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SUMMARIZATION OF RECENT LITERATURE PERTAINING TO AN OCCUPATIONAL HEALTH STANDARD FOR EPICHLOROHYDRIN

Final Report

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I. INTRODUCTION

In September 1976, the National Institute for Occupational Safety and Health (NIOSH) published a criteria document on occupational exposure to epichlorohydrin (1). That document reviewed the available information on toxic effects in animals and humans, work practices, sampling and analysis, and control technology and, on the basis of that information, recommended an occupational health standard including an environmental exposure limit of 0.5 ppm (2 mg/cu m) measured as a timeweighted average. Occupational exposure to epichlorohydrin was defined as exposure to airborne concentrations of one-half the recommended environmental exposure limits.

This report summarizes pertinent information about epichlorohydrin in the areas of human and animal toxicology, analytical and sampling methods, work practices, and engineering controls. Published and unpublished research results appearing since preparation of the criteria document were considered, but only those results that may affect the recommended standard are included. In addition, this report notes deficiencies in present knowledge concerning effects of exposure to epichlorohydrin and outlines research designed to fill those gaps.

This literature summary supplements but does not replace the extensive review in the NIOSH criteria document, which contained comprehensive surveys of all the literature available when the document was prepared, as well as recommendations for an occupational health standard. Although this report does not recommend exposure limits, work practices, or analytical methods, it provides information that will assist NIOSH in determining if there is sufficient new information to consider revising the recommended standard for epichlorohydrin.

II. SUMMARY AND CONCLUSIONS

Environmental health aspects of epichlorohydrin toxicity are confined to occupational exposures to the liquid or vapors of the chemical. The toxic effects of epichlorohydrin have been well documented by NIOSH (1,2).

The results of recent research on epichlorohydrin toxicity suggest that epichlorohydrin should be considered to be a potential human carcinogen. A retrospective mortality study conducted at Shell Oil Company by Enterline and Henderson (3) and Enterline et al. (28) has shown an increase in the number of respiratory cancer deaths and leukemias among epichlorohydrin-exposed workers. These results are not statistically significant, however, and are confounded by various shortcomings in the study's design (i.e., exposure to other industrial chemicals, relatively young age of study cohort, short latency period of study cohort, inadequate smoking histories). A similar survey of Dow Chemical workers conducted by Shellenburger et al. (4) did not describe any trend of increased risk of developing cancers of any type. There were a number of design deficiencies in this study, the most serious of which were the fairly young age and short exposure period of the study cohort. A latency period of roughly 15 years has been suggested by the studies of Enterline and Henderson (3) and Enterline et al. (28). Brown and Rinsky (27) have re-evaluated and confirmed the findings of Enterline and Henderson (3).

Cytogenetic studies by Czechoslovakian (10-16) and American researchers (17-21) in human lymphocytes have shown an increased chromosome aberration associated with occupational exposure to epichlorohydrin. A number of deficiencies in experimental protocols (i.e., use of questionable growth media for culturing human lymphocytes, inappropriate criteria in establishing a study cohort, inappropriate control and reference data) suggest that the reliability

of the results should be questioned. These deficiencies in methodology preclude analysis of the human data to absolutely confirm or refute the cytogenetic or carcinogenic risks associated with occupational exposure to epichlorohydrin. Results of studies involving experimental animals, however, provide more reliable data from which to assess the carcinogenic and cytogenetic effects of epichlorohydrin.

Researchers at New York University's Institute of Environmental Medicine (45,46) have identified epichlorohydrin as a potent carcinogen to the nasal turbinates of rats upon inhalation of 100 ppm of the chemical; the highly significant incidence among study animals of this ordinarily rare type of tumor should provide strong evidence for the carcinogenic potential of epichlorohydrin. Detailed inhalation studies conducted at Dow Chemical by Smith et al. (40) and Quast et al. (47,52) provide evidence that epichlorohydrin inhaled at concentrations of 25, 50, or 100 ppm has a substantial effect on nasal tissue in two strains of rats and one mouse strain. Varying degrees of renal toxicity were evident in rats, but not in mice. Weigel et al. (48) have detailed the pharmacokinetics of epichlorohydrin given orally or through inhalation. Sram (16) has described cytogenetic studies in which rodent lymphocytes have shown increased chromosomal aberrations induced by epichlorohydrin. But as with the human cytogenetic data, these data may be questioned because of the use in these studies of certain types of culture media. The mutagenic properties of epichlorohydrin have been tested in a number of microbial and vascular plant assays (16,25,39,41,42).

NIOSH (5) has recently recommended that epichlorohydrin be considered a human carcinogen, and that controls and work practices be undertaken to substantially minimize occupational exposure to the chemical.

III. HUMAN STUDIES

NIOSH (1,2,5) and ACGIH (6) have documented the ability of epichlorohydrin to irritate the eyes, skin, and respiratory tract upon contact with vapor or liquid. In addition, systemic absorption may occur by passage of epichlorohydrin across the respiratory epithelium or the skin, resulting in gastrointestinal disturbances, hepatic irritation, labored breathing, cough, cyanosis, and chemical pneumonitis. Epichlorohydrin has been implicated in the allergic contact dermatitis associated with the handling of epoxy resins, although Nater and Gooskens (7) and Askarova and Muryseva (8) have disagreed with the idea that epichlorohydrin was the causative agent. No cases of human deaths have been reported as a result of acute exposure to epichlorohydrin. Santodonato et al. (9) have prepared an extensive review of epichlorohydrin and epibromohydrin.

A. Cytogenetic Studies

Based on recent cytogenetic studies (14,16), NIOSH (5) considers epichlorohydrin a potential occupational hazard. Czechoslovakian researchers (10-16) have extensively examined epichlorohydrin's cytogenetic effects on cultured human lymphocytes. Kucerová (10,11) has examined peripheral lymphocytes of workers occupationally exposed to epichlorohydrin. Blood samples taken from workers before exposure to epichlorohydrin in a chemical production plant were compared with to blood samples taken one year after exposure to epichlorohydrin. The results of the findings are presented in Table 1. Cells were cultured by a "routine cytogenetic technique" and chromosal aberrations analyzed by either Giemsa stain or trypsin banding procedures. The authors concluded that this type of cytogenetic evaluation of workers exposed to suspected mutagens may be a sensitive indicator of human risk associated with such exposure.

Table 1. Effects on Peripheral Lymphocytes in Workers Exposed to Epichlorohydrin for one Year (Kucerova, 10,11)

	Number of cells scored	Cells with Aberrations		Number and Types of Aberration				No. Aberrations per 100 cells	No. Breaks per 100 cells	No. Gaps
				Chromatid		Chromosome				
		No.	%	breaks	exchanges	breaks	exchanges			
Before Exposure	3573	41	1.2	31	1	7	4	1.2	1.3	14
One Year After Exposure	3336	67	2.0*	34	5	21	7	2.0	2.4	19

*Significantly higher than controls ($P<0.01$, X^2 test)

Kucerová et al. (12) established that chromosome changes occur in cultured human lymphocytes (Hungerford method of cultivation) exposed to epichlorohydrin either in vitro or in vivo. Cells were stained according to standard Giemsa techniques. Studies of cultured human lymphocytes exposed to epichlorohydrin for 24 hours at concentrations ranging from 10^{-4}M to 10^{-11}M established dose-dependent and time-dependent chromosome damage. Chromatid breaks and chromosome breaks were the more common aberrations observed, while chromatid exchanges and chromosome exchanges were rare. The results of this work are summarized in Table 2. The results showed a specific sensitivity of lymphocytes to epichlorohydrin treatment at different phases of the mitotic cycle; the application of the chemical for the last 24 hours of cell cultivation (G_1S and G_2 phase) caused increased chromatid breaks as compared with chromosomal breaks.

The 0.9% saline solution with dimethylsulphoxide (DMSO) that was used as a dilutant for epichlorohydrin mixtures, however, did produce a positive cytogenetic effect that was significant at the 0.05 level in the G_0 phase of the cell cycle. Epichlorohydrin concentrations of 10^{-5}M to 10^{-10}M caused an increase in chromosomal aberrations and breaks. At concentrations of 10^{-4}M and 10^{-5}M, there was a trend of increased impaired chromosome numbers from the G_0 to G_1S to G_2 phases of the cell cycle; toxic results were obtained at a concentration of 10^{-4}M when cells were exposed during the G_1SG_2 phase.

Kucerová and Polívková (13) in a second report cultured human lymphocytes for a total of 52 hours and stained them with Giemsa or banded them by the Barkholder and Commings method. Previous to staining or banding, cultured cells were exposed 10^{-6}M epichlorohydrin in DMSO or 200R X-ray radiation.

Table 2. Mutagenic Effect of Epichlorohydrin *In Vitro* Testing of Human Lymphocytes (Kucerova *et al.*, 12)

	Number of cells scored	Cells with Aberrations		Number and Types of Aberration				No. Aberrations per 100 cells	No. Breaks per 100 cells	No. Gaps
				Chromatid		Chromosome				
		No.	%	breaks	exchanges	breaks	exchanges			
Concentration										
Control	700	5	0.7	3	0	1	1	0.7	0.9	7
Control with DMSO	200	2	1.0	2	0	0	0	1.0	1.0	0
Epichlorohydrin										
10^{-5} M	360	28	7.8	16	1	13	2	8.9	9.7	8
10^{-6} M	300	9	3.0	8	0	2	0	3.3	3.3	5
10^{-7} M	300	8	2.7	5	0	4	0	3,0	3.0	5
10^{-8} M	300	4	1.3	0	3	1	0	1.3	2.3	2
10^{-9} M	300	3	1.0	1	1	1	0	1.0	1.3	3
10^{-10} M	300	5	1.7	3	1	0	1	1.7	2.3	0
10^{-11} M	300	2	0.7	1	0	1	0	0.7	0.7	1

Radiation effects were characterized by a predominance of chromosome breaks and exchanges. Chemical-induced effects were characterized by chromosomal and, especially, chromatid breaks that remained open. Conventional Giemsa staining revealed 3 and 2 aberrations per 100 cells for cells exposed during the G_0 and G_1SG_2 phases of the cell cycle, while the banding technique revealed 7 and 28 aberrations per 100 cells, respectively. The chemical-induced cytogenic effect was more pronounced when exposure was during the G_1SG_2 phases of the cell cycle.

The distribution of epichlorohydrin-induced chromosome breaks was non-random, suggesting that certain segments of chromosomes were more susceptible to damage than others. The 9q12 band (Paris nomenclature) appeared to be the most fragile chromosome and the Y chromosome the most resistant to breakage. About 85% of all broken bands were G-negative. The banding technique revealed only a small number of chromosomal aberrations not detected by conventional Giemsa staining following exposure to epichlorohydrin. DMSO was used to dilute the epichlorohydrin and caused chromosomal impairment at the rate of 1.0/100 cell as opposed to a rate of 0.6 abnormal cells per 100 cells examined for controls without DMSO.

Kucerová *et al.* (14) and Kucerová and Zhurkov (15) have examined 35 workers (23-54 years of age) occupationally exposed to epichlorohydrin. Subjects were examined for chromosomal aberrations in their peripheral lymphocytes. Blood samples were taken from the workers before and after exposure to epichlorohydrin on the job, and lymphocytes cultured by the Hungerford technique for 56 to 58 hours prior to analysis. Staining of slides followed conventional Giemsa techniques. Epichlorohydrin exposure in these workers ranged from 0.5 to 5.0 mg/m^3 ($\sim$0.13 - 1.3 ppm). The study cohort was reported as not having

been exposed to radiation or other known mutagens. Cytogenetic analyses revealed that the percentage of aberrant cells collected before the start of epichlorohydrin exposure did not differ from those in a reference population.* Blood samples taken after one year of exposure and after two years of exposure showed statistically significant increases of 1.91 and 2.69 percent respectively in the number of cells with chromosome defects. Blood samples obtained before exposure to epichlorohydrin in a newly constructed chemical production plant were reported as displaying an abnormal cell rate of 1.37/100 cells. Therefore the preexposure data served as control data for subsequent years of study. Table 3 summarizes the significant findings of this research. As in previous related results of *in vitro* tests, chromatid and chromosomal breaks were the most frequent aberrations observed. Although the authors indicate that the workers had not been concurrently exposed to radiation or other known mutagens, it is not known to what extent simultaneous exposure to other chemicals in the workplace may have affected the results. As in previously reviewed Czechoslovakian studies, DMSO was used as a component of the epichlorohydrin diluting system and could potentially affect the results. Sram *et al.* (16) has included a report of the data presented by Kucerová *et al.* (12) but no further interpretation of the data was presented.

A study conducted in the United States concerning potential mutagenic hazards resulting from exposure to epichlorohydrin has created divergent lines of thought between the assigned investigators and others who subsequently reanalyzed the data.

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*The level of aberrant cells spontaneously occurring in human peripheral lymphocytes in a complex study concerned with the incidence of spontaneous chromosomal aberrations in human populations (West Germany and Eastern European).

Table 3. Comparison of the Percent Occurrence of Number of Chromosome and Chromatid Breaks and the Total Number of Abnormal Cells in Three Cytogenetic Studies Examining the Cytogenetic Effects of Epichlorohydrin in Occupational Settings

Cytogenetic Parameter	Kucerová et al. (14)			Picciano (17)		Barna-Lloyd et al. (19)						Glycerin Workers[d]	
	Production Workers			Epoxy Resin Workers		Epoxy Resin Workers							
						Group I Reevaluated Unadjusted[a]		Group IA Reevaluated Adjusted[b]		Group IF Follow-up of Group IA[c]			
	Pre-Exposure Control	1 yr-post Exposure Worker	2 yr-post Exposure Worker	Control (Pre-employ)	Worker	Control (Pre-employ	Worker	Control (Pre-employ)	Worker	Control (Pre-employ)	Worker	Control (Pre-employ)	Worker
Number of Workers Examined	35	33	31	75	96	26	76	18	61	46	19	37	115
Chromatid Breaks	0.97	1.05	1.62*	2.15	4.34*	2.40	4.36	1.03	2.35	1.35	2.45	1.08	1.47
Chromosome Breaks	0.28	0.61	1.04*	0.51	0.96*	0.58	0.93	0.52	0.66	0.51	0.79	0.39	0.55
Abnormal Cells	1.37	1.91	2.69*	2.38	4.25*	2.69	4.18*	1.61	2.51	1.83	2.76	1.43	1.74

*Statistically significant results (see text for individual explanation)

[a] Original Dow Chemical data re-evaluated, but not adjusted for experimental influence(s)

[b] Barna-Lloyd data (re-evaluated) excluding all results in which the TC199 media was used for culturing cells

[c] Follow-up of workers originally displaying abnormally high results.

[d] Controls from Dow Chemical studies were from a pre-employment health examinations of subsequent employees previously not exposed to epichlorohydrin.

Picciano (17) reports significant chromosomal aberrations among workers exposed to epichlorohydrin. Ninety-three workers in the Dow Chemical U.S.A. epoxy resin plant in Freeport, Texas exhibited no adverse health effects, but had twice as many chromosomal aberrations as compared to 75 pre-employment control workers who had no previous epichlorohydrin exposure. Exposure concentrations for the 93 coworkers in the study cohort were not detailed, but were assumed to be consistently below 5 ppm (20 mg/m^3). A summary of these findings are found in Table 3. Cells were cultured using "standard cell culture techniques," however, no details about the type(s) of media employed were provided. Likewise, procedures for the harvesting and preparation of metaphase smears were not discussed. Details as to the criteria used to select workers included in the study cohort were not presented. The average age of the pre-employment control group (25.2 years) was considerably younger than the average 35.8 year age of the study cohort. Exposure histories to chemicals other than epichlorohydrin were not detailed.

One anonymous report (18) of these findings states that Dow Chemical officials have confirmed the results of Picciano, but added that the persons examined by Picciano (17) were exposed to several other chemicals and that epichlorohydrin "is only a suspect." The report further states that Dow's concerns led to a follow-up study in 1977 of some workers previously displaying chromosome aberrations. Significant improvements were shown suggesting that such abnormalities may be reversible.

Barna-Lloyd et al. (19) have conducted similar studies on Dow Chemical workers exposed to epichlorohydrin, and re-evaluated the results of the earlier Picciano (17) study. Their findings indicate that among 76 workers exposed to

epichlorohydrin in epoxy resin production plants and 115 workers exposed to the chemical in glycerine production, there were no sustained increases in chromosome aberrations as a result of occupational exposure to epichlorohydrin. Data were obtained for 76 epoxy resin workers who had been among the 93 individuals examined by Picciano (17). Subsequent re-evaluation of the data on the original 93 workers by Barna-Lloyd et al. (19) called for the exclusion of 17 individuals from the epoxy resin cohort because of failure to meet criteria set forth for the cohort. Control groups were selected from a group of subsequently-hired Dow employees during pre-employment physical examinations and were sampled contemporaneously with that study group.

Three different culture media were utilized in the culturing of the human lymphocytes: GIBCo Chromosome Medium #4 or 1A, Difco TC 199 Chromosome Medium, and a Dow Chemical in-house preparation of the TC 199 Media. Prepared slides were stained with Giemsa stain. A summary of the re-evaluated data on epoxy resin workers is presented in Table 3.

Analysis of variance for the exposed study group vs. comparison group revealed a significant unadjusted difference in the occurrence of chromosomal aberrations ($P=0.04$ for abnormal cells). Further analyses of the data did not reveal any significant effects dependent upon duration of exposure, intensity of exposure, or person(s) scoring the chromosomal tests. A highly significant effect, however, was seen to result from the type of growth media used for cell culture ($p<0.001$). A statistically significant occurrence of chromosome aberrations was attributed to the use of a TC 199 growth medium prepared by Dow Chemical as a replacement for commercial media, thus invalidating the use of this material for chromosome studies. When these results were adjusted for

effects due to the type of growth media employed, there was no significant effect (P = 0.31). The adjusted result, however, still showed a higher incidence of chromosomal aberrations among exposed workers.

Further investigations among 115 employees working in glycerine departments revealed increased numbers of chromosomal aberrations relative to the comparison group; however, differences were not statistically significant. These findings are summarized in Table 3.

The background level of 2.69% abnormal cells for Dow Chemical's initial pre-employment comparison group was not substantially different from the 2.96% abnormal cell occurrence observed by Kucerová et al. (14) in individuals after two years of occupational exposure to epichlorohydrin. The subsequent analysis of 115 glycerine workers, however, resulted in a much lower background value (1.43% abnormal cells) that was comparable to a background level of 1.42% abnormal cells reported in the Kucerová et al. (14) study. This leads to some serious questions about the validity of the control data in the Picciano (17) and of the re-evaluation of this data by Barna-Lloyd (19). An additional discrepancy was that Picciano used 75 pre-employment controls, but only 20 such controls were analyzed by the Barna-Lloyd (19) re-evaluation. Subsequent repeat cultures from the 76 epoxy resin employees in the original study group, were TC 199 medium was not used, revealed no significant differences between the exposed and comparison populations.

It was the opinion of Barna-Lloyd et al. (19) that the original findings of Picciano (17) were confounded by the use of different culture media, discrepancies in criteria for selection of a study cohort, questionable laboratory practices, and the possibility of some individuals in the cohort

being exposured to other chemicals, and this may have been responsible for the observed chromosomal aberrations initially reported. It should be noted that control data for both Dow studies were obtained from pre-employment medical examinations of Dow workers that had no known exposure to epichlorohydrin. The Czechoslovakian control data was obtained from a group of workers before being exposed to epichlorohydrin, and pre-exposure data served as control data for subsequent medical evaluation.

Poole (21) has commented on the deficiencies in the methodology of both the Picciano (17) and Barna-Lloyd (19) studies. Their reliance on concurrent external control groups for comparison rather than on the use of pre-exposure determinations among the study cohort was criticized. Walker (20) has criticized the Picciano (17) data as having been prematurely released without the benefit of full scientific or statistical scrutiny.

Kapp et al. (23) have reported evidence of genetic toxicity (Y-chromosome non-disjunction) in the sperm of 18 workers exposed to dibromochloropropane. Workmen exposed to the chemical had significantly reduced sperm counts. The extent to which epichlorohydrin was involved in producing these effects on humans is unknown.

Thurman et al. (25) have investigated the effects of organic compounds, including epichlorohydrin, that are used in the manufacture of plastics on the immunological responsivity of murine and human lymphocytes. Epichlorohydrin was measured as non-specifically cytotoxic at 60 µg/0.2 ml lymphocyte medium. At lower concentrations, it was suppressive to the Con A* and PWM,** but not PHA-P*** parameters of lymphocyte responsiveness. The concentration

*Concanavalian A stimulated both immature and mature T-cells.

**Pokeweed mitogen is stimulator of both T and B cells, and is used as a partial indication of B cell responsivity.

***Phytohemagglutinin stimulates mainly T-cells.

range of epichlorohydrin was 0.6 to 60 µg/0.2 ml. Epichlorohydrin was most potent in its action on human lymphocytes that had not yet reached their full stages of maturity. Indications were that the inhibitory effect was not reached until the concentration approached 60 µg/2 ml. Further research investigating the effects of epichlorohydrin on the immune system may thus be warranted to monitor for possible immunological impairment in exposed workers.

B. Epidemiology

Detailed epidemiological studies on epichlorohydrin have not been reported in the scientific literature; however, several studies conducted on epichlorohydrin workers have recently been summarized.

Enterline and Henderson (3) have conducted a mortality study on 864 active or retired Shell Chemical Company workers (average age = 48 years) exposed to epichlorohydrin for at least six months during the period from 1948 to 1965. Mortality information was gathered on the entire cohort through 1977. This report suggests a possible carcinogenic risk for workers exposed to epichlorohydrin. The results of this study are summarized in Table 4. Out of a total of 52 deaths in this cohort, nine (17.3%) were due to respiratory cancer. This is not statistically significant ($P>0.05$), however, when compared to the expected respiratory cancer death rate of 6 to 7 percent for men in this age group. Although these results were considered to be "highly suggestive of a carcinogenic risk of epichlorohydrin," it was also recognized that unresolved difficulties complicated the analysis of results. These problems include the lack of accurate pathological diagnosis in certain cases, the absence of quantitative monitoring and exposure data, the absence of tobacco smoking and alcohol consumption histories, and the relatively young age of the study cohort.

Table 4. Observed Deaths From Cancer, Expected Deaths and Standard Mortality Ratios Among 864 Male Shell Oil Workers Exposed to Epichlorohydrin

Plant Location	Total			Deer Park			Norco		
Number	864			475			389		
Exposure Period	1948 - 1977			1948 - 1977			1956 - 1977		
Cause of Death[1]:	Observed	Expected[2]	SMR	Observed	Expected	SMR	Observed	Expected	SMR
All Causes	52	97.33	53.4	33	57.15	57.7	19	40.18	47.3
All Cancers:	14	17.51	80.0	10	10.44	95.8	4	7.07	56.6
Buccal & Pharyngea (140-148)	0	0.57	0.0	0	0.32	0.0	0	0.25	0.0
Digestive (150-159)	2	3.81	52.5	2	2.34	85.5	0	1.47	0.0
Respiratory (160-164)	9	6.04	131.6	6	3.95	151.9	3	2.89	103.8
Urinary (180,181)	0	0.65	0.0	0	0.41	0.0	0	0.24	0.0
Leukemia (204)	2	0.89	224.7	1	0.57	175.4	1	0.32	312.5
Lymphoma (202,203,205)	0	1.40	0.0	0	0.71	0.0	0	0.69	0.0
All Other	1	3.35	29.8	1	2.14	46.4	0	1.21	0.0
Person-Years	18483.5			10,862.2					

[1] Deaths coded to the International Classification of Diseases

[2] Expected deaths calculated from age specific, white, male death rates for Louisiana and Texas.

In the update of analysis of the mortality data, an additional two years of follow-up of the study cohort revealed an almost doubled rate of respiratory cancer in workers exposed for 15 years or longer.

Deisler (26) has commented on the same shortcomings of this preliminary report by Enterline and Henderson (3) of the possible carcinogenic risk associated with occupational exposure to epichlorohydrin.

Recently, Brown and Rinsky (27) from NIOSH conducted a re-analysis of the Enterline and Henderson (3) study. Several factors differing in the Brown and Rinsky interpretation of data provided by Enterline and Henderson included:

1) 17 individuals with an unknown vital status dropped by the Enterline and Henderson (3) study were included in the Brown and Rinsky (27) report as being alive as of December 31, 1977.

2) Brown and Rinsky (27) used age-specific death rates derived from U.S. mortality rates for white males. The Enterline and Henderson (3) report used age-specific death rates for Texas and Louisiana. The average annual death rate from lung cancer for 1950-1969 was $51.97/10^5$ in Louisiana, $38.52/10^5$ in Texas, and $37.98/10^5$ for the entire United States.

3) Slight variations in cause of death groupings were unavoidable because of differences in the Brown and Rinsky (27) analytic program.

In general, the Brown and Rinksy (27) data yielded lower than expected values for all causes of death due to the differences in person-years and U.S. death rates rather than Texas/Louisiana death rates. Lung cancer rates were elevated in both the Norco and Deer Park Plants, but were not statistically different. Table 5 summarizes the re-evaluation of the data of Enterline and Henderson (3) by Brown and Rinsky (27).

All but one of the lung cancers from both study populations occurred after a 15-year period with standard mortality rates increasing from 69 to 201

Table 5. Observed Deaths Resulting From Cancer, Expected Deaths, and Standard Mortality Rates Among Shell Oil Workers Exposed to Epichlorohydrin for more than Three Months (380 Norco Workers and 470 Deer Park Workers) (27)

Cause of Death[1]	Total			Deer Park			Norco		
	Observed	Expected[2]	SMR	Observed	Expected	SMR	Observed	Expected	SMR
All Causes	51	81.68	63**	33	50.60	65*	8	31.08	58*
All Cancers (140-205)	13	14.15	92	10	8.82	113	3	5.33	56
Buccal & Pharnyx (140-148)	0	0.43	--	0	0.28	---	0	0.15	--
Digestive (150-159)	2	3.44	58	2	2.19	91	0	1.25	--
Respiratory (160-164)	8	5.18	154	6	3.31	181	2	1.87	107
Lung (162-163)	8	4.92	163	6	3.14	191	2	1.78	112
Urinary (180-181)	0	0.63	--	0	0.40	---	0	0.23	--
Lymphatic and Hemato (200-205)	2	1.94	103	1	1.19	83	1	0.75	183
All Other	1	2.79	36	1	1.72	58	0	1.07	--
Person Years		18,173			10,720			7,452	

[1] Deaths coded to the International Classification of Diseases

[2] Expected deaths calculated from age specific, white, male death rates for the United States.

*P<0.05

**P<0.01

among those with a greater than 15 years from date of first exposure. The average length of exposure to epichlorohydrin for the 8 lung cancer deaths was 5.83 $\pm$ 5.04 (S.D.) years with a range of 6 months to 15 years 11 months. It has been verified that at least four of the workers who died had been exposed to isopropyl alcohol as well as to epichlorohydrin.

Brown and Rinksy (27) have concluded that their analyses agree with those of Enterline and Henderson (3). While an elevated number of lung cancer deaths was observed in older individuals, Brown and Rinsky observed no statistically significant association between lung cancer and exposure to epichlorohydrin. Occupational exposure to isopropyl alcohol confounds the data on exposure associated with lung cancer risk. The continued follow-up of these study cohorts was recommended; a more detailed characterization of exposure groups with respect to variables in their histories that might affect results was called for.

Enterline et al. (28) have recently submitted a detailed description of their analysis of cancers among Shell workers exposed to epichlorohydrin in two production plants. Smoking histories were obtained retrospectively from individuals who had some knowledge of the smoking habits of the deceased workers in question. Within a subpopulation of cancer deaths among workers exposed to epichlorohydrin, 12 of 14 examined cancer victims had some history of cigarette smoking, with 6 of 9 lung cancer victims known to be cigarette smokers.

Shellenberger et al. (4) have conducted a retrospective study of a cohort of 553 white male epoxy resin and glycerine production workers occupationally exposed to epichlorohydrin. Slightly more than 83% of the study cohort was under the age of 50 years, and the duration of exposure to epichlorohydrin ranged from 3 months to 181 months; a majority of the study cohort was

exposed for 18 months or less. Detailed exposure histories were not available, but it was concluded by the authors that airborne levels of the pollutant were below 5 ppm, with most exposure being less than a TWA of 1 ppm. Age specific death rates were used to determine an overall standardized mortality ratio. Within the cohort there were 12 reported deaths. Standardized mortality ratios indicated no association between epichlorohydrin exposure and increased mortality. The number of accidental deaths observed--five--was greater than expected. Workers exposed to both epichlorohydrin and allyl chloride had higher standardized mortality ratios, but the small number of persons in this category made statistical assessment difficult. Also, previous exposure to other chemicals in occupational settings was acknowledged among the study cohort. Smoking histories revealed that about 63% of the cohort smoked on a routine basis, and all victims of nonaccidental death were smokers. The distribution of observed deaths by cause for 553 epichlorohydrin workers is as follows:

	Observed	Expected	S.M.R.
All Deaths	12	20.70	58
Cancer	2	3.50	--
Adenocarcinoma	1	--	--
Bronchopneumonia in individual with metastatic malignant melanoma	1	--	--
Cardiovascular Disease	5	7.25	69
Accidents	5	4.10	122
Other	0	5.85	--

The cohort described in this study was young, and had been exposed for a relatively short period of time so that effects on mortality from chronic disorders such as cancers and cardiovascular disease might not be expected to manifest themselves. Poole (21) has raised the question of a relatively young

study cohort with a relatively short exposure period in his critical assessment of this Dow Chemical study (4).

C. Limited Occupational Exposures

Sargent et al. (29), Ruhe et al. (30), and Ferguson (31) have conducted environmental health hazards evaluations at several occupational settings in which exposure to epichlorohydrin was suspected. In all three studies, concentrations of epichlorohydrin in air samples was below the limit of detection, and standardized health surveys did not reveal any toxic threats resulting from possible exposure to epichlorohydrin. Ferguson (31) did point out that insufficient ventilation and poor housekeeping and safety procedures made the threat of accidental exposure to epichlorohydrin as well as other chemicals a possibility.

D. Reproductive Toxicology

A recent anonymous report (32) concerning epichlorohydrin workers at Shell Oil Company's Deer Park, Texas and Norco, Louisiana plants examined potential effects of exposure on male fertility. Sperm counts taken from 128 volunteers showed no variation from that of a control group of non-exposed workers. Similarly, measured hormone levels in these workers did not differ significantly from those of controls. Sperm counts did not correlate with either the duration or the intensity of exposure to epichlorohydrin.

Venable and McClimans (33) have examined the fertility of 64 male employees engaged in the production of chlorinated carbon compounds in the Glycerine Department of Dow Chemical in Freeport, Texas. Sperm counts, sperm morphology, and blood hormone levels were determined for workers exposed for more than five years to: epichlorohydrin and allyl chloride; allyl chloride

and 1,3-dichloropropane; or epichlorohydrin, allyl chloride, and 1,3-dichloropropane. The results indicated that there was no statistical association between altered test parameters and exposure to allyl chloride, epichlorohydrin, or 1,3-dichloropropane. Workers in the same plant who were not exposed to chlorinated hydrocarbons served as a control group.

Results of this study did reveal, however, that the study group exhibited a higher sperm count per cc of seminal fluid collected than did the control group. The percentage of motile sperm was significantly lower in the exposed workers ($P = 0.05$, T-test); however, the number of motile sperm/cc was higher. The higher total sperm count per cc of seminal fluid in the study group is responsible for the higher number of motile sperm/cc in the study group when compared to the control group.

A subgroup among the exposed study cohort, classified as distribution workers, had a lower average sperm count than other members of the study, while also being among a low exposure group. These workers are pending further analysis.

Certain aspects of the study need clarification before a more complete analysis of the data can be made: 1) A more complete history of exposure of both the study and control groups to industrial chemicals is needed, and 2) additional information regarding time at which semen samples were collected is required because experimental evidence indicates that epichlorohydrin effects on sperm production may be transitory. Production of samples at the end of a weekend or vacation period may have some influence on sperm density. The study did cite, however, that 3 days had passed since the last ejaculation before collection of the sample.

Poole (21) states in a critical assessment of this study that the findings of a lower percentage of motile sperm in the study group deserves additional consideration. The exclusion of data collected on 20 workers holding more than one job in the Glycerine Department was questioned, and a suggestion was made that data from this group should have been reported in a separate category.

Hine Incorporated (34) has summarized various parameters potentially affected adversely by occupational exposure to epichlorohydrin. Work history records of 680 Dow Chemical employees provided a study cohort of 507 individuals with a presumed exposure of at least 6 months to epichlorohydrin between 1955 and 1974. The cohort was divided into minimal and moderate exposure groups. No control data were reported. The average age of the 110 people in the moderate exposure group was 27 years 7 months upon entry into the work facility in December of 1966 (average calendar date of entry). The average age of the 397 people in the minimal exposure group was 30 years 11 months upon entry into the facility in November of 1965. Exposure data and histories were not provided. Both study groups were exposed to a wide variety of other unidentified industrial chemicals.

Variables examined in the study included: 1) employee reported contact exposures (eyes and skin); 2) illness episodes; 3) electrocardiogram; 4) X-ray examination; 5) basic urine analysis (casts, protein, red blood cells); 6) blood analyses (hematocrit, white blood cell count, partial white cell differentiation); 7) blood chemistry (lactate dehydrogenase, alkaline phosphatase, albumin/globulin ratio, SGOT, SGPT, BUN, and creatinine levels); and 8) pulmonary function tests.

Significant findings of the Hine Incorporated (34) study included an increase in the white blood cell count in the moderate exposure group. Values for both groups fell within normal ranges. One significant increase in the monocyte count of moderately exposed workers was obtained three years after entry into the epichlorohydrin facility ($P = 0.05$, T-test). Pulmonary function tests were similar in both study groups. There was an observed trend, however, of a greater frequency of reported respiratory-related illnesses among the moderate exposure group. Critical evaluation of the data is hampered by the lack of an appropriate comparison population.

Poole (21) has commented on the results of the Hine (34) study, stating that the trend toward increased white blood cell production in the moderate exposure group may be an important finding worth further consideration. This, plus an indication of increased respiratory illnesses among the same study group, may bear some relationship to the stimulation of infection, or direct chemical threat. Criticism was leveled at the lack of a rigid sampling protocol in the initial selection of the study and control populations and at subsequent medical evaluations.

E. Dermatological Effects

Further evidence implicating epichlorohydrin as a dermatologic irritant has been reported by Nater and Gooskens (7). The preplant soil fumigant D-D which contains chlorinated C3 hydrocarbons including 1,3-dichloropropene-1; 1,2-dichloropropane and epichlorohydrin has been reported to produce an erythematous and itching eruption on the extremities of three farm workers. Patch tests of pure D-D on one healthy volunteer showed an erythematous and infiltrated patch after 24 hours, and development of a tense blister after 48 hours. Patch

tests were performed on three volunteers using 10% concentrations of D-D in acetone developed erythematous and infiltrated responses, while a 1% concentration of D-D in five volunteers gave no reaction. In subsequent patch tests with a 1% epichlorohydrin solution, two of these subjects reacted negatively. The propene of the D-D mixture, rather than the epichlorohydrin, was thought to have caused the dermatological disorders noted in accidental and laboratory exposures.

IV. ANIMAL STUDIES

A. Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetics of epichlorohydrin in mammalian systems has only recently been explored in detail. Weigel et al. (48) have examined the tissue distribution and excretion of [1,3-^{14}C]-epichlorohydrin following an oral dose of 10 mg/kg given to 3 male and 3 female Charles River CD rats. Various body tissues were examined at 2, 8, 12, 24, 48, and 72 hours post-administration in an attempt to: (1) determine major routes of excretion; (2) observe any sex-related differences in distribution and excretion; and (3) correlate the known target organ effects of epichlorohydrin with the tissue distribution of the compound. In a separate study, the respiratory excretion of orally administered [^{14}C]-epichlorohydrin was determined by the measurement of $^{14}CO_2$ and unchanged [^{14}C]-epichlorohydrin in expired air at various intervals following exposures.

Interpretation of these results is complicated by the fact that recovery of administered radioactivity was low. Nevertheless, it was apparent that absorption of [^{14}C]-epichlorohydrin was rapid, with peak tissue concentrations being reached at 2 hours in males and 4 hours in females. In general, the site with the highest level of radioactivity was the kidney, followed in decreasing order by the liver, pancreas, adrenals, and spleen. The distribution of the ^{14}C label, 72 hours after a 10 mg/kg oral dose of epichlorohydrin, is summarized in Table 6.

The major route of excretion for [^{14}C]-epichlorohydrin-derived radioactivity was via the kidneys, accounting for 38-40% of the administered dose within 72 hours. Excretion of $^{14}CO_2$ in expired air accounted for 18-21%

Table 6. Distribution of Radioactive ^{14}C after Oral Administration of [^{14}C-]Epichlorohydrin (Weigel, et al., 48)

	µg/g Tissue or µg/ml Fluid		Percent of Dose	
	Male	Female	Male	Female
Lungs	1.29 ± 0.10	1.44 ± 0.08	0.06 ± 0.01	0.10 ± 0.01
Heart	1.15 ± 0.04	3.33 ± 1.73	0.04 ± *	0.14 ± 0.07
Liver	2.48 ± 0.18	3.40 ± 0.41	0.42 ± 0.03	2.04 ± 0.30
Spleen	1.30 ± 0.10	1.56 ± 0.08	0.04 ± 0.01	0.05 ± *
Pancreas	1.31 ± 0.03	1.52 ± 0.21	0.03 ± *	0.06 ± *
Andrenals	0.69 ± 0.04	4.81 ± 1.28	--	--
Kidneys	4.17 ± 0.43	8.68 ± 3.60	0.14 ± 0.05	0.85 ± 0.34
Testes/Ovaries	0.86 ± 0.10	1.39 ± 0.26	0.06 ± 0.01	0.01 ± *
Brain	0.71 ± 0.05	1.00 ± 0.05	0.06 ± *	0.10 ± *
Blood	1.14 ± 0.23	1.20 ± 0.03	0.61 ± 0.22	1.09 ± 0.03
Suprarenal Fat	0.96 ± 0.16	1.18 ± 0.13	0.60 ± 0.04	0.71 ± 0.08
Muscle	1.66 ± 0.16	1.14 ± 0.00	3.30 ± 0.24	4.60 ± 0.40
Skin	1.15 ± 0.07	0.94 ± 0.11	0.69 ± 0.07	1.61 ± 0.18
Stomach	Not Reported		*	0.43 ± 0.12
Sm. Intestine			0.12 ± 0.02	0.61 ± 0.03
Cecum & Lg Intestine			0.36 ± 0.10	0.33 ± 0.07
Urine			33.18 ± 0.78	35.49 ± 5.8
Feces			3.82 ± 0.62	3.59 ± 0.98

* less than 0.01%

of the administered radioactivity (24 hours), whereas fecal excretion accounted for less than 4% of the dose over a 72 hour period. The rapid appearance of large amounts of $^{14}CO_2$ in expired air suggested a rapid and extensive metabolism of [^{14}C]-epichlorohydrin by the rat.

Smith et al. (40) at Dow Chemical have studied the comparative pharmacokinetics of epichlorohydrin administered to rats orally or by inhalation. Single oral doses of 1 or 100 mg/kg [1,3-^{14}C]-epichlorohydrin were administered to two groups of four male Fischer 344 rats, or inhaled doses of 100 ppm vapor were administered for 6 hours to four male rats, and three male rats were exposed to 1 ppm levels for the same time interval. Orally treated rats (100 mg/kg) sacrificed 72 hours after treatment had retained 7-10% of the radioactivity in the body; 51% had been excreted in urine, and 38% had been expired in the air as $^{14}CO_2$.

The small percentage of the dose expired as intact epichlorohydrin and the large percentage of $^{14}CO_2$ eliminated in expired breath indicates an extensive and fairly rapid metabolism of epichlorohydrin. Administration of [3-^{14}C-]epichlorohydrin resulted in a similar percentage of the 100 mg/kg dose expired as $^{14}CO_2$, suggesting that the contributions of the 1- and 3- position carbons to $^{14}CO_2$ metabolite production are nearly equal. Pretreatment of animals with oral doses of 5, 25, or 50 ppm epichlorohydrin for 6 hours per day, 5 days per week, for 90 days had no statistical effect on the fate of labelled epichlorohydrin administered orally. Total recovery of the 1 or 100 mg/kg oral dose was 102.77 $\pm$ 0.94% and 104.25 $\pm$ 4.12%, respectively.

Excretion of radioactivity in the two vapor exposure groups (1 or 100 ppm epichlorohydrin) was similar. The percentages of total radioactivity

recovered in urine and expired air as $^{14}CO_2$ were 46% and 33% in the 1 ppm group, and 54% and 25% in the 100 ppm group, respectively. This elimination pattern was similar to that of orally treated rats. Total recovery of the inhaled 1 or 100 ppm dose was 104.25 $\pm$ 4.12% and 97.17 $\pm$ 4.58% respectively.

Patterns of excretion of total radioactivity are similar regardless of dose or route of administration. In the first 24 hours after oral dosing, 83% and 79% of the radioactivity was excreted in the 1 and 100 mg/kg dose groups, and 72% was excreted in 24 hours in both the 1 and 100 ppm inhaled dose groups. Excretion curves were biphasic. For the 1 and 100 ppm exposure levels, the rate of uptake was 15.48 and 1394 µg/hr and dose received was 0.37 and 33 mg/kg, respectively.

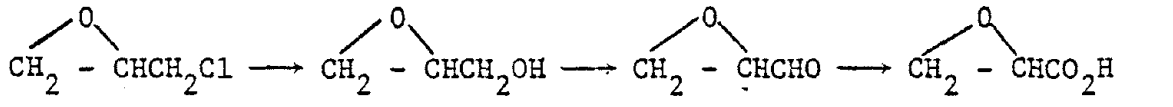
Blood samples taken six hours after inhalation of 1 or 100 ppm epichlorohydrin revealed 0.46 $\pm$ 0.19 and 27.8 $\pm$ 4.7 µg epichlorohydrin/ml plasma, respectively. Plasma levels of inhaled epichlorohydrin demonstrated increasing concentrations during exposure and a biphasic elimination after exposure. The half-life for the slow phase of elimination from the plasma was not given with great confidence, because of standard deviations greater than mean values, but were reported to be consistent with the 26-hour half-life obtained for elimination of radioactivity in the urine.

Urine samples were obtained from both exposure routes and analyzed for metabolites by liquid chromatography. A total of nine identifiable peaks were obtained. The major metabolite after oral administration was peak 7, ranging from 13% to 21% of the dose. Metabolite excretion following inhaled doses were similar to that following oral dosage except that no peak 6 was observed, and the major metabolite(s) for the 1 ppm dose was observed at peaks 4 and 5. Thus it was apparent that quantitative but not qualitative differences

occur in the patterns of metabolism of epichlorohydrin following oral and inhalation exposures. A study is underway at Dow Chemical to identify the major epichlorohydrin metabolites.

In summation, the pharmacokinetic profile of epichlorohydrin described by Smith et al. (40) indicates that the chemical was readily absorbed, metabolized and excreted. Regardless of dosage or route of administration, about half of the dose was excreted in the urine and consists of nine metabolites in orally treated animals and eight metabolites in inhalation dosed animals. Tissue distribution studies revealed little direct correlation between radioactivity levels and known target organs, except for high concentrations in the nasal turbinates after inhalation and in the stomach after oral dosage.

Possibilities for intermediates in epichlorohydrin metabolism have been suggested by Van Duuren (49) with the following pathway postulated:



Epichlorohydrin — Glycidol — Glycidaldehyde — Epoxy-propionic acid

Kozhemyakin et al. (50) have reported that prolonged inhalation of epichlorohydrin initially increased then decreased the cyclic-AMP content of the liver, brain, and heart of rats. Such changes in cyclic-AMP levels may reflect a primary adaptive mechanism to the toxicity of epichlorohydrin in individual cells and in the organism as a whole, or may reflect generalized stress.

B. Toxicity, Acute, Subacute and Chronic

Quast et al. (47) at Dow Chemical have conducted a 90-day inhalation study of epichlorohydrin in laboratory rodents. The subchronic effects of

inhaled epichlorohydrin at 0, 5, 25, and 50 ppm 6 hours per day, 5 days per week for 3 months were examined in Fisher 344 rats, Sprague-Dawley rats, and B6C3F1 mice. For each species and strain, twenty males and twenty females were exposed to epichlorohydrin vapor generated by metering the liquid at a controlled rate into a warmed vaporization flask (120°C). The vapor was then swept into an 8' x 8' x 8' (14.5 m^3) chamber in which the animals were exposed. Data were collected regarding changes in body weight, hematology, urinalysis, clinical chemistry, organ weights, gross pathology, and histopathology examination of tissues. The significant results of the study are summarized in Table 7.

Inhalation of 5 ppm epichlorohydrin did not result in any toxicologically significant effects in rats or mice as measured by the stated clinical parameters. Concentrations of 25 or 50 ppm epichlorohydrin produced consistent and apparent degenerative, inflammatory, and reactive histopathological changes in the epithelium of the nasal turbinates in all strains of rodents tested. Such lesions were reported to include: increased numbers of inflammatory cells, considerable degree of suppurative rhinitis, epithelial cells characterized by focal erosion, hyperplasia and metaplasia with a squamous appearance. Males appeared to be more adversely affected than females. Lesions in the nasal turbinates were most severe in the Sprague-Dawley rat, intermediate in the Fischer 344 rat, and least severe in the B6C3F1 mouse. Additional epichlorohydrin-induced effects included:

F-344, Male, Rats:
- minimal hepatocellular damage not resulting in degeneration or necrosis
- minimal degree of focal tubular nephrosis, dilated tubules, and swollen epithelial cells in the renal cortex
- increased cytoplasmic vacuolation of cells in the zone fasiculata of adrenal cortex (indicative of stress related to treatment)

F-344, Female, Rats:
- hepatic and renal histopathology similar to that of males

Table 7. Effects on the Nasal Turbinates of Rodents Exposed to Epichlorohydrin Vapors 6 hours per day, 5 days per week for a 90-day Interval (Quast, 47)

RATS

	Sprague-Dawley Concentration (ppm)								Fischer 344 Concentration (ppm)							
	Male				Female				Male				Female			
	0	5	25	50	0	5	25	50	0	5	25	50	0	5	25	50
30 Day Interim Necropsy:																
Number of tissues examined	5	-	--	5	5	-	--	5	5	-	--	5	5	-	--	5
Gross pathology - discoloration of nostril area	-	-	--	--	-	-	--	--	-	-	--	--	-	-	--	--
No microscopic lesions	-	-	--	--	-	-	--	--	-	-	--	--	-	-	--	--
Focal subepithelial mononuclear cell infiltrate	5	-	--	0	5	-	--	0	5	-	--	0	5	-	--	1
Changes in respiratory epithelial region: minimal	-	-	--	--	0	-	--	2	0	-	--	2	0	-	--	3
mild	-	-	--	--	-	-	--	--	-	-	--	--	-	-	--	--
moderate	0	-	--	3	0	-	--	2	0	-	--	2	0	-	--	1
severe	0	-	--	2	0	-	--	1	0	-	--	1	-	-	--	--
Changes in olfactory epithelial region	0	-	--	4	0	-	--	2	0	-	--	3	0	-	--	1
Suppurative inflammatory exudate or mucus in lumen	0	-	--	2	-	-	--	--	-	-	--	--	-	-	--	--
90 Day Terminal Necropsy:																
Number of tissues examined	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Gross pathology - discoloration of nostril area	-	-	--	--	-	-	--	--	-	-	--	--	-	-	--	--
No microscopic lesions	-	-	--	--	-	-	--	--	-	-	--	--	0	1	0	0
Focal subepithelial mononuclear cell infiltrate	10	10	1	0	10	10	--	--	10	10	1	0	10	9	2	0
Changes in respiratory epithelial region: minimal	0	0	9	0	0	0	9	0	0	0	7	0	0	0	7	0
mild	-	-	--	--	-	-	--	--	-	-	--	--	-	-	--	--
moderate	0	0	0	5	0	0	1	7	0	0	2	8	0	0	1	9
severe	0	0	0	5	0	0	0	3	0	0	0	2	0	0	0	1
Changes in olfactory epithelial region	0	0	1	10	0	0	0	10	0	0	0	9	0	0	0	6
Suppurative inflammatory exudate or mucus in lumen	0	0	0	5	0	0	0	7	0	0	0	1	-	-	--	--

Table 7. Effects on the Nasal Turbinates of Rodents Exposed to Epichlorohydrin Vapors 6 hours per day, 5 days per week for a 90-day Interval (Quast, 47) (Cont'd)

		MOUSE B6C3F1 Concentration (ppm)							
		Male				Female			
		0	5	25	50	0	5	25	50
30 Day Interim Necropsy:									
Number of tissues examined		5	-	--	5	5	-	--	5
Gross pathology - discoloration of nostril area		-	-	--	--	-	-	--	--
No microscopic lesions		1	-	--	0	0	-	--	2
Focal subepithelial mononuclear cell infiltrate		4	-	--	0	-	-	--	--
Changes in respiratory epithelial region:	minimal	0	-	--	4	0	-	--	5
	mild	-	-	--	--	-	-	--	--
	moderate	0	-	--	1	-	-	--	--
	severe	-	-	--	--	-	-	--	--
Changes in olfactory epithelial region		0	-	--	1	-	-	--	--
Suppurative inflammatory exudate or mucus in lumen		0	-	--	1	0	-	--	1
90 Day Terminal Necropsy:									
Number of tissues examined		10	9	8	10	9	9	10	9
Gross pathology - discoloration of nostril area		-	-	--	--	-	-	--	--
No microscopic lesions		8	8	0	0	-	-	--	--
Focal subepithelial mononuclear cell infiltrate		2	1	0	0	9	9	0	0
Changes in respiratory epithelial region:	minimal	0	0	8	10	-	-	10	9
	mild	-	-	--	--	-	-	--	--
	moderate	-	-	--	--	-	-	--	--
	severe	-	-	--	--	-	-	--	--
Changes in olfactory epithelial region		-	-	--	--	-	-	--	--
Suppurative inflammatory exudate or mucus in lumen		-	-	2	1	-	-	--	--

Sprague-Dawley, Male, Rats:	- minimal hepatocellular damage - kidneys of both interm and terminal kills displayed a moderate to severe focal tubular nephrosis with increased numbers of dilated renal tubules at 50 ppm - increased cytoplasmic vaculoation of cells in the zona fasiculata of adrenal cortex - epididymides containing normal sperm and increased numbers of nucleated cells and/or amorphous eosinophilic staining material
Sprague-Dawley, Female, Rats:	- kidney effects reported as minimal focal focal nephrosis, dilated renal tubules, and swollen epithelium
B6C3F1, Male, Mice:	- minimal treatment related hepatocellular effects at interm, but not terminal kill - no treatment related renal effects at either interm or terminal kill
B6C3F1, Female, Mice:	- effects similar to those reported in male mice

No toxicologically significant effects were reported at the 5 ppm dose. Both strains of rats and the mouse strain showed trends of decreased weight gains at 50 ppm.

Quast et al. (52) at Dow Chemical have further examined the effects of epichlorohydrin in a 12-day inhalation study in laboratory rodents. The acute toxicity of inhaled epichlorohydrin was examined at exposure levels of 0 and 100 ppm, six hours per day, five days per week, for a total of nine exposures. Test species included both sexes of Fischer 344 and Sprague-Dawley rats, and B6C3F1 mice. For each species and strain, five males and five females were exposed to epichlorohydrin vapor generated by metering the liquid at a controlled rate into a temperature regulated vaporization flask (120°C). The vapor was then introduced into the inlet of a 4.3 m^3 stainless steel and glass Rochester-type inhalation chamber. As the vapor was swept into the chamber, it was further diluted to the desired concentration by tempered

air. Observations on changes in body weight, hematology, urinalysis, clinical chemistry, organ weights, gross pathology, and histopathology were made. The significant results of the study are summarized in Table 8.

Inhalation of 100 ppm epichlorohydrin included clinical evidence of nasal irritation, decreased body weight gain, leucocytosis secondary to nasal inflammation in rats and mice, decreased specific gravity of urine in rats, and increased kidney weights in rats. As in the 90-day inhalation study, histopathological examination of tissues revealed detectable changes in the nasal turbinates with degeneration, inflammation, hyperplasia, and squamous metaplasia present to some degree in both exposed rats and mice. Effects noted in this group of exposed animals were more severe than those noted in the 90-day study. The effects on the nasal turbinates were characterized by suppurative rhinitis, epithelial erosion, and ulceration. No effect on lung tissue was detected.

Kidney toxicity in both strains of rats was observed, but not in the mice. Other epichlorohydrin-induced effects included: thymic atrophy and nondegenerative liver effects in rats and mice, and adrenal gland changes in male Sprague-Dawley rats attributed as a secondary effect to stress; and slight changes of the epididymides in both strains of rats (continuing normal sperm, increased numbers of nucleated cells, and/or amorphous eosinophilos staining material). A difference in toxic response was observed, with Sprague-Dawley rats being most susceptible to epichlorohydrin vapor and B6C3F1 mice being most resistant to the vapor; Fisher 344 rats were intermediate in toxic response.

Table 8. Effects on the Nasal Turbinates of Rodents Exposed to 0 or 100 ppm Epichlorohydrin 6 hours per day, 5 days per week over a 12-day Interval (Quast, 52)

	Rats								Mouse			
	Sprague-Dawley				Fischer 344				B6C3F1			
	Concentration (ppm)				Concentration (ppm)				Concentration (ppm)			
	Male		Female		Male		Female		Male		Female	
	0	100	0	100	0	100	0	100	0	100	0	100
Number of tissues examined	5	5	5	5	5	5	5	5	4	5	-	-
Gross pathology - discoloration of nostril area	0	5	0	5	0	5	0	5	-	-	-	-
No microscopic lesions	-	-	1	0	-	-	0	3	-	-	-	-
Focal subepithelial mononuclear cell infiltrate	5	0	4	0	5	0	2	0	3	0	-	-
Changes in respiratory epithelial region: minimal	-	-	-	-	-	-	-	-	0	2	-	-
mild	-	-	-	-	-	-	-	-	-	-	-	-
moderate	-	-	0	3	-	-	-	-	0	2	-	-
severe	0	5	0	2	0	5	0	5	0	1	-	-
Changes in olfactory epithelial region	0	5	0	5	0	5	0	5	0	5	-	-
Suppurative inflammatory exudate or mucus in lumen	0	5	0	5	0	5	0	5	0	3	-	-

The results of these studies conducted at Dow Chemical by Quast et al. (47,52) indicate that acute, short-term exposure to 100 ppm epichlorohydrin results in substantial alterations in the nasal turbinates of rats and mice, with kidney toxicity in rats, but not in mice. Repeated exposure to 100 ppm epichlorohydrin exceeds the maximum tolerated dose in these two species. Subchronic exposures of 25 and 50 ppm epichlorohydrin also resulted in significant cellular damage to the nasal epithelium, with lesser effects in rat kidneys. None of the strains exposed to 5 ppm displayed adverse effects in any parameters examined. These studies provided further evidence of the toxic effect on nasal tissue of inhalation of epichlorohydrin vapors.

Snyder (46), at New York University, exposed male Sprague-Dawley rats to concentrations of epichlorohydrin vapors ranging from 0 to 500 ppm in inhalation chambers. An LC_{50} estimate of 360 ppm was obtained. A sharp demarcation in lethal effects was observed between concentrations of 339 and 369 ppm, which suggested a critical ceiling exposure level. Necropsy reports indicated hemorrhage and edema of the lungs. Survivors examined 4 weeks post-exposure exhibited some evidence of reversibility in tissue damage.

Snyder (46) has performed additional inhalation studies in which male Sprague-Dawley rats were exposed to 100 ppm epichlorohydrin for 30 days. Although the treated animals had a reduced rate of survival, their rate of weight gain was greater than for controls. Substantial weight loss among control animals may indicate some deficiency in the design or implementation of the experiment. Rhinitis and squamous cell metaplasia were evident upon examination of the nasal mucosa. Chronic exposures to 30 ppm epichlorohydrin for more than 734 days or 10 ppm epichlorohydrin for more than 670 days resulted in increased survival of treated groups versus controls. Those rats

exposed to 30 ppm, however, exhibited significant weight losses. Mucosal changes in male Sprague-Dawley rats are summarized below:

		30 Exposures			Exposed for Life		
Concentration (ppm)		0	100	0	10	0	30
Number of observations		8	86	43	66	46	81
Observations:							
Bronchial:	% Hyperplasia	100	92	88	80	83	84
	% Squamous Metaplasia	13	5	2	2	2	4
Tracheal:	% Hyperplasia	25	22	19	21	13	26
	% Squamous Metaplasia	0	1	0	0	0	1
Laryngeal:	% Hyperplasia	0	17	19	11	22	14
	% Squamous Metaplasia	--	--	0	2	0	1
Nasal Cavity:	% Hyperplasia	--	--	--	--	--	--
	% Squamous Metaplasia	--	7	--	--	--	--
	% Squamous Carcinoma	--	9	--	--	--	--

Grigorowa et al. (53) demonstrated an increased toxic action of epichlorohydrin at 30 mg/m^3 in air upon heat stress at 35° and 50% relative humidity in rat inhalation studies. This work confirms previous reports of Grigorowa et al. (54) in which a 35° heat stress effected rats and mice in acute and subacute studies.

John et al. (51) at Dow Chemical has investigated the effects of inhaled epichlorohydrin on pregnant rats and rabbits. Animals were exposed to 0, 25, 50, or 100 ppm epichlorohydrin vapor for 7 hours per day during the 6th through 15th day (rats) or 6th through 18th day (rabbits) of gestation. One day after the last exposure, surviving animals were sacrificed and examined for gross pathological changes. Rats exposed to 50 or 100 ppm epichlorohydrin showed decreased maternal weight gain. Pathological examination revealed decreased intra-abdominal fat, decreased size of thymus, and increased occurrence of pale kidneys. No deaths were reported among exposed rats.

Pregnant rabbits appeared more susceptible than rats to epichlorohydrin. At the 100 ppm dose there were three maternal deaths; there was one maternal death at 50 ppm. Necropsy of those rabbits that died during exposure revealed severe pneumonia. Respiratory tract irritation and varying degrees of pneumonia or suppurative rhinitis were observed in most rabbits exposed to 50 or 100 ppm epichlorohydrin. At 25 ppm, one rabbit displayed evidence of focal pneumonia at necropsy.

Subsequent inhalation studies using 2.5 or 25 ppm epichlorohydrin were performed for seven hours per day during the 6th-15th or 6th-18 day of gestation in rats and rabbits, respectively. Tissue samples from nasal turbinates, trachea, and lungs were obtained at the termination of the experiment, but have yet to be examined pending completion of the teratologic evaluation. Female rat weight gains were significantly less ($p<0.05$) than control rats for the 25 ppm exposure group. Among the rabbits exposed to 25 ppm, one maternal death was reported, and attributed to an advanced pneumonic process. Weight gains in all rabbit groups were comparable to those of controls.

C. Allergic Reactivity

Thorgeirsson and Fregert (55) have investigated the allergenic response to the epoxy resins of diglycidylether-Bisphenol A type, to Bisphenol A-(2,2-bis(p-hydroxyphenyl)propane), and to epichlorohydrin in the guinea pig. The results showed that epichlorohydrin sensitized 60% of the animals, which classifies this compound as a moderate (grade III) sensitizer. The animals sensitized to epichlorohydrin or bisphenol A were not sensitive to epoxy resins; those animals sensitized to epoxy resins did not react to either epichlorohydrin or bisphenol A. These results suggest that neither the epichlorohydrin

component nor the bisphenol A component of the epoxy resins is responsible for the sensitization capacity of the resins. Rather, the authors suggested that the resin of MW 340, present in varying concentrations in all resin mixtures, was responsible. This conclusion was based on the fact that as the average molecular weight of the resins increased, the number of positive responses elicited decreased.

D. Developmental and Reproductive Effects

John et al. (51) at Dow Chemical have reported interim results on the effects of epichlorohydrin inhaled by pregnant mothers on the embryonic and fetal development in rats and rabbits. Adult female Sprague-Dawley rats (225-300g) were exposed to 0, 2.5, or 25 ppm epichlorohydrin during the 6th through the 15th days of gestation for seven hours per day. Adult New Zealand White rabbits (3.5 to 4.5 kg) were exposed to epichlorohydrin at the same concentrations during the 6th through the 18th day of gestation. The incidence of resorbed fetuses was not altered by exposure of pregnant rats or rabbits to 2.5 or 25 ppm epichlorohydrin. The results of the teratogenic study are not complete to date; however, preliminary findings indicate that epichlorohydrin is neither embryotoxic, fetotoxic, nor teratogenic in Sprague-Dawley rats or New Zealand White rabbits at maternal exposures levels of 2.5 or 25 ppm, for seven hours per day during the 6th through 15th or 6th through 18th days of gestation, respectively.

The effects of epichlorohydrin on pregnant Sprague-Dawley rats and New Zealand White rabbits is discussed elsewhere in the present report (Section IV.B.).

E. Mutagenicity and Cytogenetic Effects

The two literature reviews by Fishbein (35,36) provide a brief overview of the studies that have investigated the mutagenic, cytogenetic, and carcinogenic effects of epichlorohydrin in microbial or animal systems.

Without prior metabolism (i.e., metabolic activation), epichlorohydrin has been shown to cause reverse mutations in several microorganisms. The Ames Salmonella typhimurium assay has been the test most commonly used in the following studies. Information on the dose-response of epichlorohydrin exposure to mutagenesis has been provided by Elmore et al. (37) and Sram et al. (16). In Salmonella typhimurium strain TA100 (used to detect base-pair substitutions), Elmore et al. (37) found a dose-related increase in the number of revertant colonies per plate after a 48-hour incubation period. Plotted on log-log paper, this increase was linear over a concentration range of about 30 micromolar (which resulted in about 800 revertant colonies per plate). In the same study, epichlorohydrin did not inhibit the growth of a repair deficient strain of Bacillus subtilis.

Following the observation of a positive mutagenic effect of epichlorohydrin in Salmonella typhimurium spot tests over concentrations of 1-100%, Sram et al. (16) more closely examined a dose effect relationship in tester strains G56 and TA100 at doses ranging from 5.4×10^{-1} to 1.08×10^{-4} M epichlorohydrin. Controls were reported as a 0.0 M dose group. Dose effect relationships in both strains were demonstrated by the absolute number of revertants. Concentrations of 5.4×10^{-1} and 1.8×10^{-1} M were toxic in strains G56 and TA100, respectively. Base substitutions, not frame shift mutations, were induced. The mutagenicity of epichlorohydrin was further demonstrated in an ICR mouse host-mediated assay, where female mice were

injected subcutaneously or intramuscularly with 50 or 100 mg/kg epichlorohydrin. The 100 mg/kg dose produced a 5 fold increase, as determined in subsequent mutagenic analysis in S. typhimurium strain G46.

Loprieno (38) has reported that the results of a 1976 National Cancer Institute (NCI) bioassay that determined the carcinogenicity of trichloroethylene in mice but not in rats may have been affected by the use of epichlorohydrin as a stabilizer in the technical grade trichloroethylene used in the NCI carcinogenesis assay. Preliminary results of mutagenicity experiments reveal that pure trichloroethylene is not mutagenic, whereas trichloroethylene containing additives as used by the NCI at the same concentrations (including 0.09% epichlorohydrin) was mutagenic. Experiments have indicated that, on a quantitative basis, the mutagenicity of trichloroethylene that contains additives can be correlated to the amount of epichlorohydrin present in the sample. Publication of these findings is forthcoming.

Bridges (41) has reviewed the mutagenic properties of epichlorohydrin in microbial assays, and provides some cautionary statements concerning methodology of Ames-type assays. Various modifications in standard exposure techniques of cultures were examined. Relative sensitivities for detecting the mutagenic activity of epichlorohydrin in the Salmonella typhimurium G-46 *his* reversion system, as modified, are summarized below:

Method	Strain	Minimum detectable mutagenic concentration
Treat and Plate, 60 min[1]	G-46	1000 µg/ml medium
Treat and Plate, 60 min	TA100	<100 µg/ml agar
Agar incorporation (sealed)[2]	TA1535	0.2 µg/ml agar
Atmospheric exposure (sealed)[3]	TA1535	7 µg/l (≈0.2 µg/ml agar[4])
Atmospheric exposure (sealed)	TA100	3 µg/l air (≈0.1 µg/ml agar)
Atmospheric exposure (sealed, glass plates)	TA100	1.25 µg/l air (≈0.04 µg/ml agar)

[1] bacteria suspended in epichlorohydrin solution and plated on medium

[2] epichlorohydrin incorporated in agar, plates sealed in gas-tight jar

[3] epichlorohydrin externally added to plates, allowed to evaporate into gas-tight jar, bacteria spread on surface

[4] hypothetical concentration assuming total absorption by and even distribution throughout agar

Laumbach et al. (42) have examined the mutagenicity of epichlorohydrin and potential mode of action of this compound. Epichlorohydrin was shown to be directly mutagenic at a concentration of 4.746 nM/plate in tests using the Salmonella strain TA100. At this highest effective non-toxic concentration, an average of 2856 revertants per plate were obtained. Further experiments examined the effects of epichlorohydrin with and without metabolic activation on four different DNA repair deficient strains of B. subtilis. Epichlorohydrin at 0.997 molar concentration showed no inhibition of any of the strains; however, it was capable of moderate reactivity in the presence of a liver-derived metabolic activation system as indicated by a 3.0 mm zone of growth inhibition in the MC-1 B. subtilis strain. Because of its lower toxicity, epichlorohydrin exhibited a broader range of concentrations over which mutations were seen. Evidence was also obtained that higher levels of mutation were produced in cultures actively replicating DNA as opposed to

cultures arrested in DNA replication. The results also demonstrated that the mode of action for epichlorohydrin differed from that of vinyl chloride metabolites.

Biles et al. (22) have indicated that the mutagenic properties of technical grade dibromochloropropane in standard Ames tests for mutagenicity without metabolic activation may be attributed to the presence of small quantities of epichlorohydrin (1.5%) in the technical grade solution. Purification of dibromochloropropane by either distillation or dessication eliminated the mutagenic activity of the dibromochloropropane. The presence of epichlorohydrin in technical grade solutions accounted for all observed mutagenic activity. Upon metabolic activation, however, pure dibromochloropropane exhibited a strong mutagenic effect.

Kilian et al. (24) have found an elevation of mutagenic activity in S. typhimurium assay system using the urine of two Dow Chemical workers exposed after an industrial spill to a concentration of epichlorohydrin in excess of 25 ppm. In other tests, mutagenic activity in any of the 5 tester strains was obtained using the urine of workers exposed to 0.8 to 4.0 ppm epichlorohydrin, even in pooled and concentrated samples. No additional information was available in this meeting abstract.

In the dominant lethal assay, epichlorohydrin has yielded negative results. This assay system, however, is not highly sensitive to many mutagens. Sram et al. (16) administered epichlorohydrin to male ICR mice with the following results:

Dose (mg/kg)	Route	Effect
5, 10, 20	Single intraperitoneal	No observed effect in 8 weeks when compared to DMSO controls
20, 40	Single per oral	
1	5 repeated intraperitoneal	Decreased male fertility in 2nd week
4, 4, 16	5 repeated per oral	No observed effect

Epichlorohydrin, administered by either route, induced no changes characteristic of dominant lethality over the range of concentrations employed. Reduced fertility, however, was noted among males repeatedly treated with 1 mg/kg epichlorohydrin.

Sram et al. (16) have observed increased cytogenetic aberrations in bone marrow cells of ICR female mice following intraperitoneal injection of 5 to 100 mg/kg or oral administration of 5 to 100 mg/kg epichlorohydrin. Dose-effect relationships were obtained after single intraperitoneal injections ranging from 1 to 20 mg/kg, or 5 repeated injections of doses ranging from 5 to 20 mg/kg given during a 7 day period. At equal doses, epichlorohydrin administered intraperitoneally induced approximately twice as many chromosome aberrations as did epichlorohydrin administered perorally. The results are summarized in Table 9.

Dabney et al. (39) have performed a cytogenetic evaluation of bone marrow cells taken from rats exposed to epichlorohydrin for four weeks. Groups of 10 male and 10 female Fischer 344 rats were exposed to 0, 5, 25, or 50 ppm epichlorohydrin for 6 hours per day, 5 days per week for 4 weeks.

Table 9. Epichlorohydrin Induced Aberrations in Mouse Bone Marrow Cells (Sram et al., 16)

Dose mg/kg	h	Total number of cells	Abnormal cells %	Breaks % cells	B/C*	Gaps % cells	G/C*
Single i.p. application							
1	24	250	5.2	2.8	0.033	3.2	0.040
3	24	250	8.4	6.0	0.084	3.2	0.040
5	24	250	10.8	10.0	0.112	3.2	0.032
10	24	250	21.6	16.0	0.360	7.2	0.095
20	24	250	28.4	27.2	0.488	3.2	0.040
50	24	250	27.6	20.4	0.360	9.2	0.124
50	6	250	32.8	30.0	0.560	12.8	0.204
50	48	250	22.0	23.6	0.392	6.4	0.088
Repeated doses i.p. (interval between doses 24 h)							
5 x 10	6	250	35.2	20.8	0.350	12.8	0.170
Repeated i.p. doses (5 doses per 7 days)							
5 x 5	6	250	38.0	37.2	0.692	7.2	0.072
5 x 10	6	250	36.0	33.6	0.600	9.2	0.124
5 x 20	6	250	80.4	78.8	2.176	5.2	0.080
Control DMSO		500	4.0	0.6	0.006	3.8	0.038
Single p.o application							
5	24	250	6.0	4.8	0.064	2.0	0.020
20	24	250	24.0	23.2	0.372	3.2	0.036
40.	24	250	22.4	17.6	0.288	9.2	0.132
100	24	250	29.5	25.2	0.372	12.4	0.176
100	6	250	30.0	23.2	0.350	12.8	0.175
100	48	250	34.0	32.0	0.648	4.4	0.052
Repeated p.o. doses (interval between doses 24 h)							
5 x 20	6	250	30.4	26.0	0.450	12.8	0.185
Repeated p.o. doses (5 doses per 7 days)							
5 x 20	6	250	36.0	29.2	0.460	12.8	0.184
Control DMSO		500	4.0	0.6	0.006	3.8	0.038

*B/C, G/C -- Breaks, gaps per cell

The results from males suggested a trend towards a higher number of chromosomal aberrations in those animals exposed to 25 and 50 ppm. Such differences, however, were not significant at the 5% level by any of the statistical tests employed. Major findings are summarized below:

No. Animals	Dose	Cells Scored	Chromatid Breaks	Chromosome Breaks	Misc.	Abnormal Cells
Males:						
10	0	2000	2 (0.1%)	0	1 (0.05%)	3 (0.15%)
8	5	1600	1 (0.06%)	0	0	1 (0.06%)
10	25	2000	6 (0.3%)	0	0	6 (0.3%)
8	50	1600	5 (0.3%)	0	0	5 (0.3%)
Females:						
9	0	1800	8 (0.4%)	0	0	8 (0.4%)
5	50	1000	3 (0.3%)	1 (0.1%)	0	4 (0.4%)

Smith et al. (40) have demonstrated that about 50% of an inhaled dose of epichlorohydrin is absorbed in rodents. Therefore, the described exposure protocol employed by Dabney et al. (39) would correspond approximately to 12 and 24 mg/kg/day for the 25 and 50 ppm exposures, respectively.

The scoring of gaps in chromosome analyses by Sram (16) resulted in a higher background frequency. The Dabney et al. (39) study did not include the scoring of these abnormalities, and this should be considered in the evaluation of chromosomal aberrations attributed to exposure to epichlorohydrin. Other major differences between the Sram (16) study and Dabney et al. (39) study include: species used (mouse vs. rat), routes of exposure (oral or intraperitoneal vs. inhalation), and treatment regimens (single acute vs. continuous 6 hr/day, 5 days/week for 4 weeks).

F. Carcinogenicity

NIOSH (5) has recently recommended that epichlorohydrin be treated as if it were a potential human carcinogen, pending further evaluation of its

carcinogenic potential. This recommendation was based, in part, on reports of significant increases in nasal carcinomas seen in rat inhalation studies.

Long-term epichlorohydrin inhalation studies in male Sprague-Dawley rats have been performed at the New York University Institute of Environmental Medicine (43-46). The results indicated that exposure to epichlorohydrin caused a statistically significant occurrence of tumors to the nasal passages. Two different experimental designs were employed.

Nelson (44) reports that among 40 rats exposed to 100 ppm epichlorohydrin vapor for 6 hours per day, 5 days per week for 30 days, three animals died between 460 and 596 days from initial exposure. Pathological confirmation of squamous cell carcinoma of the nasal epithelium was noted in all three animals. One additional animal, which died at 391 days, had developed squamous cell papilloma of the nasal epithelium.

Synder (46) has reported the early findings of testing of epichlorohydrin vapors in rats at concentrations of 100, 30, and 10 ppm. An additional 100 animals have been exposed to 100 ppm epichlorohydrin for 6 hours per day, 5 days per week for 30 days. In this aspect of the ongoing study, four additional cancers of the nasal cavity were noted. Times to first tumor formation (462 and 495 days) were quite similar for the 40 animals initially tested and the 100 animals subsequently examined. Mucosal changes observed in rats exposed to 100 ppm epichlorohydrin were reported as (percent occurrence):

	100 ppm	Control
Number	86	8
Bronchial Hyperplasia	92	100
Bronchial Squamous Metaplasia	5	13
Tracheal Hyperplasia	22	25
Tracheal Squamous Metaplasia	1	0
Laryngeal Hyperplasia	17	0
Nasal Cavity Squamous Metaplasia	7	--
Nasal Cavity Carcinoma	9	--

In the 100 ppm exposure groups, survival was markedly decreased from that of controls. Exposed animals also demonstrated increased weight gains compared to controls.

Synder (46) reports preliminary findings among 200 rats in two groups exposed to 30 or 10 ppm epichlorohydrin. At the time of the report, the 30 ppm study had been in progress for 734 days (484 exposures), and the 10 ppm study had been in progress for 670 days (441 exposures). Survival for both exposure groups was better than for the 50 control animals (air). In the 30 ppm group, weight loss occurred but, in the 10 ppm group, weight changes paralleled those of controls. No respiratory tumors had been reported.

Nelson (45) communicated further results of the Synder study (47) to NIOSH and EPA. Of a total of 140 rats, 14 squamous cell carcinomas, one papilloma, and two unconfirmed swellings of nasal tissue were observed. The inhalation studies performed at New York University Medical Center have shown a statistically significant correlation between exposure to epichlorohydrin vapors and an increased incidence of nasal cancers at the $P<0.05$ level. No such tumors were observed in 50 control animals.

Life-time exposure tests, involving two groups of 100 rats each exposed to 30 or 10 ppm 6 hours per day, 5 days per week for the entire life of the animal, have produced two tumors among the animals in the 30 ppm group -- one a squamous cell carcinoma, the other a papilloma of the larynx. Neither the presence nor absence of tumors in the 10 ppm group was reported. Quast et al. (47) have reported a personal communication with Dr. Arthur Sellakumar of NYU indicating that, after two years of exposure, the 10 ppm group had not developed any tumors at any location.

Nelson (44,45) has commented on the rarity of spontaneous squamous cell carcinoma of the nasal epithelium in Sprague-Dawley rats. The incidence of such cancers in the NYU studies had led Nelson (45) to conclude that "[the] findings strongly suggest a potential risk to workers from exposure to epichlorohydrin."

These preliminary reports released by several investigators at NYU (43-46) have briefly described the results of ongoing studies in regard to the inhalation of epichlorohydrin vapors in rats. A detailed description of the experimental protocol is lacking, especially details concerning control data. Synder (46) has pointed out that survival of 50 control animals in the chronic life-time tests was reduced as compared to animals exposed to either 30 or 10 ppm epichlorohydrin. It was also reported that the occurrence of bronchial squamous metaplasia was elevated among controls, when compared to the test group receiving an inhaled dose of 100 ppm epichlorohydrin. The lack of further discussion of mortality and morbidity data among these various studies makes conclusive evaluation of the data difficult. Pending publication of the completed data, any interpretation of the results should consider the lack of reported details on control animals. The findings as reported to date, however, tend to demonstrate a carcinogenic risk associated with exposure to vapors of epichlorohydrin.

V. WORK PRACTICES AND ENGINEERING CONTROLS

NIOSH (5) has identified epichlorohydrin as a potential human carcinogen. In light of recent scientific findings, it has been recommended that engineering controls and work practices should reflect the toxic nature of this chemical. It is recommended that exposures to epichlorohydrin be limited to as few workers as possible and that exposure levels be minimized. Exposure monitoring should be diligently pursued to insure that exposures are reduced to the lowest technologically feasible limit. Reducing worker exposures may be undertaken by one or more of the following standard means:

(1) Substitution of alternative compounds with lower potential health risks

(2) Increased ventilation

(3) Employee isolation from highly contaminated areas

(4) Proper personal hygiene to include:
    personal protective equipment
    employee education

Bales (56) has conducted an industrial hygiene survey concerning the use and manufacture of epichlorohydrin. Various employee operations were examined in detail in two plants manufacturing and using epichlorohydrin, and in three plants using epichlorohydrin. The document states that the potential for respiratory and skin exposure exists at all of the plants examined. It was noted that safety precautions are generally utilized to prevent contact with the chemical; the dangers of the chemical were recognized by workers and acute hazards associated with exposure were appreciated by experienced personnel.

Housekeeping appeared to be a particular problem, especially in production plants where prevention of spills was difficult. The use of inappropriate solvents in cleaning epichlorohydrin spills presents a serious fire hazard

it itself, and may also induce some minor health problems. Most accidental exposure results from spillage or leaks. Prolonged contact results from contaminated clothing and/or shoes. Bales (57) recommends designing production facilities to reduce the likelihood of spills and leaks.

Bales (56) has made the following recommendations in establishing appropriate industrial hygiene practices:

(1) Maintenance of present industrial hygiene surveillance control measures,

(2) Design and installation of leak-resistant enclosed process systems,

(3) Use of vapor return lines and improved equipment in tank car filling areas,

(4) Proper use of respiratory protection and protective clothing,

(5) Instruction of employees as to the nature of the material and proper use of protective equipment,

(6) Reduction of allyl chloride concentrations (used in conjunction with epichlorohydrin),

(7) Discontinuation of the use of bulk solvents in an uncontrolled and indiscriminate manner in cleaning up spills

Additional information warning of the carcinogenic and mutagenic nature of epichlorohydrin should be placed on labels.

Nelson and Harder (57) have examined the service life of organic vapor respirator cartridges for several organic vapors and gases. Calculated 10% breakthrough time (Mecklenburg equation) for 1000 ppm epichlorohydrin at a flow rate of 53.3 1/min at 22°C and relative humidity of 50% was determined to be 145 minutes, deviating +32% from observed data for a North American Carbon Inc. G212 Coconut Type 1 organic vapor cartridge.

Walker (20) has made 21 suggested recommendations and revisions of the NIOSH (1) criteria document for epichlorohydrin. A majority of the recommendations call for changes in procedures for control, labeling and handling, and medical surveillance associated with exposures to epichlorohydrin.

VI. ANALYTICAL METHODS

Several studies have appeared in the recent literature on colorimetric analyses for epichlorohydrin quantitation. Two works discussed modification of a periodate oxidation procedure, which was reviewed in the criteria document (1). This procedure initiates with epichlorohydrin hydrolysis to yield the corresponding chloropropanediol. Subsequent reaction of the diol with periodate yields formaldehyde (HCHO), which is derivatized and quantified by colorimetry. Kolesnik et al. (58) described a new oxidant composition (KIO_4 plus H_2SO_4). Eminger and Vlacil (59) descibed a formaldehyde derivatization method with acetylacetone (2,4-pentane-dione), which utilizes absorbance at 412 nm. Urbanski (60) described a different method for colorimetric analysis; epichlorohydrin in chloroform-dioxane (3:2) is treated with 2,4-dinitrobenzenesulfonic acid. The epichlorohydrin derivative is quantified by its absorbance at 400 nm.

Although three papers have appeared that describe methods for measuring epichlorohydrin by gas chromatography, none of those methods significantly alters information already reviewed in the criteria document (1). Van Lierop (61) has described mass spectral quantitation that utilizes the epichlorohydrin fragment at m/e 49. The method was developed to analyze for epichlorohydrin that leaches from can coatings (polymers) into water. The epichlorohydrin is extracted from water with diethylether. Then, 5 µl of the etheral solution is injected into a Finnigan 4000 GC-MS equipped with a column of 0.2% Carbowax 1500 on Carbopack C at 100° (isothermal). Response was linear from 100 ppb epichlorohydrin and the detection limit was 6 ppb. Ermolaeva et al. (62) described a method for measuring epichlorohydrin in water that parallels the NIOSH recommended method for air analysis (1). Water is passed through a

bed of activated carbon (2.5-3.0 g) at 15-20 ml/min. The sorbed organics are desorbed with ethyl ether in a soxhlet extractor and the extract is concentrated. Analysis by gas chromatography utilizes a 7% FC-169 fluorosilicon grease column. Quantitation, which uses a flame-ionization detector, measures epichlorohydrin at concentrations of 10^{-6} to 10^{-7} percent with a relative error of ≈30%. Narizhnaya and coworkers (63) described a gas chromatographic method for determining epichlorohydrin in solvent systems. The method is not suitable, however, for trace analysis.

VII. INFORMATION GAPS

1. The recent epidemiology data base seems to conflict with the results of animal studies, which indicate a definite carcinogenic threat. These discrepancies should be resolved.

2. A reliable biological indicator of epichlorohydrin exposure has not been reported.

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Abstract (Limit: 200 words)

this report summarizes pertinent information about epichlorohydrin in the areas of human and animal toxicology, analytical and sampling methods, work practices, and engineering controls. published and unpublished research results appearing since preparation of the cr teria document were considered, but only those results that may affect the recommended stan are included. In addition, this report notes deficiencies in present knowledge concerning effects of exposure to epichlorohydrin and outlines research designed to fill thòse gaps.

This literature summary supplements but does not replace the extensive review in the NIOSH criteria document, which contained comprehensive surveys of all the literature available when the document was prepared, as well as recommendations for an occupational health standard. Although this report does not recommend exposure limits, work practices, or analytical methods, it provides information that will assist NIOSH in determining if there is sufficient new information to consider revising the recommended standard for epichlorohydrin.

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