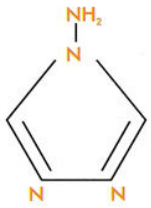
Triazole Antifungal Agents

A number of triazoles are broad spectrum antifungal agents used as pesticides and pharmaceuticals. They inhibit the biosynthesis of ergosterol, which is an essential component of fungal membranes. Triazole antifungal agents are extensively used. The general population can be exposed as a result of the use of triazole pharmaceuticals and through consumption of food or water containing triazole pesticide residues. Occupational exposure may occur to workers involved in the manufacture or use of triazole antifungal agents.



Triazole moiety

Triazole antifungal agents (as a chemical group) passed the animal data screen, underwent a preliminary toxicological evaluation, and are being brought to the Carcinogen Identification Committee (CIC) for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation. The CIC is being asked to advise OEHHA on whether triazole antifungal agents as group, or any individual triazoles, should be brought to the committee for a full evaluation of the carcinogenicity evidence at a future meeting.

Epidemiological data

No cancer epidemiology studies on triazole antifungal agents were identified.

Animal carcinogenicity data

Tables 1 and 2 present animal carcinogenicity data for several triazole antifungal agents. Triazole antifungal agents are hepatotoxic, with many producing liver tumors in mice. Some produce thyroid and other tumors in rats.

Table 1. Tumor findings in dietary carcinogenicity studies of several triazole antifungal agents

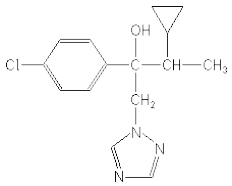
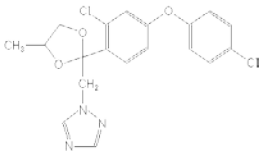
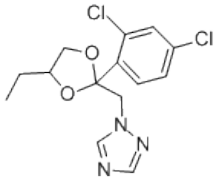
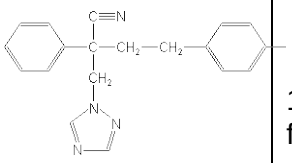
Chemical (CAS Number)	Structure	Animal data	Reference
Cyproconazole (113096-99-4)		88-week study in male and 92-week study in female CD-1 mice ▪ *Increases in liver adenoma (by pairwise comparison) and combined adenoma and carcinoma (by pairwise comparison and trend) in males and females* Two-year studies in male and female rats ▪ *No treatment-related tumor findings*	U.S. EPA (1991; 1992; 2008)
Difenoconazole (119446-68-3)		78-week studies in male and female CD-1 mice ▪ *Increases in liver adenoma, carcinoma and combined adenoma and carcinoma (by pairwise comparison and trend) in males and females* 104-week studies in male and female Sprague-Dawley rats ▪ *No treatment-related tumor findings*	U.S. EPA (1994)
Etaconazole (60207-93-4)		Two-year studies in male and female mice *Increases in hepatocelluar adenoma, carcinoma and combined adenoma and carcinoma in males and females*	U.S. EPA (1998)
Fenbuconazole (114369-43-6)		78-week studies in male and female CD-1 mice ▪ *Increase in combined liver adenoma and carcinoma (by pairwise comparison) in females* 104-week studies in male and female Sprague-Dawley rats ▪ *Increase in combined benign and malignant thyroid follicular cell tumors (by pairwise comparison) in males*	U.S. EPA (2001a)

Table 1. Tumor findings in dietary carcinogenicity studies of several triazole antifungal agents (continued)

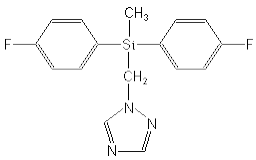
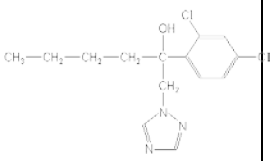
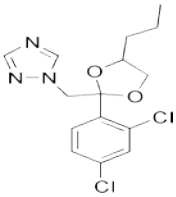
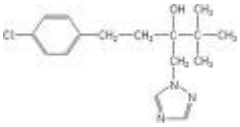
Chemical (CAS Number)	Structure	Animal data	Reference
Flusilazole (85509-19-9)		18-month studies in male and female CD-1 mice ▪ *Increase in combined hepatocelluar adenoma and carcinoma (by pairwise comparison and trend) in females* Two-year studies in male and female Sprague-Dawley rats ▪ *Increases in combined transitional cell papilloma and carcinoma of the urinary bladder (by pairwise comparison and trend) in males and females* ▪ *Increase in Leydig cell tumors (by pairwise comparison and trend) in males*	IPCS (1995)
Hexaconazole (79983-71-4)		Two-year studies in male and female mice ▪ *Marginal increase in hepatocelluar tumors* Two-year studies in male and female Wistar rats ▪ *Increase in benign Leydig cell tumors in males*	U.S. EPA (1998)
Propiconazole (60207-90-1)		Two-year studies in male and female CD-1 mice ▪ *Increase in liver adenoma and combined adenoma and carcinoma (by pairwise comparison and trend) and liver carcinoma (by trend) in males* 18-month dietary study in male CD-1 mice ▪ *Increase in liver adenoma and combined adenoma and carcinoma (by pairwise and trend) in males* Two-year studies in male and female Sprague-Dawley rats *No treatment-related tumor findings*	U.S.EPA (2003, 2006)
Tebuconazole (10754-96-3)		21-month studies in male and female NMRI mice ▪ *Increases in hepatocellular adenoma, carcinoma and combined adenoma and carcinoma (by pairwise comparison) in males and females* Two-year studies in male and female Wistar rats ▪ *No treatment-related tumor findings*	U.S. EPA (2010)

Table 1. Tumor findings in dietary carcinogenicity studies of several triazole antifungal agents (continued)

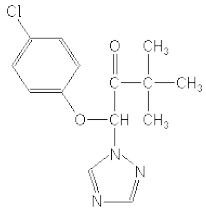
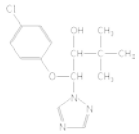
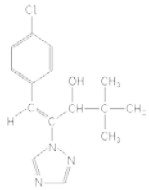
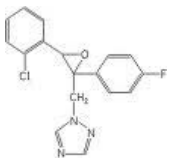
Chemical (CAS Number)	Structure	Animal data	Reference
Triadimefon (43121-43-3)		21-month studies in male and female NMRI mice ▪ *Increases in hepatocelluar adenoma (by pairwise comparison) in males and females* Two-year studies in male and female Wistar rats ▪ *Increase in thyroid follicular cell adenoma (by pairwise comparison) in males*	U.S. EPA (1998)
Triadimenol (55219-65-3)		Two-year studies in male and female mice ▪ *Increase in hepatocelluar adenoma (by pairwise comparison) in females* Two-year studies in male and female rats ▪ *No treatment-related tumor findings*	U.S. EPA (1998)
Uniconazole (83657-22-1)		78-week studies in male and female mice ▪ *Increase in hepatocellular adenoma, carcinoma and combined adenoma and carcinoma in males* Two-year studies in male and female rats ▪ *No treatment-related tumor findings*	U.S. EPA (1998)

Table 2. Tumor induced by triazole antifungal agent listed as a carcinogen under Proposition 65

Chemical (CAS Number)	Structure	Animal data	Year Listed
Epoxiconazole (135319-73-2) (U.S. EPA, 2001b)		Male Mice: ▪ Liver adenoma and carcinoma Female Mice: ▪ Liver adenoma and carcinoma Male Rats: ▪ Liver tumors; adrenal cortex tumors Female Rats: ▪ Adrenal cortex tumors; liver cholangiomas; ovarian tumors	2011

Other relevant Data

- Genotoxicity: See Table 3

Table 3. Genotoxicity findings for various triazole antifungal agents

Chemical	Gene mutation		Chromosomal effects		UDS
	Salmonella	**Other**	**Micronucleus**	**Other**	
Cyproconazole (U.S. EPA, 1991; 1992; 2008)	-	-	-	+ (CHO cells)	NA
Difenoconazole (U.S. EPA, 1994)	-	-	-	NA	-
Etaconazole (U.S. EPA, 1998; 2000)	-	-	NA	NA	NA
Fenbuconazole (U.S. EPA, 2001a)	-	-	NA	-	-
Fluconazole (Fucic *et al*., 2008)	NA	NA	+ (*in vivo*: mouse)	NA	NA
Flusilazole (IPCS, 1995)	-	-	-	-	-
Hexaconazole (U.S. EPA, 2000)	-				-
Myclobutanil (Ross *et al*., 2009)	-	-	NA	-	-
Propioconazole (Ross *et al.,* 2009)	-	+ (*in vivo:* mouse)	-	-	-
Tebuconazole (U.S. EPA, 2010; CDPR, 2003)	-	-	-	-	-
Triadimefon (Ross *et al.,* 2009)	-	+ (*in vivo:* mouse)	+ (*in vivo*: rat)	+ (*in vivo*: rat)	-
Triadimenol (U.S. EPA, 1998; CDPR, 2000)	-	-	-	-	-
Uniconazole (U.S. EPA, 1998; 2000)	-	-	+ (*in vivo*: mouse)	+ (CHO cells)	-

UDS = Unscheduled DNA synthesis
NA = Not available

Table 4. Genotoxicity findings for triazole antifungal agent listed as a carcinogen under Proposition 65

Chemical	Gene mutation		Chromosomal effects		DNA effects	
	Salmonella	**Other**	**Micronucleus**	**Other**	**UDS**	**Other**
Epoxiconazole (U.S. EPA, 2001b)	-	-	-	-	-	-

- Other mechanistic considerations
    - Triazole antifungal agents induce and inhibit cytochrome P450 (CYP) enzymes. Transcriptional analysis of liver tissue from genomic studies of triazole antifungal agents suggests these compounds induce constitutive androstane receptor (CAR) and pregnane x receptor (PXR) activation, CYP induction, oxidative stress, dysregulation of cholesterol biosynthesis and alteration in cell signaling, cell growth, cell proliferation and apoptosis pathways (Nesnow *et al*., 2009; Goetz and Dix, 2009; Nesnow *et al*., 2011).

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Fucic A, Markovic D, Herceg Z, Gamulin M, Katic J, Stojkovic R, Ferencic Z, Mildner B, Jazbec AM, Dobranic T (2008). Developmental and transplacental genotoxicology: fluconazole. *Mutat Res* **657**:43-47.

Goetz AK, Dix DJ (2009). Mode of action for reproductive and hepatic toxicity inferred from a genomic study of triazole antifungals. *Toxicol Sci* **110**(2):449-462.

International Programme on Chemical Safety (IPCS**,** 1995)**.** Flusilazole **(**Pesticide residues in food**:** 1995 evaluations Part II (Toxicological and Environmental), available at www.inchem.org/documents/jmpr/jmpmono/v89pr09.htm (accessed June 2, 2011).

Nesnow S, Padgett WT, Moore T (2011). Propiconazole induces alterations in the hepatic metabolome of mice: Relevance to propiconazole-induced hepatocarcinogenesis. *Toxicol Sci* **120**:297-309.

Nesnow S, Ward W, Moore T, Ren H, Hester SD (2009). Discrimination of tumorigenic triazole conazoles from phenobarbital by transcriptional analysis of mouse liver gene expression. *Toxicol Sci* **110**:68-83.

Ross JA, Moore T, Leavitt SA (2009). *In vivo* mutagenicity of conazole fungicides correlates with tumorigenicity. *Mutagenesis* **24**:149-152.

[1] Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.

U.S. Environmental Protection Agency (U.S. EPA, 1991). Second carcinogenicity peer review meeting on Cyproconazole. Health Effects Division. Office of Pesticides and Toxic Substances.

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