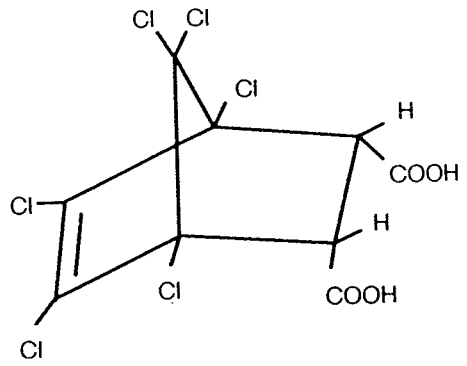
CHLORENDIC ACID

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 115-28-6
Chem. Abstr. Name: Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid, 1,4,5,6,7,7-hexachloro-
IUPAC Systematic Name: 1,4,5,6,7,7-Hexachloro-5-norbornene-2,3-dicarboxylic acid
Synonyms: HET acid; hexachloro-*endo*-methylenetetrahydrophthalic acid; 1,4,5,6,7,7-hexachlorobicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acid

1.2 Structural and molecular formulae and molecular weight



$C_9H_4Cl_6O_4$ Mol. wt: 388.85

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: White crystalline powder (Occidental Chemical Corp., 1987)

(*b*) *Melting-point*: 208-210°C, sealed tube; 230-235°C, open tube (Gupta *et al.*, 1978; Occidental Chemical Corp., 1987)

(*c*) *Spectroscopy data*: Infrared (prism [14020], grating [28088]), nuclear magnetic resonance (proton [12020]) and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Chemical Information Systems, 1988).

(*d*) *Solubility*: Slightly soluble in water (0.3% by weight at 21°C) and in nonpolar organic solvents (e.g., benzene); readily soluble in methanol, ethanol and acetone (National Toxicology Program, 1987; Occidental Chemical Corp., 1987)

(*e*) *Stability*: Loses water in a heated open system to give the anhydride (Gupta *et al.*, 1978); emits chlorine when heated to decomposition (Occidental Chemical Corp., 1987)

(*f*) *Octanol/water partition coefficient (P)*: log P, 2.30 (Chemical Information Systems, 1988)

1.4 Technical products and impurities

Trade names: Hetron 92; Hetron 92C

Chlorendic acid is available at >97% purity (Morton Thiokol, 1985). Common impurities in technical-grade chlorendic acid are maleic anhydride (maximum, 0.25%), water (maximum, 0.25%) and hexachlorocyclopentadiene (maximum, 50 ppm; Occidental Chemical N.V., 1988). Commercial chlorendic anhydride typically contains 1-3% chlorendic acid (Velsicol Chemical Corp., 1982).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Chlorendic acid is prepared in a closed system by the Diels-Alder reaction of hexachlorocyclopentadiene and maleic anhydride in a solvent, followed by hydrolysis of the anhydride (Larsen, 1980).

The US Environmental Protection Agency (1986) reported that, in 1977, 1400-14 000 tonnes of chlorendic acid were produced in the USA. In 1980, less than 4% of the 140 thousand tonnes of maleic anhydride produced in the USA was used in the manufacture of chlorendic acid and anhydride (Anon., 1980; US International Trade Commission, 1981).

Chlorendic acid is currently manufactured in Belgium (Occidental Chemical N.V., 1988), and chlorendic anhydride is manufactured in the USA, in each case by a single manufacturer. Combined production in 1987 was over 2000 tonnes but has been declining since the early 1980s (US International Trade Commission, 1988).

(*b*) *Use*

Chlorendic acid is used primarily as a chemical intermediate in the manufacture of unsaturated polyester resins, with special applications in electrical systems, panelling, engineering plastics and paints (Makhlouf, 1982). A major use is in fibreglass-reinforced resins for process equipment in chemical industries. Chlorendic acid is also used to impart flame resistance to polyurethane foams when reacted with nonhalogenated glycols to form halogenated polyols and can be used in the manufacture of alkyd resins for special paints and inks (Gupta *et al.*, 1978; Larsen, 1980; Talbot, 1984; Occidental Chemical N.V., 1988).

In Europe, 80% of the chlorendic acid produced is used in composites for flame-retardant building and transport materials. The remainder is used in composites for the manufac-

ture of anti-corrosion equipment, such as tanks, piping and scrubbers. In the USA, Latin America and the Far East, the usage pattern is reversed; 70-80% is used for anti-corrosion equipment and 20-30% for flame-retardant applications (Occidental Chemical N.V., 1988).

In the textile industry, the primary use for chlorendic acid is for flame-retardant treatment of wool fabrics. The natural flame resistance of wool is enhanced by finishing treatments with chlorendic acid in dimethylformamide (see Friedman *et al.*, 1973; Whitfield & Friedman, 1973; Seredina & Kryazhev, 1987; IARC, 1989).

(*c*) *Regulatory status and guidelines*

No data were available to the Working Group.

2.2 Occurrence

(*a*) *Natural occurrence*

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

(*b*) *Occupational exposure*

No data were available to the Working Group.

(*c*) *Environmental exposure*

It has been suggested that chlorendic acid may be released by hydrolytic degradation of polyesters that contain it. Chlorendic acid has been reported in the leachate of a landfill (National Toxicology Program, 1987). It is also an oxidation product of heptachlor and its metabolites (Cochrane & Forbes, 1974) and of endosulfan (Martens, 1972).

2.3 Analysis

In a method for determining chlorendic anhydride in water (also applicable to the acid), the sample is adsorbed on activated charcoal, extracted with ethanol in a Soxhlet apparatus, concentrated by evaporation and analysed by gas chromatography with a flame ionization detector (Ermolaeva *et al.*, 1976).

In a method for the determination of chlorendic anhydride in air (also applicable to the acid), the anhydride is separated and hydrolysed to the acid, which is methylated with diazomethane; the methyl ester is estimated by gas chromatography (Pilenkova & Fat'yanova, 1980).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, eight weeks of age, were fed 0, 620 or 1250 ppm (mg/kg) chlorendic acid (purity, >98%) in the diet for 103 weeks. All survi-

vors were killed at 112 weeks of age. The estimated mean daily intakes of chlorendic acid were 89 and 185 mg/kg bw for low-dose and high-dose males and 100 and 207 mg/kg bw for low-dose and high-dose females, respectively. Survival and feed consumption of treated mice of each sex were similar to those of controls, although mean body weights of high-dose males and females were lower than those of controls. The incidences of hepatocellular adenomas and carcinomas were significantly increased (incidental tumour test for trend) in males: adenomas occurred in 5/50 controls, 9/49 low-dose animals and 10/50 at the high dose ($p = 0.041$); carcinomas occurred in 9/50 controls, 17/49 low-dose animals and 20/50 high-dose animals ($p = 0.023$). Hepatocellular carcinomas metastasized to the lung in 2/50 male controls, 4/49 low-dose males and 7/50 high-dose males. The combined incidence of alveolar/bronchiolar adenomas and carcinomas in females was 1/50 controls, 5/50 low-dose animals and 6/50 high-dose animals ($p = 0.037$). The incidence of follicular-cell adenomas of the thyroid was significantly elevated in high-dose females: control, 0/50; low-dose, 0/47; high-dose, 3/50 ($p = 0.039$; National Toxicology Program, 1987).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, eight weeks of age, were fed 0, 620 or 1250 ppm (mg/kg) chlorendic acid (purity, >98%) in the diet for 103 weeks. All survivors were killed at 112 weeks of age. The estimated mean daily intakes of chlorendic acid were 27 and 56 mg/kg bw for low-dose and high-dose males and 39 and 66 mg/kg bw for low-dose and high-dose females, respectively. Survival and feed consumption of treated rats were similar to those of controls, although mean body weights of high-dose males and females were lower than those of controls. The incidences of neoplastic nodules of the liver [adenomas; Maronpot *et al.*, 1986] were significantly increased (incidental tumour test for trend) in both males and females: in males they occurred in 2/50 controls, 21/50 low-dose and 23/50 high-dose animals ($p < 0.001$); and in females in 1/50 controls, 3/49 low-dose and 11/50 high-dose animals ($p = 0.001$); the incidence of hepatocellular carcinomas was significantly increased in females: in 0/50 controls, 3/49 low-dose and 5/50 high-dose animals ($p = 0.023$). In males, the incidence of acinar-cell adenomas of the pancreas was significantly increased: in 0/49 controls, 4/50 low-dose and 6/50 high-dose animals ($p = 0.014$), as was the incidence of alveolar/bronchiolar adenomas: in 0/50 controls, 3/50 low-dose and 5/50 high-dose animals ($p = 0.014$). The incidences of carcinomas of the preputial gland in males were: control, 1/50; low-dose, 8/50; high-dose, 4/50; the trend is not significant (National Toxicology Program, 1987).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

^{14}C-Chlorendic acid in a solution of a polyoxyethylated vegetable oil, ethanol and water (3 mg/kg bw) was given to male Fischer 344 rats by intravenous injection or oral intubation. Following intravenous injection, more than 50% of the administered radioactivity was found in the liver within 15 min. Biliary excretion was the primary route of removal of radioactivity from the liver, which occurred with a half-life of 1.19 h. The blood contained 20% of the administered radioactivity at 1 h, and this declined with a half-life of 0.84 h. Muscle con-

tained 14% of the administered radioactivity at 15 min, and this level fell rapidly, with a half-life of 0.57 h. Smaller amounts were detected in other organs. The highest specific activity per gram of tissue (wet weight) was noted in the adrenal gland early after administration. Administration of the same solution of ^{14}C-chlorendic acid by oral intubation resulted in a somewhat higher liver concentration and a lower blood concentration at 24 h than those seen after the same time following intravenous administration. The majority of the radioactivity was found in the faeces (78% of the total dose) or large intestine. The ^{14}C-chlorendic acid-derived radioactivity in the bile, urine and faeces was attached mainly to parent compound or conjugates resistant to β-glucuronidase and aryl sulfatase (Decad & Fields, 1982).

(ii) *Toxic effects*

Male and female Fischer 344/N rats and B6C3F$_1$ mice were fed diets containing chlorendic acid for 14 days, 13 weeks or two years. In the 14-day studies, animals received diets containing 3100-50 000 ppm (mg/kg); deaths occurred only in male and female rats and in male mice given the highest dose. No treatment-related gross lesion was observed at necropsy (National Toxicology Program, 1987).

In the 13-week studies, rats received concentrations of 620-10 000 ppm (mg/kg) in the diet and mice received 1250-20 000 ppm (mg/kg); all animals survived, but reduced weight gain was noted at the higher doses. In rats, the occurrence of hepatocytomegaly and bile-duct hyperplasia was dose-dependent. Liver lesions also occurred in mice and included centrolobular cytomegaly and coagulative necrosis. The liver lesions occurred mainly in rats given 5000 and 10 000 ppm and in mice given 10 000 and 20 000 (National Toxicology Program, 1987).

Non-neoplastic lesions observed in the two-year studies (see section 3.1) included increased incidences of liver cystic degeneration and bile-duct hyperplasia in male rats and liver granulomatous inflammation and pigmentation and bile-duct hyperplasia in female rats. Liver lesions also occurred in mice and included increased incidences of necrosis in treated males (National Toxicology Program, 1987).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects* (see Appendix 1)

Chlorendic acid was not mutagenic to several strains of *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system from Aroclor 1254-induced rat liver and Syrian hamster liver (National Toxicology Program, 1987).

Chlorendic acid was mutagenic at the TK locus in cultured L5178Y mouse lymphoma cells in the absence of an exogenous metabolic system (National Toxicology Program, 1987).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Chlorendic acid is used primarily as a chemical intermediate in the manufacture of unsaturated polyester resins that have applications in electrical systems, panelling, engineering plastics and paints. It is also used in the textile industry for flame-retardant treatment of wool. No data on occupational exposure levels were available.

4.2 Experimental carcinogencity data

Chlorendic acid was tested for carcinogenicity by oral administration in one strain of mice and one strain of rats. It produced hepatocellular adenomas and carcinomas in male mice and an increase in the incidence of alveolar/bronchiolar tumours and follicular-cell adenomas of the thyroid gland in female mice. In rats, it induced hepatocellular adenomas in animals of each sex and hepatocellular carcinomas in females; in male rats, it induced an increase in the incidence of alveolar/bronchiolar adenomas and of acinar-cell adenomas of the pancreas.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

Hepatocytomegaly was observed in mice and rats fed chlorendic acid for 13 weeks.

In single studies, chlorendic acid induced mutations in mammalian cells in culture but was not mutagenic to bacteria in the presence or absence of an exogenous metabolic system.

4.5 Evaluation[1]

There is *sufficient evidence* for the carcinogenicity of chlorendic acid in experimental animals.

No data were available from studies in humans on the carcinogenicity of chlorendic acid.

Overall evaluation

Chlorendic acid is *possibly carcinogenic to humans (Group 2B)*.

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[1]For description of the italicized terms and criteria for making the evaluation, see Preamble pp. 25-29.

Summary table of genetic and related effects of chlorendic acid

Nonmammalian systems													**Mammalian systems**																													
Proka-ryotes		Lower eukaryotes				Plants			Insects				*In vitro*														*In vivo*															
													Animal cells								Human cells								Animals							Humans					
D	G	D	R	G	A	D	G	C	R	G	C	A	D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
	–[1]													+[1]																											

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the table, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

–[1] considered to be negative, but only one valid study was available to the Working Group

+[1] considered to be positive, but only one valid study was available to the Working Group.

5. References

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