1,2-DIBROMO-3-CHLOROPROPANE

Data were last reviewed in IARC (1979) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

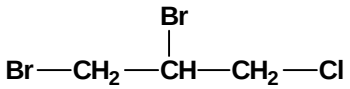
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 96-12-8
Chem. Abstr. Name: 1,2-Dibromo-3-chloropropane
IUPAC Systematic Name: 1,2-Dibromo-3-chloropropane
Synonyms: DBCP; dibromochloropropane

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_3H_5Br_2Cl$ Relative molecular mass: 236.33

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Brown liquid with a pungent odour (Budavari, 1996)
(*b*) *Boiling-point*: 196°C (Lide, 1997)
(*c*) *Melting-point:* 6°C (Agency for Toxic Substances and Disease Registry, 1992)
(*d*) *Solubility*: Slightly soluble in water; miscible with oils, dichloropropane and isopropanol (Budavari, 1996)
(*e*) *Vapour pressure*: 106 Pa at 21°C; relative vapour density (air = 1), 2.09 at 14°C (Verschueren, 1996; United States National Library of Medicine, 1997)
(*f*) *Flash point*: 76.6°C, open cup (Agency for Toxic Substances and Disease Registry, 1992)
(*g*) *Conversion factor:* $mg/m^3 = 9.7 \times ppm$

1.2 Production and use

Estimates of annual production of 1,2-dibromo-3-chloropropane in the United States during 1974–75 ranged from eight to nine thousand tonnes. Commercial production is believed to have ceased worldwide (Agency for Toxic Substances and Disease Registry, 1992).

1,2-Dibromo-3-chloropropane has been used as a pesticide, nematocide and soil fumigant (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

No current data on numbers of exposed workers were available to the Working Group. Occupational exposures to 1,2-dibromo-3-chloropropane have occurred during its production and use.

1.3.2 *Environmental occurrence*

Use of 1,2-dibromo-3-chloropropane as a pesticide, soil fumigant and a nematocide resulted in the direct release of this compound to the environment. Its production and use as an intermediate in organic synthesis also may have resulted in its release to the environment through various waste streams. It has been detected at low levels in ambient and urban air, groundwater, drinking-water and soil samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The United States Occupational Safety and Health Administration (OSHA) (1996) has established 0.0001 mg/m^3 as the permissible exposure limit for occupational exposures to 1,2-dibromo-3-chloropropane in workplace air.

The World Health Organization has established an international drinking-water guideline for 1,2-dibromo-3-chloropropane of 1 μg/L (WHO, 1993).

2. Studies of Cancer in Humans

2.1 Cohort studies

A group of some 3500 workers classified as having had exposure to several brominated chemicals, including 1,2-dibromo-3-chloropropane, was studied in four facilities in the United States. Among the 1034 workers ever exposed to 1,2-dibromo-3-chloropropane, nine respiratory cancers were observed compared with 5.0 expected; of these seven were due to lung cancer (4.8 expected) (IARC, 1987).

Olsen *et al*. (1995) studied mortality among a cohort of 548 male 1,2-dibromo-3-chloropropane production workers. This was an update of an earlier study performed by Hearn *et al*. (1984). The workers were identified on the basis of employment records or self-declaration of exposure to 1,2-dibromo-3-chloropropane and were followed from 1957 through 1989. A total of 68 deaths were identified (standardized mortality ratio (SMR), 0.8) and overall cancer mortality was similar to expected (SMR, 1.0; n = 19), based on mortality of white men in the United States. There were seven lung cancer deaths compared with 7.1 expected (SMR, 1.0; 95% confidence interval (CI), 0.4–2.0), but an excess of lung cancer (SMR, 3.4; 95% CI, 0.7–9.6), based on three cases, was

observed among the 81 workers categorized as having been directly exposed for one or more years. Exposure levels were not reported.

Brown (1992) conducted a cohort mortality study of workers employed at four pesticide manufacturing plants. The 1158 workers employed at Plant 3 of the study, which produced aldrin and dieldrin, were also potentially exposed to 1,2-dibromo-3-chloropropane produced at the plant between 1975 and 1976. The cohort included all white males employed for six or more months before 1964 with follow-up through 1987. Although overall cancer mortality at Plant 3 was not elevated (SMR, 0.9; 95% CI, 0.7–1.1; $n = 72$), an excess of liver and biliary tract cancer was observed (SMR, 3.9; 95% CI, 1.3–9.2; 5 observed). All of the deaths occurred at least 15 years after first employment (SMR, 4.9), but no association was observed with duration of employment. The SMR for lung cancer was 0.7 (95% CI, 0.4–1.0). Levels of exposure were not reported. Amoateng-Adjepong *et al*. (1995) reported the results of an update of the same cohort with three additional years of follow-up. No new association was reported.

Wesseling *et al*. (1996) reported the results of a retrospective cohort study of cancer incidence among banana plantation workers in Costa Rica where 1,2-dibromo-3-chloropropane was used as a soil fumigant. Other pesticides were also used. The cohort consisted of 29 565 men and 4892 women on the payrolls of banana companies, as reported to the social security system, at any time between 1972 and 1979. Follow-up was performed using national cancer registry records from 1981 to 1992. Duration of employment during the period 1972–79 period was also available. Overall cancer rates for both men and women were less than expected based on national rates. The standardized incidence ratio (SIR) for lung cancer among men was 1.1 (95% CI, 0.7–1.5; 30 cases). Excesses were observed for melanoma (SIR, 2.0; 95% CI, 0.9–3.6; 10 cases) and penile cancer (SIR, 1.5; 95% CI, 0.6–3.2; 6 cases) among men and for cervical cancer (SIR, 1.8; 95% CI, 1.2–2.4; 36 cases) and leukaemia (SIR, 2.7; 95% CI, 0.9–6.4; 5 cases) among women. Excesses, based on small numbers, were observed among men employed for three or more years for lung (SIR, 1.7; 95% CI, 0.9–2.9; 12 cases), melanoma (SIR, 3.2; 95% CI, 0.9–3.3; 4 cases), penile (SIR, 2.0; 95% CI, 0.3–1.4; 2 cases) and brain cancer (SIR, 2.3; 95% CI, 0.9–5.0; 6 cases), and among women for leukaemia (SIR, 5.6; 95% CI, 0.7–20.3; 2 cases). It was not possible to link cancer incidence results to specific exposures and exposure levels were not reported.

2.2 Case–control studies

Wong *et al*. (1989) performed both ecological analyses and case–control studies to examine the relationship between gastric cancer and leukaemia and 1,2-dibromo-3-chloropropane contamination of drinking-water in Fresno County, California (United States). The concentration of 1,2-dibromo-3-chloropropane was estimated based on water systems by census tract (Whorton *et al.*, 1987). The studies were precipitated by public concern over 1,2-dibromo-3-chloropropane contamination of drinking-water wells in various farming areas of the county, and an analysis by the Department of Health suggesting elevated stomach cancer and leukaemia mortality in the county. In the ecological

analyses, no correlation between gastric cancer and leukaemia rates from 1960 to 1983 and estimated 1,2-dibromo-3-chloropropane concentration in water based on census tracts and residence at time of death was observed after adjustment for age, sex and race. For the case–control analyses, fatal gastric cancer (n = 263) and leukaemia (n = 259) cases were identified and 203 and 225 were included in the study. Three or four controls for each case, matched on age, race and year, were randomly chosen from among other Fresno County deaths. Attempts were made through the use of mailed questionnaires and residential directories to identify the residence of cases and controls at time of death and at one year and ten years before death. No association was observed with estimated 1,2-dibromo-3-chloropropane levels based on census tract. Nonsignificant increased risks of both gastric cancer (odds ratio, 3.1; 95% CI, 1.0–9.8) and leukaemia (odds ratio, 3.9; 95% CI, 0.7–21.5) were associated with estimated 1,2-dibromo-3-chloropropane concentrations above 1.0 ppb (μg/L) based on the water system data alone, 10 years before death in multiple logistic regression analysis.

3. Studies of Cancer in Experimental Animals

1,2-Dibromo-3-chloropropane was tested in one experiment in mice and one in rats by oral administration. It produced squamous-cell carcinomas of the forestomach in animals of both species and adenocarcinomas of the mammary gland in female rats (IARC, 1979).

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F_1 mice, four to five weeks of age, were administered 1,2-dibromo-3-chloropropane (96% pure), containing small amounts of epichlorohydrin (0.6%) and 1,2-dibromoethane (0.07%), by whole-body inhalation at concentrations of 0 (control), 0.6 or 3 ppm [0, 4 or 29 mg/m^3] for 6 h per day on five days per week for 76–103 weeks. Survival was significantly decreased in all treated groups. 1,2-Dibromo-3-chloropropane increased the incidence of lung and nasal tumours, as shown in Table 1 (United States National Toxicology Program, 1982).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344 rats, five to six weeks of age, were administered 1,2-dibromo-3-chloropropane (96% pure), containing small amounts of epichlorohydrin (0.6%) and 1,2-dibromoethane (0.07%), by whole-body inhalation at concentrations of 0 (control), 0.6 or 3 ppm [0, 4 or 29 mg/m^3] for 6 h per day on five days per week for 84–103 weeks. Survival of high-dose rats was reduced and all surviving rats were killed at week 84. Increased incidence of tumours of the nasal cavity and of the tongue in both sexes and of the pharynx in females was observed, as shown in Table 2 (United States National Toxicology Program, 1982).

Table 1. Primary tumour incidence in B6C3F$_1$ mice exposed by inhalation to 1,2-dibromo-3-chloropropane

Site/tumour	Animals with tumours					
	Males			Females		
	Chamber control	0.6 ppm	3.0 ppm	Chamber control	0.6 ppm	3.0 ppm
Lung/bronchus/bronchiole[a,b]	0/41	3/40	11/45[c]	4/49	12/48[d]	18/47[c]
Nasal cavity[a,e]	0/45	1/42	18/48[c]	0/50	11/50[c]	38/50[c]

From United States National Toxicology Program (1982)
[a] Dose-related trends ($p < 0.001$)
[b] Papillary adenoma or carcinoma, squamous-cell carcinoma, alveolar/bronchiolar adenoma or carcinoma
[c] Greater than controls ($p < 0.001$)
[d] Greater than controls ($p < 0.05$)
[e] Carcinoma, squamous-cell papilloma or carcinoma, adenocarcinoma, adenomatous polyp, unspecified malignant neoplasm

Table 2. Primary tumour incidence in Fischer 344 rats exposed by inhalation to 1,2-dibromo-3-chloropropane

Site/tumour	Animals with tumours					
	Males			Females		
	Chamber control	0.6 ppm	3.0 ppm	Chamber control	0.6 ppm	3.0 ppm
Adrenal gland cortical adenoma	1/49	6/49	3/48	0/50	7/50[a]	5/48[b]
Mammary gland fibroadenoma	0/50	0/50	0/49	4/50	13/50[b]	4/50
Nasal cavity and turbinates[c,d]	0/50	32/50[e]	39/49[e]	1/50	21/50[e]	42/50[e]
Pharynx squamous-cell papilloma or carcinoma[f]	0/50	3/50	1/49	0/50	0/50	6/50[b]
Tongue squamous-cell papilloma or carcinoma[c]	0/50	1/50	11/49[e]	0/50	4/50	9/50[e]

From United States National Toxicology Program (1982)
[a] Greater than controls ($p < 0.01$)
[b] Greater than controls ($p < 0.05$)
[c] Dose-related trends ($p < 0.001$)
[d] Carcinoma, squamous-cell papilloma or carcinoma, adenoma, adenocarcinoma, adenomatous polyp and carcinosarcoma
[e] Greater than controls ($p < 0.001$)
[f] Dose-related trend, females ($p < 0.001$)

3.2 Other systems

Fish: A group of 100 *Danio rerio* (H) fish of both sexes, 10–12 months old, were exposed to 20 µg/L water 1,2-dibromo-3-chloropropane (purity, > 95%) (equivalent to 0.2 $LD_{50/30}$) added to the water every two weeks for eight weeks, after which the fish were kept in fresh water without 1,2-dibromo-3-chloropropane for 12 more weeks. A negative control group of 40 fish received dimethyl sulfoxide (DMSO) at a concentration of 90 mg/L water [exact test regimen not reported]. A positive-control group of 100 fish received *N*-nitrosodimethylamine (NDMA) at a concentration of 50 mg/L water [exact test regimen not reported]. Twenty-one fish in the 1,2-dibromo-3-chloropropane group, 39 fish in the DMSO group and 51 in the NDMA group lived for 20 weeks, the minimum duration required for the appearance of the first liver tumour. The incidences of liver tumours were 9/21, 0/39 and 22/51 for the 1,2-dibromo-3-chloropropane, DMSO and NDMA groups, respectively. The nine liver tumours in the 1,2-dibromo-3-chloropropane group consisted of seven hepatocellular carcinomas and two cholangiocarcinomas (Belitsky *et al*., 1994).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Several purified human GST forms readily metabolized 1,2-dibromo-3-chloropropane in descending order of activity from GST A1-2 > A2-2 ≈ A1-1 > M1a-1a > M3-3 ≈ P1-1 (Søderlund *et al*., 1995).

The in-vitro metabolic activation of 1,2-dibromo-3-chloropropane, measured as radio-label covalently bound to macromolecules, is three-fold faster in rat testicular cells than in human testicular cells (Bjørge *et al*., 1996a).

4.1.2 *Experimental systems*

In rats, 1,2-dibromo-3-chloropropane is rapidly absorbed after oral administration in water (T_{max}, 0.20 h after 1 mg/kg bw); corn oil as a vehicle delays absorption (T_{max}, 1.56 h), but does not affect bioavailability. 1,2-Dibromo-3-chloropropane is distributed and eliminated biexponentially, mainly as metabolites with a half-life of 2–3 h. There is no saturation of absorption, distribution or elimination up to 10 mg/kg bw (Gingell *et al*., 1987).

Metabolism of 1,2-dibromo-3-chloropropane proceeds via oxidation by cytochrome P450 enzyme(s) and conjugation with glutathione (Omichinski *et al*., 1987, 1988; Simula *et al*., 1993; Weber *et al*., 1995). The metabolism is measurable as formation of water-soluble metabolites (mainly several *N*-acetylcysteine conjugates in bile and urine) and metabolites covalently bound to macromolecules (Kato *et al*., 1979; Dohn *et al*., 1988; Pearson *et al*., 1990a,b; Weber *et al*., 1995). Metabolism to water-soluble products

occurs in isolated rat liver, kidney and testicular cells, the rate of formation decreasing in this order (Søderlund *et al.*, 1995). Various testicular cell types isolated from rats show differences in their rates of activation of 1,2-dibromo-3-chloropropane to metabolites that bind to macromolecules (Bjørge *et al.*, 1995). Rats and guinea-pigs seem to be more sensitive than Syrian hamsters and mice to testicular damage because of a higher ability to activate 1,2-dibromo-3-chloropropane to DNA-damaging species (Låg *et al.*, 1989a).

1,2-Dibromo-3-chloropropane is metabolically activated into several products (see Figure 1; Pearson *et al.*, 1990a,b). The principal adduct in rat and mouse tissues after in-vivo administration was *S*-[1-(hydroxymethyl)-2-(*N*7-guanyl)-ethyl]glutathione, which was also detected in several rat tissues, both target and non-target, after in-vivo administration of 1,2,3-trichloropropane, a structurally related chemical (La *et al.*, 1995). Several studies suggest that cytochrome P450-mediated metabolism is of minor importance for organ toxicity (Omichinski *et al.*, 1987; Låg *et al.*, 1989b; Søderlund *et al.*, 1995).

4.1.3 *Comparison of human and rodent data*

The rate of metabolic activation of 1,2-dibromo-3-chloropropane in human testicular cells is abour one-third that of rat cells. No other data are available for comparison. Nevertheless, since P450 isoenzymes and several GST enzymes are rather similar in terms of substrate selectivity between humans and rats, it is expected that human tissues should be capable of activating 1,2-dibromo-3-chloropropane via both P450- and GST-mediated pathways.

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

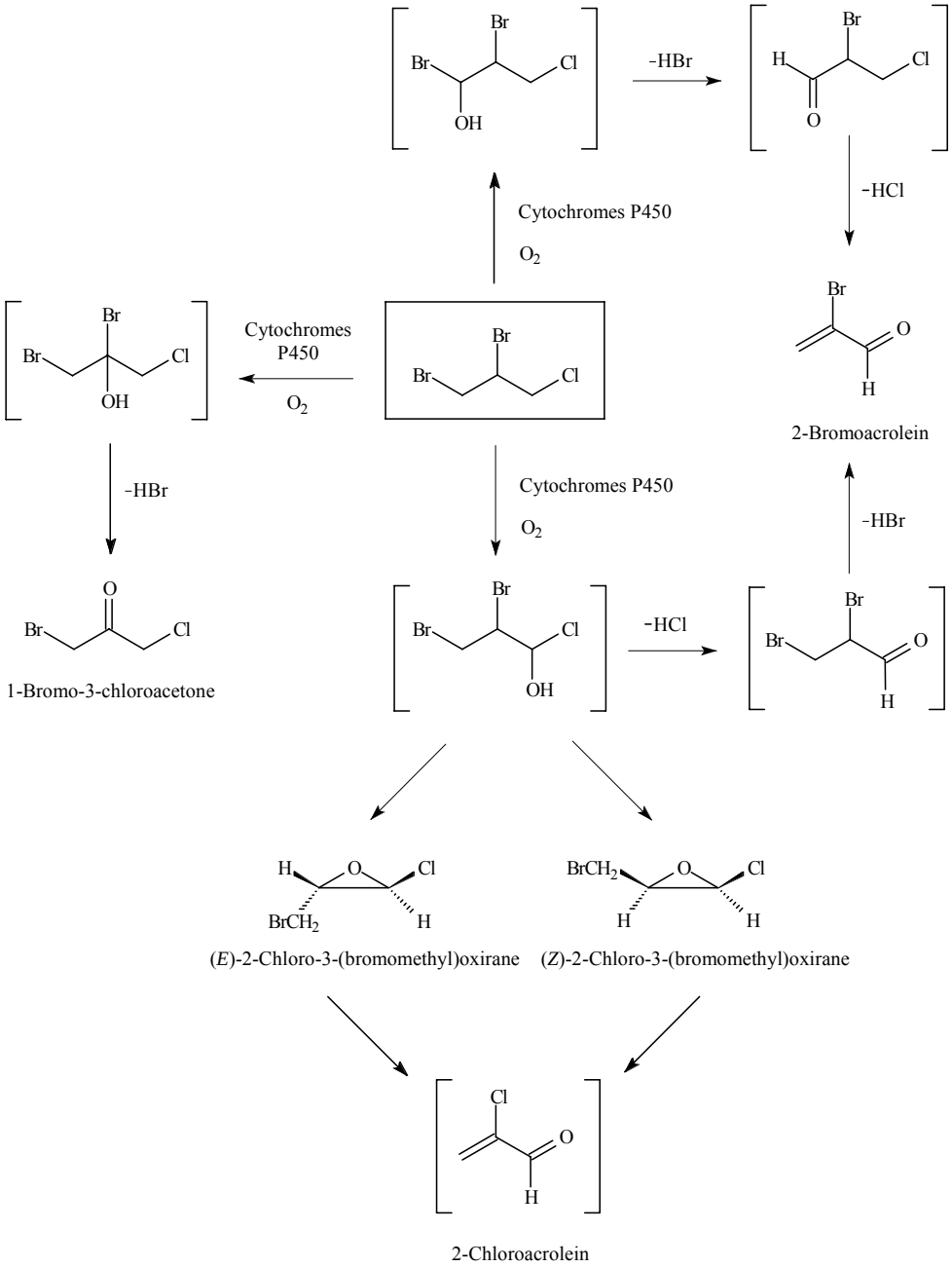
4.2.2 *Experimental systems*

Groups of rats were exposed by inhalation to 1,2-dibromo-3-chloropropane for 7 h per day on five days per week for 10 weeks. The testis was the primary target for toxicity, atrophy being observed at concentrations of 10 ppm [97 mg/m^3] and above (Torkelson *et al.*, 1961).

Extensive renal necrosis and elevated plasma urea and creatinine levels were noted in male Mol:WIST rats 48 h after intraperitoneal administration of 170–340 mmol/kg bw [40.2–80.3 mg/kg bw] 1,2-dibromo-3-chloropropane (Søderlund *et al.*, 1990). In the same study, significantly less damage was found in male Bom:NMRI mice and male Mol:DH guinea-pigs after higher doses (up to 680 mmol/kg bw [160.7 mg/kg bw]). No nephrotoxicity was detected in male Lak:LVG/SYR Syrian hamsters at doses of 170–680 mmol/kg bw. In guinea-pigs and mice, the high doses (> 510 mmol/kg bw) of 1,2-dibromo-3-chloropropane resulted in central nervous system depression and death in a number of animals.

Male Fischer 344 rats dosed by gavage with 29 mg/kg bw 1,2-dibromo-3-chloropropane on five days per week for two weeks developed hyperkeratosis and hyperplasia of

Figure 1. Proposed oxidative metabolism pathway for 1,2-dibromo-3-chloro-propane



From Pearson *et al.* (1990a)
Bracketed structures have not been isolated.

the forestomach. A lower dose 915 mg/kg bw had no significant effect (Ghanayem *et al*., 1986).

Necrosis and atrophy of the olfactory epithelium in the nasal cavity resulted from inhalation exposure to 5 and 25 ppm [50 and 240 mg/m^3] 1,2-dibromo-3-chloropropane for 6 h per day on five days per week for 13 weeks in both male and female Fischer 344 rats and B6C3F$_1$ mice. At 1 ppm, respiratory changes were observed that included cytomegaly, focal hyperplasia and, to lesser extents, squamous metaplasia and loss of cilia (Reznik *et al*., 1980).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

Several studies have found decreased sperm counts, altered sperm morphology and decreased spermatogenic activity in workers occupationally exposed to 1,2-dibromo-3-chloropropane, with the drop in sperm count correlating with the length of exposure, but other studies have failed to find any effect (reviewed by Whorton & Foliart, 1988). Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were increased from 7.9 and 14.0 ImU/mL to 29.0 and 21.7 ImU/mL, respectively, in highly exposed men (physicians' estimation of exposure) (Olsen *et al*., 1990). The hormonal effects of 1,2-dibromo-3-chloropropane appear to be reversible after 12–16 months of cessation of exposure in many cases of oligospermia and in some cases of azospermia (Whorton & Milby, 1981; Eaton *et al*., 1986; Olsen *et al*., 1990; Potashnik & Porath, 1995). It has been reported that the use of 1,2-dibromo-3-chloropropane in the 1970s caused the sterilization of approximately 1500 banana workers (approximately 20–25% of the workforce) in Costa Rica (Thrupp, 1991).

4.3.2 *Experimental systems*

Groups of male Sprague-Dawley rats were given subcutaneous injections of 1,2-dibromo-3-chloropropane at 7, 30 or 90 days of age either once (50 mg/kg bw) or repeatedly (20 mg/kg bw once a week for three weeks) (Sod-Moriah *et al*., 1990). Results were similar following either single or repeated injections. In the 7- and 90-day-old rats, the weights of the testes, epididymis, prostate and seminal glands were significantly reduced. Additionally, the plasma FSH and LH levels were significantly increased. Little change in reproductive organs or hormone levels was observed in the 30-day-old rats. No changes in the weights of non-reproductive organs were observed.

In a study on the effects of fetal exposure to 1,2-dibromo-3-chloropropane, pregnant Sprague-Dawley rats were treated with 25 mg/kg bw 1,2-dibromo-3-chloropropane for two, four or six days beginning on gestational days 18.5, 16.5 or 14.5, respectively (Warren *et al*., 1988). A decrease in testicular weights of 75% to > 90% was found in adult males treated *in utero* that related to the duration of treatment. Many of the adults treated with 1,2-dibromo-3-chloropropane on gestational days 16.5–18.5 lacked seminiferous tubules. In-utero treatment for six days reduced intratesticular testosterone level by 50%.

Adult males treated *in utero* on gestational days 16.5–18.5 also exhibited increased feminine behaviour and decreased masculine behaviour.

There are species differences in sensitivity to 1,2-dibromo-3-chloropropane-mediated testicular damage. Låg *et al*. (1989a) found marked necrosis and atrophy of seminiferous epithelium in male Mol:WIST rats and male Mol:DH guinea-pigs 10 days after a single injection of 340 mmol/kg bw [80 mg/kg bw] 1,2-dibromo-3-chloropropane and no significant difference in the seminiferous epithelium of male Bom:NMRI mice or Lak:LVG/SYR Syrian hamsters. Indicators of testicular DNA damage correlated with the relative susceptibilities of the different species to 1,2-dibromo-3-chloropropane-induced testicular damage.

In a continuous breeding study, exposure of Swiss CD-1 mice to 100 mg/kg bw 1,2-dibromo-3-chloropropane was found to produce a minor decline in the number of litters per F_0 pair and reduced epididymis and prostate weights in the F_1 mice. These effects were considered to be relatively minor compared with the effects seen in rats (Lamb *et al*., 1997).

In female Wistar rats, subcutaneous administration of 1,2-dibromo-3-chloropropane during gestation did not affect oogenesis (Shaked *et al*., 1988).

4.4 Genetic and related effects

The genetic toxicology of 1,2-dibromo-3-chloropropane has been reviewed (Teramoto & Shirasu, 1988).

4.4.1 *Humans*

Kapp *et al.* (1979) reported the presence of Y-chromosomal non-disjunction in 1,2-dibromo-3-chloropropane-exposed workers using a quinacrine-staining technique. [There was no indication of the level of exposure to 1,2-dibromo-3-chloropropane or whether other exposures were present.] The frequency of sperm with two spots (indicating two Y chromosomes) was 1.2% (range, 0.8–1.8%) in 15 controls and 3.8% (range, 2.0–5.3%) in 18 samples from exposed men.

In preparations from human organ transplant donors, no DNA single-strand breaks were detected in testicular germ cells treated with 1,2-dibromo-3-chloropropane up to 300 μM, which is in contrast to rat cells, in which breaks were increased after exposure to 3 μM (Bjørge *et al*., 1996a,b).

4.4.2 *Experimental systems* (see Table 3 for references)

1,2-Dibromo-3-chloropropane is mutagenic to *Salmonella typhimurium* strains, particularly strain TA100 and usually in the presence of an exogenous metabolic activation system. The occasional significant responses in strain TA1535 in the absence of such an activation system are probably due to the presence of epichlorohydrin (see this volume), which was used as a stabilizer (Biles *et al*., 1978). The mutagenicity of 1,2-dibromo-3-chloropropane in *S. typhimurium* TA100 was greatly increased if the strain was modified to express the human glutathione-*S*-transferase genes A1-1 or P1-1. It

Table 3. Genetic and related effects of 1,2-dibromo-3-chloropropane

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAF, *Salmonella typhimurium* BA13, forward mutation (Ara test)	–	+	3.9	Roldán-Arjona, *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	50	Blum & Ames (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	30	Stolzenberg & Hine (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	1180	Stolzenberg & Hine (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	50	Moriya *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	236	Miller *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	2.5	McKee *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	2.5	Ratpan & Plaumann (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	24	Holme *et al.* (1989)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	1.2	Låg *et al.* (1994)
SA0, *Salmonella typhimurium* TA100 expressing human GST A1-1 or P1-1, reverse mutation	–	+	1.25	Simula *et al.* (1993)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	(+)	10.5	Prival *et al.* (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	25	Biles *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	0.5	McKee *et al.* (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	0.5	Ratpan & Plaumann (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	100	McKee *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	50	Ratpan & Plaumann (1988)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	10450	Rosenkranz (1975)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	525	Prival *et al.* (1977)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	+	50	McKee *et al.* (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	100	McKee *et al.* (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	50	Ratpan & Plaumann (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	1180	Stolzenberg & Hine (1979)

Table 3 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50	Ratpan & Plaumann (1988)
SAS, *Salmonella typhimurium* TA1530, reverse mutation	+	NT	200	Rosenkranz (1975)
DMG, *Drosophila melanogaster*, genetic crossing over or recombination	+		2400 mg/m^3 vap. × 0.5 h	Kale & Baum (1982)
DMG, *Drosophila melanogaster*, genetic crossing over or recombination	+		23.6 feed	Vogel & Nivard (1993)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		7.2% vap. 5 min	Inoue *et al*. (1982)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		600 mg/m^3 vap. × 0.5 h	Kale & Baum (1982)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		200 ppm feed	Yoon *et al*. (1985)
DMH, *Drosophila melanogaster*, heritable translocations	–		3000 mg/m^3 vap. × 0.5 h	Kale & Baum (1982)
DMH, *Drosophila melanogaster*, heritable translocations	+		200 ppm feed	Yoon *et al*. (1985)
DIA, DNA strand breaks/cross-links, rat testicular germ cells *in vitro*	+	NT	17.3	Bradley & Dysart (1985)
DIA, DNA strand breaks, rat testicular cells *in vitro*	+	NT	0.6	Brunborg *et al*. (1988)
DIA, DNA strand breaks, male Wistar rat hepatocytes *in vitro*	+	NT	0.2	Holme *et al*. (1989)
DIA, DNA strand breaks, rat testicular cells *in vitro*	+	NT	1.2	Låg *et al*. (1989a)
DIA, DNA strand breaks, male Wistar rat hepatocytes *in vitro*	+	NT	0.2	Holme *et al*. (1991)
DIA, DNA strand breaks, male New Zealand white rabbit lung cells (Clara cells, type II cells and alveolar macrophages) *in vitro*	+	NT	7.0	Becher *et al*. (1993)
DIA, DNA strand breaks, Wistar rat testicular germ cells *in vitro*	+	NT	0.7	Bjørge *et al*. (1996a)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	+	20	McKee *et al*. (1987)
GIA, Gene mutation, Fischer 344 rat ARL-13 hepatocytes, *hprt* locus *in vitro*	(+)	NT	95	Belitsky *et al*. (1994)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	NT	2.4	Tezuka *et al*. (1980)

Table 3 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	+	10	Loveday *et al*. (1989)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	+	NT	24	Tezuka *et al*. (1980)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	+	50	Loveday *et al*. (1989)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	NT	7	McKee *et al*. (1987)
DIH, DNA strand breaks, cross-links or related damage, human testicular cells *in vitro*	–	NT	71	Bjørge *et al*. (1996a)
CIH, Chromosomal aberrations, human sperm cells *in vitro*	+	NT	NG[c]	Kapp *et al*. (1979)
BFA, Bile from dosed rats, *Salmonella typhimurium* TA1535, reverse mutation	–		5 iv × 1	Connor *et al*. (1979)
DVA, DNA strand breaks, Fischer 344 rat testicular cells *in vivo*	+		35 ip × 1	Bradley & Dysart (1985)
DVA, DNA strand breaks, rat testicular cells *in vivo*	+		20 ip × 1	Brunborg *et al*. (1988)
DVA, DNA strand breaks, rat and guinea-pig testicular cells *in vivo*	+		40 ip × 1	Låg *et al*. (1989a)
DVA, DNA strand breaks, female Sprague-Dawley rat liver cells *in vivo*	+		35 po × 2	Kitchin & Brown (1994)
DVA, DNA strand breaks, male rat liver and kidney cells *in vivo*	+		5 ip × 1	Brunborg *et al*. (1996)
DVA, DNA strand breaks, rat lung, spleen, brain, urinary bladder, stomach, duodenum, colon, bone marrow, testis *in vivo*	+		10 ip × 1	Brunborg *et al*. (1996)
UVR, Unscheduled DNA synthesis, male Fischer 344 rat spermatocytes *in vivo*	+		150 ip × 1	Bentley & Working (1988)
MST, Mouse spot test, male PW and female C57BL/6 mice	+		106 ip × 1	Sasaki *et al*. (1986)
SLP, Mouse specific locus test, postspermatogonia, male (101 × C3H) or (C3H × 101)F_1 mice	–		150 ip × 1	Russell *et al*. (1986)
SLO, Mouse specific locus test, spermatogonia, (101 × C3H) or (C3H × 101)F_1 mice	–		150 ip × 1	Russell *et al*. (1986)
MVM, Micronucleus test, CD-1 and male CCBF_1 mouse bone marrow *in vivo*	–		150 po × 1	Albanese *et al*. (1988)

Table 3 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MVM, Micronucleus test, male SHR mouse bone marrow *in vivo*	+		25.7 po × 2	Belitsky *et al*. (1994)
MVM, Micronucleus test, male SHR mouse forestomach *in vivo*	(+)		54.4 po × 4	Belitsky *et al*. (1994)
MVR, Micronucleus test, male PVG and Alpk rat bone marrow *in vivo*	+		75 po × 1	Albanese *et al*. (1988)
MVR, Micronucleus test, male PVG rat bone marrow *in vivo*	+		75 po × 1	George *et al*. (1990)
CGG, Chromosomal aberrations, male rat spermatogonia *in vivo*	+		7.3 po × 5	Kapp *et al*. (1979)
DLM, Dominant lethal test, female BDF_1 mice	–		150 po × 5	Teramoto *et al*. (1980)
DLM, Dominant lethal test, male $(C3H \times 101)F_1$ mice	–		200 sc × 1	Generoso *et al*. (1985)
DLR, Dominant lethal test, male Sprague-Dawley rats	+		10 po × 5	Teramoto *et al*. (1980)
DLR, Dominant lethal test, male Sprague-Dawley rats	+		50 po × 5	Saito-Suzuki *et al*. (1982)
DLR, Dominant lethal test, male and female Sprague-Dawley rats	+		8 inh 6 h/d, 5 d/w, 14 wk	Rao *et al*. (1983)
DLR, Dominant lethal test, male Sprague-Dawley rats	+		10 po × 5	Au *et al*. (1990)
BVD, Binding (covalent) to DNA, rat liver *in vivo*	+		200 ip × 1	Humphreys *et al*. (1991)
BVD, Binding (covalent) to DNA, rat kidney and testis *in vivo*	–		200 ip × 1	Humphreys *et al*. (1991)
SPM, Sperm morphology, $(C57BL/6 \times C3H)F_1$ mice *in vivo*	–		150 ip × 5	Osterloh *et al*. (1983)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; NG, not given; iv, intravenous; ip, intraperitoneal; po, oral; inh, inhalation; sc, subcutaneous

[c] Cells collected from exposed workers

appears that both oxidation and conjugation are requirements for bacterial mutagenicity. Activation was proportional to cytochrome P450 concentration and was reduced by exogenous reduced glutathione (Miller *et al*., 1986). However, the synthetic glutathione conjugate of 1,2-dibromo-3-chloropropane itself was not mutagenic to *S. typhimurium* TA100 (Humphreys *et al*., 1991).

The compound is mutagenic to *Drosophila melanogaster*, in which it induced sex-linked recessive lethal mutations, mitotic recombinations and heritable translocations.

In cultured mammalian cells, several studies have demonstrated the induction of DNA strand breaks (including one study with human primary testicular cell cultures), while (usually) single studies have demonstrated increases in the frequencies of gene mutations, sister chromatid exchanges, chromosomal aberrations and cell transformation.

In vivo, it is clear that rats are more sensitive than mice to the genotoxic effects of 1,2-dibromo-3-chloropropane. DNA strand breaks were induced in cells of many organs of rats dosed by intraperitoneal injection, as well as in testicular cells of guinea-pigs. Unscheduled DNA synthesis was also induced in rat spermatocytes in one study. In-vivo mutation assays have been conducted only in mice, in which somatic cell mutations were induced in one study, but specific locus mutations were not induced in either spermatogonial stem cells or post-spermatogonial cell stages in another study. Micronuclei were induced in bone-marrow cells of rats, and of mice in one of two studies, and there was evidence of micronucleus induction in the forestomach of orally dosed mice in one study. Dominant lethal effects were induced in orally dosed rats, but not in mice dosed either orally or by subcutaneous injection. Sperm of abnormal morphology were not more frequent in 1,2-dibromo-3-chloropropane-dosed mice than in controls.

In a study of DNA adducts, intraperitoneal injection of rats with 1,2-dibromo-3-chloropropane (200 mg/kg bw) produced *N7*-guanine adducts in the liver at a level of 1 pmol/mg DNA, whereas adducts were not found in either kidney or testis.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to 1,2-dibromo-3-chloropropane has occurred during its production and use as a pesticide, nematocide and soil fumigant; however, production is believed to have ceased. It has been detected at low levels in ambient air, water and soil.

5.2 Human carcinogenicity data

Four cohort studies and one population-based case–control study have examined the risk of cancer among populations exposed to 1,2-dibromo-3-chloropropane, among other chemicals. In two of the cohort studies, an excess of lung cancer was observed based on small numbers of cases. In a third cohort study, an excess of liver and biliary tract cancers was found, while in the fourth an excess of cervical cancer and a non-significant excess of melanoma and leukaemia were observed. However, in both of the last two studies, it

was unclear what proportion of the population was exposed to 1,2-dibromo-3-chloropropane, and there was exposure to multiple pesticides. In the case–control study, there was a non-significant association of gastric cancer and leukaemia with exposure to 1,2-dibromo-3-chloropropane in groundwater.

5.3 Animal carcinogenicity data

1,2-Dibromo-3-chloropropane has been tested by oral administration and inhalation in mice and rats. After oral administration, it produced squamous-cell carcinomas of the forestomach in animals of each species and adenocarcinomas of the mammary gland in female rats. After inhalation, it induced nasal cavity and lung tumours in mice, and nasal cavity and tongue tumours in rats of each sex and pharynx in females. In fish, an increased incidence of liver tumours was found.

5.4 Other relevant data

1,2-Dibromo-3-chloropropane is metabolically activated via cytochrome P450-catalysed oxidation and glutathione conjugation to form several protein- and DNA-binding products in the rat and mouse. It is also activated in human testicular cells *in vitro*. It disturbs spermatogenesis and has caused male infertility in humans. 1,2-Dibromo-3-chloropropane is a bacterial mutagen in the presence of metabolic activation. It causes DNA damage and genotoxicity in animal cells *in vitro* and *in vivo*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 1,2-dibromo-3-chloropropane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2-dibromo-3-chloropropane.

Overall evaluation

1,2-Dibromo-3-chloropropane is *possibly carcinogenic to humans (Group 2B)*.

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