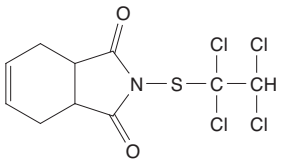
Captafol

CAS No. 2425-06-1

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)

Also known as Difolatan (formerly a registered trademark of Chevron Chemical Company)



Carcinogenicity

Captafol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data on mechanisms of carcinogenesis.

Cancer Studies in Experimental Animals

Oral exposure to captafol caused tumors at several different tissue sites in rats and mice. Long-term feeding studies were conducted with two mouse strains (CD-1 and $B6C3F_1$) (Ito *et al*. 1984, Quest *et al*. 1993, NTP 2008) and two rat strains (Crl:CD and F344) (Nyska *et al*. 1989, Tamano *et al*. 1990, Quest *et al.* 1993, NTP 2008). In mice of both sexes, tumors were predominantly of the vascular system, gastrointestinal system, and liver; they included (1) cancer of the lymphoid tissue (lymphosarcoma) in CD-1 mice, (2) blood-vessel cancer (hemangiosarcoma) in $B6C3F_1$ and CD-1 mice, (3) benign tumors of blood vessels of the spleen (splenic hemangioma) in $B6C3F_1$ mice, (4) benign and malignant tumors of the small intestine in $B6C3F_1$ mice, and (5) liver cancer (hepatocellular carcinoma) in $B6C3F_1$ mice. Benign Harderian-gland tumors (adenoma) also were observed in CD-1 males (Ito *et al.* 1984, Quest *et al.* 1993). In rats, captafol caused liver and kidney tumors in several studies and benign mammary-gland tumors (fibroadenoma) in female Crl:CD rats in one study (Nyska *et al.* 1989, Tamano *et al.* 1990, Quest *et al.* 1993). Benign liver tumors (hepatocellular adenoma) were observed in female Crl:CD rats and in F344 rats of both sexes, and a significant dose-related trend was observed for malignant liver tumors (hepatocellular carcinoma) in female F344 rats (Tamano *et al.* 1990, Quest *et al.* 1993, NTP 2008). Captafol caused benign kidney tumors (renal-cell adenoma) in F344 rats of both sexes and malignant kidney tumors (renal-cell carcinoma) in F344 males (Nyska *et al.* 1989, Tamano *et al.* 1990). In Crl:CD rats, the combined incidence of benign and malignant kidney tumors (renal-cell adenoma and carcinoma) was increased in males, and a significant dose-related trend was observed for malignant kidney tumors (renal-cell carcinoma) in both sexes (Quest *et al.* 1993, NTP 2008).

Captafol was shown to be hepatotoxic and to induce potentially preneoplastic glutathione S-transferase placental form positive (GST-P+) foci in the liver of male F344 rats (NTP 2008) in both the initiation and promotion phases of studies of tumor development. In addition, promotion with captafol increased the incidences of hyperplasia of the forestomach and adenoma of the small intestine (Uwagawa *et al.* 1991), thyroid follicular-cell adenoma (Ito *et al.* 1996), and the expression of a marker of cell proliferation (proliferating-cell nuclear antigen) in the kidney (Kim *et al.* 1997) in F344 rats.

Studies on Mechanisms of Carcinogenesis

In rodents, captafol is absorbed through the gastrointestinal tract and lung and to a lesser extent through the skin; however, the available data indicate that captafol and its metabolites do not accumulate in the tissues of animals and are rapidly eliminated, primarily in the urine. The metabolism and disposition of captafol after oral absorption is anticipated to be similar in experimental animals and humans (NTP 2008). Two metabolic pathways, based primarily on oral absorption, have been proposed; one pathway involves reaction of captafol with cellular thiol-containing molecules such as glutathione and cysteine, and the other involves hydrolysis of the N–S bond. Both pathways are relevant to the mechanism of carcinogenesis, as the reaction of captafol with thiol groups can lead to cytotoxicity, and metabolites derived from the side chain have been shown to be carcinogenic. Tetrahydrophthalimide is a product of both reaction pathways and has been identified in blood, urine, and feces of rats, dogs, and monkeys (Hayes 1982). However, tetrahydrophthalimide has not been tested in carcinogenicity bioassays. Dichloroacetic acid (previously shown to be carcinogenic in mice) was identified as a minor metabolite of captafol in rodents (NTP 2008). Another reported metabolite of captafol is 2-chloro-2-methyl-thioethylene sulfonic acid (which is derived from the side chain) (IPCS 1990). The proposed mechanism for formation of this metabolite is through transient formation of an episulfonium ion, a DNA alkylating agent (IPCS 1990, Williams 1992, Bernard and Gordon 2000).

Short-term *in vitro* and *in vivo* genotoxicity studies support mutagenicity as a mechanism of carcinogenesis. Captafol is an alkylating agent and has produced genotoxic effects in a variety of systems (NTP 2008). It caused mutations in *Salmonella typhimurium* (base-pair mutations) and *Escherichia coli* and in non-mammalian *in vivo* systems (*Aspergillus nidulans* and *Drosophila melanogaster*). In *in vitro* studies with cell lines from rodents and other mammals, captafol caused DNA single-strand breaks, sister chromatid exchange, chromosomal aberrations, micronucleus formation, polyploidy (in one of two studies), mitotic spindle disturbances, and cell transformation. In human cells *in vitro*, it caused DNA single-strand breaks, sister chromatid exchange, micronucleus formation, and chromosomal aberrations. In rodents exposed *in vivo,* captafol caused DNA strand breaks, micronucleus formation (Robbiano *et al.* 2004), and dominant lethal mutations in rats (Collins 1972) but did not cause mutations in the host-mediated assay in rats or dominant lethal mutations in albino mice (Kennedy *et al.* 1975).

In addition to direct genotoxic activity, epigenetic mechanisms, such as cytotoxicity as a result of reduced cellular content of thiol groups (nonprotein and protein), inhibition of enzymes involved in DNA replication (DNA topoisomerases and polymerases), inhibition of DNA and RNA synthesis, and induction of cytochrome P450 mono-oxygenases may also be involved in the pathogenesis of tumor formation (NTP 2008).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to captafol. One case-control study (Clary and Ritz 2003) directly addressed captafol exposure. This study was based upon an ecologic (group-level) exposure assessment and included 17 other chlorinated pesticides. A statistically nonsignificant increase in pancreatic cancer was reported among residents who had lived for over 20 years in geographical areas with high captafol use; however, confounding by other cancer risk factors could not be ruled out, and the study was limited by imprecise measures of exposure and diseases.

Properties

Captafol is a broad-spectrum nonsystemic fungicide that is categorized as a phthalimide fungicide based on its tetrahydrophthalimide chemical ring structure (other phthalimide fungicides include captan and folpet). Captafol exists as white, colorless to pale-yellow, or tan (technical grade) crystals or as a crystalline solid or powder, with a slight characteristic pungent odor. It is practically insoluble in water but is soluble or slightly soluble in most organic solvents. Captafol reacts with bases, acids, acid vapors, and strong oxidizers (HSDB 2010). It hydrolyzes slowly in aqueous emulsions or suspensions, but rapidly in acidic and basic aqueous alkaline media (Akron 2010). Captafol will not burn, but when heated to decomposition, it emits toxic fumes, including nitrogen oxides, sulfur oxides, phosgene, and chlorine (IPCS 1993). Physical and chemical properties of captafol are listed in the following table.

Property	Information
Molecular weight	349.1[a]
Density	1.64 ± 0.1 g/cm^3 at 20°C (calculated from molar volume)[b]
Melting point	160°C to 161°C (decomposes slowly)[c]
Log K_{ow}	3.8 at 25°C[a]
Water solubility	1.4 mg/L at 20°C; 2.24 mg/L at 25°C[d]
Vapor pressure (mm Hg)	8.27×10^{-9} at 20°C[d]
Vapor density relative to air	12[e]
Dissociation constant (pK_a)	–2.67 ± 0.20 at 25°C[b]

Sources: [a]HSDB 2010, [b]CAS 2008, [c]BCPC 2006, [d]Kim *et al.* 1997, [e]Akron 2010.

Use

Captafol is a nonsystemic fungicide used to control fungal diseases of fruits, vegetables, ornamental plants, and grasses and as a seed treatment. It also was used in the timber industry to control woodrot fungi on logs and wood products (IARC 1991, IPCS 1990). Captafol was produced and used as a fungicide in the United States until 1987, when all registrants of captafol products requested voluntary cancellation of their registrations. Legal use of existing stocks was allowed after 1987; however, in 1999, the U.S. Environmental Protection Agency further restricted its use, and all captafol tolerances were revoked except those for onions, potatoes, and tomatoes. These remaining tolerances were revoked in 2006. Although many countries banned its use, captafol was still used as of the mid 2000s in several countries that exported agricultural products to the United States, including Mexico and Brazil; however, by 2010, no countries were identified that still allowed the use of captafol on food crops.

Production

Captafol is produced by the reaction of tetrahydrophthalimide and 1,1,2,2-tetrachloroethylsulfenyl chloride in the presence of aqueous sodium hydroxide (IARC 1991). It was first registered and produced commercially in the United States in 1961 as Difolatan (IPCS 1993). From 1979 to 1981, annual U.S. production of captafol was estimated to be 3,600 to 4,500 metric tons (8 million to 10 million pounds) (as active ingredient), of which about half was exported (IARC 1991). In 1983, captafol was produced by one U.S. company, whose annual production capacity was 12 million pounds (SRI 1984). Production in 1985 was estimated at 6,600 metric tons (14.5 million pounds) (IARC 1991). In 2010, no producers of captafol were identified worldwide (SRI 2010), but Difolatan (a captafol fungicide) was available from ten suppliers, including five in the United States, one in France, one in Hong Kong, two in India, and one in South Africa. In addition, Captafol Pestanal (an analytical standard for captafol) was available from two U.S. suppliers and one Swiss supplier (Chem Sources 2010).

Exposure

In the past, exposure to captafol occurred by ingestion, inhalation, or dermal contact. The potential for exposure of both the general population and agricultural workers would have been greatest from the late 1970s through the mid 1980s, when annual domestic usage was estimated to be at least 4 million pounds. In the past, the general population was potentially exposed to captafol through ingestion of contaminated groundwater or agricultural products sprayed with captafol, through exposure to topsoil, or through its application in nearby agricultural settings. In the United States, captafol was no longer produced after 1987 or used after 2006. It is possible, though highly unlikely, that individuals could be exposed by ingestion of imported fruits or vegetables treated with captafol. The U.S. Food and Drug Administration's Pesticide Residue Monitoring Program and the U.S. Department of Agriculture's Pesticide Data Program detected captafol at low levels in food samples in the 1980s and 1990s, but have not detected it since 1998. No captafol residues were detected in the FDA's Total Diet Study (FDA 1988, 1989, 1993, Yess *et al.* 1993, Gunderson 1995). Between 1993 and 2003, captafol was detected once in animal feed, at a concentration of 0.036 ppm in a barley sample from Maryland in 1999 (FDA 2000).

In air, captafol is expected to exist solely in the particulate phase, based on its vapor pressure; however, some reports suggest that it exists in the vapor phase. In water, captafol is expected to adsorb to sediment and suspended solids. In soil, captafol is expected to have slight mobility, based on its soil organic carbon–water partition coefficient (HSDB 2010). Volatilization from soil is not expected to be an important fate process. Reported values for captafol's half-life in soil vary among sources, ranging from less than 3 days to around 11 days (Extoxnet 1995, HSDB 2010). Captafol has been detected in the vicinity of agricultural uses outside the United States; it was detected in air in Canada (Frank *et al.* 1994), in surface water in Spain (Picó *et al.* 1994, Vioque-Fernandez *et al.* 2007) and Italy (Readman *et al.* 1997), and in soil in India (Venkatramesh and Agnihothrudu 1988). Runoff losses of captafol with natural rainfall were less than 0.1% of the amount applied (Kim *et al.* 1996).

U.S. workers previously were exposed to captafol during its production, formulation, or application to agricultural fields; on reentry to a sprayed field; or when working with treated timber products (IPCS 1993, HSDB 2010). In a study of worker exposure to Difolatan 80 Sprills (80% captafol) in central Florida orange groves, aerosolized captafol concentrations averaged 56 μg/m^3 for mixer-loaders and 34 μg/m^3 for spray applicators. Hourly dermal exposure levels were approximately 1 to 10 μg/cm^2 for the hands, legs, and arms; however, levels of up to 20 μg/cm^2 were seen when direct contact with captafol solution was evident. Whole-body exposures ranged from 15 to 116 mg/h, with a mean of 40 mg/h; the hands accounted for about 40% of total exposure (Popendorf 1988).

Captafol toxicity was reported in exposed workers. Peoples *et al.* (1978) presented 37 brief case reports of exposure during the manufacture and application of captafol that had been reported to the California Department of Food and Agriculture from 1974 through 1976. The reports reflected toxic outcomes of possible captafol exposure that were reported by physicians, including systemic, skin, and eye toxicity. Positive patch tests for captafol or a history of occupationally induced dermatitis were reported in studies of workers who packed captafol (Camarasa 1975), workers exposed to captafol in timber-treatment plants (Stoke 1979), agricultural workers and former agricultural workers (Lisi *et al.* 1986, 1987, Guo *et al.* 1996, Rademaker 1998), flower-shop workers (Thiboutot *et al.* 1990), and laboratory chemists (Brown 1984).

Regulations

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Limitations: Daily discharge maximum = 4.24×10^{-6} kg/kkg (kg/metric ton); monthly average discharge maximum = 1.31×10^{-6} kg/kkg.

Federal Insecticide, Fungicide, and Rodenticide Act

Classified as Group B, probable human carcinogen based on mammary-gland and liver tumors in female Sprague-Dawley rats, kidney tumors in both male and female rats, and lymphosarcoma and hemangiosarcoma in both male and female CD-1 mice, with Harderian-gland tumors in male mice.

Food and Drug Administration (FDA, an HHS agency)

Tolerance levels have been revoked for all foods, thereby making it illegal to import or introduce into commerce any foods with captafol residue.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 mg/m^3.
Potential for dermal absorption.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Recommended exposure limit (REL) = 0.1 mg/m^3.
Potential for dermal absorption.
Listed as a potential occupational carcinogen.

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