Ciprofibrate

(RS)-2-[4-(2,2-dichlorocyclopropyl)phenoxy]-2-methylpropanoic acid

Ciprofibrate is a hypolipidemic drug used to lower plasma lipid levels. It modulates lipid metabolism through activation of peroxisome proliferator-activated receptor-alpha (PPARα).

Ciprofibrate 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

- 60-week dietary studies
  - Male F344 rats: Rao *et al*. (1984)
    - *Increase in liver tumors (by pairwise comparison)*
  - Male F344 rats: Rao and Subbarao (1997)
    - *Increase in liver tumors (by pairwise comparison)*
  - Male F344 rats: Rao and Subbarao (1999)
    - *Increase in liver tumors (by pairwise comparison)*

- 70-week dietary studies
  - Male F344 rats: Rao *et al*. (1986)
    - *Increase in liver tumors (by pairwise comparison)*

- Two-year dietary studies
  - Male and female F344 rats: Spencer *et al*. (1989)
    - *Increase in rare carcinoid tumors of the fundus of the stomach (by pairwise comparison and trend)*
    - *One rare carcinoid tumor of the fundus of the stomach occurred in females*

- 14- to 22-month dietary studies
  - Male F344 rats: Milano *et al*. (1987)
    - *Increases in liver tumors and metastasis to the lung (by pairwise comparison)*

- 22-month dietary studies
  - Male F344 rats: Rao and Subbarao (1995)
    - *No findings of treatment-related pancreatic and testicular tumors. Other sites not examined.*

- 18- and 21-month dietary studies
  - Male C57BL/6N mice: Rao *et al*. (1988)
    - *Increase in liver tumors (by pairwise comparison and trend)*

- Two-year dietary studies
  - Male B6C3F_1 mice: Hegi *et al*. (1993)
    - *Increase in liver tumors (by pairwise comparison)*

- 155-week gavage studies
  - Male and female marmosets: Graham *et al*. (1994)
    - *No findings of treatment related tumors in three animals. (Comment: small numbers and study duration was < 25% of marmoset lifespan)*

Other relevant data

- Genotoxicity
  - Rat hepatocyte sister chromatid exchanges, chromosome aberrations, and micronuclei *(positive)*: Reisenbichler and Eckl (1993)
  - DNA alterations and 8-hydroxydeoxyguanosine adduct formation *in vivo* in rat liver *(positive)*: Kasai *et al*. (1989), Randerath *et al*. (1991), Huang *et al*. (1994)
  - DNA synthesis *in vivo* in rat liver *(positive)*: Yeldandi *et al*. (1989)

- Mechanistic considerations
  - H- and K-*ras* gene mutations in ciprofibrate mouse liver tumors *(differ from mutations in spontaneous tumors)*: Hegi *et al*. (1993)
  - Gene expression profiling in rat liver slices *(expression profile of ciprofiprate is similar to that of other peroxisome proliferators)*: Werle-Schneider *et al*. (2006)
  - Transcription factor NF-κB activity in rat liver *in vivo (increased)*: Li *et al*. (1996)
  - NF-κB and AP-1 activities in mouse liver *in vivo (increased)*: Nilakantan *et al*. (1998)
  - Chromatin sphingomyelin alterations in rat liver *in vivo (induced)*: Albi *et al*. (2003)
  - Reviews of PPARα agonists and human relevance of rodent liver tumors: IARC (1994), Guyton *et al.* (2009)

- Structure activity considerations
    - Structurally similar to two other fibrate compounds that induce liver tumors in rodents and are Proposition 65 carcinogens: clofibrate and gemfibrozil

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[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.

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