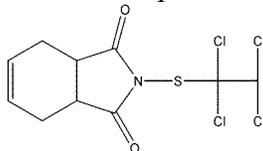


Captafol

CAS No. 2425-06-1

Reasonably anticipated to be a human carcinogen

First listed in the 12th Report on Carcinogens



Carcinogenicity

Captafol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting mechanistic data. Captafol induced tumors at multiple tissue sites in rats and mice. Long-term feeding studies have been conducted in two strains (CD-1 and B6C3F₁) of mice (Quest *et al.* 1993, Ito *et al.* 1984, NTP 2008) and two strains (CrI:CD and F344) of rats (Nyska *et al.* 1989, Tamano *et al.* 1990, Quest *et al.* 1993, NTP 2008) of both sexes. In mice of both sexes, tumors were primarily in the vascular system, gastrointestinal system, and liver. Neoplasms (abnormal groups of cells) observed in different strains of mice fed captafol included: (1) lymphosarcoma (lymph node cancer) (CD-1), (2) hemangiosarcoma (blood vessel cancer) (B6C3F₁, CD-1), (3) splenic hemangioma (benign tumor of blood vessels in the spleen) (B6C3F₁), (4) benign and malignant lesions in the small intestine (B6C3F₁), (5) hepatocellular carcinoma (liver cancer) (B6C3F₁), and (6) Harderian gland adenoma (benign tumor of a tear-producing gland in the eyelid) (CD-1, in males only) (Ito *et al.* 1984, Quest *et al.* 1993).

In rats, liver and kidney neoplasms have been reported in multiple studies, and one study reported significantly increased mammary-gland fibroadenomas (benign tumors of the connective tissue of the milk-producing gland) in CrI:CD female rats (Nyska *et al.* 1989, Tamano *et al.* 1990, Quest *et al.* 1993). Hepatic neoplastic nodules were reported in female CrI:CD rats, and in both sexes of F344 rats, with an increasing trend for hepatocellular carcinomas in female F344 rats (Quest *et al.* 1993, Tamano *et al.* 1990). Renal-cell adenomas were induced in F344 rats of both sexes, with carcinomas in males only (Tamano *et al.* 1990, Nyska *et al.* 1989). In CrI:CD rats, an increased incidence of renal-cell carcinoma and adenoma combined was observed in males, and a significant trend was noted for renal-cell tumors in both sexes.

Captafol has been shown to be hepatotoxic and to induce potentially preneoplastic glutathione S-transferase placental form positive (GST-P+) foci in the liver in F344 male rats (NTP 2008) in both the initiation and promotion phases of experimental studies of tumor development. In addition, promotion with captafol significantly increased the incidences of forestomach hyperplasia and adenoma of the small intestine (Uwagawa *et al.* 1991), thyroid follicular 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.

The available data from epidemiological studies are inadequate to evaluate the relationship of human cancer and specific exposure 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 non-significant increase in pancreatic cancer was reported among residents living for greater than 20 years in geographical areas with high captafol usage; however, confounding could not be ruled out, and the study was limited by imprecise measures of exposure and diseases.

Additional Information Relevant to Carcinogenicity

In rodents, captafol is absorbed through the gastrointestinal tract and lung and to a lesser extent through the skin, but available data indicate that the chemical 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 in 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 the hydrolysis of the N-S bond. Tetrahydrophthalimide is a product of both reaction pathways and has been identified in blood, urine, and feces in rats, dogs, and monkeys (reviewed by Hayes 1982). Dichloroacetic acid (a chemical previously shown to be carcinogenic in mice) has been identified as a minor metabolite of captafol in rodent studies (NTP 2008). Another reported metabolite of captafol is 2-chloro-2-methylthioethylene sulfonic acid (which is derived from the side-chain) (WHO 1990). The proposed mechanism for formation of this metabolite is through transient formation of an episulfonium ion, a DNA alkylating agent (WHO 1990, Williams 1992, Bernard and Gordon 2000).

Short-term genotoxicity studies *in vivo* and *in vitro* 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* strains that detect base-pair change, in *Escherichia coli*, and in non-mammalian *in vivo* systems (the fungus *Aspergillus nidulans* and the fruit fly *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 (one positive and one negative study), 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 mammalian *in vivo* studies, captafol administered to rats caused DNA strand breaks and micronucleus formation (Robbiano *et al.* 2004), and dominant lethal mutations (Collins 1972), but did not cause mutations in the host-mediated assay (Kennedy *et al.* 1975). Captafol did not cause 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 P-450 monooxygenases may also be involved in the pathogenesis of tumor formation (NTP 2008).

Properties

Captafol is a nonsystemic broad-spectrum fungicide (i.e., it is applied topically and works outside the plants to which it is applied). Captafol is categorized as a phthalimide fungicide based on its tetrahydrophthalimide chemical ring structure. Other phthalimide fungicides include captan and folpet (HSDB 2006).

Captafol exists as white, colorless to pale yellow, or tan (technical grade) crystals, 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 2006). It hydrolyzes slowly in aqueous emulsions or suspensions, but rapidly in acidic and basic aqueous alkaline media (UAkron 2004). Captafol will not burn, but when heated to decomposition, it emits toxic fumes such as nitrogen oxides, sulfur oxides, phosgene, and chlorine (WHO 1993). The physical and chemical properties of captafol are summarized in the following table.

Property	Information
Molecular weight	349.1
Melting point	160°C–161°C (slow decomposition)
Octanol-water partition coefficient (log K_{ow})	[3.2]–3.8; at 25°C
Density	[1.64 ± 0.1 g/cm ³ at 20°C] (calculated from molar volume)
Water solubility	1.4 mg/L at 20°C; 2.24 mg/L at 25°C
Vapor pressure (mm Hg)	8.27 × 10 ⁻⁹ at 20°C (calculated)
Vapor density relative to air	12
pK _a	-2.67 ± 0.20 at 25°C (calculated)

Source: HSDB 2006, BCPC 2006, CAS 2008, Kim *et al.* 1997, UAkron 2004.

Use

Captafol is a protective 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 wood-rot fungi on logs and wood products (IARC 1991, WHO 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 (EPA) further restricted its use, and all captafol tolerances were revoked except those for onions, potatoes, and tomatoes. These

remaining tolerances were revoked by the EPA in 2006. Although many countries banned its use, as of the mid-2000s, it is still used in several countries that export to the United States, such as Mexico and Brazil.

Exposure

Exposure to captafol can occur by ingestion, inhalation, or through skin exposure. Potential occupational exposure to captafol in the United States occurred during its production, through formulating or applying the fungicide to agricultural fields or after reentry of a sprayed field, or through working with treated timber products (HSDB 2006, WHO 1993). Sources of worker exposure to Difolatan 80 Sprills (80% captafol) in central Florida orange groves were assessed by Popendorf (1988). Aerosolized captafol concentrations averaged $56 \mu\text{g}/\text{m}^3$ for mixer-loaders and $34 \mu\text{g}/\text{m}^3$ for spray applicators. Dermal exposure levels were approximately 1 to $10 \mu\text{g}/\text{h}$ per cm^2 for the hands, legs, and arms; however, the authors noted that levels up to $20 \mu\text{g}/\text{h}$ per cm^2 were seen when direct contact with captafol solution was evident. Whole-body exposures had a mean of 40 mg/h and ranged from 15 to 116 mg/h, with the hands accounting for approximately 40% of total exposure.

Evidence of captafol toxicity comes from case reports of workers exposed to captafol. Peoples *et al.* (1978) presented 37 brief case reports of exposures from the manufacture and application of captafol that were reported to the California Department of Food and Agriculture for the years 1974 through 1976. The reports reflected toxic outcomes of possible captafol exposure that were reported by physicians and included systemic, skin, and eye illnesses. Positive patch tests for captafol or a history of occupationally-induced dermatitis have been 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 (Guo *et al.* 1996, Lisi *et al.* 1986, 1987, Rademaker 1998), floral shop workers (Thiboutot *et al.* 1990), and laboratory chemists (Brown 1984).

The general population may potentially be exposed to captafol from drinking contaminated ground water, from exposure to topsoils sprayed with captafol, or from ingestion of foods sprayed with captafol. In the past, the general public was potentially exposed to captafol through application in nearby agricultural settings or through ingestion of foods that had been treated with captafol.

Captafol is predicted to exist solely in the particulate phase in the atmosphere based on its vapor pressure (HSDB 2006); however, some reports suggest that captafol might be present in air or might act through the vapor phase. In water, captafol is expected to adsorb to sediment and suspended solids (HSDB 2006). Captafol is expected to have slight mobility in soil, based on its soil organic carbon-water partition coefficient (K_{oc}) value (HSDB 2006). Volatilization from soil is not expected to be an important fate process. Reported values for soil half-life vary among sources and range from less than 3 days to around 11 days (Exttoxnet 1995, HSDB 2006). 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

Agnihotrudu 1988). In a study of pesticide runoff from the soil surface, Kim *et al.* (1996) reported that runoff losses of captafol with natural rainfall were less than 0.1% of the amount applied.

Although captafol is no longer produced or used in the United States, the ingestion of imported foods treated with captafol remains a potential source of exposure to the general population. Captafol has been used in other countries that export agricultural commodities to the United States. Based on data reported through the U.S. FDA Pesticide Residue Monitoring Program and the U.S. Department of Agriculture (USDA) Pesticide Data Program, captafol was detected at low levels in food in the 1980s and 1990s, but has not been detected by the FDA or USDA in food samples since 1998. No captafol residues were identified above the detection limit in the FDA Total Diet Study (FDA 1988, 1989, 1993, Gunderson 1995, Yess *et al.* 1993).

In addition to monitoring foods for human consumption, FDA also samples and analyzes domestic and imported animal feeds for pesticide residues. For the time-period 1993 to 2003, captafol was detected once in animal feed: in 1999 at a level of 0.036 ppm for a barley sample from Maryland.

Regulations

U.S. 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 Food, Drug, and Cosmetic Act

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) limit = 0.1 mg/m³ (skin; not classifiable as a human carcinogen)

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen

Recommended exposure limit (REL) = 0.1 mg/m³ (skin)

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