Chloroprene: Observations of Carcinogenesis and Mutagenesis

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In 1931, 2-chlorobutadiene, more commonly called chloroprene, was introduced into American commerce. This colorless liquid is used for the manufacture of a synthetic rubber, polychloroprene. Worldwide, an estimated one billion pounds of chloroprene is currently being produced annually (Lloyd et al. 1976). In the United States alone, an estimated 400 million pounds of polychloroprene, marketed under the trade name Neoprene, is produced annually (Lloyd et al. 1975). It has been estimated that approximately 2500–3000 workers in the United States are currently being exposed to chloroprene during its manufacture and polymerization. It is not known how many thousands of individuals may be exposed to chloroprene as a result of working daily with Neoprene or with the liquid polymer (latex). Because of the close structural similarity between chloroprene and vinyl chloride (VC) (Fig. 1), the latter a known carcinogen (Waxweiler et al. 1976) and mutagen (Rannug et al. 1974; McCann et al. 1975; Bartsch et al. 1975a; Greim et al. 1975; Garro et al. 1976; Andrews et al. 1976; Loprieno et al. 1976), it was only natural that scientific attention should be focused on the assessment of potential adverse effects associated with exposure to chloroprene. With this in mind, the National Institute for Occupational Safety and Health (NIOSH) initiated in 1976 an intensive search and synthesis of chloroprene-related research from sources both within and outside the United States.

Observations of Carcinogenesis

Laboratory Observations

One animal study has addressed itself to the carcinogenicity of chloroprene (Zilfian et al. 1975). In three series of experiments, the authors reported that skin application of chloroprene to mice and subcutaneous and stomach-tube administration to rats did not induce tumors. For several of the test series, the authors did not state the specific period of time required for tumor ob-

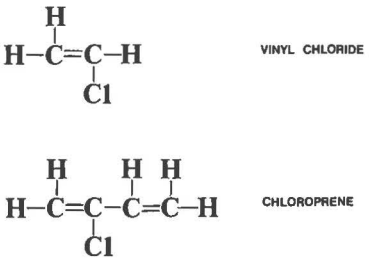

Figure 1
Chemical structures of vinyl chloride and chloroprene.

servation, making it impossible to determine the number of animals surviving for specific periods of time on which observations were based. The investigators indicated that pure chloroprene rather than technical grade chloroprene was administered to the animals. Since workers are exposed to technical grade chloroprene, which may contain other contaminants, it is difficult to determine the public health significance of these results.

Human Observations

The earliest assessment of the possible carcinogenicity of chloroprene was undertaken by Khachatryan in the Yerevan district of the Soviet Union (Khachatryan 1972a,b). A gradient of exposure to chloroprene was established. As shown in Table 1, a zero exposure level was assumed for group 1, and the relatively highest exposure level was assumed for group 5 (Khachatryan 1972a). The prevalence rate of skin cancer during the period 1956–1970 was directly related to the degree of chloroprene exposure. The rate increased from 0.13% in exposure group 1, composed of cultural and civic workers; to 0.40% in group 2, composed of nonchemical-industry workers such as electricians, carpenters, and tinsmiths; to 0.67% in group 3, composed of nonchloroprene-chemical workers such as truck drivers and service station attendants; to 1.69% in group 4, composed of chloroprene-derivative workers; to 3.07% in group 5, composed of chloroprene-production workers having extensive exposure. An inverse relationship was demonstrated between mean age at diagnosis of skin cancer and degree of chloroprene exposure; i.e., the groups having relatively greater exposure to chloroprene had an earlier age at diagnosis of skin cancer. A similar inverse relationship was also demonstrated for duration of employment; i.e., higher exposure groups had a shorter duration of employment at the time of skin cancer diagnosis.

As shown in Table 2, during this same time period (1956–1970) lung cancer morbidity was also directly associated with the degree of chloroprene exposure (Khachatryan 1972b). This increased from 0.06% in group 1 to 0.71% and 2.63% in groups 4 and 5, respectively. As in the study of skin cancer, similar inverse relationships between degree of exposure to chloroprene and mean age at diagnosis of lung cancer and mean duration of employment were observed.

Although these findings were reported to have been instrumental in the decision by the Soviet Union to lower the maximum allowable concentration (MAC) for chloroprene from 20 mg/m^3 to 2 mg/m^3, 5 ppm to 0.5 ppm (Prosser 1975), recent correspondence from the Soviet Union indicates that a reevaluation of this study has detected some methodological errors (Savelev

Table 1
Prevalence of Skin Cancer

	Exposure group				
	1 no industry	*2 non-chemical industry*	*3 unrelated chemical industry*	*4 chloroprene derivatives*	*5 chloroprene production*
Number examined	8520	8755	4780	2250	684
Number with skin cancer	11	35	32	38	21
Percent	0.13	0.40	0.67	1.69	3.07
Mean age of cases	72.1	68.9	64.4	59.1	59.6
Mean length of employment for cases (yr)	16.3	15.4	13.8	8.7	9.5

The data shown are for workers over 25 years of age in the Yerevan district of the Soviet Union, 1956–1970 (Khachatryan 1972a).

Table 2
Prevalence of Lung Cancer

	Exposure group				
	1 no industry	*2 non-chemical industry*	*3 unrelated chemical industry*	*4 chloroprene derivatives*	*5 chloroprene*
Number examined	6220	6045	4780	2250	684
Number with lung cancer	4	11	22	16	18
Percent	0.06	0.18	0.46	0.71	2.63
Mean age of cases	60.2	59.3	54.9	44.5	
Mean length of employment for cases (yr)	18.5	14.9	10.3	8.7	

The data shown are for workers over 25 years of age in the Yerevan district of the Soviet Union, 1956–1970 (Khachatryan 1972b).

1975). To date, however, a reanalysis of the data has not been released, and attempts to discuss the study results with the author, other medical personnel involved, and toxicologists have been unsuccessful (Zapp 1975).

Since no mention is made of adjustments for age and sex differences in comparisons among the groups, these variables may account for some of the methodological aspects needing reconsideration. Although reference is made to length of employment for cancer cases (both lung and skin) in these reports, no consideration was given to the importance of latency. Total employment histories also appear to be lacking, as suggested by a difference of 40–50 years between mean age of cases and mean length of employment for cases. If one assumes that most workers begin employment in their mid-20s, the differences between mean age of cases and mean length of employment should be less than 25 years.

More recently, S. Pell (unpubl.) has reported preliminary analyses from a study of mortality among workers in the United States exposed to chloroprene. In this study (Table 3), the cohort consisted of 1661 men who were on the payroll as chloroprene workers at a single facility on June 30, 1957. Although no significant excesses are reported, the data do show an excessive risk of respiratory cancer at each calendar time period for the total study cohort.

Four deaths from lung cancer have been observed among the maintenance mechanics (Table 3). In addition, four currently active maintenance mechanics have been diagnosed as having lung cancer, and these data are not shown in the table. The eight lung cancers in this subcohort account for 40% (8/20) of the lung cancer cases in the total study cohort. Since only 17% of the total study cohort is composed of maintenance mechanics (S. Pell, unpubl.), this observation may be highly significant. (Two respiratory cancer deaths in the total cohort apparently were categorized as other than lung cancer.) Since the task of the maintenance mechanics is to replace leaking pipe fittings, to install equipment, and to do general maintenance in the reactor areas, this group of workers would be expected to have relatively high chloroprene exposure.

In terms of methodology for this study, data for chloroprene-monomer-production workers and polymerization workers were combined, making it impossible to determine the relative contribution from each of these groups to the risk of lung cancer in the total study cohort. (The greatest cancer risk in the VC industry was identified in polymerization workers, not in monomer-production workers. Thus it would seem essential that data for these groups be analyzed separately in the chloroprene-rubber industry.) Since the study cohort included any active worker who was on the chloroprene payroll on June 30, 1957, it is not clear whether any person classified as a member of the control group may have had extensive exposure to chloroprene at a much earlier date. Also, adequate consideration was not given to length of exposure and latency, two variables of prime importance in the epidemiologic study of occupationally related cancer.

In the absence of adequate consideration of these variables, a final evaluation of the carcinogenicity of chloroprene cannot be made. The importance of exposure duration and latency has been demonstrated clearly by Nelson (this volume) in his report on lung cancer among workers occupationally exposed to BCME and by Selikoff (this volume) in his report on lung cancer

Table 3
Preliminary Findings for Respiratory Cancer Deaths among Workers Exposed to Chloroprene

	All years 1957–1974			*1957–1962*			*1963–1968*			*1969–1974*		
	obs.	*exp.*	*SMR*	*obs.*	*exp.*	*SMR*	*obs.*	*exp.*	*SMR*	*obs.*	*exp.*	*SMR*
Total cohort	18	13.2	136	3	2.2	136	4	3.1	129	11	7.9	139
Maintenance mechanics	4	2.8	143	1	0.4	250	1	0.7	143	2	1.7	118
Chemical operators	3	2.8	107	1	0.4	250	0	0.6	—	2	1.8	111
Other high exposures	2	1.4	143	0	0.3	—	0	0.3	—	2	0.8	250

Data shown are for total cohort and specific exposure areas, by period of death (S. Pell, unpubl.). Obs. = observed deaths; exp. = expected deaths (based on company records); SMR = standardized mortality ratio.

and mesothelioma among populations exposed to asbestos from both occupational and environmental sources.

Case Report of Liver Angiosarcoma

More recently, a confirmed case of liver angiosarcoma in a worker who had extensive exposure to finished polychloroprene (Neoprene) has been identified (Herbert 1976). The worker had been employed as a roll builder from 1952 to 1967. During this period, he applied Neoprene to metal cylinders, which were then vulcanized. After this procedure, the material often would be cut to the desired size with a metal saw. Dust control was attempted by means of water sprays, but the worker did not wear a mask. A history of exposure indicated that this worker never had occupational exposure to vinyl chloride, nor had he ever received Thorotrast, an agent also associated with liver angiosarcoma (da Silva Horta et al. 1965). Because of the structural similarity of vinyl chloride and chloroprene and the rare occurrence of angiosarcoma, this observation is considered of great public health concern. It also indicates the need to determine the amount of residual chloroprene in polychloroprene, as well as the need to identify other industrial populations which may have potential exposure to chloroprene from working with finished polychloroprene or the liquid polymer (latex). The latter material is estimated to contain 5000 ppm chloroprene (J. A. Zapp, pers. comm.). After 45 years of occupational exposure to chloroprene, not one investigation addressed to its carcinogenic potential, through either epidemiologic or animal study, by either government or industry, has been completed in the United States.

Observations of Mutagenesis

Laboratory Observations

Because of the lack of data on the carcinogenic potential of chloroprene, efforts have been undertaken to assess existing data regarding the potential for mutagenic effects of chloroprene. This approach seemed scientifically appropriate given the high correlation between carcinogenesis and mutagenesis (McCann et al. 1975) and the close similarity in chemical structure between chloroprene and VC, an agent for which there is strong evidence for both carcinogenicity and mutagenicity.

As far back as 1936, Von Oettingen et al. of DuPont's Haskell Laboratories reported infertility associated with chloroprene inhalation by male mice (Von Oettingen et al. 1936). As shown in Table 4, the fertility rate in mice exposed to levels ranging from 12 to 150 ppm was 43% versus 100% for controls. (Most exposures were at relatively lower levels.) In rats, the fertility rate was 32% at higher levels versus 100% for controls.

This report served as the basis for the U.S. Public Health Service recommending in 1945 a 25-ppm maximum allowable concentration of chloroprene in the work environment (Cook 1945). With the passage of the Occupational Safety and Health Act in 1971, this 25-ppm level was established as the legal occupational standard for chloroprene in the United States.

As shown in Table 5, the first in-depth industrial hygiene air-monitoring program conducted at a chloroprene polymerization facility in 1973 revealed

Table 4
Effect of Inhalation of Chloroprene on the Fertility of Male Mice and Rats, 1936

Species	*No. of animals*	*Pregnancies*	*Fertility rate (%)*
Mice			
0.042–0.548 mg/l (11.6–151.4 ppm)	14	6	43
controls	6	5	83
Rats			
0.434–22.419 mg/l (120–6194 ppm)	19	6	32
controls	5	5	100

Data from Von Oettingen et al. (1936).

mean concentrations to be as high as 1000 ppm, with individual samples ranging as high as 6760 ppm (NIOSH, unpubl.). Data for cancer mortality among personnel employed at this plant were presented above (S. Pell, unpubl.).

In 1972, Davtyan reported the mutagenic effects of chloroprene on male rats at an exposure level of 0.04 ppm. He observed a dominant lethal effect, i.e., a significant excess of embryonic mortality following only male rat exposure, testicular atrophy, and a reduction in the numbers and motility of sperm in animals with nonatrophied testicles.

A year later, Davtyan et al. (1973) reported the results of exposure of male rats to chloroprene at concentrations of 1.0 ppm (Table 6). Again, a dominant lethal effect was observed. Chromosomal aberrations in the bone marrow cells of these same animals were also increased. The authors concluded that both germinal and somatic cells were sensitive to the mutagenic action of chloroprene at these low levels. In 1974, observations of chromosomal aberrations in bone marrow cells of chloroprene-exposed rats were also reported by Bagramyan and Babayan (1974).

Bartsch et al. (1975b) have reported chloroprene vapor to be mutagenic in *Salmonella typhimurium,* TA100, both with and without metabolic activation, when plates containing the bacteria and the mouse liver microsomal fraction

Table 5
Atmospheric Chloroprene Concentrations at a Polymerization Plant, 1973

Area	*No. of samples*	*Range (ppm)*	*Mean (ppm)*
Makeup	10	14–1420	554
Reactor	21	130–6760	1015
Monomer recovery	2	6–440	223
Latex	2	113–252	205

Grab samples collected with glass sampling flasks; analysis by gas chromatography.

were incubated with gaseous mixtures of 2-chlorobutadiene in air. Vogel (1976 and this volume) has demonstrated that chloroprene induces sex-linked recessive lethal mutations in *Drosophila.*

These reports thus indicate that chloroprene is mutagenic in bacteria, is recessive lethal in *Drosophila,* and causes dominant lethality as well as chromosomal aberrations in bone marrow cells of rats. Chloroprene in very low concentrations has been associated with sterility (Von Oettingen et al. 1936), and with decreases in numbers and motility of sperm and testicular atrophy (Davtyan 1972; Davtyan et al. 1973), in mice and rats.

The question facing society is whether such data are scientifically adequate to institute a prudent public health policy for controlling worker exposure to toxic substances. If such data from laboratory studies of mutagenicity are not sufficient to allow for a decision at this time to control exposure to chloroprene as a mutagen, then genetic toxicologists will have to come forward and indicate the data set they would accept as adequate for the prediction of potential mutagenic response in humans.

Human Observations

Recently, data have surfaced regarding the cytogenetic and genetic effects of chloroprene in humans (Table 6). Katosova (1973) has reported a significant excess of chromosomal aberrations in chloroprene workers. As reported at an international conference held in 1975 by the Environmental Mutagen Society, N. P. Bochkov (unpubl.) found a significant excess of chromosomal aberrations in workers exposed to chloroprene as compared to controls. Sanotsky (1976) has reported two additional important observations: (1) a threefold excess of miscarriages among the wives of chloroprene workers and (2) a reduction in the numbers and motility of sperm following occupational exposure to chloroprene.

Chloroprene Data vs. Vinyl Chloride Data for Mutagenesis

Given the mutagenic capacity of chloroprene, demonstrated first by laboratory assay and subsequently by observations in humans, and given the close chemical similarity between chloroprene and VC, it seems to follow that one should compare the mutagenicity data for chloroprene and the data available for VC (Table 7). VC has demonstrated mutagenicity in several microbial test systems (Rannug et al. 1974; Greim et al. 1975; McCann et al. 1975; Bartsch et al. 1975a; Andrews et al. 1976; Loprieno et al. 1976; Garro et al. 1976). Recessive lethal mutations associated with VC exposure have also been observed in *Drosophila* (Sobels and Vogel 1976; Magnusson and Ramel 1976) as well as in plants (A. H. Sparrow, pers. comm.). VC metabolites have induced mutations in Chinese hamster cells (Huberman et al. 1975). Several studies have demonstrated excessive chromosomal aberrations in circulating lymphocytes among workers exposed to VC as compared to controls (Ducatman et al. 1975; Funes-Cravioto et al. 1975; Purchase et al. 1975; E. Loken and E. Thiis-Evensen, unpubl.). In addition, excessive miscarriages have been reported among the wives of male workers exposed to VC as compared to industrial controls (Infante et al. 1976a,b). Although these observations

Table 6
Laboratory Studies Indicating Cytogenetic, Mutagenic, or Reproductive Effects of Chloroprene

	Observation	*Investigators*
Laboratory test system		
Mice and rats	sterility	Von Oettingen et al. (1936)
Rat	1. dominant lethal 2. effects on sperm 3. testicular atrophy	Davtyan (1972)
Rat	1. chromosomal aberrations 2. dominant lethal	Davtyan et al. (1973)
Rat	chromosomal aberrations	Bagramyan and Babayan (1974)
S. typhimurium	mutagenic	Bartsch et al. (1975b)
Drosophila	recessive lethal	Vogel (1975)
Human studies		
Workers	chromosomal aberrations	Katosova (1973)
Workers	chromosomal aberrations	N. P. Bochkov (unpubl.)
Workers	1. decrease in motility and numbers of sperm 2. threefold excess of miscarriages in wives of male workers	Sanotsky (1976)

Table 7
Evidence for Cytogenetic, Mutagenic, or Reproductive Effects of Vinyl Chloride and Chloroprene

Test system	*Agent*	
	vinyl chloride	*chloroprene*
Laboratory observations		
Microbial		
E. coli,[a] *S. pombe*,[a] *S. typhimurium*	+	+
Insect		
recessive lethal in *Drosophila*	+	+
Plant		
Tradescantia	+	?
Mammals		
metabolites in hamster cells	+	?
chromosomal aberrations in male rats	?	+
reproduction interference following exposure of male mice and rats	−	+
decrease in motility and numbers of sperm in rats	?	+
Human observations		
Chromosomal aberrations in male workers	+	+
Excess miscarriages in wives of male workers	+	+
Decrease in motility and numbers of sperm in workers	?	+

[a] Mutagenic activity of chloroprene has not been tested in these organisms.

document overwhelmingly the mutagenicity of VC, even more data are available (Table 7) to demonstrate that chloroprene is mutagenic and reaches the germinal tissue in mammals, including man.

SUMMARY

Even though observations of excessive lung and skin cancer associated with chloroprene production were reported in the Russian literature in 1972, it was not until 1974, with the identification of the epidemic of liver, brain, and lung cancer among VC polymerization workers (Waxweiler et al. 1976), that government, labor, and industry in the United States began to focus attention upon the carcinogenic potential of chloroprene. Unfortunately, data sources and reports currently available do not permit the development of valid inferences regarding the carcinogenicity of chloroprene. Given the consistency of positive response for the mutagenicity of chloroprene in several test systems, plus the observations of adverse effects on the reproduction process among workers occupationally exposed to chloroprene, whether or not chloroprene is carcinogenic may be only of academic interest from a public health point of view.

Even more striking is the fact that 46 years after the introduction of this

toxic agent into industry and 40 years after the report by Von Oettingen et al. (1936) which indicated adverse effects on reproduction, not one epidemiologic study of the effects of chloroprene on reproduction among worker populations in the United States has been reported. These observations clearly indicate the need for regulation of toxic substances prior to their introduction into the work environment. Perhaps the data for VC and chloroprene may now serve as the basis for a more aggressive role by genetic toxicologists in the assay of industrial chemicals and in the utilization of these assay results for making prudent public health policy decisions to control industrial environmental mutagens that are impacting on present and future generations.

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Origins of Human Cancer

BOOK A
Incidence of Cancer in Humans

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COLD SPRING HARBOR CONFERENCES ON CELL PROLIFERATION
VOLUME 4

Cold Spring Harbor Laboratory
1977

Origins of Human Cancer

International Standard Book Number 0-87969-119-0
Library of Congress Catalog Card Number 76-57915

Printed in the United States of America

Cover and book design by Emily Harste

This publication was supported in part by
grants from the Rita Allen Foundation and
the Charles E. Merrill Trust.