

CAPTAFOL

1. Exposure Data

1.1 Chemical and physical data

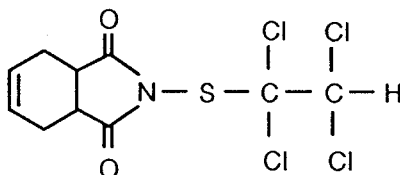
1.1.1 Synonyms, structural and molecular data

Chem. Abstr. Serv. Reg. No.: 2425-06-1

Chem. Abstr. Name: 3 α ,4,7,7 α -Tetrahydro-2-[(1,1,2,2-tetrachloroethyl)thiol]-1*H*-isoin-dole-1,3-(2*H*)dione

IUPAC Systematic Name: *N*-[(1,1,2,2-Tetrachloroethyl)thio]cyclohex-4-ene-1,2-dicar-boximide

Synonyms: *N*-[(1,1,2,2-Tetrachloroethyl)thio]-4-cyclohexene-1,2-dicarboximide; tetra-chloroethylthiotetrahydrophthalimide; *N*-(tetrachloroethylthio)tetrahydrophthalimide; *N*-(1,1,2,2-tetrachloroethylthio)- δ 4-tetrahydrophthalimide; 3 α ,4,7,7 α -tetrahydro-*N*-(1,1,2,2-tetrachloroethanesulfenyl)phthalimide



$C_{10}H_9Cl_4NO_2S$

Mol. wt: 349.06

1.1.2 Chemical and physical properties

- Description:* Colourless to pale-yellow crystals (Royal Society of Chemistry, 1989). The technical material is light-tan with a slight pungent odour (Pack, 1967).
- Melting-point:* 162°C (pure compound) (US Environmental Protection Agency, 1984a)
- Spectroscopy data:* Infrared spectroscopy data have been reported (US Environmental Protection Agency, 1975).
- Solubility:* Practically insoluble in water (1.4 mg/l at 20°C); slightly soluble in most organic solvents (g/kg): isopropanol, 13; benzene, 25; toluene, 17; xylene, 100; acetone, 43; methyl ethyl ketone, 44; dimethyl sulfoxide, 170 (Royal Society of Chemistry, 1989)
- Stability:* Slowly hydrolysed in aqueous emulsion or suspension; rapidly hydrolysed in acidic and alkaline media; decomposes slowly at the melting-point; corrosive to metals (Royal Society of Chemistry, 1989)
- Vapour pressure:* Negligible at room temperature (Royal Society of Chemistry, 1989)
- Conversion factor for airborne concentrations*¹: $mg/m^3 = 14.28 \times ppm$

¹Calculated from: $mg/m^3 = (\text{molecular weight}/24.45) \times ppm$, assuming standard temperature (25°C) and pressure (760 mm Hg [101.3 kPa])

1.1.3 Trade names, technical products and impurities

Some examples of common trade names are: Alfloc; Arborseal; CS 5623; Difolatan; Folcid; Foltaf; Haipen 50; Merpafol; Nalco 7046; Ortho 5865; Proxel EF; Santar SM; Terrazol (Worthing & Walker, 1987; Meister, 1990).

In the USA, the technical-grade product must contain at least 97% captafol as the sole active ingredient (US Environmental Protection Agency, 1984a). It has been formulated as dusts, emulsifiable concentrates, flowable suspensions, wettable powders and water-dispersible granules. The usual carriers are clay, talc (see IARC, 1987a), silica (see IARC, 1987b) and water (US Environmental Protection Agency, 1984b).

Formulated captafol products registered in European countries include coating agents, liquid formulations, pastes, suspension concentrates and wettable powders (Royal Society of Chemistry, 1986).

Captafol may be combined with most commonly used insecticides and fungicides, with the exception of strongly alkaline materials and oil sprays (Meister, 1990). It has been formulated in the USA in combination with triadimefon, carbendazim, folpet, ofurace, flutriafol, ethirimol, diclobutrazol, propiconazole, copper oxychloride, cymoxanil and halacrinat (Worthing & Walker, 1987). Formulations have also contained oxadiyl fenpropimorph, pyrazophos, captan (see IARC, 1983, 1987c), triadimenol and thiabendazole (Royal Society of Chemistry, 1986).

1.1.4 Analysis

Selected methods for the analysis of captafol in various matrices are given in Table 1.

Table 1. Methods for the analysis of captafol

Sample matrix	Sample preparation	Assay procedure ^a	Limit of detection	Reference
Specified fruits and vegetables	Extract with benzene; clean-up with thin-layer chromatography on silica gel or silicic acid column chromatography with or without preliminary hexane-acetonitrile partitioning	GC/ECD	0.1 ppm (mg/kg)	US Food and Drug Administration (1989a)
Maize, peanuts, tomatoes	Extract with ethyl acetate; clean-up by acetonitrile-hexane partitioning, acetonitrile-water-hexane partitioning and Florisil column chromatography	GC/ECD	0.1 ppm	US Food and Drug Administration (1989b)
Formulations	Extract with dichloromethane; centrifuge; filter	HPLC/UV	Not reported	Zweig & Sharma (1978)
Fruits, vegetables and oils	Extract with ethyl acetate; clean-up with either acetate-water, acetonitrile-hexane, or acetonitrile-water-hexane partitioning and Florisil column chromatography	GC/ECD or FID	Not reported	US Food and Drug Administration (1989c)

^aAbbreviations: GC/ECD, gas chromatography/electron capture detection; GC/FID, gas chromatography/flame ionization detection; HPLC/UV, high-performance liquid chromatography/ultraviolet detection

1.2 Production and use

1.2.1 Production

Captafol is prepared by the reaction of tetrahydrophthalimide and 1,1,2,2-tetrachloroethylsulfenyl chloride in the presence of aqueous sodium hydroxide (Pack, 1967). It was first produced commercially and registered for use in the USA in 1961 (County NatWest WoodMac, 1990). It is produced currently by two companies in India (Meister, 1990).

Production of captafol in the USA was estimated to be 3600-4500 tonnes (active ingredient) per year in 1979-81, of which half was exported (US Environmental Protection Agency, 1982). The sole US producer had a production of 6600 tonnes in 1985 (County NatWest WoodMac, 1990); that manufacturer ceased production in 1987 (Agriculture Canada, 1990).

1.2.2 Use

Captafol is a fungicide which has been used for the control of fungal diseases of fruits, vegetables, ornamental plants and turf grasses. It is also used to control certain seed- and soil-borne organisms (Pack, 1967). Captafol and/or its metabolites and degradates are absorbed by roots and shoots of plants and translocated in plant tissue as a result of seed treatment, soil treatment and foliar application (US Environmental Protection Agency, 1984b).

Captafol is used to control scab of pome fruit, shot-hole of stone fruit, peach leaf curl, downy mildew and black rot of vines, early and late blights of potatoes, *Alternaria* and mildew of carrots, celery leaf spot, *Septoria* of wheat, *Rhynchosporium* of barley and various diseases of tomatoes, coffee, groundnuts, citrus fruit, pineapples, macadamia nuts, onions, cucurbits, maize, sorghum, etc. Captafol is also used as a seed treatment for control of *Pythium* and *Phoma* species and other emergence diseases of beetroot, cotton, groundnuts and rice. In addition, it is used as a protector for grafting and pruning wounds and cankers on trees and in the timber industry as a wood preservative (Royal Society of Chemistry, 1989).

Types and methods of application include dusting, spraying, misting and dipping under pressure for wood treatment (US Environmental Protection Agency, 1984b).

In the USA, annual use of captafol (active ingredient) as a pesticide in 1979-81 was about 500 tonnes for apples, 500 tonnes for cherries, 410 tonnes for citrus fruits, 240 tonnes for potatoes, 200 tonnes for tomatoes, 110 tonnes for sweet maize, 60 tonnes for plums, 10 tonnes for watermelon and 110 tonnes for other crops (US Environmental Protection Agency, 1982).

1.3 Occurrence

Some 1520 samples were analysed for captafol residues as part of the Canadian national surveillance programme between 1984 and 1989. Residues were found in nine samples: one of eight peaches, five of 200 pears and three of 97 tomatoes, at levels of 0.01-0.8 mg/kg (Government of Canada, 1990). Apples grown in Ontario (305 samples) were monitored for terminal residues of pest control chemicals on raw fruit offered for sale during the period 1978-86. On the 0.4% of crops treated with captafol, no residue was detected (detection limit, 0.02 mg/kg) (Frank *et al.*, 1989).

When fruit and vegetables were monitored in the United Kingdom at the point of sale, in 1981-82, residues of captafol at 0.02-0.7 mg/kg were found in six of 33 domestic potato samples and at 0.02-0.2 mg/kg in three of 16 imported potato samples (FAO/WHO, 1986a).

1.4 Regulations and guidelines

National and regional pesticide residue limits for captafol in foods are presented in Table 2.

Table 2. National and regional pesticide residue limits for captafol in food^a

Country or region	Residue limit (mg/kg)	Commodities
Argentina	10	Sour cherries
	5	Cucumber, tomato, melon, peach, watermelon
	2	Plum, sweet cherry
	0.5	Grapefruit, mandarin, orange
	0.25	Apple, pear
Austria	0.1	Vegetables
Belgium	0 ^b (0.05)	All foodstuffs of vegetable origin
Brazil	15	Peaches
	5	Apples, pears, eggplants, tomatoes
	2	Squash, honeydew melons, cucumbers, nectarines, watermelons
	1.0	Grapes, pineapples (treatment of seedlings)
	0.5	Carrots, citrus fruit, coffee, onions, peanuts (shelled), potatoes
	0.2	Wheat, rice
	0.1	Cottonseed, green beans, strawberries (treatment of seedlings)
	0.05	Peanuts
0.04	Field beans	
Chile	15	Peaches
	10	Plums
	5	Apples, pears, tomatoes
	2	Cherries
	0.5	Carrots, onions, potatoes
	0.2	Wheat
	0.1 ^c	Carcasses ^d (sheep, hogs, goats and cattle), milk
Czechoslovakia ^e	15	Peaches
	10	Sour cherries
	5.0	Tomatoes
	2.0	Cherries, cucumbers, melons
Denmark	0.05 ^c	All other foods, berries and small fruits, carrots, cereals, citrus fruits, leafy vegetables, other fruits, other root vegetables and onions, pome and stone fruits, potatoes
European Community	0.05	All products
Finland	2	Other (except cereal grains)
	0.5	Carrots, onions, potatoes
France	0.05	Cereal grains, fruits and vegetables
Germany	0.05	All foods of plant origin

Table 2 (contd)

Country or region	Residue limit (mg/kg)	Commodities
Hungary	15 ^e	Peaches
	10 ^e	Grapefruits, lemons, mandarins, oranges
	5	Apples, Brussels' sprouts, cabbage cauliflower, celery leaf, cherries, grapes, green beans, greenhouse tomatoes, green paprikas, kohlrabi, lettuce, pears, savoy, strawberries, tomatoes
	2.0	Cantaloupe, cucumbers, pumpkin, watermelons, wine grapes
	0.5	Beetroot, carrots, celery, horseradish, onion (green, red), parsley root, radish
Ireland	0.05	All products
Israel	5	Apples, eggplant, pears
	2	Pumpkin
	0.5	Carrots, onions, potatoes
	0.1	Almonds
Italy	8	Leafy garden vegetables, tobacco
	5	Hops, other fruit and garden vegetables
	2	Potatoes, root vegetables
	0.2	Cereals, sugar beets
	0.05	Fruit and garden vegetables
Japan	5	Apples, Japanese pear, fruit ^f
	1.0	Cabbage, garden radish, garden radish leaves, potatoes ^f , tea ^f , vegetables ^f , etc.
Kenya	15	Peaches
	10	Sour cherries
	5	Tomatoes
	2	Melons (whole), sweet cherries
	1.0	Cucumbers (whole)
	0.5	Apricots
	0.2	Plums
Netherlands	8	Leaf vegetables
	5	Fruit, other vegetables
	2	Root, tuber vegetables
	0.05 ^g	Cereals
	0 (0.05) ^h	Other
Singapore	15	Apricots, nectarines, peaches
	5.0	Other fruits and vegetables
South Africa	10	Pineapples
	5	Avocados
	3	Coffee, tomatoes
	0.5	Potatoes
Spain	0.05 ⁱ	All plant products
Sweden	0.05 ^c	Cereals and hulled grains, flakes and flour made from cereals, fruits and vegetables, potatoes
Switzerland	0.1	Cereals, potatoes

Table 2 (contd)

Country or region	Residue limit (mg/kg)	Commodities
Taiwan	1.0	Berries, melons
	0.5	Citrus fruits, fruit vegetables, nut fruits, pome and stone fruits, tropical fruits
	0.1	Root vegetables
	0.01	Rice
United Kingdom	0.05 ⁱ	Apples, bananas, barley, beans, black currants, Brussels' sprouts, cabbage, carrots, cauliflower, celery, cucumber, grapes, leeks, lettuce, maize, mushrooms, nectarines, oats, onions, oranges, other cereals, other citrus, paddy rice, pears, peaches, peas, plums, potatoes, raspberries, rye, strawberries, swedes, tomato, turnips, wheat
USA	50	Sour cherries
	35	Blueberries
	30	Apricots, peaches
	15	Tomatoes
	8	Cranberries
	5	Melons
	2	Cucumbers, nectarines, peanuts (hulls), plums (fresh prunes), sweet cherries
	0.5	Citrus fruits, potatoes
	0.25	Apples
	0.1	Fresh corn, macadamia nuts, onions, pineapples
	0.05	Peanuts (meats hulls removed)
	0.02	Taro (corn)
Yugoslavia	3.0	Fruit, vegetables
	0.1	Other food commodities

^aFrom Health and Welfare Canada (1990)

^bThe figure in parentheses is the lower limit for determining residues in the corresponding product according to the standard method of analysis.

^cDose at detectable limit or close to same

^dMuscle tissue including attached adipose tissue

^eIn imported produce

^fStandards for withholding established registration

^gA pesticide may be used on an eating or drinking ware or raw material without a demonstrable residue remaining behind. The value listed is considered the highest concentration at which this requirement is deemed to have been met.

^hResidues shall be absent; value in parentheses indicates highest concentration at which requirement is met.

ⁱExtraneous residue limit

^jAt the limit of detection except for peaches, nectarines and plums

International temporary maximum residue limits for captafol residues in raw agricultural commodities, ranging from 0.05 to 50 ppm (mg/kg), established by the Codex Committee on Pesticide Residues (US Environmental Protection Agency, 1984b) and the temporary acceptable daily intake values established by the Joint Meeting on Pesticide Residues in 1982 (FAO/WHO, 1983) were deleted in 1985 (FAO/WHO, 1986a).

The occupational exposure limit for captafol is 0.1 mg/m³ (time-weighted average) in Denmark, Mexico, the Netherlands, Switzerland, the United Kingdom, the USA and Venezuela, with a skin notation in Mexico, the Netherlands, Switzerland, the United Kingdom and the USA (Cook, 1987; Arbejdstilsynet, 1988; American Conference of Governmental Industrial Hygienists, 1989; US Occupational Safety and Health Administration, 1989).

The FAO/WHO Joint Meeting on Pesticide Residues evaluated permethrin at its meetings in 1969, 1973, 1974, 1976, 1977, 1982 and 1985 (FAO/WHO, 1970, 1974, 1977, 1978, 1983, 1986a,b). The technical product captafol was classified by the WHO (1990) as 'extremely hazardous'. Several countries have banned the use of this pesticide, including Canada (1987) and Germany (1988) (Agriculture Canada, 1990; County NatWest WoodMac, 1990).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Oral administration

Mouse: Groups of 50-51 male and 50-51 female B6C3F₁ mice, six weeks old, were fed a diet containing captafol (94.9% pure; [impurities unspecified]) at 0, 0.075, 0.15 or 0.3% (maximum tolerated dose) for 96 weeks and the basal diet for a further eight weeks. Survivors were killed at 104 weeks. Dose-related retardation of body weight gain and increased mortality (particularly in the high-dose group) were observed. Mice surviving at week 104 were: males—33/50 control, 34/51 low-dose, 34/51 mid-dose and 0/51 high-dose; females—35/50 controls, 39/51 low-dose, 23/51 mid-dose and 0/51 high-dose. A dose-related increase in the incidence of heart haemangioendothelioma was observed in animals of each sex. Significant increases in the incidences of tumours were also seen at some other sites: forestomach papillomas in high-dose females and small intestinal adenoma, hepatocellular carcinoma and splenic angioma in males and females (Table 3). The increase in the incidence of small intestinal adenocarcinomas in males and females was possibly dose-related, although the incidence in the mid-dose group was higher than that in the high-dose group, probably due to earlier death in the latter, in which significant mortality was seen at approximately 80 weeks (Ito *et al.*, 1984).

Rat: Four groups of 49-50 male and 49-50 female Fischer 344 rats, four weeks of age, received a diet containing 0, 500, 2000 or 5000 mg/kg captafol (Merpafol; 97% pure) for 104 weeks, after which time they were killed. The high-dose group was sacrificed after 98 weeks of treatment, due to excess mortality (78% in males and 60% in females at week 96). A dose-related increase in the incidence of nonneoplastic renal lesions was found in males and females (tubular cystic dilatation, glomerulonephropathy, cystic tubules lined by cells with giant nuclei). Renal tumours were found only in treated males: one, three and 12 carcinomas in the low-, mid- and high-dose groups, respectively (positive trend, $p < 0.001$) (Nyska *et al.*, 1989).

Table 3. Occurrence of tumours in B6C3F₁ mice fed captafol in the diet^a

Site and type of tumour	Control	Concentration (%) of captafol		
		0.075	0.15	0.3
<i>Males</i>				
Effective number of mice	47	51	46	47
Heart haemangioendothelioma	0	1	4*	20*** ^b
Forestomach papilloma	0	2	3	2
Forestomach squamous cell carcinoma	0	0	1	2
Small intestinal adenoma	0	3	0	4*
Small intestinal adenocarcinoma	0	7**	32***	22***
Hepatocellular carcinoma	8	23**	15	1
Splenic haemangioma	0	0	5*	0
<i>Females</i>				
Effective number of mice	48	50	49	51
Heart haemangioendothelioma	0	2	2	11*** ^b
Forestomach papilloma	0	1	1	4*
Forestomach squamous cell carcinoma	0	0	0	1
Small intestinal adenoma	0	3	3	5*
Small intestinal adenocarcinoma	0	3	13***	7**
Hepatocellular carcinoma	2	13**	12**	0
Splenic haemangioma	0	2	4*	0

^aFrom Ito *et al.* (1984)

^b[Positive trend test ($p < 0.01$)]

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Groups of 50 male and 50 female Fischer 344/DuCrj rats, six weeks of age, were fed diets containing 0, 750 or 1500 mg/kg captafol (97.5% pure) for 104 weeks and then the normal diet for a further eight weeks, after which time the experiment was terminated. Mean body weights in males and females of the high-dose group and in females of the low-dose group were reduced. There was no difference in survival times between control and treated rats; about 60% of rats survived to week 112. Statistically significant increased incidences of tumours of the kidney and liver were observed in treated rats, as shown in Table 4 (Tamano *et al.*, 1990).

4. Other Relevant Data

The toxicokinetics and toxicity of captafol have been reviewed (FAO/WHO, 1970, 1974, 1978, 1983, 1986a,b).

4.1 Absorption, distribution, metabolism and excretion

No published data were available to the Working Group.

Table 4. Occurrence of tumours in Fischer 344/DuCrj rats fed captafol in the diet^a

Site and type of tumour	Control	Concentration (%) of captafol	
		750	1500
<i>Males</i>			
Effective number of rats	50	49	50
Renal-cell adenoma	0	26***	38***
Renal-cell carcinoma	0	1	8**
Hyperplastic (neoplastic) nodule (liver)	2	8*	21***
Hepatocellular carcinoma	2	0	1
Forestomach papilloma	0	0	3
<i>Females</i>			
Effective number of rats	50	50	50
Renal-cell adenoma	0	8**	6*
Renal-cell carcinoma	0	0	0
Hyperplastic (neoplastic) nodule (liver)	3	14**	34***
Hepatocellular carcinoma	0	0	4
Forestomach papilloma	0	1	0

^aFrom Tamano *et al.* (1990)

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

4.2 Toxic effects

4.2.1 Humans

Contact dermatitis has been reported after exposure to captafol (Takamatsu *et al.*, 1968; Groundwater, 1977; Stoke, 1979; Matsushita *et al.*, 1980; Brown, 1984).

4.2.2 Experimental systems

The oral LD₅₀ for captafol in rats is 2500-6200 mg/kg bw, and the dermal LD₅₀ in rabbits is 15 400 mg/kg bw (Ben-Dyke *et al.*, 1970).

In rats, single intraperitoneal doses of captafol at 5 mg/kg bw decreased liver monoxygenase content and activity and increased plasma transaminase levels (Dalvi & Mutinga, 1990).

Captafol was given in the diet at 3000 mg/kg for six weeks, two weeks after a single intraperitoneal dose of *N*-nitrosodiethylamine (200 mg/kg bw) to male Fischer rats that were also subjected to a two-thirds hepatectomy three weeks after the start of the study. Significant increases were seen in the number and area of glutathione *S*-transferase-positive liver foci at eight weeks compared to rats treated with *N*-nitrosodiethylamine and partial hepatectomy alone (Ito *et al.*, 1988).

4.3 Reproductive and developmental effects

4.3.1 Humans

No data were available to the Working Group.

4.3.2 Experimental systems

Captafol has an *N*-substituted phthalimide-like structure similar to hydrolysis products of thalidomide. It was shown to have no teratogenic effect in two thalidomide-sensitive strains of rabbits (New Zealand white and Dutch belted) (Kennedy *et al.*, 1968) or in thalidomide-sensitive rhesus monkeys (Vondruska *et al.*, 1971). The rabbits received oral doses on days 6-16 of gestation of up to 75 mg/kg bw daily (Dutch belted) and on days 6-18 of up to 150 mg/kg bw daily (New Zealand). The monkeys received up to 25 mg/kg bw per day on days 22-32 of gestation. [The Working Group noted that the low doses used were reported to cause no systemic maternal toxicity in the monkeys, and no mention was made of the doses at which metabolites similar to those of thalidomide would occur in relevant concentrations.]

In Syrian hamsters, increased maternal and fetal lethality and teratogenic effects (fused ribs, short or curved tail, limb defects) were observed at oral doses of 200 mg/kg bw and above on days 7 or 8 of gestation (Robens, 1970).

4.4 Genetic and related effects (see also Table 5 and Appendices 1 and 2)

4.4.1 Humans

No data were available to the Working Group.

4.4.2 Experimental systems

Captafol caused DNA damage and gene mutation in bacteria; exogenous metabolic systems reduced or abolished the activity, as did rat blood or cysteine when captafol was tested in an *Escherichia coli* reverse mutation assay. [Only a few experiments have been performed with an exogenous metabolic system; their effect is supported by more extensive data on captan, a structural analogue.] In a single study with *Aspergillus nidulans*, captafol induced mitotic recombination and gene mutation, but not aneuploidy. Captafol induced sister chromatid exchange, micronucleus formation and chromosomal aberrations in cultured mammalian and human cell lines.

In dominant lethal tests in rats, captafol induced a small, but significant, trend towards increased numbers of early deaths per pregnancy (males treated intraperitoneally or orally). No such effect was observed in a single study in mice given one intraperitoneal injection of captafol. [The apparent species difference may be attributable to the doses and route of administration used.]

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Captafol is a fungicide that has been widely used since 1961 for the control of fungal diseases in fruits, vegetables and some other plants.

Table 5. Genetic and related effects of captafol

Test system	Result ^a		Dose ^b LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BSD, <i>Bacillus subtilis</i> rec strain (H17 vs M45), differential toxicity	+	0	0.1000	Shirasu <i>et al.</i> (1976)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	2500.0000	Moriya <i>et al.</i> (1983)
SAF, <i>Salmonella typhimurium</i> SV3, arabinose resistance	-	-	0.3000	Ruiz-Vásquez <i>et al.</i> (1978)
SA2, <i>Salmonella typhimurium</i> TA102, reverse mutation	+	+	0.0800	Barrueco & de la Peña (1988)
SA3, <i>Salmonella typhimurium</i> TA1530, reverse mutation (spot test)	+	0	0.0000	Seiler (1973)
SA4, <i>Salmonella typhimurium</i> TA102, reverse mutation	-	-	0.3000	Barrueco & de la Peña (1988)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	-	0	0.0000	Kada <i>et al.</i> (1974)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutatin	-	0	25.0000	Shirasu <i>et al.</i> (1976)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation (spot test)	-	-	200.0000	Carere <i>et al.</i> (1978)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	-	-	2500.0000	Moriya <i>et al.</i> (1983)
SA7, <i>Salmonella typhimurium</i> TA1537, reverse mutation	-	0	0.0000	Kada <i>et al.</i> (1974)
SA7, <i>Salmonella typhimurium</i> TA1537, reverse mutation (spot test)	-	-	200.0000	Carere <i>et al.</i> (1978)
SA7, <i>Salmonella typhimurium</i> TA1537, reverse mutation	-	-	2500.0000	Moriya <i>et al.</i> (1983)
SA8, <i>Salmonella typhimurium</i> TA1538, reverse mutation	-	0	0.0000	Kada <i>et al.</i> (1974)
SA8, <i>Salmonella typhimurium</i> TA1538, reverse mutation (spot test)	-	-	200.0000	Carere <i>et al.</i> (1978)
SA8, <i>Salmonella typhimurium</i> TA1538, reverse mutation	-	-	2500.0000	Moriya <i>et al.</i> (1983)
SA9, <i>Salmonella typhimurium</i> TA98, reverse mutation	-	-	2500.0000	Moriya <i>et al.</i> (1983)
SAS, <i>Salmonella typhimurium</i> his G46, reverse mutation (spot test)	+	0	0.0000	Seiler (1973)
SAS, <i>Salmonella typhimurium</i> TA1531, reverse mutation (spot test)	-	0	0.0000	Seiler (1973)
SAS, <i>Salmonella typhimurium</i> TA1532, reverse mutation (spot test)	-	0	0.0000	Seiler (1973)
SAS, <i>Salmonella typhimurium</i> TA1534, reverse mutation (spot test)	-	0	0.0000	Seiler (1973)
SAS, <i>Salmonella typhimurium</i> TA1536, reverse mutation	-	0	0.0000	Kada <i>et al.</i> (1974)
SAS, <i>Salmonella typhimurium</i> TA1536, reverse mutation (spot test)	-	-	200.0000	Carere <i>et al.</i> (1978)
EC2, <i>Escherichia coli</i> B/r WP2, reverse mutation	+	0	50.0000	Kada <i>et al.</i> (1974)
EC2, <i>Escherichia coli</i> WP2, reverse mutation	+	0	25.0000	Shirasu <i>et al.</i> (1976)
EC2, <i>Escherichia coli</i> WP2 <i>hcr</i> , reverse mutation	+	0	25.0000	Shirasu <i>et al.</i> (1976)
EC2, <i>Escherichia coli</i> WP2 <i>hcr</i> , reverse mutation	+	-	26.0000	Moriya <i>et al.</i> (1978)
EC2, <i>Escherichia coli</i> WP2 <i>hcr</i> + cysteine, reverse mutation	-	0	26.0000	Moriya <i>et al.</i> (1978)

Table 5 (contd)

Test system	Result ^a		Dose ^b LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
EC2, <i>Escherichia coli</i> WP2 <i>hcr</i> , reverse mutation	+	+	2.5000	Moriya <i>et al.</i> (1983)
ANG, <i>Aspergillus nidulans</i> , genetic crossing-over	+	0	0.2000	Bignami <i>et al.</i> (1977)
* <i>Aspergillus nidulans</i> , non-disjunction	-	0	2000.0000	Bignami <i>et al.</i> (1977)
ANF, <i>Aspergillus nidulans</i> , forward mutation	+	0	20.0000	Bignami <i>et al.</i> (1977)
SIC, Sister chromatid exchange, Chinese hamster V79 cells <i>in vitro</i>	+	0	0.7000	Tezuka <i>et al.</i> (1980)
SIC, Sister chromatid exchange, Chinese hamster Don cells <i>in vitro</i>	+	0	3.5000	Sasaki <i>et al.</i> (1980)
MIA, Micronucleus test, Chinese hamster Don cells <i>in vitro</i>	+	0	3.5000	Sasaki <i>et al.</i> (1980)
CIC, Chromosomal aberrations, Chinese hamster V79 cells <i>in vitro</i>	+	0	3.5000	Tezuka <i>et al.</i> (1980)
CIC, Chromosomal aberrations, Chinese hamster CHL cells <i>in vitro</i>	+	-	4.0000	Ishidate (1988)
SIH, Sister chromatid exchange, human HE 2144 cells <i>in vitro</i>	+	0	3.5000	Sasaki <i>et al.</i> (1980)
MIH, Micronucleus test, human HE 2144 cells <i>in vitro</i>	+	0	3.5000	Sasaki <i>et al.</i> (1980)
CIH, Chromosomal aberrations, human HE 2144 cells <i>in vitro</i>	+	0	3.5000	Sasaki <i>et al.</i> (1980)
HMM, Host-mediated assay, <i>Salmonella typhimurium</i> G46, CR mouse	-	0	250.0000 × 1 i.p.	Kennedy <i>et al.</i> (1975)
DLM, Dominant lethal test, CD mouse	-	0	3.0000 × i.p.	Kennedy <i>et al.</i> (1975)
DLR, Dominant lethal test, Osborne-Mendel rat	(+)	0	10.0000 × 5 i.p.	Collins (1972)
DLR, Dominant lethal test, Osborne-Mendel rat	(+)	0	200.0000 × 5 p.o.	Collins (1972)

*Not displayed on profile

^a+, positive; (+), weakly positive; -, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

^bIn-vitro tests, µg/ml; in-vivo tests, mg/kg bw

It has been formulated for use as dusts, emulsifiable concentrates, flowable suspensions and water-dispersible granules, and also in combination with other pesticides.

Exposure can occur during its production and application and, at much lower levels, from consumption of foods containing residues.

5.2 Carcinogenicity in humans

No data were available to the Working Group.

5.3 Carcinogenicity in experimental animals

Captafol was tested for carcinogenicity in one study in mice and in two studies in rats by oral administration. In mice, it produced a high incidence of adenocarcinomas of the small intestine and of vascular tumours of the heart and spleen; the increase in tumours of the heart was dose-related for animals of each sex. Increases in the incidence of hepatocellular carcinomas were also observed in animals of each sex. In two studies in rats, captafol produced a dose-related increase in the incidence of renal carcinomas in males; in one of these, it also induced dose-related increases in the incidence of benign renal tumours in females and of liver tumours in males and females.

5.4 Other relevant data

In one study, captafol increased the frequency of enzyme-positive foci in rat liver.

Captafol did not affect embryonic development in rabbits or monkeys but was embryolethal and teratogenic at high doses in hamsters.

No data were available on the genetic and related effects of captafol in humans.

Administration of captafol induced dominant lethal effects in rats. Captafol induced positive results in various short-term tests in human and mammalian cells *in vitro*, including gene mutation and chromosomal aberrations. It induced DNA damage and gene mutation in fungi and bacteria.

5.5 Evaluation¹

No data were available from studies in humans.

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

In making the overall evaluation, the Working Group took into consideration the following supporting evidence: Captafol is active in a wide range of tests for genetic and related effects, including the generally insensitive in-vivo assay for dominant lethal mutation.

Overall evaluation

Captafol is *probably carcinogenic to humans (Group 2A)*.

¹For definition of the italicized terms, see Preamble, pp. 26-28.

6. References

- Agriculture Canada (1990) *Cancellation of Captafol Fungicide*, Ottawa, Food Production and Inspection Branch, Pesticide Directorate
- American Conference of Governmental Industrial Hygienists (1989) *Threshold Limit Values and Biological Exposure Indices for 1988-1989*, Cincinnati, OH, p. 13
- Arbejdstilsynet (Labour Inspection) (1988) *Graensevaerdier for Stoffer og Materialer* (Limit Values for Compounds and Materials) (No. 3.1.0.2), Copenhagen, p. 13 (in Danish)
- Barrueco, C. & de la Peña, E. (1988) Mutagenic evaluation of the pesticides captan, folpet, captafol, dichlofluanid and related compounds with the mutants TA102 and TA104 of *Salmonella typhimurium*. *Mutagenesis*, 3, 467-480
- Ben-Dyke, R., Sanderson, D.M. & Noakes, D.N. (1970) Acute toxicity data for pesticides (1970). *World Rev. Pest Control*, 9, 119-127
- Bignami, M., Anlicino, F., Velcich, A., Carere, A. & Morpurgo, G. (1977) Mutagenic and recombinogenic action of pesticides in *Aspergillus nidulans*. *Mutat. Res.*, 46, 395-402
- Brown, R. (1984) Contact sensitivity to difolatan (captafol). *Contact Derm.*, 10, 181-182
- Carere, A., Ortali, V.A., Cardamone, G., Torracca, A.M. & Raschetti, R. (1978) Microbiological mutagenicity studies of pesticides *in vitro*. *Mutat. Res.*, 57, 277-286
- Collins, T.F.X. (1972) Dominant lethal assay. II. Folpet and difolatan. *Food Cosmet. Toxicol.*, 10, 363-371
- Cook, W.A., ed. (1987) *Occupational Exposure Limits—Worldwide*, Washington DC, American Industrial Hygiene Association, pp. 20, 49, 85, 168-169
- County NatWest WoodMac (1990) *Update of the Agrochemical Products Section*, Parts 1 and 2, London, County NatWest Securities Limited Incorporating Wood Mackenzie & Co., Agrochemical Service
- Dalvi, R.R. & Mutinga, M.L. (1990) Comparative studies of the effects on liver and liver microsomal drug-metabolizing enzyme system by the fungicides captan, captafol and folpet in rats. *Pharmacol. Toxicol.*, 66, 231-233
- FAO/WHO (1970) *1969 Evaluations of Some Pesticide Residues in Food. The Monographs* (FAO/PL:1969/M/17/1; WHO/Food Add./70.38), Rome
- FAO/WHO (1974) *1973 Evaluations of Some Pesticide Residues in Food. The Monographs* (FAO/AGP/1973/M/9/1; WHO Pesticide Residues Series No. 3), Rome
- FAO/WHO (1977) *1976 Evaluations of Some Pesticide Residues in Food. The Monographs* (FAO/AGP/1976/M/14), Rome
- FAO/WHO (1978) *Pesticide Residues in Food: 1977 Evaluations* (FAO Plant Production and Protection Paper 10 Sup.), Rome
- FAO/WHO (1983) *Pesticide Residues in Food—1982. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues* (FAO Plant Production and Protection Paper 46), Rome
- FAO/WHO (1986a) *Pesticide Residues in Food—1985. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues* (FAO Plant Production and Protection Paper 72/1), Rome
- FAO/WHO (1986b) *Pesticide Residues in Food—1986. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues* (FAO Plant Production and Protection Paper 77), Rome

- Frank, R., Braun, H.E. & Ripley, B.D. (1989) Monitoring Ontario-grown apples for pest control chemicals used in their production, 1978-86. *Food Addit. Contam.*, 6, 227-234
- Government of Canada (1990) *Report on National Surveillance Data from 1984/85 to 1988/89*, Ottawa
- Groundwater, J.R. (1977) Difolatan dermatitis in a welder; nonagricultural exposure. *Contact Derm.*, 3, 104
- Health and Welfare Canada (1990) *National Pesticide Residue Limits in Food*, Ottawa, Bureau of Chemical Safety, Food Directorate, Health Protection Branch
- IARC (1983) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 30, *Miscellaneous Pesticides*, Lyon, pp. 295-318
- IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*, Lyon, pp. 349-350
- IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*, Lyon, pp. 341-343
- IARC (1987c) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*, Lyon, p. 59
- Ishidate, M., Jr (1988) *Data Book of Chromosomal Aberration Test In Vitro*, rev. ed., Amsterdam, Elsevier, p. 79
- Ito, N., Ogiso, T., Fukushima, S., Shibata, M. & Hagiwara, A. (1984) Carcinogenicity of captafol in B6C3F₁ mice. *Gann*, 75, 853-865
- Ito, N., Tsuda, H., Tatematsu, M., Inoue, T., Tagawa, Y., Aoki, T., Uwagawa, S., Kagawa, M., Ogiso, T., Masui, T., Imaida, K., Fukushima, S. & Asamoto, M. (1988) Enhancing effect of various hepatocarcinogens on induction of preneoplastic glutathione S-transferase placental form positive foci in rats—an approach for a new medium-term bioassay system. *Carcinogenesis*, 9, 387-394
- Kada, T., Moriya, M. & Shirasu, Y. (1974) Screening of pesticides for DNA interactions by 'rec-assay' and mutagenesis testing, and frameshift mutagens detected. *Mutat. Res.*, 26, 243-248
- Kennedy, G., Fanchier, O.E. & Calandra, J.C. (1968) An investigation of the teratogenic potential of captan, folpet and difolatan. *Toxicol. appl. Pharmacol.*, 13, 420-430
- Kennedy, G.L., Jr, Arnold, D.W. & Keplinger, M.L. (1975) Mutagenicity studies with captan, captafol, folpet and thalidomide. *Food Cosmet. Toxicol.*, 13, 55-61
- Matsushita, T., Nomura, S. & Wakatsuki, T. (1980) Epidemiology of contact dermatitis from pesticides in Japan. *Contact Derm.*, 6, 255-259
- Meister, R.T., ed. (1990) *Farm Chemicals Handbook '90*, Willoughby, OH, Meister Publishing Company, p. C56
- Moriya, M., Kato, K. & Shirasu, Y. (1978) Effects of cysteine and liver metabolic activation system on the activities of mutagenic pesticides. *Mutat. Res.*, 57, 259-263
- Moriya, M., Ohta, T., Watanabe, K., Miyazawa, T., Kato, K. & Shirasu, Y. (1983) Further mutagenicity studies on pesticides in bacterial reversion assay systems. *Mutat. Res.*, 116, 185-216
- Nyska, A., Waner, T., Pirak, M., Gordon, E., Bracha, P. & Klein, B. (1989) The renal carcinogenic effect of merpafor in the Fischer 344 rat. *Isr. J. med. Sci.*, 25, 428-432
- Pack, D.E. (1967) Difolatan. In: Zweig, G., ed., *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives*, Vol. 5, *Additional Principles and Methods of Analysis*, New York, Academic Press, pp. 293-304

- Robens, J.F. (1970) Teratogenic activity of several phthalamide derivatives in the golden hamster. *Toxicol. appl. Pharmacol.*, *16*, 24-34
- Royal Society of Chemistry (1986) *European Directory of Agrochemical Products*, Vol. 1, *Fungicides*, Cambridge, pp. 46-56
- Royal Society of Chemistry (1989) *The Agrochemicals Handbook* [Dialog Information Services (File 306)], Cambridge
- Ruiz-Vásquez, R., Pueyo, C. & Cerdá-Olmedo, E. (1978) A mutagen assay detecting forward mutations in an arabinose-sensitive strain of *Salmonella typhimurium*. *Mutat. Res.*, *54*, 121-129
- Sasaki, M., Sugimura, K., Yoshida, M.A. & Abe, S. (1980) Cytogenetic effects of 60 chemicals on cultured human and Chinese hamster cells. *Kromosomo II*, *20*, 574-584
- Seiler, J.P. (1973) A survey on the mutagenicity of various pesticides. *Experientia*, *29*, 622-623
- Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A. & Kada, T. (1976) Mutagenicity screening of pesticides in the microbial system. *Mutat. Res.*, *40*, 19-30
- Stoke, J.C.J. (1979) Captafol dermatitis in the timber industry. *Contact Derm.*, *5*, 284-292
- Takamatsu, M., Futatsuka, M., Arimatsu, Y., Maeda, H., Inuzuka, T. & Takamatsu, S. (1968) Epidemiological survey on dermatitis from a new fungicide used in tangerine orchards in Kumamoto Prefecture. *J. Kumamoto med. Soc.*, *42*, 854-859
- Tamano, S., Kurata, Y., Yamada, M., Yamamoto, A., Hagiwara, A., Cabral, R. & Ito, N. (1990) Carcinogenicity of captafol in F344/DuCrj rats. *Jpn. J. Cancer Res.*, *81*, 1222-1231
- Tezuka, H., Ando, N., Suzuki, R., Terahata, M., Moriya, M. & Shirasu, Y. (1980) Sister-chromatid exchanges and chromosomal aberrations in cultured Chinese hamster cells treated with pesticides positive in microbial reversion assays. *Mutat. Res.*, *78*, 177-191
- US Environmental Protection Agency (1975) Infrared spectra of pesticides. In: *Manual of Chemical Methods for Pesticides and Devices*, Arlington, VA, Association of Official Analytical Chemists
- US Environmental Protection Agency (1982) *Preliminary Quantitative Usage Analysis of Captafol*, Washington DC, Office of Pesticide Programs
- US Environmental Protection Agency (1984a) *Guidance for the Registration of Pesticide Products Containing Captafol as the Active Ingredient* (EPA Case Number 116), Washington DC
- US Environmental Protection Agency (1984b) *Pesticide Fact Sheet: Captafol*, Washington DC
- US Food and Drug Administration (1989a) Captafol method II. In: *Pesticide Analytical Manual*, Vol. II, *Methods Which Detect Multiple Residues*, Washington DC, US Department of Health and Human Services, pp. 1-9
- US Food and Drug Administration (1989b) Captafol method IIa. In: *Pesticide Analytical Manual*, Vol. II, *Methods Which Detect Multiple Residues*, Washington DC, US Department of Health and Human Services, pp. 10-14
- US Food and Drug Administration (1989c) Captafol method A. In: *Pesticide Analytical Manual*, Vol. II, *Methods Which Detect Multiple Residues*, Washington DC, US Department of Health and Human Services, pp. 15-17
- US Occupational Safety and Health Administration (1989) Air contaminants—permissible exposure limits. *US Code fed. Regul.*, Title 29, Part 1910.1000
- Vondruska, J.F., Fanchier, O.E. & Calandra, J.C. (1971) An investigation into the teratogenic potential of captan, folpet and difolatan in nonhuman primates. *Toxicol. appl. Pharmacol.*, *18*, 619-624
- WHO (1990) *The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 1990-91*, Geneva, p. 11

- Worthing, C.R. & Walker, S.B., eds (1987) *The Pesticide Manual: A World Compendium*, 8th ed., Thornton Heath, British Crop Protection Council, pp. 121-122
- Zweig, G. & Sherma, J., eds (1978) *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. X, *New and Updated Methods*, New York, Academic Press, pp. 171-173