CHLOROTHALONIL

This substance was considered by previous working groups, in 1982 (IARC, 1983) and 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

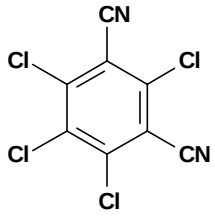
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 1897-45-6
Deleted CAS Reg. Nos: 37223-69-1; 101963-73-9
Chem. Abstr. Name: 2,4,5,6-Tetrachloro-1,3-benzenedicarbonitrile
IUPAC Systematic Name: Tetrachloroisophthalonitrile
Synonyms: 1,3-Dicyanotetrachlorobenzene; tetrachlorobenzene-1,3-dicarbonitrile; 2,4,5,6-tetrachloro-1,3-dicyanobenzene; 2,4,5,6-tetrachloroisophthalonitrile; 2,4,5,6-tetrachloro-1,3-isophthalonitrile

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_8Cl_4N_2$ Relative molecular mass: 265.91

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White, crystalline solid (National Library of Medicine, 1998a)
(*b*) *Boiling-point*: 350°C (Lide, 1997)
(*c*) *Melting-point*: 250°C (Lide, 1997)
(*d*) *Density*: 1.7 g/cm^3 at 25°C (Lide, 1997)
(*e*) *Solubility*: Insoluble in water; slightly soluble in acetone and cyclohexane (Lide, 1997)
(*f*) *Volatility*: Vapour pressure, < 1 Pa at 40°C (National Toxicology Program, 1991)

(*g*) *Octanol/water partition coefficient (P)*: log P, 2.90 (Hansch *et al.*, 1995)
(*h*) *Conversion factor*: mg/m^3 = 10.88 × ppm

1.2 Production and use

Chlorothalonil has been produced commercially since 1969 (WHO, 1996). Information available in 1995 indicated that chlorothalonil was produced in China and Italy (Chemical Information Services, 1995).

Chlorothalonil is used as an agricultural and horticultural fungicide, bactericide and nematocide (Budavari, 1996). It is also used as a preservative in paints and adhesives (National Toxicology Program, 1991).

1.3 Occurrence

1.3.1 *Natural occurrence*

Chlorothalonil is not known to occur naturally.

1.3.2 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 1998), approximately 63 000 workers in the United States were potentially exposed to chlorothalonil. Occupational exposure to chlorothalonil may occur during its production and during its use as a pesticide or preservative. Crop workers may be exposed to chlorothalonil by dermal contact and inhalation of dust during application and as a result of contact with treated foliage (National Library of Medicine, 1998a).

1.3.3 *Environmental occurrence*

Chlorothalonil has been detected in some raw agricultural commodities and foods in several countries at concentrations of 0.001–7.5 mg/kg (WHO, 1996; National Library of Medicine, 1998a).

Chlorothalonil has been found in surface water, groundwater and seawater (WHO, 1996; Cox, 1997; National Library of Medicine, 1998a).

The mean concentrations of chlorothalonil in indoor air samples have been reported to range from 0.1 to 6.7 ng/m^3 and those in outdoor air samples at the same locations from 0.2 to 0.8 ng/m^3 (National Library of Medicine, 1998a).

According to the Environmental Protection Agency Toxic Chemical Release Inventory for 1987, 9600 kg chlorothalonil were released into the air and 110 kg were discharged into water from manufacturing and processing facilities in the United States. By 1996, 7100 kg were released into the air, 10 kg were discharged into water, and 760 kg were released onto the land (National Library of Medicine, 1998b).

1.4 Regulations and guidelines

No occupational exposure limits have been proposed for chlorothalonil in workplace air in the United States, and no international guidelines for chlorothalonil in drinking-water have been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Previous evaluation

Chlorothalonil was tested in one experiment in both rats and mice by oral administration. It produced adenomas and adenocarcinomas of the renal tubular epithelium at low incidence in male and female rats. No carcinogenic effect was found in mice (IARC, 1983).

New studies

Oral administration

Mouse: Groups of 60 male and 60 female CD-1 mice [age unspecified] were given diets containing chlorothalonil at doses of 0, 125, 250 or 550 mg/kg bw per day for 24 months. Survival was unaffected by treatment. Chlorothalonil increased the incidence of renal tubular tumours in male mice, but without a clear dose–response relationship, the incidences being: control, 0/60; low dose, 6/60, intermediate dose, 4/60; and high-dose, 5/60. No renal tumours were seen in females. There was a close association between renal tubular hyperplasia and renal tumour incidence in males, and a much lower incidence of tubular hyperplasia in females. Animals of each sex showed increased incidences of forestomach tumours, again with no clear dose–response relationship, the incidences being: males—control, 0/60; low dose, 2/60; intermediate dose, 5/60; and high dose, 2/60; females—control, 0/60; low dose, 2/60; intermediate dose, 4/60; and high dose, 5/59. Forestomach tumours were associated with squamous-cell hyperplasia and hyperkeratosis in all treated groups (Wilkinson & Killeen, 1996).

In a second study, male CD-1 mice were fed diets containing chlorothalonil at 1.6, 4.5, 21.3 and 91.3 mg/kg bw per day for two years. No renal tumours were observed, but there was a slight increase in the incidence of forestomach tumours at the high dose. Dose-related increases in the incidence of associated hyperplasia were seen, commencing at 21.3 mg/kg bw for the renal tubules and at 4.5 mg/kg bw for the forestomach lining (Wilkinson & Killeen, 1996).

Rat: Groups of 60 male and 60 female Fischer 344 rats were given diets containing chlorothalonil at 0, 40, 80 or 175 mg/kg bw per day for 27 months for males and for 30 months for females. Survival was unaffected by treatment. Chlorothalonil increased the incidence of renal tubular tumours (adenomas and carcinomas) in a dose-related manner at all doses in animals of each sex. The incidence of forestomach tumours (squamous-cell papillomas and carcinomas) was also increased in males and females (Table 1). A close association was seen between renal tubular hyperplasia and renal tumorigenicity

Table 1. Incidences of primary tumours in Fischer 344 rats exposed orally to chlorothalonil

Treatment (mg/kg bw per day)	Sex	Animals with tumours	
		Kidney[a]	Forestomach[b]
None	M	0/60	0/60
40		7/60	1/60
80		7/60	1/60
175		19/60	3/60
None	F	0/60	0/60
40		3/60	1/60
80		6/60	2/60
175		23/60	7/60
None	M	1/55	0/55
1.8		1/54	0/54
3.8		1/54	3/54
15		4/54	2/54
175		23/55	5/55
None	F	0/55	1/55
1.8		0/54	1/54
3.8		0/55	2/55
15		0/53	5/53
175		32/55	9/55

From Wilkinson & Killeen (1996); no statistical analysis provided
[a] Renal tubular adenoma or carcinoma
[b] Squamous-cell papilloma or carcinoma

and between squamous-cell hyperplasia and forestomach tumorigenicity (Wilkinson & Killeen, 1996).

In a second study, groups of 55 male and 55 female Fischer 344 rats received diets containing chlorothalonil at doses of 0, 1.8, 3.8, 15 or 175 mg/kg bw for either 23–26 months (males) or 29 months (females). The incidence of renal tubular tumours and forestomach tumours was increased at the high dose in animals of each sex (Table 1; Wilkinson & Killeen, 1996).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

The toxicokinetics of chlorothalonil in rats has been reviewed (Wilkinson & Killeen, 1996). After oral administration, the amount of chlorothalonil absorbed is dose-related. Thus, while approximately 30% of an administered dose of up to 50 mg/kg bw was absorbed, absorption at higher doses decreased, being only 15% at 200 mg/kg bw. Chlorothalonil reacts readily with glutathione, and glutathione conjugation is the primary route of metabolism. The liver is the major organ for the conjugation of chlorothalonil with glutathione: 9 and 18 h after oral administration of 5000 mg/kg bw chlorothalonil to rats, hepatic glutathione was depleted by 20 and 40%, respectively. The major urinary metabolites are trithiomonochloroisophthalonitrile and dithiomonochloroisophthalonitrile and the corresponding methylthio derivatives. The di- and triglutathione conjugates of chlorothalonil formed in the liver may be secreted into the bile, undergo enterohepatic circulation as intact glutathione conjugates or cysteine conjugates, return to the liver for further processing and be transported directly to the kidney, as demonstrated by their presence in blood. The chlorothalonil metabolites arriving in the kidney consist of a mixture of di-and tri-glutathione conjugates, cysteine *S*-conjugates and possibly some mercapturic acids. The glutathione conjugates are completely cleaved in the proximal tubules by γ-glutamyl transpeptidase and dipeptidases to the cysteine *S*-conjugates, which are subsequently cleaved by β-lyases to the corresponding thiol derivatives. Since mercapturic acids have not been identified in the urine, these compounds are probably deacetylated to the corresponding cysteine *S*-conjugates, which may undergo bioactivation to a reactive thiol by β-lyase (Wilkinson & Killeen, 1996).

A comparative study in rats, dogs and rhesus monkeys demonstrated that rats excrete the largest amount of thiol-derived materials in the urine. During the first 24 h after oral administration of chlorothalonil to rats, about 1.6% of the administered dose (50 mg/kg bw) was excreted in the urine as di- and trithiol-derived metabolites. In contrast, rhesus monkeys excreted less than 0.06% of the applied dose in the form of thiol derivatives during the same time, and no thiol-derived metabolites were identified in the urine of dogs (Savides *et al.*, 1991).

4.2 Toxic effects

4.2.1 *Humans*

Contact dermatitis due to exposure to chlorothalonil was diagnosed over a period of two years in three workers in greenhouses in which chlorothalonil was used (Bruynzeel & van Ketel, 1986).

Contact urticaria was reported after diagnostic application of diluted chlorothalonil (0.01% aqueous solution) to intact skin (Dannaker *et al.*, 1993). The patient had experienced immediate respiratory reactions (tight chest and throat) after entering a nursery greenhouse in which chlorothalonil and other pesticides had been applied. Chlorothalonil was present at 300 ppm in the air, while the other pesticides were not detectable. Since the patient showed skin reactions after direct application of chlorothalonil, but not after that of

the other pesticides used in the nursery, chlorothalonil can be considered the cause of the allergic reaction.

Patch tests for chlorothalonil were performed in two groups of field workers in banana plantations in Panama: 39 workers with erythema-dyschromicum-perstans-like dermatitis (ashy dermatitis) and 41 control workers without skin symptoms (Penagos *et al.*, 1996). Thirty-four (87%) of the 39 workers with dermatitis and none of the controls showed positive reactions to chlorothalonil; the difference was highly significant. The group with dermatitis did not have positive reactions to 16 additional pesticides used in the banana plantations.

4.2.2 *Experimental systems*

Daily oral administration of approximately equimolar doses of chlorothalonil (75 mg/kg bw per day) or the monoglutathione conjugate of chlorothalonil (150 mg/kg bw per day) to male Fischer 344 rats over 90 days resulted in significantly increased kidney weights and histopathological signs of nephrotoxicity: proximal tubular hyperplasia, tubular dilatation, vacuolar degeneration and interstitial fibrosis. The parent compound also induced gross and microscopic changes in the forestomach, which were not seen with the glutathione conjugate (Wilson *et al.*, 1990).

Fischer 344 rats fed diets containing chlorothalonil at 175 mg/kg bw per day for up to 91 days showed multifocal ulceration and erosion of the stomach mucosa, which subsequently progressed to hyperplasia and hyperkeratosis. The first evidence of kidney damage was seen on day 4, as marked vacuolization of the proximal tubular epithelial cells; this was followed on day 14 by tubular hyperplasia (Wilkinson & Killeen, 1996).

Chlorothalonil administered in the diet of dogs at daily doses of up to 500 mg/kg bw for 12 months did not induce proliferative or degenerative changes in the kidney (Wilkinson & Killeen, 1996).

Incubation of hepatocytes from male Sprague-Dawley rats for up to 90 min with 0.1 mmol/L chlorothalonil reduced the non-protein sulfhydryl content to 13% that of controls and stimulated lipid peroxidation, as evidenced by malondialdehyde production, while cell viability was reduced to only 84% that of the controls. Chlorothalonil at 1 mmol/L reduced the non-protein sulfhydryl content of hepatocytes to 4.8% that of controls and the cell viability to 14% that of controls. The cytotoxic effects on isolated hepatocytes were probably directly associated with a reduction in non-protein sulfhydryls, since addition of dithiothreitol prevented the cytotoxicity of chlorothalonil (Yamano & Morita, 1995).

A comparative investigation in isolated Wistar rat hepatocytes of cytotoxicity and induction of lipid peroxidation, as assessed by measuring the content of hydroperoxide in phospholipid, showed chlorothalonil to be one of the most potent of 10 pesticides. At 1 mmol/L, chlorothalonil reduced survival to practically zero and increased the phosphatidylcholine hydroperoxide concentration by 23-fold when compared with controls, indicating oxidative damage (Suzuki *et al.*, 1997).

Feeding diets containing chlorothalonil at doses of 125, 250 or 550 mg/kg bw per day to CD1 mice for 24 months resulted in renal tubular tumours, cortical tubular degeneration and proximal tubular hyperplasia in males at all doses and a low incidence of the non-neoplastic changes in female mice (Wilkinson & Killeen, 1996).

Male CD1 mice fed diets containing chlorothalonil at doses of 1.6, 4.5, 21.3 or 91.3 mg/kg bw per day for 24 months showed no renal tumours, but the incidence of tubular hyperplasia was slightly increased at doses ≥ 21.3 mg/kg bw per day. Forestomach tumours were found at the highest dose, and dose-related increases in hyperplasia and hyperkeratosis of the forestomach epithelium were observed at doses ≥ 4.5 mg/kg bw per day (Wilkinson & Killeen, 1996).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 2 for references)

Chlorothalonil was not mutagenic to *Salmonella typhimurium* or *Escherichia coli* WP2 *hcr*. It induced point mutations in strains *biA1*, *meth G1* and 118 of *Aspergillus nidulans* in the absence of metabolic activation. Chlorothalonil did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*. It weakly induced forward mutation in L5178Y $tk^{+/-}$ mouse lymphoma cells in the absence of metabolic activation in two of three independent experiments. It increased the frequency of sister chromatid exchange in Chinese hamster ovary cells in the presence but not in the absence of a liver microsomal preparation from Aroclor 1254-induced rats. Chlorothalonil induced chromosomal aberrations in Chinese hamster ovary cells.

A statistically significant, dose-dependent increase in DNA damage, as evaluated in the comet assay, was observed in peripheral blood lymphocytes of humans exposed to chlorothalonil.

Chlorothalonil did not form adducts in calf thymus DNA when incubated with rat liver microsomes, as tested by ^{32}P-postlabelling.

A dose-dependent increase in the 8-hydroxy-2-deoxyguanosine concentration in liver DNA, indicative of oxidative damage, was observed in rats treated *in vivo*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to chlorothalonil may occur during its production and during its application as a fungicide, bactericide and nematocide. It has been detected in some foods.

Table 2. Genetic and related effects of chlorothalonil

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without metabolic activation	With metabolic activation		
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	–	–	7.64 µg/plate	Wei (1982)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	–	–	5000 µg/plate	Moriya *et al*. (1983)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, reverse mutation	–	–	10 µg/plate	Mortelmans *et al*. (1986)
Escherichia coli WP2, reverse mutation	–	–	5000 µg/plate	Moriya *et al*. (1983)
Aspergillus nidulans (strains biA1, methG1 and 118), forward mutation	+	NT	0.4	Martinez-Rossi & Azevedo (1987)
Drosophila melanogaster, sex-linked recessive lethal mutations	–		10 000	Yoon *et al*. (1985)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	(+)	NT	0.12	McGregor *et al*. (1988)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	+	2.50	Galloway *et al*. (1987)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	+	0.5	Galloway *et al*. (1987)
DNA strand breaks, cross-links or related damage (comet assay), human lymphocytes *in vitro*	+	NT	2.7	Lebailly *et al*. (1997)
DNA damage, rat liver *in vivo*	+		0.13 po × 10	Lodovici *et al*. (1997)
Binding (covalent) to DNA *in vitro*	NT	–	266	Shah *et al*. (1997)

[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 per day; po, oral

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Chlorothalonil was tested by oral administration in the diet in three experiments in mice and three experiments in rats. It produced renal tubular tumours (adenomas and carcinomas) in males of each species and in female rats. The incidences of forestomach papillomas and carcinomas were increased in males and females of each species.

5.4 Other relevant data

Chlorothalonil is metabolized in rats by conjugation to glutathione in the gastrointestinal tract and liver. After biliary excretion, uptake and metabolism of these conjugates in the kidney by the action of γ-glutamyl transpeptidase and cysteine–conjugate β-lyase results in the production of di- and tri-thiols, which are thought to be responsible for the toxicity seen in the kidney. Sustained cytotoxicity and the resultant regenerative response in the kidney are found in conjunction with tumour formation after long-term exposure.

There may be less activity of γ-glutamyl transpeptidase and cysteine–conjugate β-lyase in humans than in rats.

Forestomach tumours produced by chlorothalonil were associated with squamous hyperplasia and local irritation.

No data were available on reproductive or developmental effects.

No data were available on the genetic and related effects of chlorothalonil in humans or in rodents *in vivo*. In one study, 8-oxydeoxyguanosine products were observed in the livers of mice exposed *in vivo*. There is some evidence for genotoxicity in mammalian cells *in vitro*. Chlorothalonil was not mutagenic to bacteria.

5.5 Evaluation

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

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

Overall evaluation

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

6. References

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