DICHLOROACETIC ACID

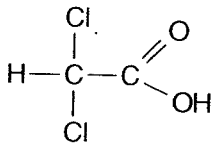
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 79-43-6
Deleted CAS Reg. No.: 42428-47-7
Chem. Abstr. Name: Dichloroacetic acid
IUPAC Systematic Name: Dichloroacetic acid
Synonyms: Bichloracetic acid; DCA; DCA (acid); DCAA; dichloracetic acid; dichlorethanoic acid; dichloroethanoic acid; 2,2-dichloroethanoic acid

1.1.2 Structural and molecular formulae and relative molecular mass



$C_2H_2Cl_2O_2$ Relative molecular mass: 128.94

1.1.3 Chemical and physical properties of the pure substance

From Lide (1993), unless otherwise noted

(*a*) *Description*: Colourless to slightly yellowish liquid with a pungent acid-like odour (Budavari, 1989; Hoechst Chemicals, 1990)

(*b*) *Boiling-point*: 194 °C

(*c*) *Melting-point*: 13.5 °C

(*d*) *Density*: 1.5634 at 20 °C/4 °C

(*e*) *Spectroscopy data*: Infrared (prism [2806]; grating [36771]), nuclear magnetic resonance (proton [166], C-13 [500]) and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*f*) *Solubility*: Soluble in water, acetone, ethanol and diethyl ether; also soluble in ketones, hydrocarbons and chlorinated hydrocarbons (Hoechst Chemicals, 1990). In aqueous solution, dichloroacetic acid and dichloroacetate exist as an equilibrium mixture, the proportions of each depending primarily on the pH of the solution. The pK_a of dichloroacetic acid is 1.48 at 25 °C.

(*g*) *Volatility*: Vapour pressure: 0.19 mbar [19 Pa] at 20 °C (Hoechst Chemicals, 1990)

(*h*) *Reactivity*: Highly corrosive and attacks metals; releases hydrogen chloride gas (see IARC, 1992) when heated (Hoechst Chemicals, 1990)

(*i*) *Octanol:water partition coefficient (P)*: log P, 0.92 (Hansch *et al.*, 1995)

(*j*) *Conversion factor*: $mg/m^3 = 5.27 \times ppm$[1]

1.1.4 Technical products and impurities

Dichloroacetic acid is available commercially at a purity of 99% with a maximum of 0.3% water (Hoechst Chemicals, 1990; Spectrum Chemical Mfg Corp., 1994).

1.1.5 Analysis

Two ion chromatography methods are available for determining haloacetic acids, including dichloroacetic acid. The first is based on anion-exchange separation with suppressed electrical conductivity detection. The second is based on anion-exclusion separation with ultraviolet detection. The detection limits for dichloroacetic acid were 16.0 µg/L with the ion-exchange method and 8.0 µg/L with the ion-exclusion method (Nair *et al.*, 1994).

A high-performance liquid chromatography method has been used to separate and quantify dichloroacetic acid. The samples were chromatographed with aqueous ammonium sulfate as the mobile phase, and the chromatograph was equipped with an ultraviolet-visible radiation detector set at 210 nm (Husain *et al.*, 1993).

A method for the microdetermination of chloroacetic acids, including dichloroacetic acid, in water involved conversion to the difluoroanilide derivative by reaction with difluoroaniline and dicyclohexylcarbodiimide. The derivative was extracted into ethyl acetate and determined by gas chromatography with electron capture detection. The detection limit for dichloroacetic acid was about 1 µg/L (Ozawa & Tsukioka, 1990).

A multi-channel, microwave-induced plasma atomic spectroscopic gas chromatographic detector has been used to characterize the profiles of chlorinated humic acid on capillary columns and the content of carbon, chlorine and bromine in drinking-water. This technique makes it possible to estimate the empirical formulae of separated compounds with sufficient accuracy for useful peak identification. Dichloroacetic acid was among the compounds characterized by this method (Italia & Uden, 1988).

The United States Environmental Protection Agency (1990) reported a method for the determination of haloacetic acids, including dichloroacetic acid, in drinking-water, groundwater, raw water and water in any intermediate treatment stage. The method involves adjusting the pH to 11.5 and extraction with methyl-*tert*-butyl ether to remove neutral and basic organic compounds. The aqueous sample is then acidified to a pH of 0.5, and the acids are extracted into methyl-*tert*-butyl ether. The acids are then converted to their methyl esters with diazomethane.

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[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa)

The methyl esters are determined by capillary gas chromatography with electron capture detection. The detection limit for this method is 0.015 μg/L.

1.2 Production and use

1.2.1 Production

The most efficient method for producing dichloracetic acid is hydrolysis of dichloroacetyl chloride produced by oxidation of trichloroethylene (see monograph, this volume) (Koenig *et al.*, 1986). Dichloroacetic acid is also prepared by hydrolysis of pentachloroethane (see IARC, 1987a) with concentrated sulfuric acid, by oxidation of 1,1-dichloroacetone with nitric acid and air or by catalytic dechlorination of trichloroacetic acid (see monograph, this volume) with hydrogen over a palladium catalyst. Dichloroacetic acid can be produced in the laboratory by reacting chloral hydrate (see monograph, this volume) with potassium or sodium cyanide (Koenig *et al.*, 1986).

Figures for the production and use of dichloroacetic acid throughout the world are not available (Koenig *et al.*, 1986). In the Member States of the European Union, 3000 tonnes were estimated to have been produced and used in 1984 (Environmental Chemicals Data and Information Network, 1993). Dichloroacetic acid is produced by two companies in Japan and by one company each in Germany and India (Chemical Information Services, Inc., 1994).

1.2.2 Use

Dichloroacetic acid is presently of little economic importance. Its acid chloride and methyl ester, however, are used as intermediates in the manufacture of agrochemicals and the pharmaceutical, chloramphenicol (see IARC, 1990) (Koenig *et al.*, 1986). Dichloroacetic acid is also a starting material for the production of glyoxylic acid, dialkyloxy and diaryloxy acids and sulfonamides. The compound is used as a test reagent for analytical measurements during the manufacture of poly(ethylene terephthalate) and as a medical disinfectant, in particular as a substitute for formaldehyde (Koenig *et al.*, 1986). It has been considered for use in the treatment of lactic acidosis, diabetes mellitus, hyperlipoproteinaemia and several other disorders; however, it has never been marketed for any of these purposes (Budavari, 1989; Stacpoole, 1989).

1.3 Occurrence

1.3.1 Natural occurrence

Dichloroacetic acid is not known to occur as a natural product.

1.3.2 Occupational exposure

The National Occupational Exposure Survey conducted between 1981 and 1983 indicated that 1592 employees in the United States were potentially exposed to dichloroacetic acid in 39 facilities (United States National Institute for Occupational Safety and Health, 1994).

1.3.3 Air

No data were available to the Working Group.

1.3.4 Water

Dichloroacetic acid is produced as a by-product during aqueous chlorination of humic substances (Christman *et al.*, 1983; Miller & Uden, 1983; Legube *et al.*, 1985; Reckhow *et al.*, 1990). Consequently, it may occur in drinking-water after chlorine disinfection of raw waters containing natural organic substances (Hargesheimer & Satchwill, 1989; see IARC, 1991a). The concentrations of dichloroacetic acid measured in various water sources are summarized in Table 1. It has been identified as a major chlorinated by-product of the photocatalytic degradation of tetrachloroethylene in water but a minor by-product of the degradation of trichloroethylene (Glaze *et al.*, 1993).

Table 1. Concentrations of dichloracetic acid in water

Water type (location)	Concentration range (μg/L)	Reference
Drinking-water (chlorinated tap water) (USA)	63.1–133	Uden & Miller (1983)
Chlorinated treated water (Australia)	200 max	Nicholson *et al.* (1984)
Drinking-water (chlorinated surface, reservoir, lake and groundwater) (USA)	5.0–7.3	Krasner *et al.* (1989)
Chlorinated surface water (USA)	9.4–23	Jacangelo *et al.* (1989)
Chlorinated drinking-water (USA)	8–79	Reckhow & Singer (1990)
Chlorinated drinking-water (Japan)	4.5	Ozawa (1993)
Rainwater (Germany)	1.35	Clemens & Schöler (1992a)
Swimming pool (Germany)	indoors: 0.2–10.6 open air: 83.5–181.0[a]	Clemens & Schöler (1992b)
Surface water (downstream from a paper mill) (Austria)	< 3–522	Geist *et al.* (1991)
Biologically treated kraft pulp mill effluent (Malaysia)	14–18	Mohamed *et al.* (1989)

[a]The higher levels found in open-air swimming pools may be due to the input of organic material by swimmers.

1.3.5 Other

In humans, dichloroacetic acid is a reactive intermediate metabolite of trichloroethylene and an end-metabolite of 1,1,2,2-tetrachloroethane (see IARC, 1987b). As dichloroacetic acid has also been reported as a biotransformation product of methoxyflurane (Mazze & Cousins, 1974) and dichlorvos (see IARC, 1991b; WHO, 1989), it may occur in the tissues and fluids of animals treated with dichlorvos for helminthic infections (Schultz *et al.*, 1971).

Dichloroacetic acid has been detected in spruce needles from the Black Forest in Germany and the Montafon region in Austria, both considered to be relatively unpolluted areas, in the range of ten to several hundreds of micrograms per kilogram (Frank *et al.*, 1989).

1.4 Regulations and guidelines

In most countries, no limits have been recommended for exposure to dichloroacetic acid. A guideline limit of 4 mg/m^3 for short-term occupational exposure has been set in the Russian Federation (ILO, 1991).

The United States Environmental Protection Agency (1994) proposed that the maximal level of haloacetic acids (the sum of the concentration of mono-, di- and trichloroacetic acids and mono- and dibromoacetic acids) in drinking-water be 0.06 mg/L.

WHO (1993) recommends a provisional guideline value for dichloroacetic acid in drinking-water of 50 µg/L.

2. Studies of Cancer in Humans

No studies were available on people exposed to dichloroacetic acid. In view of the fact that it is a metabolite of trichloroethylene and tetrachloroethylene, the results of studies on populations exposed to those compounds may be relevant (see pp. 95 and 176). In particular, urinary levels of dichloroacetic acid were measured in one descriptive study of a population exposed to trichloroethylene and tetrachloroethylene in drinking-water (Vartiainen *et al.*, 1993).

3. Studies of Cancer in Experimental Animals

Oral administration

Mouse: A group of 26 male B6C3F1 mice, four weeks of age, received drinking-water containing 5 g/L dichloroacetic acid (purity, > 99%) neutralized with sodium hydroxide to a pH of 6.5–7.5. A control group of 27 mice received drinking-water containing 2 g/L sodium chloride. Both groups were kept for 61 weeks, at which time they were killed and necropsied. Two of 22 control mice had hepatic adenomas and none had hepatic carcinomas, whereas 25/26 mice that received dichloroacetic acid had hepatic adenomas and 21/26 had hepatocellular carcinomas ($p < 0.01$; Fisher's exact test) (Herren-Freund *et al.*, 1987). [The Working Group noted that this study also included groups pretreated with intraperitoneal injections of *N*-nitrosoethylurea in order to test for promoting effects of dichloroacetic acid; however, because of

the high incidence and early appearance of liver tumours induced by dichloroacetic acid alone, promoting effects could not be evaluated.]

Groups of male and female B6C3F1 mice, 37 days old, received dichloroacetic acid in drinking-water (neutralized to pH 6.8-7.2 with sodium hydroxide) for up to 52 weeks, at which time the experiment was terminated. A group of 11 male mice received a dose of 1 g/L for 52 weeks, 24 male mice received 2.0 g/L for 52 weeks, and a further group of 11 males received 2.0 g/L for 37 weeks and then water alone until week 52 . Two groups of 35 and 11 male control mice were kept until the end of the experiment. Groups of 10 female mice received either 0 or 2.0 g/L dichloroacetic acid for 52 weeks. Livers and kidneys were weighed and examined macroscopically. Microscopic examination was undertaken only of lesions found in the livers of 35 male control mice, the 11 male mice treated with 2.0 g/L dichloroacetic acid for 37 weeks and other groups [numbers unspecified] chosen at random. The lesions were classified histologically as hyperplastic nodules, adenomas or hepatocellular carcinomas. The incidences of these lesions were increased in mice receiving 2 g/L dichloroacetic acid (see Table 2). Only hyperplastic nodules and adenomas were found in mice treated for 37 weeks, and only hyperplastic nodules were observed in 3/10 treated female mice [no further details reported]. Other pathological signs seen at 37 or 52 weeks in males and females treated with dichloroacetic acid included cytomegaly, massive accumulation of glycogen and focal necrotic lesions (Bull *et al.*, 1990). [The Working Group noted that histopathological examination was limited to selected macroscopic lesions.]

Table 2. Lesions in the livers of male B6C3F1 mice given dichloroacetic acid in the drinking-water

Dose (g/L) × no. of weeks	No. of mice	No. with macroscopic lesions	Total no. of lesions	No. of macroscopic lesions examined histologically (no. of mice)	No. of hyperplastic nodules (no. of mice)	No. of hepatic adenomas (no. of mice)	No. of hepatocellular carcinomas (no. of mice)
Control × 52 (water alone)	35	2	2	2 (2)	1 (1)	0	0
1 × 52	11	2	3	1 (1)	1 (1)	0	0
2 × 52	24	23	92	23 (10)	15 (9)	2 (2)	6 (5)
2 × 37	11	7	23	19 (7)	15 (6)	2 (2)	0

From Bull *et al.* (1990)

Groups of 50 male B6C3F1 mice, four weeks old, were given 0.05, 0.5 or 5 g/L dichloroacetic acid (purity, > 99%; adjusted to pH 6.8–7.2 by the addition of 10 N sodium hydroxide) in the drinking-water. A control group of 50 mice was given drinking-water containing 2 g/L sodium chloride. In a second experiment, groups of 50 male B6C3F1 mice were given drinking-water containing either 3.5 g/L dichloroacetic acid or 1.5 g/L acetic acid (control group) in order to examine the metabolic appropriateness of an alternative control group. Interim kills of five

mice were made in all treatment groups at four, 15, 30 and 45 weeks, except in the group given 3.5 g/L dichloroacetic acid. After 60 weeks of treatment, nine mice treated with 2 g/L saline or with 0.05 or 0.5 g/L dichloroacetic acid and 30 mice given 5.0 g/L dichloroacetic acid were killed. The remaining animals were killed at 75 weeks. In the second experiment, 12 mice receiving 3.5 g/L dichloroacetic acid and 10 mice given acetic acid were killed at 60 weeks. [The fate of the remaining mice in these two groups is not described.] Drinking-water intake and final body weight were lower in the groups receiving 3.5 or 5.0 g/L dichloroacetic acid than among their respective controls; there was no difference in survival. Proliferative lesions of the liver were classified as hyperplastic nodules, hepatocellular adenomas or hepatocellular carcinomas; the prevalence of the two tumour types was reported only as percentages on the basis of the number of animals examined. Hyperplastic nodules occurred mainly among animals receiving dichloroacetic acid; the prevalence rates [presented graphically] at 60 weeks were 58% among those given 3.5 g/L and 83% for those given 5.0 g/L. Hepatocellular carcinomas were first observed at 30 weeks in mice at 3.5 g/L. At 60 weeks, the group given 5.0 g/L dichloroacetic acid had prevalences of 80% hepatic adenomas and 83% hepatocellular carcinomas ($p < 0.001$); the prevalences in the group given 3.5 g/L were 100% hepatic adenomas and 67% hepatocellular carcinomas [combined prevalence of tumours at 60 and 75 weeks] ($p < 0.001$). In contrast, the prevalences of hepatic adenomas and carcinomas (combined) were 11.1% in the group given 0.5 g/L dichloroacetic acid and 24.1% in that given 0.05 g/L; these values were not significantly different from that in the saline controls (7.1%). No liver tumours were found in 10 controls given acetic acid and killed at 60 weeks (DeAngelo *et al.*, 1991). [The Working Group noted the unconventional design and reporting of the study.]

A group of 33 male B6C3F1 mice (initially two groups of 23 and 10 mice but analysed as one), four weeks of age, received 0.5 g/L dichloroacetic acid (purity, > 95%; impurities unspecified; pH adjusted to 6.8–7.2 with 10 N sodium hydroxide) in distilled drinking-water (pooled estimated mean dose, 88 mg/kg bw per day) for 104 weeks; 33 control mice received distilled water only. Five mice per group were killed at 30 weeks and a further five in the control group at 60 weeks, for interim evaluation. Three control mice and four treated mice died before week 104. Of the animals killed at week 104, 15/24 treated mice and 2/20 controls had hepatocellular carcinomas [$p = 0.001$, Fisher's exact test]; 10/24 treated mice and 1/20 control mice had hepatocellular adenomas [$p = 0.005$]; and 18/24 treated mice and 3/20 controls had carcinomas or adenomas [$p = 0.001$]. Two treated mice had hyperplastic liver nodules; 8/24 treated mice and 1/20 controls had hepatocellular necrosis, and 22/24 treated mice and 1/20 controls had cytomegaly (Daniel *et al.*, 1992).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

Oral or intravenous administration of 50 mg/kg bw dichloroacetic acid to healthy volunteers resulted in the excretion of oxalate and dichloroacetic acid itself as the major urinary com-

ponents; however, only 5% of the administered dose was found in the urine. The plasma half-life of dichloroacetic acid after a single oral or intravenous dose was 0.5–2 h. Negligible amounts of dichloroacetic acid appear to bind to plasma proteins (Curry *et al.*, 1985; Stacpoole, 1989). Identification of oxalate as a metabolite in urine indicates cytochrome P450-dependent dechlorination to glyoxylate, which can be converted to oxalate either directly or via glycolate. The plasma half-life of dichloroacetic acid is several times longer after repeated than after single oral or intravenous administration, possibly because of enzyme inhibition by dichloroacetic acid or its metabolites (Curry *et al.*, 1985).

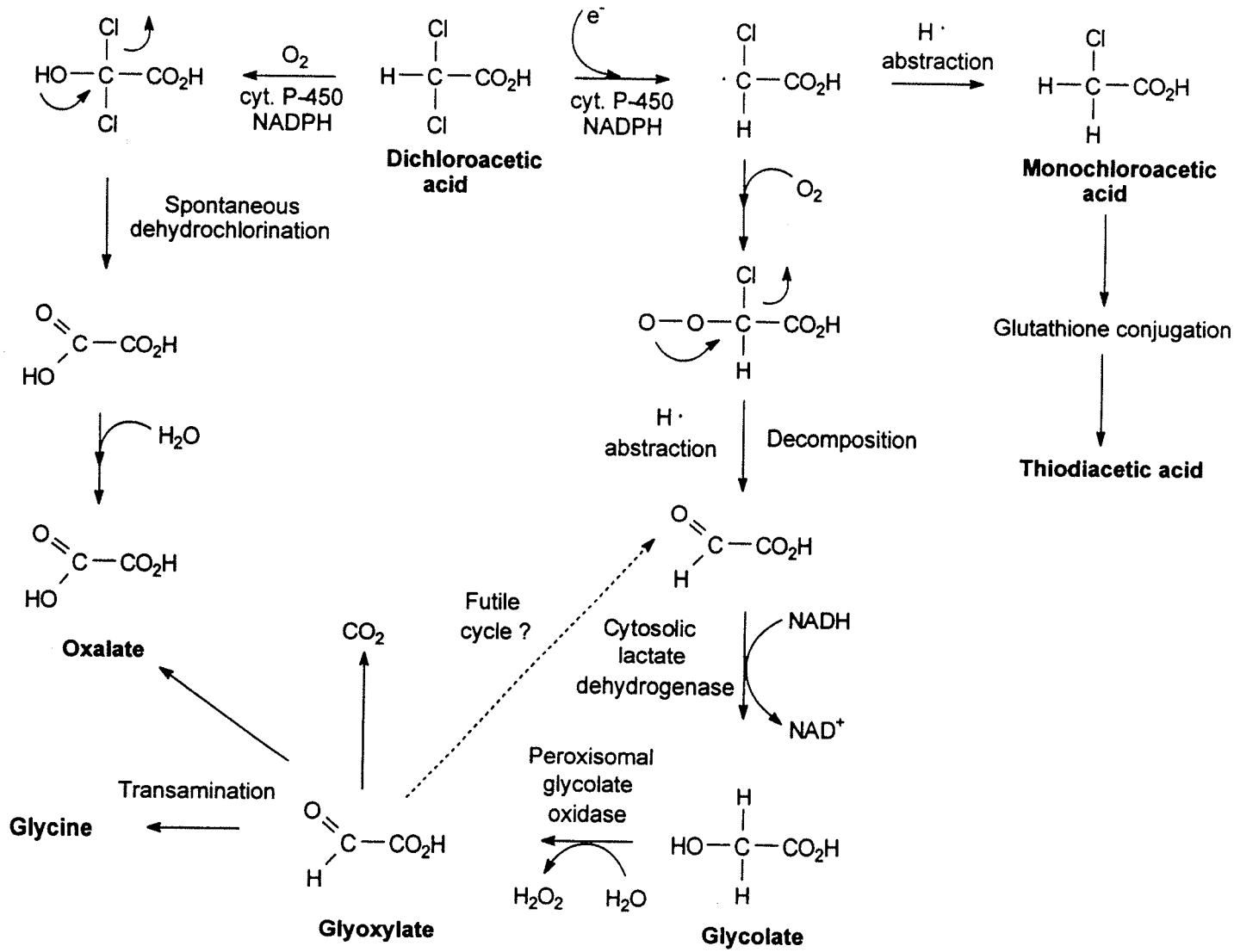
4.1.2 Experimental systems

The toxicokinetics of dichloroacetic acid were investigated in male Fischer 344 rats during 48 h after oral administration of 28.2 or 282 mg/kg bw ^{14}C-dichloroacetic acid (Lin *et al.*, 1993). The percentage of radiolabel excreted in the urine increased from 12.7% at the lower dose to 35.2% at the high dose. Unmetabolized dichloroacetic acid comprised > 20% of the urinary radiolabel at the high dose and < 1% at the low dose. The percentage of the dose excreted as carbon dioxide decreased from 34.4% at the lower dose to 25% at the higher. Significant percentages of the administered dose were retained in the liver (4.9–7.9%), muscle (4.5–9.9%), skin (3.3–4.5%) and intestines (1.0–1.7%). [The Working Group noted that the tissue retention might be related to the formation of one-carbon fragments.]

After dichloroacetic acid was administered as a single oral dose in water at 5, 20 or 100 mg/kg bw to male Fischer 344 rats and male B6C3F1 mice, only 2% was found unchanged in urine, indicating that it is extensively metabolized in both species. The total radiolabel in the urine comprised about 20–24% of the administered dose in rats and 28% in mice; the mean plasma half-life of dichloroacetic acid in both species was 0.9–1.6 h. The blood concentration over time was much greater in rats than in mice. Since this difference was magnified by increasing dose, the clearance mechanisms for dichloroacetic acid are probably more susceptible to saturation in rats than in mice (Larson & Bull, 1992a,b).

Dichloroacetic acid is metabolized by both oxidative and reductive pathways (Figure 1). Both pathways lead ultimately to oxalate and carbon dioxide, glycolate and glyoxylate being probable intermediate metabolites in the reductive pathway. Reductive dechlorination of dichloroacetic acid to monochloroacetate, followed by glutathione conjugation to give thiodiacetic acid as the ultimate metabolite, has also been demonstrated. Oxalic, glycolic and thiodiacetic acids are the major urinary metabolites of dichloroacetic acid in both rats and mice. The metabolic reactions possibly involve free-radical intermediates (Crabb & Harris, 1979; Stacpoole *et al.*, 1990; Larson & Bull, 1992a). The ability of dichloroacetic acid to elicit a lipid peroxidative response in liver was therefore investigated in male Fischer 344 rats and male B6C3F1 mice after administration of a single oral dose of 100–2000 mg/kg bw in water. A dose-dependent response was induced up to 300 mg/kg bw dichloroacetic acid in both species. A further increase to 1000 mg/kg bw resulted in only minimal increases in the lipid peroxidative response in mice and in a decreased response in rats (Larson & Bull, 1992a).

Figure 1. Metabolism of dichloroacetic acid



From Larson and Bull (1992a)

4.1.3 Comparison of humans and animals

Both humans and rodents metabolize dichloroacetic acid to glyoxylate by oxidative dechlorination; the plasma half-life of the parent compound is 0.5–2 h. A significantly greater percentage of the dose is excreted in the urine of rodents (about 20–30%), however, than by humans. Since only a negligible percentage of administered radiolabel is bound to plasma proteins or taken up by erythrocytes, dichloroacetic acid and its metabolites may be distributed to other tissues, although there is no direct evidence for this suggestion. Administration of repeated doses results in a marked decrease in the clearance of dichloroacetic acid from human plasma, but a similar inhibition by dichloroacetic acid of its own metabolism has not been reported in rodents.

4.2 Toxic effects

4.2.1 Humans

The pharmacological and toxic effects of dichloroacetic acid in humans have been studied extensively owing to the potential use of this chloroacetic acid for the treatment of various disorders (see section 1.2.2). Dichloroacetic acid lowers blood sugar levels in animals and humans with diabetes mellitus by stimulating peripheral glucose use and inhibiting gluconeogenesis. In addition, long-term administration of dichloroacetic acid reduces plasma triglyceride and cholesterol levels (a particularly important effect in patients with congenital hypercholesterolaemia, who have no cholesterol receptors), and it facilitates oxidation of lactate by activating pyruvate dehydrogenase in patients with acquired and congenital forms of lactic acidosis. Its capacity to activate pyruvate dehydrogenase also made dichloroacetic acid a candidate for use in the treatment of conditions involving myocardial ischaemia, because when oxygen delivery to heart muscle is limited, a shift from fatty acid to carbohydrate oxidation may increase the ratio of ATP production:oxygen consumption (Stacpoole, 1989).

The neurotoxic effects of dichloroacetic acid observed repeatedly in experimental animals have rarely been documented in clinical trials. Drowsiness is a fairly frequent side-effect of dichloroacetic acid and has been observed in healthy volunteers, adults with type II diabetes and patients with lactic acidosis. A patient with homozygous familial hypercholesterolaemia who received single doses of 50 mg/kg bw dichloroacetic acid daily for four months developed reversible peripheral neuropathy characterized by loss of reflexes and muscle weakness; the effect subsided several weeks after cessation of administration of dichloroacetic acid (Moore *et al.*, 1979).

4.2.2 Experimental systems

More total radioactivity was associated with albumin and haemoglobin in male Fischer 344 rats than in male B6C3F1 mice 4–120 h after a single oral dose of 5 mg/kg bw ^{14}C-dichloroacetic acid. In contrast, incorporation of radiolabelled amino acids resulting from the metabolism of chloroacetate (glycine being derived from glyoxylic acid) was more extensive in mice; this result is consistent with the more extensive metabolism in this species (Stevens *et al.*, 1992).

Exposure of male and female Sprague-Dawley rats to dichloroacetic acid at target doses of 10–600 mg/kg bw per day in the drinking-water for 14 days resulted in reduced weight gain only in the group given the highest dose. Treatment also increased urinary excretion of ammonia and changed the activities of enzymes of ammoniagenesis, indicating renal compensation for an acid load (Davis, 1986).

Male Sprague-Dawley rats administered dichloroacteic acid in the drinking-water for 90 days at concentrations providing daily doses of about 4, 35 or 350 mg/kg bw had decreased body weights. Animals given the high dose also showed histological and biochemical signs of liver and kidney damage and increased hepatic peroxisomal β-oxidation activity (Mather *et al.*, 1990).

Male Sprague-Dawley rats were given dichloroacetic acid in the drinking-water at a concentration of 80.5 mmol/L [10 g/L] to provide an approximate intake of 1100 mg/kg bw per day. After 90 days, body weights were decreased, and there was an 11% increase in liver weight and a 34% decrease in testicular weight; histopathological changes were seen in the liver and lung (Bhat *et al.*, 1991).

Ocular toxicity was observed in beagle dogs (which are susceptible to drug-induced cataract formation) that were treated for 13 weeks with an approximate dose of 1100 mg/kg bw dichloroacetic acid in the drinking-water. No similar organ-specific effect has been seen in other studies or in other species (Katz *et al.*, 1981).

Administration of the sodium salt of dichloroacetic acid at a target dose of 50 or 1100 mg/kg bw to male Sprague-Dawley rats in the drinking-water for seven weeks resulted in severe hind limb weakness, demyelinization of cerebral and cerebellar parenchyma and thiamine depletion in the group at the high dose. The neurotoxic effects could be partially prevented by providing thiamine supplementation during the treatment period (Stacpoole *et al.*, 1990). These results confirmed the observed association between neurotoxicity induced by dichloroacetic acid and the histopathological changes in the brain seen in thiamine deficiency. The underlying mechanism may involve stimulation of thiamine-dependent enzymes by dichloroacetic acid, resulting in increased turnover of this vitamin (Katz *et al.*, 1981; Yount *et al.*, 1982). Oxalate, a metabolite of dichloroacetic acid in humans and rodents, has been shown to cause both peripheral neuropathy and cataracts; however, the renal and testicular oxalate crystals seen commonly in such cases have not been observed after administration of high doses of dichloroacetic acid (Yount *et al.*, 1982; Stacpoole *et al.*, 1990).

Dichloroacetic acid, trichloroacetic acid and chloroform are formed during the chlorination of drinking-water (see IARC, 1991a). After concomitant administration of dichloroacetic acid (at 0.92 and 2.45 mmol [118 and 316 mg]/kg bw by gavage, three times over 24 h) and chloroform (one intraperitoneal injection of 0.75 mg/kg bw once after the last dose of dichloroacetic acid) to male and female Sprague-Dawley rats, the toxicity of chloroform to the liver and kidney was increased (Davis, 1992).

Exposure of male and female B6C3F1 mice to dichloroacetic acid at 1000 and 2000 mg/L in drinking-water for up to 52 weeks induced severe cytomegaly associated with extensive accumulation of glycogen, the effects progressing to multiple focal areas of necrosis, regenerative cell division and hepatomegaly (Bull *et al.*, 1990; Sanchez & Bull, 1990; Bull *et al.*, 1993).

Induction of peroxisome proliferation has been repeatedly associated with the chronic toxicity and carcinogenicity of dichloroacetic acid to the liver (DeAngelo *et al.*, 1989). It can induce peroxisome proliferation in the livers of both mice and rats, as indicated by increased activities of palmitoyl-coenzyme A oxidase and carnitine acetyl transferase, the appearance of a peroxisome proliferation-associated protein and increased volume-density of peroxisomes after exposure to dichloroacetic acid for 14 days.

4.3 Reproductive and prenatal effects

4.3.1 Humans

No data were available to the Working Group.

4.3.2 Experimental systems

Dichloroacetic acid and its metabolites accumulate in rat fetuses after treatment of the dam (Roth *et al.*, 1991). The main effect of maternal doses of 140–2400 mg/kg bw per day on days 6–15 of gestation was altered development of the heart and major vessels and, less frequently, the kidneys and the orbits of the eyes (Randall *et al.*, 1991; Smith *et al.*, 1991; Epstein *et al.*, 1992; Smith *et al.*, 1992).

Long-term administration of dichloroacetic acid orally at up to 72 mg/kg bw per day to dogs and 80.5 mmol/L [10 g/L] in drinking-water to rats (calculated dose, 1100 mg/kg bw per day) for 90 days induced testicular toxicity in both species, with degeneration of the seminiferous epithelium (Bhat *et al.*, 1991; Cicmanec *et al.*, 1991). Earlier studies in rats, including one with a similar dose (1100 mg/kg bw per day for seven weeks), showed normal testicular histopathology and sperm production (Yount *et al.*, 1982; Stacpoole *et al.*, 1990). In male Long-Evans rats given 0, 31.3, 62.5 or 125 mg/kg bw per day by gavage for 10 weeks, toxic effects were seen on the male reproductive accessory organs (preputial glands and epididymes) and sperm at 31.3 or 62.5 mg/kg bw, whereas toxic effects on the testis and a reduction in late-step spermatid head count were observed only in the group given the highest dose. The number of viable implants on day 14 of gestation after an overnight mating with unexposed controls was decreased only in group at the high dose (Toth *et al.*, 1992).

4.4 Genetic and related effects

4.4.1 Humans

No data were available to the Working Group.

4.4.2 Experimental systems (see also Table 3 and Appendices 1 and 2)

Dichloroacetic acid did not induce differential toxicity in DNA repair-deficient strains of *Salmonella typhimurium* but did induce prophage in *Escherichia coli* in one study. It was mutagenic to *S. typhimurium* TA100 and TA98 in single studies. Most of the mutations in 400 revertants of dichloroacetic acid-treated *S. typhimurium* TA100 cultures were GC→AT transitions (DeMarini *et al.*, 1994).

Table 3. Genetic and related effects of dichloroacetic acid

Test system	Result[a]		Dose[b]	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
PRB, λ Prophage induction, *Escherichia coli* WP2s	–	+	2500	DeMarini *et al.* (1994)
SAD, *Salmonella typhimurium*, DNA repair-deficient TS24 strain	–	–	31 000	Waskell (1978)
SAD, *Salmonella typhimurium*, DNA repair-deficient TA2322 strain	–	–	31 000	Waskell (1978)
SAD, *Salmonella typhimurium*, DNA repair-deficient TA1950 strain	–	–	31 000	Waskell (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–		0.00	Herbert *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	(+)	1.0	DeMarini *et al.* (1994)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.00	Herbert *et al.* (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.00	Herbert *et al.* (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	0.00	Herbert *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	(+)	(+)	5	Herbert *et al.* (1980)
DIA, DNA strand breaks, B6C3F1 mouse hepatocytes *in vitro*	–	0	2580	Chang *et al.* (1992)
DIA, DNA strand breaks, Fischer 344 rat hepatocytes *in vitro*	–	0	1290	Chang *et al.* (1992)
DIH, DNA strand breaks, human CCRF-CEM cells *in vitro*	–	0	1290	Chang *et al.* (1992)
DVA, DNA strand breaks, B6C3F1 mouse hepatic cells *in vivo*	+		13 po × 1	Nelson & Bull (1988)
DVA, DNA strand breaks, B6C3F1 mouse hepatic cells *in vivo*	+		10 po × 1	Nelson *et al.* (1989)
DVA, DNA strand breaks, B6C3F1 mouse hepatic cells *in vivo*	–		1290 po × 1	Chang *et al.* (1992)
DVA, DNA strand breaks, B6C3F1 mouse splenocytes *in vivo*	–		1290 po × 1	Chang *et al.* (1992)
DVA, DNA strand breaks, B6C3F1 mouse epithelial cells from stomach and duodenum *in vivo*	–		1290 po × 1	Chang *et al.* (1992)
DVA, DNA strand breaks, B6C3F1 mouse hepatic cells *in vivo*	–		830 dw × 7–14 d	Chang *et al.* (1992)
DVA, DNA strand breaks, Sprague-Dawley rat hepatic cells *in vivo*	+		30 po × 1	Nelson & Bull (1988)
DVA, DNA strand breaks, Fischer 344 rat hepatic cells *in vivo*	–		645 po × 1	Chang *et al.* (1992)
DVA, DNA strand breaks, Fischer 344 rat hepatic cells *in vivo*	–		250 dw × 30 weeks	Chang *et al.* (1992)

[a]+, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative; 0, not tested

[b]LED, lowest effective dose; HID, highest effective dose. In-vitro tests, μg/ml; in-vivo tests, mg/kg bw; 0.00, dose not reported; po, orally; dw, drinking water

DNA strand breaks were not induced in mammalian cells *in vitro* in the absence of an exogenous metabolic activation system, but contradictory results were obtained *in vivo*. No effect was seen in either mouse or rat hepatic cells after single or repeated dosing, and no effects were observed in epithelial cells from spleen, stomach or duodenum after a single dose (Chang *et al.*, 1992).

DNA strand breaks were reported in one laboratory in the livers of mice and rats treated 4 h previously with dichloroacetate. None were observed 24 h after a single dose of 500 mg/kg bw or after repeated daily dosing (Nelson & Bull, 1988; Nelson *et al.*, 1989). Peroxisome proliferation, as indicated by β-oxidation of palmitoyl-coenzyme A, was observed only after induction of DNA damage (Nelson *et al.*, 1989). In another laboratory, DNA strand breakage was not observed in the livers of either mice or rats, while there was increased peroxisomal enzyme activity (Chang *et al.*, 1992). [The reasons for the contrasting results obtained using similar techniques are unclear.]

Mutations of proto-oncogenes in tumours induced by dichloroacetic acid

A group of 110 male B6C3F1 mice, eight weeks of age, were administered dichloroacetic acid, neutralized with sodium hydroxide, at a concentration of 0.5% in their drinking water for up to 76 weeks. Of two concurrent control groups, each consisting of 50 male mice, one was untreated and the other received corn oil at a dose of 10 ml/kg bw; 10 mice in each group were killed at 76 weeks and the remainder at 96, 103 and 134 weeks [numbers not stated]. At death, liver tumours measuring ≥ 0.5 cm in diameter were taken for histological examination and for oncogene analysis. At the time of the terminal kill, there were 24 untreated controls, 32 corn oil controls and 89 treated animals. The numbers of hepatocellular adenomas per mouse in these three groups were 0.9 ± 0.06 (8%), 0.13 ± 0.06 (13%) and 4.98 ± 0.38 (93%). The corresponding numbers of hepatocellular carcinomas were 0.09 ± 0.06 (8%), 0.12 ± 0.06 (12%) and 1.73 ± 0.17 (74%). The authors noted numerous foci of cellular alteration (presumed preneoplastic lesions) in the livers of treated mice but only rare foci in the livers of controls. No neoplasms related to treatment were found at other sites. The frequency of mutations in codon 61 of H-*ras* was not significantly different in the hepatocelluar tumours from 64 treated mice (62%) and in those from 74 combined historical and concurrent controls (69%); however, the spectra of these mutations showed a significant decrease in AAA and an increase in CTA in the treated mice in comparison with the controls. No other H-*ras* mutations were found, and only one K-*ras* mutation was detected in tumours from the treated and concurrent control groups. The authors interpreted these findings as suggesting that exposure to dichloroacetic acid provides the environment for a selective growth advantage for spontaneous CTA mutations in codon 61 of H-*ras* (Anna *et al.*, 1994).

Expression of c-*myc*, and c-H-*ras* in mRNA was studied by in-situ hybridization in the livers of male B6C3F1 mice treated with dichloroacetate at 1 or 2 g/L in the drinking-water for 52 weeks. Expression of c-*myc*, corrected for the background frequency, was increased by about three times in hepatic hyperplastic nodules and hepatic carcinomas in comparison with normal liver. A similar comparison of c-H-*ras* expression showed no significant increase in hyperplastic nodules but an approximately fourfold increase in hepatic carcinomas (Nelson *et al.*, 1990). [The

Working Group considered that the changes in proto-oncogene expression could not be attributed conclusively to dichloroacetic acid.]

5. Summary and Evaluation

5.1 Exposure data

Dichloroacetic acid is produced commercially in small quantities for use as an intermediate in the production of glyoxylic acid, dialkyloxy and diaryloxy acids and sulfonamides. Human exposure may occur during the production and use of dichloroacetic acid and from drinking chlorinated water.

5.2 Human carcinogenicity data

The available data were too limited to form the basis for an evaluation of the carcinogenicity of dichloroacetic acid to humans.

5.3 Animal carcinogenicity data

Neutralized dichloroacetic acid was tested by oral administration in males of one strain of mice in four studies. Increased incidences of hepatocellular adenomas and carcinomas were observed in all of the studies.

5.4 Other relevant data

Dichloroacetic acid is metabolized in humans and experimental animals, and oxalate, thiodiacetic acid and unchanged dichloroacetic acid are excreted in urine. Clearance is decreased in humans after repeated administration. Species differences in the clearance of dichloroacetic acid are observed in rodents: clearance in rats is much slower than in mice. Dichloroacetic acid induces peroxisome proliferation in the livers of both rats and mice.

No data were available on the effects of dichloroacetic acid on human reproduction. In rats and dogs, testicular degeneration can occur after exposure to this compound. The development of the heart, major vessels and kidney of rats can be affected by exposure *in utero*.

The evidence for induction of DNA strand breaks in liver cells of rodents exposed to dichloroacetic acid *in vivo* was inconclusive. Strand breaks were not induced in human or rodent cells *in vitro*. The results of assays for mutagenesis in bacteria were inconsistent.

The spectrum of mutations in H-*ras* proto-oncogenes in hepatic tumours from mice treated with dichloroacetic acid was different from that seen in hepatic tumours from untreated mice.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of dichloroacetic acid.

There is *limited evidence* in experimental animals for the carcinogenicity of dichloroacetic acid.

Overall evaluation

Dichloroacetic acid *is not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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[1]For definition of the italicized terms, see Preamble, pp. 22–26.

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