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Mutagenic and Carcinogenic Risks Associated With Halogenated Olefins

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Recent experimental evidence indicates that structural analogs of vinyl chloride namely, vinylidene chloride and trichloroethylene, are mutagenic. Carcinogenic response also has been observed in experimental animals following exposure to vinylidene chloride, trichloroethylene, and perchloroethylene. More recent observations demonstrate low-level vinyl chloride-induced mammary carcinoma.

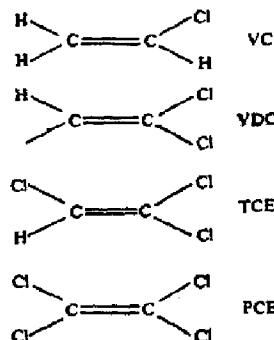
An additional chlorinated olefin, chloroprene, has demonstrated a mutagenic response in several test systems. Likewise, several studies have indicated significant excesses of chromosomal aberrations as well as adverse effects on reproductive function following male exposure to chloroprene. Although reports have indicated an increased incidence of lung and skin cancer among workers occupationally exposed to chloroprene, adequately designed studies have not been carried out which would allow the development of valid inferences regarding its carcinogenicity.

The question facing the scientific community and society is whether observations in subhuman species are adequate to institute prudent public health practice by controlling these agents as carcinogens or mutagens or whether, once again, post-hoc epidemiologic enumeration of the toll will be required.

Since the early 1940's, there has been a tremendous proliferation of man-made chemicals into the workplace. Because of the lack of concern or knowledge of the adverse effects of these chemicals on workers, this proliferation of toxic agents has extended into the environment from out-plant emissions and from consumer end-product use. A majority of these chemicals has not been evaluated for potential danger as carcinogens, mutagens or teratogens. Although carcinogens have been identified from studies of finite occupational groups, the insensitivity of currently employed epidemiologic methods as well as the lack of a national policy for retention of personnel and medical records in the occupational setting necessitate the use of and reliance upon laboratory assay for the detection and prevention of adverse health effects to humans.

The observation of vinyl chloride (VC)-induced cancer, first in animals (1, 2) and subsequently in humans (3, 4) had a profound effect on the need for a rapid reduction of VC levels in the industrial setting and on the value of laboratory assay.

Subsequently, investigators have assessed the mutagenic and carcinogenic potential of the structural analogs of VC: vinylidene chloride (VDC), trichloroethylene (TCE), and perchloroethylene (PCE). With regard to mutagenicity, both vinylidene chloride and trichloroethylene have tested positive in *S. typhimurium* (5-8) (C. Ramel, personal communication) in *E. coli* (9), and TCE has tested positive in *Tradescantia* (A. H. Sparrow, personal communication). Mutagenicity testing with perchloroethylene has been negative (9).



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Table 1. Laboratory studies indicating cytogenetic, mutagenic, or reproductive effects of chloroprene.

Laboratory test system	Observation	Investigators
Mouse, rat	Sterility	von Oettingen et al. (13)
Rat	Dominant lethal: effects on sperm; testicular atrophy	Davtian (14)
Rat	dominant lethal; chromosomal aberrations in bone marrow cells	Davtian et al. (15)
Rat	Chromosomal aberrations in bone marrow cells	Bagramian and Babalian (16)
Rat	Chromosomal aberrations in bone marrow cells	Volkova et al. (17)
<i>S. typhimurium</i>	Mutagenic in TA 100 or TA 1530	Bartsch et al. (6, 18, 19)
<i>S. typhimurium</i>	Mutagenic in TA 1535	Brusick (personal communication)
<i>Drosophila</i>	Recessive lethal	Vogel (20)

With regard to carcinogenicity, VDC, TCE, and PCE all have induced cancer in experimental animals. VDC has induced angiosarcoma (10) and adenocarcinoma of kidney (11) in the mouse. TCE (12) and PCE (unpublished observations, NCI) have induced hepatocellular carcinoma in the mouse.

An additional chlorinated olefin, 2-chloro-1,3-butadiene, more commonly called chloroprene, has demonstrated adverse effects on reproduction and a mutagenic response in several test systems. Chloroprene is a colorless liquid which is polymerized into polychloroprene, a synthetic rubber.

Table 1 shows reports indicating cytogenetic, mutagenic or adverse reproductive effects of chloroprene in subhuman species. As far back as 1936, von Oettingen (13) induced sterility in male mice at air concentrations ranging from 12-152 ppm. Sterility in rats was observed at higher concentrations.

In the rat, atmospheric chloroprene concentrations ranging from 0.04 to 1.0 ppm have resulted in a dominant lethal effect (14, 15), effects on sperm (14), testicular atrophy (14), and chromosomal aberrations in bone marrow cells (15-17). Chloroprene also has demonstrated a mutagenic response in several strains of *S. typhimurium* (6, 18, 19; D. Brusick, personal communication). The report by Bartsch et al. (19) indicates that the mutagenic action of chloroprene in *S. typhimurium* was four times that of VC without metabolic activation and eight times greater with activation. In *Drosophila*, chloroprene has induced sex-linked recessive lethal mutations (20).

Observations in humans are consistent with findings in subhuman experimental systems. Table 2 lists reports indicating the cytogenetic and adverse

reproductive effects of chloroprene on workers. Three studies indicate a significant excess of chromosomal aberrations in workers exposed to chloroprene or chloroprene latexes (17, 21, 22).

Even more significant are the observations by Sanotskii (23). He reported a decrease in motility of sperm after 6-10 years of work in chloroprene and morphological disturbances of sperm after 11 years of exposure to chloroprene-based latex. He also reported that cases of spontaneous abortion occurred three times more frequently in the wives of chloroprene workers as compared to the control group. Furthermore, an industrial hygiene assessment indicated that chloroprene levels in the process ranged from only 0.28 to 1.94 ppm. This is in contrast to the current OSHA standard which allows for a 25 ppm 8-hr time-weighted average concentration. Although no single study clearly establishes that chloroprene is mutagenic, the consistency of positive mutagenic response over the numerous test systems in addition to observations, which indicate that chloroprene affects the sperm, testicles, and reproductive function as a result of male exposure only, indicates the need to control chloroprene as a potential mutagenic agent to man.

Table 2. Cytogenetic or reproductive effects among workers exposed to chloroprene.

Atmospheric chloroprene concentration, ppm	Observation	Investigator
5.0	Chromosomal aberrations	Katosova (21)
No data	Chromosomal aberrations	Bochkov (1976) (22)
0.8-2.0	Chromosomal aberrations	Volkova, et al. (17)
0.3-1.9	Decrease in motility and number of sperm; threefold excess of miscarriages in wives of male workers	Sanotskii (23)

With regard to carcinogenicity, two studies report an excess of lung and skin cancer among workers exposed to chloroprene in the Yerevan district of the Soviet Union (24, 25).

More recently, Pell (26) reported preliminary analyses from a study of mortality among workers exposed to chloroprene in the U. S. Although no significant excesses were reported, inspection of the data indicates an excessive risk of respiratory cancer for each of three 6-yr calendar time periods between 1957 and 1974 for the total study cohort. These excesses however, were not statistically significant. In addition, four deaths from cancer, plus four cases of lung cancer among currently active maintenance mechanics have been observed. 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, this observation may be highly significant. 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 exposures. However, limitations in methodology and study design in these reports preclude an assessment of the carcinogenic risk. None of the epidemiologic studies gives adequate consideration to environmental concentrations, job classification, intensity or duration of exposure, or latency, all factors known to influence the risk of cancer. In each of these studies, the investigators did not analyze their data separately for chloroprene polymerization workers. (The greatest risk in the vinyl chloride industry was identified in polymerization workers, not in monomer production workers). The studies also do not mention the method by which the cancers were diagnosed, nor are the cell types indicated for skin and lung cancers.

More recently, a confirmed case of angiosarcoma of the liver in a worker who had extensive exposure to finished polychloroprene has been identified. The worker had been employed as a roll builder during the period 1952-1967. During this period, he applied neoprene to metal cylinders, which were later vulcanized. 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 angiosarcoma of the liver (27). An industrial hygiene assessment conducted by NIOSH at the plant where this employee worked indicates average chloroprene air levels of 0.2 ppm from personal sampling and 0.14 ppm from area sampling. Because of the structural similarity of vinyl chloride and chloroprene and the rare occurrence of angiosarcoma, this observation is obvi-

ously of concern.

Although this conference pertains to VC-related compounds, new observations related to VC are also of interest. After 87 weeks of observations, Maltoni (unpublished observations) has observed angiosarcoma in rats exposed to 25 ppm VC. Mammary carcinomas were observed at lower levels. Even at 1 ppm, there appears to be a 2-fold risk of mammary carcinoma; with 120 animals exposed at each concentration, at 25 ppm there were 9 observed (8%), at 10 ppm there were 11 observed (9%), at 5 ppm there were 13 observed (11%), at 1 ppm there were 7 observed (6%), as compared to 4 observed (3%) in the control group. In another series of experiments by Maltoni, a 50 ppm exposure to VC resulted in 43/300 (14%) of the rats developing mammary carcinoma as compared to 3/100 (3%) in controls (28). Thus, there appears to be a dose-response relationship in the induction of mammary carcinomas with a 3% tumor rate in each control group.

In 1976, the results of a study of PVC fabricators conducted by Organization Resources Counselors (29) was transmitted to NIOSH. An estimated 700,000 to two million workers are employed in the production of 3.5 million tons of PVC annually. VC exposures are thought to have been low (5-15 ppm) and to have resulted only from the release of unreacted monomer trapped in the resin. Study results are based on deaths which occurred between 1964 and 1973. Causes of death for selected types of cancer in female employees are shown in Table 3. A 38% excess of breast cancer is seen among women

Table 3. Observed and expected deaths due to selected causes among employees of 17 PVC fabricators, 1964-1973.*

	White females		
	Observed	Expected	PMR ^b
All cancers	179	135.933	1.32
Selected types of cancer			
Buccal cavity and pharynx	3	1.872	1.60
Digestive	53	34.929	1.52
Respiratory	12	11.715	1.02
Breast	44	31.907	1.38
Genitals	19	22.971	0.83
Urinary	11	4.487	2.45
Lymphatic and leukemia	10	12.481	0.80

*Unpublished data (29).

^bProportionate mortality ratio.

employed in the fabrication of PVC into finished products.* These observations, combined with ani-

*The author has recently become aware of a limited case-control study which suggests that the increased risk of breast cancer among PVC fabricators may not be related to vinyl chloride exposure.

mal studies indicating VC-induced mammary carcinomas at 1 ppm, raise serious health concern for the possibility of yet another type of cancer induced by vinyl chloride from low level exposures.

The question facing the scientific community is whether observations in subhuman species are adequate to institute prudent public health practice by controlling these agents as carcinogens or mutagens or whether, once again, post-hoc epidemiological enumeration of the toll will be required.

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