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## Toxicologic Investigations of 1,2-Dibromo-3-Chloropropane

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The following is a joint report of two independent toxicologic investigations of 1,2-dibromo-3-chloropropane,  $\text{CH}_2\text{BrCHBrCH}_2\text{Cl}$ , conducted concurrently and independently by the Biochemical Research Laboratory of The Dow Chemical Company and the Department of Pharmacology and Experimental Therapeutics of the University of California School of Medicine in San Francisco.<sup>1</sup> This compound is sold primarily as a soil fumigant under the names of Fumazone<sup>2</sup> and Nemagon<sup>3</sup> and is very effective as a nematocide. It has the unique property of low toxicity for most plants after their roots are established and its relatively low vapor pressure and high density assure a long residence in the soil. This report summarizes the results of toxicologic studies on laboratory animals conducted in order to allow the assessment of toxic hazards associated with its manufacture, handling, and use. Included in this report are the results of studies to determine the effect of single application of the material to the eyes, single and repeated application to the skin, single and repeated oral administration, single and repeated inhalation of the vapors, and the measurement of sensory threshold values. Limited studies involving intramuscular injection and hormonal protection are also reported.

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<sup>2</sup> Trademark, The Dow Chemical Company.

<sup>3</sup> Trademark, Shell Chemical Corporation.



METHODS

1,2-Dibromo-3-chloropropane is a liquid that varies in color from amber to dark brown. It has a molecular weight of 236.4, a specific gravity of 2.09 at 20/4° C, a boiling point of 199° C at 760 mm Hg, and a vapor pressure of less than 1 mm Hg at 70° F. It has neither a flash nor a fire point.

Samples from four sources were used during the course of these studies. The purity of the test materials was reported to be between 95 and 98% 1,2-dibromo-3-chloropropane, the remainder consisting of halogenated C<sub>3</sub> compounds.

The techniques, equipment, and procedures used in these studies were essentially the same as those reported previously by the two laboratories and will not be discussed in detail here (Torkelson *et al.*, 1959, 1960; Dunlap *et al.*, 1958). Deviations from the published techniques which are considered to be of significance are noted in the summaries of results.

Laboratory A refers to the Department of Pharmacology and Experimental Therapeutics of the University of California School of Medicine in San Francisco. Laboratory B refers to the Biochemical Research Laboratory of The Dow Chemical Company, Midland, Michigan.

RESULTS

Single-Dose Oral Toxicity of 1,2-Dibromo-3-chloropropane

The results of oral intubation of 1,2-dibromo-3-chloropropane are given in Table 1.

TABLE 1  
SINGLE-DOSE ORAL TOXICITY OF 1,2-DIBROMO-3-CHLOROPROPANE GIVEN BY INTUBATION TO SEVERAL SPECIES<sup>a</sup>

Species	Sex	Laboratory A <sup>b</sup>	Laboratory B <sup>c</sup>
Rat	Male	0.17 (0.15-0.20) <sup>b</sup>	0.30 (0.23-0.37)
Mouse	Female	0.26	0.41 (0.27-0.62)
Guinea pig	Male	—	0.21 (0.15-0.30)
Rabbit	Male	—	0.18 (not calculable)
Chick	Unsorted	—	0.06 (0.04-0.10)

<sup>a</sup> Values: LD<sub>50</sub> (19/20 confidence limits) in grams per kilogram body weight.  
<sup>b</sup> Unpublished data, Stanford Research Institute.  
<sup>c</sup> Laboratory B noted that kidney degeneration was evident 2 weeks after treatment of rats with doses of 0.126 and 0.25 g/kg. Recovery was very slow.

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*Single Applications of 1,2-Dibromo-3-chloropropane in Rabbit Eyes*

When applied undiluted and as a 1% solution in propylene glycol, slight pain and irritation of the conjunctiva and iris were seen. No corneal irritation was noted. Irritation lasted for 1-2 days and healed completely. There was essentially no difference in response between an unwashed eye and one washed with water 30 seconds after exposure.

*Skin Irritation and Absorption Studies on Rabbits with 1,2-Dibromo-3-chloropropane*

A single application of 0.5 ml to the shaven back of each of 4 rabbits resulted in no irritation to the intact skin and only slight erythema of abraded areas. After a total of 20 repeated applications, only a slight crustiness was apparent. However, microscopic examination of the skin of one rabbit revealed much more severe injury. The superficial portion of the epidermis was fairly well preserved, but the entire dermis as well as the subcutaneous tissue showed extensive necrosis and was packed with polymorphonuclear leucocytes. Deeper areas were normal in appearance and no gross systemic effects or visceral abnormalities were found microscopically.

Ten repeated 24-hour applications of a 10% solution in dipropylene glycol, methyl ether, resulted only in slight hyperemia and scaliness on the uncovered ear or when bandaged on the shaven belly. The toxicity by skin absorption was studied by a modified Draize technique. An  $LD_{50}$  of 1.4 (0.80-2.5) g/kg was obtained when the material was applied undiluted for 24 hours. An  $LD_{50}$  of 0.5 (0.34-0.75) was obtained when the material was applied as a 10% solution in propylene glycol.

*Single Exposures of Rats to the Vapors of 1,2-Dibromo-3-chloropropane*

When studied in laboratory A, irritation of the eyes and respiratory passage was apparent at concentrations of 60 ppm and higher. Slight to moderate depression of the central nervous system was indicated by apathy, sluggishness, and ataxia, but complete hypnosis never occurred. Clouding of the cornea or lens was seen at the higher concentrations. All deaths occurred within 72 hours. The following  $LCT_{50}$  values (with the 19-20 confidence limits) were found: 1 hour, 368 ppm; 2 hours, 232 ppm (202-265); 4 hours, 154 ppm (135-177); and 8 hours, 103 ppm (90-118) (see Fig. 1).

The results of exposure of male rats to 1,2-dibromo-3-chloropropane in laboratory B are also shown in Fig. 1. The concentrations of 290 and

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190 ppm were determined by combustion analysis of the air during exposure. This was found necessary at these higher concentrations owing to loss of the chemical on the walls and piping of the exposure chamber. The concentrations of 100 and 50 ppm are based on the calculated values. Delayed deaths were common; recovery was very slow in all animals. The kidneys were particularly affected, permanent scarring being noted in animals exposed to concentrations as low as 50 ppm. It was noted

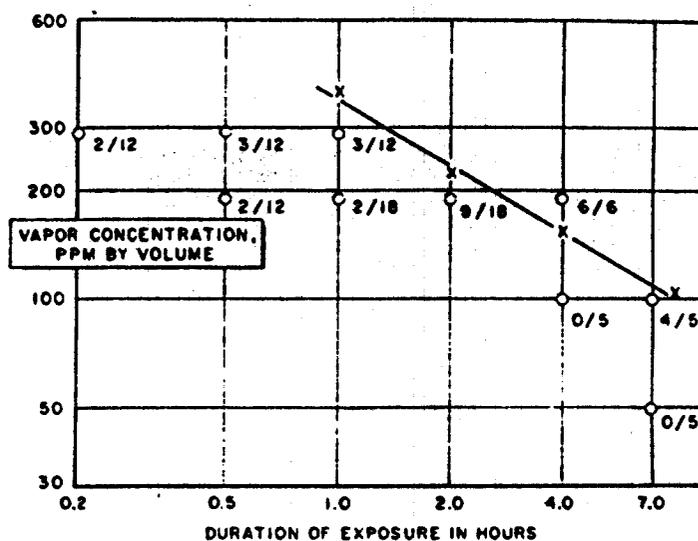


FIG. 1. The acute vapor toxicity of 1,2-dibromo-3-chloropropane for rats. The line connects the  $LCT_{50}$  values (X) reported by laboratory A. The circles represent the results of exposures made by laboratory B. The fraction by each circle represents the mortality resulting from that exposure.

that an unusually wide range of exposures caused mortality. This may have been due to secondary infections resulting from the weakened condition of the rats.

#### *Repeated Exposures of Rats to 1,2-Dibromo-3-chloropropane*

The results of repeated exposures conducted in both laboratories are summarized below and in Tables 2, 3, and 4. Exposures routinely were for 7 hours per day 5 days per week. The concentrations were determined by chemical analysis.

Thirteen of a group of 15 male rats died during fifteen exposures to

40 ppm. Survivors were emaciated and had nasal discharge. They died during the fifth week of exposure. Extensive changes were seen in the testes and kidneys. In another experiment, six exposures resulted in very poor health and loss of weight. Lung congestion, cloudy swelling of the livers, and nephritis were noted in all of a group of 5 male and 5 female rats. The testes of one male were atrophied.

Fifteen male rats exposed to 20 ppm gained very little weight. Ten died between the 35th and 48th exposures. Depilation was noted after 2 weeks and dulling of the corneas after 5 weeks. Gross lesions were seen in the lungs, intestinal mucosa, kidneys, and testes. The testes were usually atrophied (Table 2). Atelectasis and emphysema were seen in the lungs, as well as focal bronchopneumonia.

Thirteen of 15 male rats exposed to 10 ppm 50 times in 70 days survived the exposures but were adversely affected, as shown by lack of weight gain, depilation and dulling of the corneas. Pathology of this group was similar to that noted in more severe exposures. Liver and kidney:body weight ratios were elevated significantly (Table 2). The hemoglobin content of the blood and leucocyte counts were normal (Table 3).

In a larger experiment, 50-66 exposures to 12 ppm in 70-92 days were severely damaging to groups of 20 male and 20 female rats, 10 male and 10 female guinea pigs, 3 male and 3 female rabbits, and 2 female monkeys. In the male and female rats, 40 and 50% mortality occurred. Death of the rats was generally attributed to lung infections. The most striking observation at autopsy was severe atrophy and degeneration of the testes of all species. In the rats this was characterized by degenerative changes in the seminiferous tubules, an increase in Sertoli cells, reduction in the number of sperm cells, and development of abnormal forms of sperm cells.

Centrilobular congestion and dilation of the sinusoids of the liver occurred in male and female rats. Cloudy swelling of the epithelial lining of the proximal convoluted tubules, with a slight increase in interstitial tissue of the kidneys, occurred in the male rats. Since both sexes of rats showed evidence of pneumonia as well as increased lung weight, the increase in polymorphonuclear neutrophils (Table 3) was probably due to the infection.

Both monkeys developed severe secondary infections, probably as a result of a weakened condition produced by chemical exposures. The ex-

TABLE 2  
MORTALITY, WEIGHT GAIN AND ORGAN:BODY WEIGHT RATIOS OF ANIMALS GIVEN 50-66 7-HOUR EXPOSURES TO 1,2-DIBROMO-3-CHLOROPROPANE IN AIR

Species	Number of exposures	Vapor concentration (ppm)	Sex	Mortality ratio	Body weight change:	Organ weights (g/100g body wt.)					
					net gain original wt. × 100	Liver	Kidney	Lung	Spleen	Testes	Heart
Laboratory A											
Rat	50	0	M	0/15	108	3.57	0.63	0.63	—	1.02	—
	50	5	M	0/15	82 <sup>a</sup>	3.94 <sup>a</sup>	0.64	0.64	—	0.83	—
	50	10	M	2/15	15 <sup>a</sup>	4.06 <sup>a</sup>	0.83 <sup>a</sup>	0.75	—	0.53 <sup>a</sup>	—
	50	20	M	10/15	39 <sup>a</sup>	4.74 <sup>a</sup>	0.84 <sup>a</sup>	0.84	—	0.52 <sup>a</sup>	—
	15	40	M	13/15							
Laboratory B											
Rabbit	0	0	M	0/3	—	2.43	0.46	0.41	0.02	0.19	0.20
	0	0	F	0/3	—		Controls were not sacrificed				
	66	12	M	0/3	—	2.53	0.56	0.41	0.04	0.04 <sup>a</sup>	0.20
	66	12	F	0/3	—	3.07	0.48	0.39	0.04	—	0.18
Guinea pig	0	0	M	0/10	120	3.09	0.62	0.59	0.10	0.56	0.31
	0	0	F	1/10	116	3.65	0.67	0.66	0.13	—	0.28
	66	12	M	0/10	122	3.48	0.64	0.58	0.20	0.37 <sup>a</sup>	0.32
	66	12	F	0/10	113	3.45	0.68	0.69	0.14	—	0.21
Rat	0	0	M	0/20	150	3.42	0.72	0.55	0.36	0.94	0.33
	0	0	F	0/20	85	3.42	0.74	0.72	0.43	—	0.42
	50	12	M	8/20	76 <sup>a</sup>	3.67	0.83 <sup>a</sup>	1.01 <sup>a</sup>	0.36	0.99 <sup>b</sup>	0.40 <sup>a</sup>
	50	12	F	10/20	40 <sup>a</sup>	3.62	0.86 <sup>a</sup>	1.24 <sup>a</sup>	0.40	—	0.44

<sup>a</sup> Significantly different from control value ( $P < 0.05$ ).

<sup>b</sup> Not statistically significant owing to decreased body weight. Marked pathological changes occurred.

TABLE 3  
AVERAGE HEMATOLOGIC VALUES OF ANIMALS GIVEN 50-66 7-HOUR EXPOSURES TO 1,2-DIBROMO-3-CHLOROPROPANE IN AIR

Species	Number of exposures	Vapor concentration ( $\mu\text{g}/\text{m}^3$ )	Sex	Number of animals	WBC count	Hemoglobin (g/100 ml)	Packed cell volume	Differential count (%)			
								Neutrophils	Lymphocytes	Mono-cytes	Eosino-philes
Laboratory A											
Rat	50	0	M	15	5323	14.9	—	—	—	—	—
		5	M	15	7100	16.8	—	—	—	—	—
		10	M	13	6000	16.0	—	—	—	—	—
		20	M	5	3390 <sup>a</sup>	14.3	—	—	—	—	—
Laboratory B:											
Monkey	50, 60	12	F	2	140 <sup>b</sup>	12.0	14.0	—	—	—	—
Rabbit	63	0	M	2	—	—	43.0	—	—	—	—
		12	M	2	—	—	41.0	—	—	—	—
Guinea pig	66	0	M	3	—	—	44.0	—	—	—	—
		0	F	3	—	—	46.0	—	—	—	—
		12	M	2	—	—	45.0	—	—	—	—
		12	F	3	—	—	43.0	—	—	—	—
Rat	50	0	M	2	12880	14.2	48.0	15.5	82.0	2.5	0
		0	F	2	8820	13.6	42.5	15.5	81.5	3.0	0
		12	M	4	10560	14.4	47.6	29.2 <sup>a</sup>	68.8	2.0	0
		12	F	4	12480	14.6	46.6	51.0 <sup>a</sup>	48.2	0.8	0

<sup>a</sup> Significantly different from control value ( $P < 0.05$ ).

<sup>b</sup> The monkeys were moribund and extremely emaciated. Aplastic anemia was evident.

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tensive hematologic changes seen at autopsy (Table 3) were considered to be due to the secondary infections, and not a primary result of the chemical exposures. Guinea pigs were essentially unaffected except for a decrease in testicular weight and slight cloudy swelling and fatty changes in the livers. Rabbits showed only a slightly significant decrease in body weight besides the decreased testicular weight.

Sodium bromide levels of the blood serum were elevated, but not to levels of physiological significance (see Table 4). Analyses were made by the gold chloride method of Wuth (1927).

TABLE 4  
AVERAGE SERUM BROMIDE LEVELS AFTER 50-66 7-HOUR EXPOSURES TO 12 PPM OF  
1,2-DIBROMO-3-CHLOROPROPANE IN AIR<sup>a</sup>

Species	Number of exposures	Sex	NaBr (mg, 100 ml serum) <sup>b</sup>	
			Control	Exposed
Rat	50	M	0.0	10.9
		F	0.0	12.8
Guinea pig	66	M	2.3	8.2
		F	7.8	6.7
Rabbit	66	M	3.1	9.7

<sup>a</sup> Laboratory B.

<sup>b</sup> Analyses were made by the gold chloride method of Wuth (1927).

In a group of 15 male rats exposed to 5 ppm 50 times in 70 days, no deaths occurred but weight gain was significantly low (Table 2). No dulling of the cornea was noted, but two rats kept their eyes closed. At autopsy the changes noted were focal and limited to the epithelium of the testes, the collecting tubules of the kidneys, and the bronchioles. An increase in liver:body weight ratio was found. Although not statistically significant because of large internal variation within the group, the testicular weight was reduced to 50% of normal in half of the rats. The hemoglobin content and leucocyte count of the blood were normal.

#### *Repeated Intramuscular Injection—12 Days, Laboratory A*

Because the inhalation experiments indicated the possibility of changes in cellular elements of the bone marrow and upon the circulating blood cells, the effects of 1,2-dibromo-3-chloropropane were further studied by repeated intramuscular injection of male rats. Five rats (the same stock as that used in the acute studies) were given 25 mg/kg intra-

muscularly daily for 3 days; this series was repeated after a 4-day rest period. Blood samples were taken from the proximal end of the tail vein on the first, fourth, eighth, and twelfth days. After the final sample had been taken, the rats were weighed and then killed to secure the femoral bone marrow. A control group of 5 rats was given similar treatment, except that propylene glycol was substituted for the test compound.

Each blood sample was smeared on slides, and four sets of counts were made of the leucocytes; the average count was then determined. Similarly, the bone marrow smears were counted in four areas each, and the total number of nucleated cells was determined. There was no attempt to differentiate between the types of nucleated cells found.

The mean leucocyte count of the control animals rose from 10 to 14 thousand per cubic millimeter during the experimental period (Table 5).

TABLE 5  
AVERAGE HEMATOLOGIC VALUES AND BODY WEIGHTS OF GROUPS OF 5 MALE RATS RECEIVING TWO SERIES OF 3 CONSECUTIVE DAILY INTRAMUSCULAR INJECTIONS<sup>a</sup>

Group	Days on Experiment:	0	4	8	12
	Number of Injections:	0	3	4	6
Propylene glycol-injected controls	Average body weight (g)	141	145	157	152
	Leucocyte count/mm <sup>3</sup>	10,000	10,900	12,400	14,200
	Nucleated cells in femoral smear/mm <sup>3</sup>	—	—	—	170 × 10 <sup>6</sup>
Propylene glycol plus 25 mg/kg 1,2-dibromo-3-chloropropane	Average body weight (g)	171	—	177	185
	Leucocyte count/mm <sup>3</sup>	7,200	7,700	12,400	11,500
	Nucleated cells in femoral smear/mm <sup>3</sup>	—	—	—	140 × 10 <sup>6</sup>

<sup>a</sup> Data from laboratory A.

During the first series of injections, the counts of the experimental rats remained in the neighborhood of 7.5 thousand; however, the second pair of counts showed a rise to almost double this number, as did the control counts. The mean marrow-cell count of the experimental animals was  $140 \times 10^6$ , not below normal. Hence, hematologic changes noted in the vapor exposure studies may be considered to be the results of infections secondary to the chemical exposure.

#### Chronic Ingestion—90 Days, Laboratory A

The sample was the same as that used in the acute toxicity studies, and the rats were obtained from the same source. A population of approxi-

mately 200 male and female rats were maintained in the laboratory for 2 weeks prior to the start of the the experiment. Those which did not gain weight normally were discarded, and 94 rats of each sex were randomized from the remainder into five groups of 14 and one group of 10 (control). At the start of the experiment, the males ranged in weight from 105 to 145 g and the females from 80 to 125 g. They were housed in wire-bottom cages in pairs, the sexes separated.

The basic diet was powdered maintenance feed; fresh mixes with 1,2-dibromo-3-chloropropane were prepared every 2 weeks. Some loss of the compound through evaporation was anticipated, but more frequent mixing was impractical. Two samples of the mixed feed were chemically analyzed during the course of the experiment, and the loss was found to be negligible. The feed containers were metabolism jars with mesh tops and were refilled thrice weekly.

The original dietary levels were 0, 5, 20, 50, 150, and 450 ppm by weight. Subsequent to the completion of this first experiment, 14 males and 14 females were fed a diet containing 1350 ppm.

The rats were weighed individually each week and examined daily for general health and activity. At the end of 90 days all survivors were decapitated under light ether anesthesia. Liver:body weight and kidney:body weight ratios and percentage body weight gains were compared by the *t* test; significance was set arbitrarily at  $P < 0.05$ . Histologic examinations were made by the pathologist without information concerning the group to which the specimens belonged. Each slide was read twice, having been resubmitted under a code number, and the two sets of tissues were mounted and stained by two different laboratories (not laboratory B).

Male and female rats fed diets containing 150 ppm or less of 1,2-dibromo-3-chloropropane remained in excellent health throughout the 90 days, except for one male rat in the 50-ppm group which died of bronchopneumonia during the ninth week. Rats fed 450 ppm showed only vague and minor signs of physiological disturbance. Their coats were not as sleek as those of the other groups. At 1350 ppm there was moderate unthriftiness, inanition, muscular weakness, and decreased activity, but no signs referable to the central nervous system. Four males and two females fed 1350 ppm died during the course of the experiment. Their livers, kidneys, and stomachs were slightly discolored, and there was some hypotonicity and edema of the intestines. Acid hematin was found in the stomach and in the intestines.

Weight gain was significantly retarded at 150 ppm in the females and at 450 and 1350 ppm in both sexes. Rats fed 450 and 1350 ppm consumed less feed and wasted more than those fed lower concentrations. The livers of females fed 450 and 1350 ppm and the kidneys of those fed 20 ppm and higher were significantly heavier than those of the controls, but there were no significant differences among the males except in the 1350-ppm group.

Only a few, minimal changes were visible on gross examination at necropsy. Microscopically, minimal cloudy swelling was seen in the livers of five males scattered throughout the experimental groups. Scattered groups of females had mild cloudy swelling of the kidneys; however, this change appeared at all dose levels including the control and was seen only on one set of slides, and not on slides prepared by the other laboratory. Therefore, it is believed to be referable to the processing of the tissues or to scattered unrelated infection. There were no other abnormalities of interest, and no degenerative changes.

These data are summarized in Table 6.

TABLE 6  
MEAN ORGAN:BODY WEIGHT RATIOS AND WEIGHT GAIN OF MALE AND FEMALE RATS MAINTAINED FOR 90 DAYS ON DIETS CONTAINING 1,2-DIBROMO-3-CHLOROPROPANE<sup>b</sup>

Concentration in diet (ppm)	Average organ weight (g/100 g body wt.)				Body weight change: net gain		Mortality ratio	
	Liver		Kidney		× 100 original wt.			
	M	F	M	F	M	F	M	F
0	3.45	3.39	0.64	0.63	165	98	0/10	0/10
5	3.43	3.16	0.61	0.65	161	96	0/14	0/14
20	3.36	3.44	0.64	0.71 <sup>a</sup>	157	92	0/14	0/14
50	3.32	3.33	0.62	0.71 <sup>a</sup>	162	93	1/14	0/14
150	3.62	3.42	0.63	0.74 <sup>a</sup>	153	75 <sup>a</sup>	0/14	0/14
450	3.47	3.82 <sup>a</sup>	0.58	0.71 <sup>a</sup>	119 <sup>a</sup>	60 <sup>a</sup>	0/14	0/14
1350	4.70 <sup>a</sup>	5.50 <sup>a</sup>	0.98 <sup>a</sup>	1.13 <sup>a</sup>	95 <sup>a</sup>	-25 <sup>a</sup>	4/14	2/14

<sup>a</sup> Significantly different from control value ( $P < 0.05$ ).

<sup>b</sup> Data from laboratory A.

#### *Hormonal Effect on Male Rats, Laboratory B*

Because of the severe effect in the testes of animals exposed to vapors of 1,2-dibromo-3-chloropropane, an attempt was made to determine whether intramuscular injection of hormones might have a beneficial

effect. The hormones used were testosterone, cortisone, and adrenocorticotrophic hormone (ACTH).

The rats were divided into eight groups evenly matched as to age and weight and treated as shown in Table 7. No protective action against body weight loss or testicular atrophy was demonstrated either grossly or

TABLE 7  
MEAN FINAL BODY WEIGHT AND TESTICULAR WEIGHT OF MALE RATS GIVEN INTRAMUSCULAR INJECTIONS OF HORMONES AND EXPOSED FOR 36 7-HOUR PERIODS IN 51 DAYS TO 12.5 PPM OF 1,2-DIBROMO-3-CHLOROPROPANE\*

Treatment		Number of rats	Mean body weight (g)	Mean testes weight	
Injection	Exposure			Grams	g/100 g body weight
Not injected	Exposed	8	192	2.30	1.25
	Unexposed	10	274	2.98	1.10
Testosterone, 0.1 mg at 2-3- day intervals	Exposed	9	228	1.05 <sup>b</sup>	0.46 <sup>b</sup>
	Unexposed	4	274	2.30 <sup>c</sup>	0.84 <sup>c</sup>
Cortisone, 1.0 mg at 2-3- day intervals	Exposed	8	199	2.33	1.21
	Unexposed	5	262	3.03	1.18
ACTH <sup>d</sup> , 0.1 unit at 2-3- day intervals	Exposed	8	184	2.35	1.31 <sup>b</sup>
	Unexposed	5	289	3.10	1.07

\* Laboratory B.

<sup>b</sup> Significantly different from uninjected exposed controls ( $P < 0.05$ ).

<sup>c</sup> Significantly different from uninjected unexposed controls ( $P < 0.05$ ).

<sup>d</sup> ACTH = adrenocorticotrophic hormone.

microscopically. However, testosterone itself appeared to cause a decrease in testicular weight in the unexposed animals and enhanced the decrease in the exposed animals.

#### Human Sensory Threshold, Laboratory A

An analyzed concentration of 1.7 ppm was maintained in a chamber (130 cubic feet) long enough to permit two human volunteers to test the atmosphere for odors of the chemical. Both reported a definite, not unpleasant odor. This finding was confirmed in laboratory B.

#### DISCUSSION

There is good general agreement between the results of the two independent investigations. Slight differences are to be expected; they are

usually the result of differences in technique and do not materially affect the conclusions relative to the hazards of handling this material. The apparent discrepancy between the LD<sub>50</sub> values for skin absorption is probably the result of the increased penetration when the material is applied in a propylene glycol solution and is not an unusual finding.

1,2-Dibromo-3-chloropropane caused general manifestations of toxicity, including poor growth, predisposition toward secondary infection, and a specific histological alteration in the testes in male rats receiving 50 repeated 7-hour exposures to 5 ppm. This was the lowest concentration studied. The effect upon testes resulting from exposure to higher concentrations was particularly severe, resulting in atrophy, degenerative changes, reduction of spermatogenesis, and the development of abnormal sperm.

The results of the dietary feeding studies suggested a sex difference in susceptibility. In female rats an increase in kidney weight resulted from a diet containing 20 ppm, retarded weight gain from 150 ppm, and increased liver weight from 450 ppm. The males did not show retarded growth until the dietary concentration reached 450 ppm, and the other signs appeared only at 1350 ppm. Histologic changes were considered insignificant in all groups, in contrast to the results of repeated inhalation.

No consistent effects were observed on the circulating blood or on the marrow. Although bromide could be found in the blood, it was of no physiological significance and was not useful in demonstrating excessive exposure.

Since minimal effects were still apparent in animals exposed repeatedly to 5 ppm in air, it is suggested that the concentration of 1,2-dibromo-3-chloropropane be kept below 1 ppm if repeated, prolonged exposure is likely. If this precaution is observed, there would seem to be little likelihood of injury. Until further experience is obtained, close observation of the health of people exposed to this compound should be maintained.

#### SUGGESTED PRECAUTIONS FOR SAFE HANDLING

The following precautions for safe handling are made on the basis of industrial experience, previous data, and the data presented herein.

##### *Inhalation*

The concentration of 1,2-dibromo-3-chloropropane in the air of work areas should be maintained below 1 ppm. Concentrations of 1,2-dibromo-3-chloropropane in this range do not have warning properties, but may be

detected by odor by some people. Suitable analytical methods rather than sensory perception should be depended upon for control.

Concentrations that are likely to be injurious in short periods of time will be painful to the eyes and nose. The warning odor *must not* be ignored.

To prevent ill effects from inhalation, 1,2-dibromo-3-chloropropane should be handled in closed systems or with respiratory protection unless adequate ventilation is provided. If spills should occur, the area should be evacuated at once and re-entered only after thorough aeration. If it is necessary to re-enter before aeration is completed, adequate respiratory protection, such as a full-face gas mask equipped with an organic vapor (black) canister, an air- or oxygen-supplied respirator, or a self-contained breathing apparatus, should be worn.

#### *Eye Contact*

The eyes should be protected from liquid 1,2-dibromo-3-chloropropane. If the likelihood of contact exists, a minimum of side shield safety glasses should be worn to prevent getting the material in the eyes.

#### *Skin Contact*

Protective clothing impermeable to the material should be worn if the likelihood of skin contact exists. Standard rubber or neoprene gloves do not offer adequate protection and should not be relied upon for keeping the material off the skin. Compar rubber and polyethylene appear to offer the most practical protection. 1,2-Dibromo-3-chloropropane should never be allowed to remain on the skin. Clothing and shoes should not be allowed to become contaminated with the material, and if they do, they should be promptly removed and not worn again until completely free of the material.

#### *Ingestion*

All containers should be properly labeled so that ingestion due to mistaken identity cannot occur. Keep out of the reach of children and animals. Hands should be washed with soap and water before eating or smoking.

#### SUMMARY AND CONCLUSIONS

1,2-Dibromo-3-chloropropane was found to be but slightly irritating to the skin upon short single exposure. However, repeated applications caused necrosis of the dermis, the epidermis remaining fairly well preserved. The compound can be ab-

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sorbed through the skin in toxic amounts. It is not likely to cause permanent injury to the eyes on single application but probably will be painful and cause transient irritation. The compound was found to be moderate to high in toxicity from single respiratory exposure and highly toxic on repeated exposure, producing damage even at 5 ppm, the lowest level studied. Excessive exposure to the vapors resulted in damage to the liver, kidneys, and various tissues including sperm cells and seminiferous tubules, dermis, bronchioles, renal collecting tubules, lens and cornea, and alimentary canal. Injury caused by this compound was noted to be particularly slow in healing. Precautions for safe handling of this compound are discussed.

## REFERENCES

- DUNLAP, M. K., KODAMA, J. K., WELLINGTON, J. S., ANDERSON, H. H., and HINE, C. H. The toxicity of allyl alcohol. *A.M.A. Arch. Indust. Health* 18, 303-311.
- TORKELSON, T. R., WOLF, M. A., OYEN, F., and ROWL, V. K. (1959). Vapor toxicity of allyl chloride as determined on laboratory animals. *Am. Ind. Hyg. Assoc. J.* 20, 217-223.
- TORKELSON, T. R., OYEN, F., and ROWL, V. K. (1960). The toxicity of bromochloromethane (methylene chlorobromide) as determined on laboratory animals. *Am. Ind. Hyg. Assoc. J.* 21, 275-286.
- WUTE, O. (1927). Rational bromide treatment; new methods for its control. *J. Am. Med. Assoc.* 88, 2013-2017.