Clodinafop-Propargyl

(2-Propynyl (R)-2-[4-(5 chloro-3-fluoro-2-pyridiyloxy)-phenoxy]-propionate)

Clodinafop-propargyl is a phenoxy herbicide used on wheat fields for control of broad-leaved weeds. Clodinafop-propargyl is registered for use by the U.S. Environmental Protection Agency (U.S. EPA), but it is not currently registered for use in California. The U.S. EPA has established tolerances for clodinafop-propargyl on wheat and hay. Exposures to the general public may occur through consumption of food products containing residues.

Clodinafop-propargyl passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

No cancer epidemiology studies were identified.

Animal carcinogenicity data

- Long-term feeding studies in rats
    - Two-year studies in male and female albino rats: as reviewed in U.S. EPA (1999, pp. iv, 1-5; 2006, pp. 1, 5-9)
        - *Increase in prostate adenoma (by trend), and prostate adenoma and carcinoma (combined) (by pairwise comparison and trend) in males*
        - *Increase in ovarian tubular adenomas (by pairwise comparison and trend) in females (U.S. EPA, 1999)*
        - *Pathology Working Group reread found no treatment-related increase in ovarian tumors in females (U.S. EPA, 2006)*

- Long-term feeding studies in mice
    - 18-month studies in male and female albino mice: as reviewed in U.S. EPA (1999, pp. iv, 5-6, 9; 2006, pp. 2, 10-16)
        - *Increase in liver carcinoma (by trend), hepatoma and carcinoma (combined) (by pairwise comparison and trend) in males*
        - *Increase in hepatoma, and hepatoma and carcinoma (combined) (by trend), and in uncommon liver hemangioma and hemangiosarcoma (combined) above the range of historical controls in females (U.S. EPA, 1999)*
        - *Increase in angiosarcoma (all tissues) (by trend) and hemangioma and angiosarcoma (combined) (all tissues) (by pairwise comparison and trend) in females. U.S. EPA did not consider these vascular tumors to be treatment related. (U.S. EPA, 2006)*

Other relevant data

- Genotoxicity
  - as reviewed in U.*S.* EPA (1999, pp. 10-11; 2000, pp. 20-23; 2006, pp. 3, 16-17)
    - *Salmonella typhimurium* reverse mutation assays (*negative*)
    - Chinese hamster V79 forward mutation assay (*negative*)
    - *In vitro* chromosomal aberrations in cultured human lymphocytes (*inconclusive*)
    - *In vitro* chromosomal aberrations in Chinese hamster ovary cells *(positive only at cytotoxic concentrations)*
    - *In vivo* mouse bone marrow micronucleus assay (*negative*)
    - *In vitro* unscheduled DNA synthesis assay in primary rat hepatocytes (*negative*) and cultured human fibroblasts (*negative*)
  - *In vitro* interaction with DNA by intercalation (*positive*): Kashanian *et al*. (2008)

- Structure-activity considerations
  - as reviewed in U.S. EPA (1999, pp. 11-12)
    - Two of four structural analogs (*i.e*., diclofop-methyl and haloxyfop-methyl) also induce liver tumors in mice
      - Diclofop-methyl is a Proposition 65 carcinogen and has been classified by U.S. EPA since 2000 as "Likely to be carcinogenic to humans"
      - Haloxyfop-methyl is classified by U.S. EPA as a Group B2 (probable) carcinogen

- Mechanistic considerations
    - Liver tumors and peroxisome proliferator-activated receptor alpha-agonism: U.S. EPA (1999, pp. 15-18, 20-21; 2006, pp. 3, 17-24); Guyton *et al*. (2009)

Reviews

- U.S. EPA (1999)
- U.S. EPA (2006)

References[1]

Guyton KZ, Chiu WA, Bateson TF, Jinot J, Scott CS, Brown RC, Caldwell JC (2009). A Reexamination of the PPAR-α Activation Mode of Action as a Basis for Assessing

[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.

Human Cancer Risks of Environmental Contaminants. *Environ Health Perspect* **117**:1664-72.

Kashanian S, Askari S, Ahmadi F, Omidfar K, Ghobadi S, Tarighat FA (2008). *In Vitro* study of DNA interaction with clodinafop-propargyl herbicide. *DNA Cell Biol*. **27**(10):581-586.

U.S. EPA (1999). U.S. Environmental Protection Agency. Clodinafop-Propargyl (CGA 184927). Report of the Cancer Assessment Review. Health Effects Division, Office of Pesticides Programs. December 7, 1999.

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U.S. EPA (2006). U.S. Environmental Protection Agency. Clodinafop-propargyl: second report of the Cancer Assessment Review Committee. PC Code: 125203. Office of Pesticides and Toxic Substances. February 8, 2006.