mice to chloroprene produced a potent multisite carcinogenic response. Several organs that were targets of 1,3-butadiene carcinogenicity in mice were similarly affected by chloroprene, including the lung, harderian gland, liver, forestomach, and mammary gland; however, some carcinogenic effects of 1,3-butadiene in mice were not seen in the chloroprene study (Table 32). Most notable was the lack of lymphomas in mice exposed to chloroprene compared to the early occurrence and extensive development of lymphocytic lymphomas in mice exposed to 625 ppm 1,3-butadiene. This may be related to differences in exposure to the parent compound and differences in target organ dosimetry and/or reactivity of metabolic intermediates. Exposure of mice to 1,3-butadiene was also associated with the development of rarely occurring hemangiosarcomas of the heart. Although exposure to chloroprene in the present study did not induce hemangiosarcomas of the heart, there were exposure-related increases in the incidences of hemangioma and hemangiosarcoma at multiple organ sites. In addition, 1,3-butadiene, but not chloroprene, induced granulosa cell tumors of the ovary; and chloroprene, but not 1,3-butadiene, induced skin and mesentery sarcomas in female mice. Small numbers of renal tubule adenomas were observed in male mice exposed to either 1,3-butadiene or chloroprene. The present studies included a step-section evaluation of the kidneys from chamber control and exposed male mice to more clearly ascertain the potential relationship between exposure to chloroprene and kidney neoplasms. The occurrence of Zymbal's gland carcinomas in three female mice exposed to 80 ppm chloroprene is also indicative of an exposure-related effect. The four organ sites where isoprene was reported to induce neoplasms in mice (lung, liver, harderian gland, and forestomach; Melnick *et al.*, 1994) were also affected by chloroprene.

The lung was a major target organ of chloroprene-induced neoplasms in male and female mice. In addition to producing increases in the incidences of bronchiolar epithelial hyperplasia and alveolar/bronchiolar adenoma or carcinoma (combined), chloroprene exposure caused significant increases in the incidences of alveolar/bronchiolar carcinoma, multiple adenoma, and multiple carcinoma. Qinan *et al.* (1989) also observed an increase in lung neoplasm incidence and multiplicity in mice exposed to chloroprene for 7 months. Lung neoplasms including alveolar/bronchiolar carcinoma were induced in female mice exposed to 1,3-butadiene at concentrations as low as 6.25 ppm (Melnick *et al.*, 1990a; NTP, 1993). Lung neoplasms were also induced by vinyl chloride in male and female mice (Maltoni *et al.*, 1981).

The livers of most chamber control and exposed male mice contained a spectrum of lesions consistent with *Helicobacter* infection; these included karyomegaly, regeneration, and bile duct hyperplasia. The liver lesions associated with *Helicobacter* infection were not present in female mice, and an exposure-related increase in the incidences of hepatocellular carcinoma was evident. Neoplasm responses in female mice or at other sites in male mice (including hemangiosarcoma) were not considered to be affected by the *Helicobacter* infection.

Based on retrospective analyses, *Helicobacter hepaticus* was determined to have infected mice in 12 recent NTP 2-year studies (Appendix O). Of the 12 studies, mice (primarily males) from nine studies (including this chloroprene study) had *H. hepaticus*-associated hepatitis. Qualitatively, the hepatitis and silver-staining organisms within the liver were similar among the nine studies. An organism compatible with *H. hepaticus* was identified by an assay based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in studies from which adequately preserved (frozen) liver tissue was available, including livers from 5 animals in this chloroprene study. Generally, efforts to identify *H. hepaticus* from tissue fixed in formalin for over a week were not successful (Malarkey *et al.*, 1997). Because of the presence of the typical liver lesions, silver-positive helical organisms, and confirmation with PCR-RFLP-based assays, mice from the current study were determined to be infected with *H. hepaticus*.

Increased incidences of hepatocellular neoplasms in male mice have been shown to be associated with *H. hepaticus* infection when hepatitis is also present (Ward *et al.*, 1994; Fox *et al.*, 1996; Appendix O). Additionally, in NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of hemangiosarcoma were seen in the livers of male mice (Appendix O). In this study of chloroprene, hemangiosarcomas and hemangiomas, which are endothelial cell neoplasms derived from blood vessels, occurred primarily in the mesentery, subcutis of the skin, and liver; the bone and spleen were sometimes affected. Because of the association noted above, hemangiosarcomas of the liver were excluded from the analyses of circulatory (endothelial) neoplasms in males in this study. Hemangiomas did not occur in the liver of male mice in this study. Even with this exclusion, the incidences of the combined occurrence of hemangiosarcoma or hemangioma at other sites were significantly increased at all chloroprene exposure concentrations in males and in 32 ppm females. Incidences of neoplasms at other sites in this study of chloroprene were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis (Appendix O).

As with 1,3-butadiene, mammary gland neoplasms induced by chloroprene included both carcinomas and adenoacanthomas. The detection of mammary gland adenoacanthomas provides an additional indicator of an exposure-related effect because the historical incidence of these neoplasms is much less than that of mammary gland carcinoma in control female mice (0.1% versus 3.1%).

The slight increases in incidences of squamous cell papilloma of the forestomach were considered to be exposure related because there were similar increases in the incidences of this uncommon neoplasm in exposed groups of male and female mice, and these responses were accompanied by increased incidences of hyperplasia of the forestomach epithelium. The latter lesion probably represents a proliferative preneoplastic change caused by chloroprene.

As in the study of chloroprene in rats, exposure-related increases in the incidences of renal tubule hyperplasia and renal tubule adenoma were observed in male mice. Because renal tubule adenomas are uncommon in historical control $B6C3F_1$ mice (0.2%), additional sections of kidney from chamber control and chloroprene-exposed male mice were examined to verify the proliferative effects of chloroprene in this organ. The step-section data confirmed the original findings that exposure to chloroprene increased the incidences of renal tubule hyperplasia and produced an exposure-related increase in the incidences of renal tubule hyperplasia and renal tubule adenoma in males. The incidence of renal tubule adenoma in the 80 ppm group was significantly greater than that in the chamber controls, and the incidences of renal tubule hyperplasia were increased in all exposed groups of males. No renal tubule neoplasms were seen in chamber control males even after step sectioning.

Several sites of neoplasm induction by chloroprene in mice have been mentioned as sites of increased risk of human cancer associated with occupational exposure to chloroprene, including the lung, skin, and liver (Infante *et al.*, 1977; Shouqi *et al.*, 1989).

Exposure of male and female mice to 80 ppm chloroprene produced high incidences of olfactory epithelial atrophy, metaplasia, and adenomatous hyperplasia in the nose of males and females. These changes were not associated with neoplastic effects, although an adenoma of the respiratory epithelium was detected in one 80 ppm male and one 32 ppm female. Olfactory epithelial degeneration has been observed in mice exposed to 1,3-butadiene or isoprene (Melnick *et al.*, 1988; NTP, 1993).

For neoplasms in mice showing exposure-related effects, the shapes of the dose-response curves and ED_{10} values were estimated by fitting a modified Weibull model (Portier *et al.*, 1986) to the Poly-3 survival-adjusted neoplasm rates. These values for chloroprene are shown along with those for 1,3-butadiene in Table 33. If the estimated shape parameter is greater than 1, the resulting dose response has more curvature than a linear model (shape parameter equal to 1) and exhibits "threshold-like behavior." If the estimated shape parameter is less than 1, then the dose-response curve is very steep (supralinear) in the low-dose region. The ED_{10} values represent the estimated exposure concentration associated with an excess cancer risk of 10% at each site. Small differences in mean body weights between the chamber control group and groups of mice exposed to chloroprene or 1,3-butadiene were not

TABLE 33
Comparison of Dose-Response Shape Parameter and ED_{10} Values (ppm) for Chloroprene (Chl) and 1,3-Butadiene (BD) in Mice[a]

	Males				Females			
	Shape Parameter		ED_{10}-Chl	ED_{10}-BD	Shape Parameter		ED_{10}-Chl	ED_{10}-BD
	Chl	BD	(LCL, UCL)	(LCL, UCL)	Chl	BD	(LCL, UCL)	(LCL, UCL)
Lung								
Alveolar/bronchiolar Carcinoma	0.743	0.576*	3.7 (0.1, 13.7)	8.1 (1.1, 30.7)	0.686	0.456**	1.9 (0.05, 6.7)	2.8 (0.3, 7.8)
Alveolar/bronchiolar Adenoma or Carcinoma	0.682	0.459**	0.9 (<0.01, 4.8)	2.1 (0.01, 21.2)	0.597*	0.374**	0.3 (<0.01, 1.6)	0.3 (<0.01, 1.8)
All organs[b]								
Hemangioma or Hemangiosarcoma	0.292**	0.737	0.2 (<0.01, 4.8)	14.0 (14.0, 28.4)	0.329*	0.982	1.4 (<0.01, 17.4)	24.4 (11.4, 46.6)
Harderian Gland								
Adenoma or Carcinoma	0.661	0.649**	12.1 (<0.01, 39.6)	5.8 (1.4, 16.2)	0.814	0.574*	22.5 (<0.01, 79.2)	9.4 (1.0, 40.9)
Mammary Gland								
Adenoacanthoma or Carcinoma					0.844	0.706**	11.8 (0.5, 34.5)	13.1 (5.4, 24.1)
Liver								
Hepatocellular Carcinoma	0.414	0.399*	0.6 (<0.01, 20.2)	2.33 (<0.01, 29.0)	0.605	0.279*	2.7 (<0.01, 13.3)	9.1 (<0.01, 112.8)
Hepatocellular Adenoma or Carcinoma	1.330	0.362*	36.9 (11.7, 79.5)	0.7 (<0.01, 22.8)	0.584	0.315	1.9 (<0.01, 78.4)	7.2 (<0.01, 625)
Forestomach								
Squamous Cell Papilloma or Carcinoma	1.83	1.412	70.0 (51.3, 79.9)	120.4 (87.5, 172.1)	>10.0*	1.182	79.1 (76.9, 80[c])	63.9 (37.5, 185.4)
Kidney								
Renal Tubule Adenoma								
Single Section	0.773	0.247	80[c] (51, 80)	625[c] (241, 625)				
Single + Step Section	1.01		32.2 (14.2, 60.8)					

TABLE 33
Comparison of Dose-Response Shape Parameter and ED_{10} Values (ppm) for Chloroprene (Chl) and 1,3-Butadiene (BD) in Mice

	Males				Females			
	Shape Parameter		ED_{10}-Chl	ED_{10}-BD	Shape Parameter		ED_{10}-Chl	ED_{10}-BD
	Chl	BD	(LCL, UCL)	(LCL, UCL)	Chl	BD	(LCL, UCL)	(LCL, UCL)
Skin Sarcoma					0.459**	0.555	1.1 (<0.01, 6.3)	70.4 (65.1, 237.9)
Mesentery Sarcoma					0.074**	>10.0	0.02 (<0.01, 17.5)	602 (577.6, 618.4)

* Shape is significantly different ($P<0.05$) from 1 by a likelihood ratio test
** $P<0.01$
[a] Shape parameter and ED_{10} values were estimated by fitting a modified Weibull model (Portier *et al.*, 1986) to the Poly-3 survival-adjusted neoplasm rates for chloroprene and for 1,3-butadiene. The 95% lower confidence limit (LCL) and 95% upper confidence limit (UCL) are given in parentheses.
[b] Liver hemangioma and hemangiosarcoma were excluded for chloroprene-exposed male mice.
[c] Estimates and upper limits of ED_{10} values were not allowed to exceed the maximum exposure concentration.

considered to have a substantial impact on the neoplasm dose-response evaluations.

For many of the chloroprene-induced neoplastic effects that were evaluated, the dose responses were consistent with a linear model. In most instances in which a departure from linearity was evident, the shape parameter indicated a dose-response curve that was supralinear (concave downward) in the low-dose region (hemangioma and hemangiosarcoma in male and female mice, alveolar/bronchiolar adenoma or carcinoma, skin and mesentery sarcomas in female mice). Only squamous cell papilloma or carcinoma of the forestomach in female mice had evidence of a sublinear (concave upward) dose response. For 1,3-butadiene, the shape parameter values indicated supralinear dose responses for lung, harderian gland, and liver neoplasms in male and female mice and for mammary gland neoplasms in female mice.

ED_{10} values, which are central tendency estimates within the region of experimental observation, have been used to compare cancer potency between carcinogens. The data in Table 33 indicate that chloroprene is more potent than 1,3-butadiene at inducing hemangiomas or hemangiosarcomas in male and female mice and skin and mesentery sarcomas in female mice. The two chemicals were nearly equivalent in their potency to induce lung and harderian gland neoplasms in male and female mice and mammary gland, liver, and forestomach neoplasms in female mice. ED_{10} values for neoplasms induced by 1,3-butadiene but not by chloroprene (e.g., malignant lymphoma and granulosa cell tumors of the ovary) were higher than those estimated for 1,3-butadiene-induced lung neoplasms, harderian gland neoplasms, or hemangioma and hemangiosarcoma. Hence, the carcinogenic potency of chloroprene in mice appears to be equivalent to or greater than that of 1,3-butadiene.

A similar type of analysis on the dose response and potency of vinyl chloride-induced neoplasms was not possible because of differences in study design (including different strains of rats and mice and different durations of exposure) and because individual animal data were not available. However, vinyl chloride (Maltoni *et al.*, 1981) and chloroprene have several common sites of induction of neoplasms, in particular hemangiosarcomas as well as mammary gland neoplasms in rats and neoplasms of the liver, lung, mammary gland, and forestomach in mice.

Bartsch *et al.* (1975, 1979) reported that chloroprene was mutagenic to *Salmonella typhimurium* with and

without metabolic activation; however, others have found no evidence of mutagenicity for chloroprene in *S. typhimurium* (Zeiger *et al.*, 1987; Westphal *et al.*, 1994). Westphal *et al.* (1994) observed mutagenic effects in *S. typhimurium* with aged samples of chloroprene but not with freshly distilled samples. These results indicate either that chloroprene is not mutagenic to *S. typhimurium* or that in the systems used to determine its mutagenicity, the reactive alkylating intermediate did not reach the target DNA. In addition, chloroprene did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster*, nor did it induce chromosomal aberrations, sister chromatid exchanges, or micronucleated erythrocytes in bone marrow or peripheral blood of mice exposed to concentrations as high as 80 ppm. Using similar protocols, both 1,3-butadiene and isoprene induced cytogenetic changes in mice. Clearly, *in vivo* and *in vitro* genotoxicity data were not predictive of the potent multisite carcinogenic effects of chloroprene. These results reveal the inadequacy of relying on oversimplified operational classification systems, such as genotoxic versus nongenotoxic, in regard to cancer risk rather than focusing on increasing the understanding of causal relationships between exposure and cancer outcome (Melnick *et al.*, 1996b). The finding of a higher frequency of unique K-*ras* mutations, predominantly A to T transversions at codon 61 in chloroprene-induced lung and harderian gland neoplasms (Appendix N), suggests the involvement of a mutagenic event in chloroprene-induced neoplasia. A similar high frequency of A to T transversions at codon 61 of K-*ras* were detected in lung and harderian gland neoplasms induced by isoprene.

The carcinogenic effects of 1,3-butadiene have been attributed to its mutagenic epoxide intermediates (Melnick and Kohn, 1995). Similarly, the mutagenic and carcinogenic effects of vinyl chloride have been attributed to its epoxide metabolite, chlorothyleneoxide, and the rearrangement product, chloroacetaldehyde, both of which can react with DNA to form a variety of adducts (Guengerich, 1992; Singer, 1996). Neither the metabolic fate of chloroprene nor the biological properties of its metabolic intermediates have been well studied. Oxidation of chloroprene to epoxide intermediates (2-chloro-1,2-epoxybutene-3 and 2-chloro-3,4-epoxybutene-1) was suggested to occur based on the detection of alkylated 4-(4-itrobenzyl)pyridine in incubations of chloroprene and mouse liver microsomes (Haley, 1978; Bartsch *et al.*, 1979). Analogous to the formation of chloroacetaldehyde subsequent to the oxidation of vinyl chloride to chloroethylene oxide, 2-chloro-1,2-epoxybutene-3 could undergo rearrangement to form an unsaturated chloroketone. These postulated oxidative intermediates of chloroprene metabolism may be protein and/or DNA reactive and may account for the cytotoxicity and carcinogenic effects of this compound. Differences in stability, distribution, and reactivity of these various intermediates may account for differences in dose-related carcinogenic effects of chloroprene and 1,3-butadiene. Further studies are needed to understand the processes involved in chloroprene carcinogenesis.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of chloroprene in male F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, lung, and kidney were also attributed to chloroprene exposure. There was *clear evidence of carcinogenic activity* of chloroprene in female F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, mammary gland, and kidney were also attributed to exposure to chloroprene. Low incidences of urinary bladder neoplasms in male and female rats and lung neoplasms in female rats may also have been related to exposure to chloroprene.

There was *clear evidence of carcinogenic activity* of chloroprene in male B6C3F$_1$ mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), and harderian gland; increased incidences of neoplasms of the forestomach and kidney were also attributed to exposure to chloroprene. There was *clear evidence of carcinogenic activity* of chloroprene in female B6C3F$_1$ mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), harderian gland, mammary gland, liver, skin, and mesentery; increased incidences of neoplasms of the forestomach and Zymbal's gland were also attributed to exposure to chloroprene.

Exposure of male and female rats to chloroprene was associated with increased incidences of alveolar epithelial hyperplasia in the lung; nephropathy; and several nonneoplastic effects in the nose including olfactory epithelial atrophy, fibrosis, adenomatous hyperplasia, basal cell hyperplasia, chronic inflammation, respiratory metaplasia, and necrosis. Exposure of male and female mice to chloroprene was associated with increased incidences of bronchiolar hyperplasia and histiocytic cell infiltration in the lung; epithelial hyperplasia in the forestomach; renal tubule hyperplasia (males only); several effects in the nose including olfactory epithelial atrophy, respiratory metaplasia, and adenomatous hyperplasia; and hematopoietic cell proliferation in the spleen.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 14. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 16.

DISCUSSION AND CONCLUSIONS

Chloroprene was selected for study by the National Toxicology Program (NTP) because it is an important high-volume production chemical with a potential for human exposure, there is limited information available on its carcinogenic potential in experimental animals and humans, and it is the 2-chloro analogue of 1,3-butadiene. Chloroprene is also structurally similar to vinyl chloride, a human carcinogen known to induce hemangiosarcomas in the liver of laboratory animals and exposed workers. Based on results of a previous NTP study of 1,3-butadiene in mice in which neoplasms were induced at multiple organ sites (NTP, 1984; Huff *et al.*, 1985), NTP examined chloroprene and isoprene (2-methyl-1,3-butadiene) to see if either of these structural analogues of 1,3-butadiene produces effects similar to those of 1,3-butadiene. A second study of 1,3-butadiene was also conducted over an expanded exposure range to provide a better characterization of dose-response effects.

1,3-Butadiene has been studied intensely over the past 12 years, and results from those studies have raised the level of concern for humans exposed to this chemical and heightened the importance of understanding the toxicologic and carcinogenic potential of chloroprene and isoprene. This report presents the findings of 16-day, 13-week, and 2-year chloroprene inhalation studies in F344/N rats and B6C3F$_1$ mice and makes comparisons to the toxicologic effects of 1,3-butadiene.

In the two NTP long-term inhalation toxicology/carcinogenicity studies of 1,3-butadiene in B6C3F$_1$ mice, exposure concentrations ranged from 6.25 to 1,250 ppm (Huff *et al.*, 1985; Melnick *et al.*, 1990a; NTP, 1984, 1993). Particularly noteworthy in these studies were the induction of malignant lymphomas as early as 20 weeks after the start of exposure and uncommon hemangiosarcomas of the heart. Furthermore, malignant lung neoplasms were induced in female mice at all exposure concentrations. Other sites of neoplasm induction in mice included the liver, forestomach, harderian gland, ovary, mammary gland, and preputial gland. A 2-year inhalation study of 1,3-butadiene in Sprague-Dawley rats, sponsored by the International Institute of Synthetic Rubber Producers, used exposure concentrations of 1,000 and 8,000 ppm. In rats, 1,3-butadiene was carcinogenic to the mammary gland, brain, Zymbal's gland, uterus, pancreas, testis, and thyroid gland (Owen *et al.*, 1987). These studies established 1,3-butadiene as a multiple-species, multiple-organ carcinogen, with mice eliciting the more striking response. Because of differences in sites of tumor induction and in the effective exposure-related responses between rats and mice, recent research has focused on trying to understand the basis for this species difference, especially as it may relate to assessment of human risk. Based on available epidemiological and mechanistic data on 1,3-butadiene as well as the similarities in response between 1,3-butadiene and ethylene oxide, Melnick and Kohn (1995) concluded that butadiene should be considered a human carcinogen and that the mouse is an appropriate model for assessing human cancer risk.

Epidemiologic studies have consistently associated excess mortality from lymphatic and hematopoietic cancers with occupational exposure to 1,3-butadiene. Significant increases in incidences of lymphosarcoma have been observed in individuals who work in the 1,3-butadiene production industry (Divine, 1990; Ward *et al.*, 1995), whereas increases in the incidence of leukemia have been found in individuals who work in the styrene-butadiene rubber manufacturing industry (Matanoski *et al.*, 1990; Santos-Burgoa *et al.*, 1992). Recent follow-up studies of synthetic-rubber producers have confirmed the association between exposure to 1,3-butadiene and chronic leukemia (Delzell *et al.*, 1996). The finding that the risk of chronic leukemia in humans exposed to 1,3-butadiene was similar to risk estimates that were based on the induction of lymphocytic lymphoma in exposed mice supports the use of mice in studies for human risk assessment.

Based on data available on 1,3-butadiene, the Occupational Safety and Health Administration (OSHA) has recently lowered the occupational exposure standard for 1,3-butadiene from 1,000 to 1 ppm, expressed as an 8-hour, time-weighted, average workplace exposure limit, and set a 15-minute short-term exposure limit of 5 ppm (29 CFR, Parts 1910, 1915, and 1926). The current OSHA standard for chloroprene is 25 ppm, based largely on results of 4-week inhalation toxicity studies in rats and hamsters (Clary *et al.*, 1978).

16-Day and 13-Week Studies in Rats and Mice

Exposure of F344/N rats to chloroprene for 16 days at chamber concentrations ranging from 32 to 500 ppm produced several toxic effects: 1) mortality at 500 ppm and reductions in body weight gain in males exposed to 200 or 500 ppm; 2) regenerative, normocytic, normochromic anemia in males exposed to 500 ppm and in females exposed to 200 or 500 ppm; 3) centrilobular hepatocellular necrosis in the 200 and 500 ppm groups and increases in alanine aminotransferase (ALT), glutamate dehydrogenase (GDH), and sorbitol dehydrogenase (SDH) activities in 200 ppm females and 500 ppm males and females; 4) olfactory epithelial degeneration in all exposed groups and respiratory metaplasia in the 500 ppm groups; and 5) thymic atrophy. Similar effects in the liver were reported in a 4-week inhalation study of chloroprene in Wistar rats (Clary *et al.*, 1978).

The hemorrhage observed clinically (epistaxis) in this study suggests that the rapidly developing normocytic, normochromic, responsive anemia that occurred on day 4 in the 500 ppm groups may have been related to acute blood loss. The thrombocytopenia seen in this study is also consistent with the clinically observed hemorrhage. 1,3-Butadiene has also been shown to cause an anemia in mice (Irons *et al.*, 1986; Melnick *et al.*, 1990b); however, in this species the anemia was macrocytic, normochromic, and nonresponsive and was suggested to involve altered bone marrow production of erythrocytes. No hematologic effects were observed in rats exposed to 1,3-butadiene or isoprene at concentrations as high as 8,000 ppm and 7,000 ppm, respectively (Crouch *et al.*, 1979; Melnick *et al.*, 1994).

Findings from the 13-week inhalation toxicity studies of chloroprene in F344/N rats and B6C3F$_1$ mice have been reported by Melnick *et al.* (1996a). Exposure of rats to 32 ppm chloroprene or greater concentrations caused olfactory epithelial degeneration, and 80 ppm or greater caused respiratory metaplasia; exposure to 200 ppm caused anemia (characterized as normocytic, normochromic, and nonresponsive), minimal to mild hepatocellular necrosis, and reduced sperm motility. These lesions had not been observed in rats exposed to 1,3-butadiene or isoprene even at exposure concentrations as high as 8,000 and 7,000 ppm, respectively (Crouch *et al.*, 1979; Melnick *et al.*, 1994). Neurobehavioral assessments showed an increase in motor activity in exposed males but not females with no effects on grip strength or startle response in either male or female rats (Tilson, 1990).

As in the 16-day rat study, rats in the 200 ppm groups demonstrated evidence of hemorrhage, which may, in part, explain the minimal normocytic, normochromic, and nonresponsive anemia that was observed at week 13. The increase in activated partial thromboplastin time and prothrombin time on day 2 of the 13-week study suggests that coagulopathy may have contributed to the hemorrhage and subsequent anemia. The lack of a bone marrow response at the end of the 13-week study may be because the changes in erythroid parameters were not severe enough to stimulate a demonstrable erythropoietic response.

Increases in serum ALT, GDH, and SDH activities indicative of hepatocellular pathology resulting in a loss of cell membrane integrity, or cellular necrosis with subsequent enzyme release, were observed in both the 16-day and 13-week studies. These changes were transient, however, and by week 13 the activities of these serum enzymes had returned to chamber control levels. Centrilobular necrosis was also observed in the liver of rats exposed to 200 ppm or greater concentrations of chloroprene, and this would account for the increases in the serum activities of these enzymes. However, while the biochemical effects appeared to be transient, liver injury (hepatocellular necrosis) was still evident at study termination.

In the 13-week study, proteinuria and alkaline phosphatase enzymeuria occurred in the 200 ppm animals as early as day 22; these findings suggest a renal

tubule effect. There were no microscopic lesions to support these biochemical alterations, suggesting that the renal injury was too mild to result in structural damage or that the biochemical effects may precede the eventual development of microscopic lesions. Exposure-related increases in kidney weights also suggest a renal effect and support the biochemical findings. These findings suggest that the kidney is a target tissue for the inhalation toxicity of chloroprene and that the renal effects would not have been identified by microscopic evaluation alone.

In the 16-day inhalation study of chloroprene in $B6C3F_1$ mice, exposure concentrations were slightly less than those in the rat study (from 12 to 200 ppm in mice versus 32 to 500 ppm in rats). In spite of the lower exposure concentration, all mice exposed to 200 ppm died during the first 3 days of the study. Chloroprene at exposure concentrations up to 80 ppm had no effect on survival, body weight gain, hematology, or clinical chemistry parameters. Histopathologic findings in the 200 ppm group included multifocal hepatic necrosis, thymic necrosis, and focal hemorrhage, erosions, or necrosis of the glandular stomach mucosa. Squamous epithelial hyperplasia of the forestomach was observed in a small number of mice exposed to 80 ppm.

In the 13-week inhalation study in $B6C3F_1$ mice, exposure to 80 ppm caused a marginal decrease in body weight gain in males and epithelial hyperplasia of the forestomach in males and females. This lesion had also been observed in mice exposed to isoprene or 1,3-butadiene. A mild, normocytic, normochromic, nonresponsive anemia was also detected in exposed female mice. Decreases in hepatic nonprotein sulfhydryl concentrations in mice exposed to 80 ppm were not associated with any histopathologic changes in the liver.

In conjunction with these toxicity studies on chloroprene, additional groups of mice were included for evaluations of cytogenetic effects after 12 exposures over a 16-day period. Unlike the effects seen in mice exposed to 1,3-butadiene or isoprene, chloroprene did not induce cytogenetic damage in bone marrow cells of mice exposed to concentrations up to 80 ppm (Tice *et al.*, 1988). For 1,3-butadiene, this exposure concentration produced increases in sister chromatid exchanges and in the frequency of micronuclei in peripheral blood. Isoprene also produced cytogenetic effects in mice but at exposure concentrations greater than those that could be achieved with chloroprene.

The 16-day and 13-week studies indicate that chloroprene is substantially more toxic to rats and mice than either 1,3-butadiene or isoprene. This difference is reflected in the maximum tolerated exposures that were selected for long-term studies of these chemicals: 1,3-butadiene, 8,000 ppm for rats (Owen *et al.*, 1987) and 1,250 ppm for mice (NTP, 1993; Huff *et al.*, 1985); isoprene, 7,000 ppm for rats and mice (Melnick *et al.*, 1994); and chloroprene, 200 ppm for rats and 80 ppm for mice. Table 31 shows that the profile of toxicologic effects of chloroprene, in terms of target sites and effective exposures, differs considerably from that of isoprene or 1,3-butadiene; this may be due in part to differences in exposure concentrations that were used in the toxicology studies of these compounds but is also likely due to the influence of the chlorine substitution on the toxicokinetics and biotransformation of this chemical and the reactivity of metabolic intermediates with tissue macromolecules.

TABLE 31
Toxicologic Effects (Lowest-Observable-Adverse-Effect Level in ppm) of Chloroprene, 1,3-Butadiene, and Isoprene in Rats and Mice[a]

Toxic Effect	Rats			Mice		
	Chloroprene	Butadiene	Isoprene	Chloroprene	Butadiene	Isoprene
Anemia	200[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	62.5[e]	220[d]
Liver, necrosis	200[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	625[f]	neg(7,000)[d]
Nose, olfactory epithelium degeneration	32[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	625[g]	220[d]
Forestomach, squamous epithelial hyperplasia	neg(200)[b]	neg(8,000)[c]	neg(7,000)[d]	80[b]	200[e]	438[h]
Testes, atrophy	neg(200)[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	625[e]	7,000[h]
Cytogenetic damage						
Chromosomal aberrations	NS	NS	NS	neg(80)[i]	625[j]	neg (7,000)[i]
Sister chromatid exchange	NS	neg(10,000)[k]	NS	neg(80)[i]	6.25[j]	220[l]
Micronuclei	NS	neg(10,000)[k]	NS	neg(80)[i]	6.25[l]	438[i]

[a] Taken from Melnick *et al.*, 1996a. Neg = no effect. NS = not studied. The highest concentration studied is given in parentheses.
[b] The current study
[c] Crouch *et al.*, 1979
[d] Melnick *et al.*, 1994
[e] Melnick *et al.*, 1990b
[f] NTP, 1984
[g] NTP, 1993
[h] Melnick *et al.*, 1990c
[i] Tice *et al.*, 1988
[j] Tice *et al.*, 1987
[k] Cunningham *et al.*, 1986
[l] Shelby, 1990

2-Year Study in Rats

In the 2-year study of chloroprene in rats, survival rates were less in all exposed groups of males and significantly reduced in 32 and 80 ppm males relative to the chamber controls. Males exposed to 80 ppm had decreased body weights compared to the chamber controls; a large part of this difference occurred during the last month of the study. There were no differences in survival or body weights among the female exposed and chamber control rats.

Exposure of rats to chloroprene produced a multiple-organ carcinogenic response. Some sites affected by chloroprene were not affected by 1,3-butadiene, whereas other sites were affected similarly even though the exposure concentrations used in the studies of these two chemicals differed substantially (Table 32). Exposure-related carcinogenic effects of chloroprene were seen in the lung, oral cavity, thyroid gland, mammary gland, and kidney. In addition, low incidences of rare neoplasms in the urinary bladder in males and females may have been exposure related.

TABLE 32
Sites of Increased Incidences of Neoplasms in the 2-Year Inhalation Studies of Chloroprene and 1,3-Butadiene in Rats and Mice

	Chloroprene[a]		1,3-Butadiene[b]	
	Male	Female	Male	Female
Rats				
			Pancreas	
				Uterus
	Oral Cavity	Oral Cavity		
	Thyroid gland	Thyroid gland		Thyroid gland
	Lung			
		Mammary gland		Mammary gland
	Kidney	Kidney		
			Testis	
				Zymbal's gland
			Brain	
Mice				
			Hematopoietic system	Hematopoietic system
	Lung	Lung	Lung	Lung
	Circulatory system	Circulatory system		
			Heart (hemangiosarcoma)	Heart (hemangiosarcoma)
	Harderian gland	Harderian gland	Harderian gland	Harderian gland
	Forestomach	Forestomach	Forestomach	Forestomach
	Kidney		Kidney	
		Mammary gland		Mammary gland
		Liver	Liver	Liver
		Skin		
		Mesentery		
		Zymbal's gland		
			Preputial gland	
				Ovary

[a] Current study in F344/N rats and B6C3F$_1$ mice
[b] Studies in Sprague-Dawley rats at exposure concentrations of 1,000 or 8,000 ppm (Owen *et al.*, 1987) and B6C3F$_1$ mice at exposure concentrations of 6.25, 20, 62.5, 200, or 625 ppm (Melnick *et al.*, 1990a; NTP, 1993)

In rats exposed to chloroprene, increased incidences of proliferative lesions of the oral cavity included squamous cell hyperplasia, squamous cell papilloma, and squamous cell carcinoma and involved the palate, pharynx, gingiva, cheek, and tongue. In addition to the positive exposure-related trends, the incidences of squamous cell papilloma and squamous cell carcinoma (combined) increased significantly in males and females and far exceeded the NTP historical control incidence. Oral cavity neoplasms have not been reported in rats or mice exposed to 1,3-butadiene or isoprene (NTP, 1993, 1995).

Exposure-related positive trends and increased incidences of follicular cell adenoma or carcinoma (combined) in rats were indicative of a carcinogenic effect of chloroprene in the thyroid gland. Thyroid gland follicular cell neoplasms have been reported to be induced in female Sprague-Dawley rats exposed to 1,000 or 8,000 ppm 1,3-butadiene (Owen *et al.*, 1987).

The incidences of alveolar epithelial hyperplasia were increased in all exposed groups of male and female rats relative to their respective chamber control groups, and there was also a slight increase in the incidence of alveolar/bronchiolar carcinomas (4 of 50) in 80 ppm males. The NTP historical control database recorded only 6 of 654 (0.9%) chamber control male rats with alveolar/bronchiolar carcinoma. Although exposure to 1,3-butadiene or isoprene induced lung neoplasms in mice, neither of these chemicals has been reported to cause lung neoplasms in rats (NTP, 1993, 1995).

The incidences of mammary gland fibroadenoma were increased in female rats exposed to 32 or 80 ppm; however, the incidence of mammary gland carcinoma was not increased. Increases in the incidences of multiple fibroadenoma of the mammary gland in female rats support the conclusion that this effect is exposure related. Exposure of female rats to 1,3-butadiene also caused increases in the incidence and multiplicity of mammary gland fibroadenoma (Owen *et al.*, 1987; Melnick and Huff, 1992).

Slight increases in the incidences of renal tubule adenoma and renal tubule hyperplasia were observed in male and female rats exposed to chloroprene compared to the chamber controls. Renal tubule hyperplasias are thought to represent an early stage in the morphologic continuum of proliferative kidney lesions leading to renal tubule adenoma and carcinoma. Even though the severity of nephropathy was increased slightly in exposed rats compared to the chamber controls, the renal tubule hyperplasias observed in this study were distinguishable from regenerative epithelial changes associated with renal nephropathy in this strain of rat. Because renal tubule neoplasms are uncommon in chamber control F344/N rats, additional kidney sections were examined from chamber control and exposed male and female rats to provide a clearer indication of the potential effects of chloroprene in this organ. Analyses of the step-section data indicated that the incidences of renal tubule hyperplasia were increased significantly in 32 and 80 ppm males and 80 ppm females. The incidences of renal tubule adenoma or carcinoma (combined) were increased in all exposed groups of males compared to the chamber controls. Particularly unusual was the finding of renal tubule adenomas in four 80 ppm females and a renal tubule carcinoma in one 12.8 ppm male. Thus, the results from the additional kidney step sections support the evidence from the original pathology review, which indicated that chloroprene induces proliferative renal tubule lesions, including neoplasms, in male and female rats.

A variety of exposure-related nasal lesions were induced in male and female rats including necrosis, chronic active inflammation, atrophy, respiratory metaplasia, adenomatous hyperplasia, basal cell hyperplasia, and fibrosis of the olfactory epithelium. Although the incidences of many of these lesions approached or reached 100% in the 80 ppm groups, there was no evidence of progression of these lesions to neoplasms. Similar nasal lesions without neoplastic effects were seen in several other NTP 2-year studies, including 2-chloroacetophenone, *o*-chlorobenzalmalononitrile, *l*-epinephrine hydrochloride, vinyl toluene, and tetranitromethane (NTP, 1990a,b,c,d,e). Although increased cell turnover may contribute to multistage carcinogenesis, a review of 19 NTP inhalation bioassays found that chronic toxicity and cell proliferation frequently were not associated with nasal carcinogenesis (Ward *et al.*, 1993). Olfactory epithelial degeneration and respiratory metaplasia in rats had been identified as a toxic effect of chloroprene in the 13-week studies; however, nasal lesions were not observed in rats exposed to 8,000 ppm 1,3-butadiene

for 2 years (Owen *et al.*, 1987) or to 7,000 ppm isoprene for 26 weeks (Melnick *et al.*, 1994).

2-Year Study in Mice

In the 2-year study of chloroprene in mice, survival rates were less in 32 and 80 ppm males and in all exposed groups of females than in the chamber controls. Many early deaths and moribund kills were associated with chloroprene-induced neoplasms. Mean body weights of 80 ppm female mice were less than those of chamber controls after week 75.

Exposure of mice to chloroprene produced a potent multisite carcinogenic response. Several organs that were targets of 1,3-butadiene carcinogenicity in mice were similarly affected by chloroprene, including the lung, harderian gland, liver, forestomach, and mammary gland; however, some carcinogenic effects of 1,3-butadiene in mice were not seen in the chloroprene study (Table 32). Most notable was the lack of lymphomas in mice exposed to chloroprene compared to the early occurrence and extensive development of lymphocytic lymphomas in mice exposed to 625 ppm 1,3-butadiene. This may be related to differences in exposure to the parent compound and differences in target organ dosimetry and/or reactivity of metabolic intermediates. Exposure of mice to 1,3-butadiene was also associated with the development of rarely occurring hemangiosarcomas of the heart. Although exposure to chloroprene in the present study did not induce hemangiosarcomas of the heart, there were exposure-related increases in the incidences of hemangioma and hemangiosarcoma at multiple organ sites. In addition, 1,3-butadiene, but not chloroprene, induced granulosa cell tumors of the ovary; and chloroprene, but not 1,3-butadiene, induced skin and mesentery sarcomas in female mice. Small numbers of renal tubule adenomas were observed in male mice exposed to either 1,3-butadiene or chloroprene. The present studies included a step-section evaluation of the kidneys from chamber control and exposed male mice to more clearly ascertain the potential relationship between exposure to chloroprene and kidney neoplasms. The occurrence of Zymbal's gland carcinomas in three female mice exposed to 80 ppm chloroprene is also indicative of an exposure-related effect. The four organ sites where isoprene was reported to induce neoplasms in mice (lung, liver, harderian gland, and forestomach; Melnick *et al.*, 1994) were also affected by chloroprene.

The lung was a major target organ of chloroprene-induced neoplasms in male and female mice. In addition to producing increases in the incidences of bronchiolar epithelial hyperplasia and alveolar/bronchiolar adenoma or carcinoma (combined), chloroprene exposure caused significant increases in the incidences of alveolar/bronchiolar carcinoma, multiple adenoma, and multiple carcinoma. Qinan *et al.* (1989) also observed an increase in lung neoplasm incidence and multiplicity in mice exposed to chloroprene for 7 months. Lung neoplasms including alveolar/bronchiolar carcinoma were induced in female mice exposed to 1,3-butadiene at concentrations as low as 6.25 ppm (Melnick *et al.*, 1990a; NTP, 1993). Lung neoplasms were also induced by vinyl chloride in male and female mice (Maltoni *et al.*, 1981).

The livers of most chamber control and exposed male mice contained a spectrum of lesions consistent with *Helicobacter* infection; these included karyomegaly, regeneration, and bile duct hyperplasia. The liver lesions associated with *Helicobacter* infection were not present in female mice, and an exposure-related increase in the incidences of hepatocellular carcinoma was evident. Neoplasm responses in female mice or at other sites in male mice (including hemangiosarcoma) were not considered to be affected by the *Helicobacter* infection.

Based on retrospective analyses, *Helicobacter hepaticus* was determined to have infected mice in 12 recent NTP 2-year studies (Appendix O). Of the 12 studies, mice (primarily males) from nine studies (including this chloroprene study) had *H. hepaticus*-associated hepatitis. Qualitatively, the hepatitis and silver-staining organisms within the liver were similar among the nine studies. An organism compatible with *H. hepaticus* was identified by an assay based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in studies from which adequately preserved (frozen) liver tissue was available, including livers from 5 animals in this chloroprene study. Generally, efforts to identify *H. hepaticus* from tissue fixed in formalin for over a week were not successful (Malarkey *et al.*, 1997). Because of the presence of the typical liver lesions, silver-positive helical organisms, and confirmation with PCR-RFLP-based assays, mice from the current study were determined to be infected with *H. hepaticus*.

Increased incidences of hepatocellular neoplasms in male mice have been shown to be associated with *H. hepaticus* infection when hepatitis is also present (Ward *et al.*, 1994; Fox *et al.*, 1996; Appendix O). Additionally, in NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of hemangiosarcoma were seen in the livers of male mice (Appendix O). In this study of chloroprene, hemangiosarcomas and hemangiomas, which are endothelial cell neoplasms derived from blood vessels, occurred primarily in the mesentery, subcutis of the skin, and liver; the bone and spleen were sometimes affected. Because of the association noted above, hemangiosarcomas of the liver were excluded from the analyses of circulatory (endothelial) neoplasms in males in this study. Hemangiomas did not occur in the liver of male mice in this study. Even with this exclusion, the incidences of the combined occurrence of hemangiosarcoma or hemangioma at other sites were significantly increased at all chloroprene exposure concentrations in males and in 32 ppm females. Incidences of neoplasms at other sites in this study of chloroprene were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis (Appendix O).

As with 1,3-butadiene, mammary gland neoplasms induced by chloroprene included both carcinomas and adenoacanthomas. The detection of mammary gland adenoacanthomas provides an additional indicator of an exposure-related effect because the historical incidence of these neoplasms is much less than that of mammary gland carcinoma in control female mice (0.1% versus 3.1%).

The slight increases in incidences of squamous cell papilloma of the forestomach were considered to be exposure related because there were similar increases in the incidences of this uncommon neoplasm in exposed groups of male and female mice, and these responses were accompanied by increased incidences of hyperplasia of the forestomach epithelium. The latter lesion probably represents a proliferative preneoplastic change caused by chloroprene.

As in the study of chloroprene in rats, exposure-related increases in the incidences of renal tubule hyperplasia and renal tubule adenoma were observed in male mice. Because renal tubule adenomas are uncommon in historical control $B6C3F_1$ mice (0.2%), additional sections of kidney from chamber control and chloroprene-exposed male mice were examined to verify the proliferative effects of chloroprene in this organ. The step-section data confirmed the original findings that exposure to chloroprene increased the incidences of renal tubule hyperplasia and produced an exposure-related increase in the incidences of renal tubule hyperplasia and renal tubule adenoma in males. The incidence of renal tubule adenoma in the 80 ppm group was significantly greater than that in the chamber controls, and the incidences of renal tubule hyperplasia were increased in all exposed groups of males. No renal tubule neoplasms were seen in chamber control males even after step sectioning.

Several sites of neoplasm induction by chloroprene in mice have been mentioned as sites of increased risk of human cancer associated with occupational exposure to chloroprene, including the lung, skin, and liver (Infante *et al.*, 1977; Shouqi *et al.*, 1989).

Exposure of male and female mice to 80 ppm chloroprene produced high incidences of olfactory epithelial atrophy, metaplasia, and adenomatous hyperplasia in the nose of males and females. These changes were not associated with neoplastic effects, although an adenoma of the respiratory epithelium was detected in one 80 ppm male and one 32 ppm female. Olfactory epithelial degeneration has been observed in mice exposed to 1,3-butadiene or isoprene (Melnick *et al.*, 1988; NTP, 1993).

For neoplasms in mice showing exposure-related effects, the shapes of the dose-response curves and ED_{10} values were estimated by fitting a modified Weibull model (Portier *et al.*, 1986) to the Poly-3 survival-adjusted neoplasm rates. These values for chloroprene are shown along with those for 1,3-butadiene in Table 33. If the estimated shape parameter is greater than 1, the resulting dose response has more curvature than a linear model (shape parameter equal to 1) and exhibits "threshold-like behavior." If the estimated shape parameter is less than 1, then the dose-response curve is very steep (supralinear) in the low-dose region. The ED_{10} values represent the estimated exposure concentration associated with an excess cancer risk of 10% at each site. Small differences in mean body weights between the chamber control group and groups of mice exposed to chloroprene or 1,3-butadiene were not

TABLE 33
Comparison of Dose-Response Shape Parameter and ED_{10} Values (ppm) for Chloroprene (Chl) and 1,3-Butadiene (BD) in Mice[a]

	Males				Females			
	Shape Parameter		ED_{10}-Chl	ED_{10}-BD	Shape Parameter		ED_{10}-Chl	ED_{10}-BD
	Chl	BD	(LCL, UCL)	(LCL, UCL)	Chl	BD	(LCL, UCL)	(LCL, UCL)
Lung								
Alveolar/bronchiolar Carcinoma	0.743	0.576*	3.7 (0.1, 13.7)	8.1 (1.1, 30.7)	0.686	0.456**	1.9 (0.05, 6.7)	2.8 (0.3, 7.8)
Alveolar/bronchiolar Adenoma or Carcinoma	0.682	0.459**	0.9 (<0.01, 4.8)	2.1 (0.01, 21.2)	0.597*	0.374**	0.3 (<0.01, 1.6)	0.3 (<0.01, 1.8)
All organs[b]								
Hemangioma or Hemangiosarcoma	0.292**	0.737	0.2 (<0.01, 4.8)	14.0 (14.0, 28.4)	0.329*	0.982	1.4 (<0.01, 17.4)	24.4 (11.4, 46.6)
Harderian Gland								
Adenoma or Carcinoma	0.661	0.649**	12.1 (<0.01, 39.6)	5.8 (1.4, 16.2)	0.814	0.574*	22.5 (<0.01, 79.2)	9.4 (1.0, 40.9)
Mammary Gland								
Adenoacanthoma or Carcinoma					0.844	0.706**	11.8 (0.5, 34.5)	13.1 (5.4, 24.1)
Liver								
Hepatocellular Carcinoma	0.414	0.399*	0.6 (<0.01, 20.2)	2.33 (<0.01, 29.0)	0.605	0.279*	2.7 (<0.01, 13.3)	9.1 (<0.01, 112.8)
Hepatocellular Adenoma or Carcinoma	1.330	0.362*	36.9 (11.7, 79.5)	0.7 (<0.01, 22.8)	0.584	0.315	1.9 (<0.01, 78.4)	7.2 (<0.01, 625)
Forestomach								
Squamous Cell Papilloma or Carcinoma	1.83	1.412	70.0 (51.3, 79.9)	120.4 (87.5, 172.1)	>10.0*	1.182	79.1 (76.9, 80[c])	63.9 (37.5, 185.4)
Kidney								
Renal Tubule Adenoma								
Single Section	0.773	0.247	80[c] (51, 80)	625[c] (241, 625)				
Single + Step Section	1.01		32.2 (14.2, 60.8)					

TABLE 33
Comparison of Dose-Response Shape Parameter and ED_{10} Values (ppm) for Chloroprene (Chl) and 1,3-Butadiene (BD) in Mice

	Males				Females			
	Shape Parameter		ED_{10}-Chl	ED_{10}-BD	Shape Parameter		ED_{10}-Chl	ED_{10}-BD
	Chl	BD	(LCL, UCL)	(LCL, UCL)	Chl	BD	(LCL, UCL)	(LCL, UCL)
Skin Sarcoma					0.459**	0.555	1.1 (<0.01, 6.3)	70.4 (65.1, 237.9)
Mesentery Sarcoma					0.074**	>10.0	0.02 (<0.01, 17.5)	602 (577.6, 618.4)

* Shape is significantly different ($P<0.05$) from 1 by a likelihood ratio test
** $P<0.01$
[a] Shape parameter and ED_{10} values were estimated by fitting a modified Weibull model (Portier *et al.*, 1986) to the Poly-3 survival-adjusted neoplasm rates for chloroprene and for 1,3-butadiene. The 95% lower confidence limit (LCL) and 95% upper confidence limit (UCL) are given in parentheses.
[b] Liver hemangioma and hemangiosarcoma were excluded for chloroprene-exposed male mice.
[c] Estimates and upper limits of ED_{10} values were not allowed to exceed the maximum exposure concentration.

considered to have a substantial impact on the neoplasm dose-response evaluations.

For many of the chloroprene-induced neoplastic effects that were evaluated, the dose responses were consistent with a linear model. In most instances in which a departure from linearity was evident, the shape parameter indicated a dose-response curve that was supralinear (concave downward) in the low-dose region (hemangioma and hemangiosarcoma in male and female mice, alveolar/bronchiolar adenoma or carcinoma, skin and mesentery sarcomas in female mice). Only squamous cell papilloma or carcinoma of the forestomach in female mice had evidence of a sublinear (concave upward) dose response. For 1,3-butadiene, the shape parameter values indicated supralinear dose responses for lung, harderian gland, and liver neoplasms in male and female mice and for mammary gland neoplasms in female mice.

ED_{10} values, which are central tendency estimates within the region of experimental observation, have been used to compare cancer potency between carcinogens. The data in Table 33 indicate that chloroprene is more potent than 1,3-butadiene at inducing hemangiomas or hemangiosarcomas in male and female mice and skin and mesentery sarcomas in female mice. The two chemicals were nearly equivalent in their potency to induce lung and harderian gland neoplasms in male and female mice and mammary gland, liver, and forestomach neoplasms in female mice. ED_{10} values for neoplasms induced by 1,3-butadiene but not by chloroprene (e.g., malignant lymphoma and granulosa cell tumors of the ovary) were higher than those estimated for 1,3-butadiene-induced lung neoplasms, harderian gland neoplasms, or hemangioma and hemangiosarcoma. Hence, the carcinogenic potency of chloroprene in mice appears to be equivalent to or greater than that of 1,3-butadiene.

A similar type of analysis on the dose response and potency of vinyl chloride-induced neoplasms was not possible because of differences in study design (including different strains of rats and mice and different durations of exposure) and because individual animal data were not available. However, vinyl chloride (Maltoni *et al.*, 1981) and chloroprene have several common sites of induction of neoplasms, in particular hemangiosarcomas as well as mammary gland neoplasms in rats and neoplasms of the liver, lung, mammary gland, and forestomach in mice.

Bartsch *et al.* (1975, 1979) reported that chloroprene was mutagenic to *Salmonella typhimurium* with and

without metabolic activation; however, others have found no evidence of mutagenicity for chloroprene in *S. typhimurium* (Zeiger *et al.*, 1987; Westphal *et al.*, 1994). Westphal *et al.* (1994) observed mutagenic effects in *S. typhimurium* with aged samples of chloroprene but not with freshly distilled samples. These results indicate either that chloroprene is not mutagenic to *S. typhimurium* or that in the systems used to determine its mutagenicity, the reactive alkylating intermediate did not reach the target DNA. In addition, chloroprene did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster*, nor did it induce chromosomal aberrations, sister chromatid exchanges, or micronucleated erythrocytes in bone marrow or peripheral blood of mice exposed to concentrations as high as 80 ppm. Using similar protocols, both 1,3-butadiene and isoprene induced cytogenetic changes in mice. Clearly, *in vivo* and *in vitro* genotoxicity data were not predictive of the potent multisite carcinogenic effects of chloroprene. These results reveal the inadequacy of relying on oversimplified operational classification systems, such as genotoxic versus nongenotoxic, in regard to cancer risk rather than focusing on increasing the understanding of causal relationships between exposure and cancer outcome (Melnick *et al.*, 1996b). The finding of a higher frequency of unique K-*ras* mutations, predominantly A to T transversions at codon 61 in chloroprene-induced lung and harderian gland neoplasms (Appendix N), suggests the involvement of a mutagenic event in chloroprene-induced neoplasia. A similar high frequency of A to T transversions at codon 61 of K-*ras* were detected in lung and harderian gland neoplasms induced by isoprene.

The carcinogenic effects of 1,3-butadiene have been attributed to its mutagenic epoxide intermediates (Melnick and Kohn, 1995). Similarly, the mutagenic and carcinogenic effects of vinyl chloride have been attributed to its epoxide metabolite, chlorothyleneoxide, and the rearrangement product, chloroacetaldehyde, both of which can react with DNA to form a variety of adducts (Guengerich, 1992; Singer, 1996). Neither the metabolic fate of chloroprene nor the biological properties of its metabolic intermediates have been well studied. Oxidation of chloroprene to epoxide intermediates (2-chloro-1,2-epoxybutene-3 and 2-chloro-3,4-epoxybutene-1) was suggested to occur based on the detection of alkylated 4-(4-itrobenzyl)pyridine in incubations of chloroprene and mouse liver microsomes (Haley, 1978; Bartsch *et al.*, 1979). Analogous to the formation of chloroacetaldehyde subsequent to the oxidation of vinyl chloride to chloroethylene oxide, 2-chloro-1,2-epoxybutene-3 could undergo rearrangement to form an unsaturated chloroketone. These postulated oxidative intermediates of chloroprene metabolism may be protein and/or DNA reactive and may account for the cytotoxicity and carcinogenic effects of this compound. Differences in stability, distribution, and reactivity of these various intermediates may account for differences in dose-related carcinogenic effects of chloroprene and 1,3-butadiene. Further studies are needed to understand the processes involved in chloroprene carcinogenesis.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of chloroprene in male F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, lung, and kidney were also attributed to chloroprene exposure. There was *clear evidence of carcinogenic activity* of chloroprene in female F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, mammary gland, and kidney were also attributed to exposure to chloroprene. Low incidences of urinary bladder neoplasms in male and female rats and lung neoplasms in female rats may also have been related to exposure to chloroprene.

There was *clear evidence of carcinogenic activity* of chloroprene in male B6C3F$_1$ mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), and harderian gland; increased incidences of neoplasms of the forestomach and kidney were also attributed to exposure to chloroprene. There was *clear evidence of carcinogenic activity* of chloroprene in female B6C3F$_1$ mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), harderian gland, mammary gland, liver, skin, and mesentery; increased incidences of neoplasms of the forestomach and Zymbal's gland were also attributed to exposure to chloroprene.

Exposure of male and female rats to chloroprene was associated with increased incidences of alveolar epithelial hyperplasia in the lung; nephropathy; and several nonneoplastic effects in the nose including olfactory epithelial atrophy, fibrosis, adenomatous hyperplasia, basal cell hyperplasia, chronic inflammation, respiratory metaplasia, and necrosis. Exposure of male and female mice to chloroprene was associated with increased incidences of bronchiolar hyperplasia and histiocytic cell infiltration in the lung; epithelial hyperplasia in the forestomach; renal tubule hyperplasia (males only); several effects in the nose including olfactory epithelial atrophy, respiratory metaplasia, and adenomatous hyperplasia; and hematopoietic cell proliferation in the spleen.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 14. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 16.

APPENDIX E

Description of Online Searches for Chloroprene

DESCRIPTION OF ONLINE SEARCHES FOR CHLOROPRENE

Online searches for chloroprene [CASRN 126-99-8] were performed in databases on the systems of STN International, DIALOG, NLM's TOXNET, and the Chemical Information System from 1980 to date. Toxicology information was sought in the databases EMIC, EMICBACK, RTECS, TSCATS, TOXLINE, CANCERLIT, and MEDLINE (name and CASRNs combined with terms for metabolism and the MESH heading for all neoplasms). Occupational safety and health information was obtained from NIOSHTIC and HSDB. Also, the review of 1200 life sciences journals was accomplished using Current Contents on Diskette® (and cumulative issues on CD-ROM). STN Registry file and SANSS provided chemical identification information. Numerous reprints were requested and received of the chloroprene literature.

Regulatory information was obtained from the in-house FESA CD-ROM containing the latest Code of Federal Regulations and the Federal Register pertaining to the title 21 (FDA) and title 40 (EPA) regulations.

Searches were limited to 1995 [the year before the NTP bioassay (NTP, 1998), which has an extensive literature review up to 1996] through July 1997.

APPENDIX F

Report on Carcinogens (RoC), 9th Edition
Review Summary

Report on Carcinogens (RoC), 9th Edition
Review Summary

Chloroprene

NOMINATION
Review based on results of an NTP Bioassay of Chloroprene (1996), reporting clear evidence of carcinogenicity in all experimental animal groups.

DISCUSSION
Chloroprene is used as a monomer for neoprene elastomers, industrial rubber products, and as a component of adhesives in food packaging. NTP Bioassay results indicate clear evidence of benign and malignant tumor formation at multiple tissue sites in multiple species of experimental animals. However, an industry-sponsored inhalation exposure study with rats failed to find carcinogenic effects. There is limited evidence for the carcinogenicity of chloroprene in humans. Data from two studies suggest that occupational exposure to chloroprene may increase cancer risk for digestive and lymphatic/hematopoietic tumors and for liver, lung, and lymphatic tumors. An additional epidemiology report appearing since the 1997 review also suggests a link with liver cancer. The recommendation from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	list as a reasonably anticipated human carcinogen	7 yes/0 no/2 a*
NTP EC Working Group (RG2)	list as a reasonably anticipated human carcinogen	8 yes/0 no
NTP Board RoC Subcommittee	list as a reasonably anticipated human carcinogen	6 yes/0 no

*a-abstentions

Public Comments Received
A total of 2 public comments were received:

- 1 against listing as reasonably anticipated to be a human carcinogen
- 1 providing comments on the content of the background document prepared for the review of this nomination