

## Quinoxaline-1,4-dioxide Compounds and Desoxycarbadox

Quinoxaline-1,4-dioxide compounds are antimicrobial agents that are used as animal growth promoters for livestock.

- Carbadox (CAS No. 6804-07-5) has been approved by the U.S. Food and Drug Administration (FDA) since 1998 for the control of swine dysentery and bacterial swine enteritis, and to promote increased rate of weight gain and improved feed efficiency.
- Desoxycarbadox (CAS No. 55456-55-8) is an important metabolite of carbadox found in swine after carbadox intake. Desoxycarbadox is present in edible tissues and thus can be considered to be an indirect unintentional food additive.
- Olaquinox (CAS# 23696-28-8) has been banned in the European Union since 1999 and is not approved for use in the U.S. It is used in Asia and other countries as an antimicrobial added to livestock feed.
- Quinoxin or quinoxaline 1,4-dioxide (CAS No. 2423-66-7) was withdrawn from the European market in the late 1970s; it has not been used in the U.S. since the late 70's.

These chemicals have been detected in U.S. and Canadian surface waters and wastewater effluents.

Quinoxaline-1,4-dioxide compounds and desoxycarbadox passed the animal data screen, underwent a preliminary toxicological evaluation, and are 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

#### *Carbadox*

- Dietary studies
  - 26-month studies in male and female Charles River C-D rats: WHO (2003, p. 4); WHO (1991a, p. 4); FDA (1998, p. 2)
    - *Mammary tumors in females (10 animals/sex/dose) (by pairwise comparison and trend)*
  - 106-week studies in male and female Charles River C-D rats: WHO (2003, pp. 4-5); WHO (1991a, pp. 4-5); FDA (1998, p. 2)
    - *Mammary tumors in females (20 animals/sex/dose) and liver tumors in males and females combined (by pairwise comparison and trend)*

- 12-month studies in male and female Wistar rats: WHO (2003; p. 5); WHO (1991a, p. 5)
  - *Liver tumors in males and females (by pairwise comparison)*
- 10-month studies in male and female rats: WHO (2003, p. 5); WHO (1991a, p. 5); FDA (1998, p. 2)
  - *Liver tumors in males and females combined (14 animals/sex/dose) (by pairwise comparison)*
- Intraperitoneal (i.p.) studies
  - Pre-weanling male and female Wistar rats received carbadox by i.p. injection for 8-20 days, and were observed until study termination 12 months after administration of the first dose: WHO (1991a, p. 5)
    - *Liver tumors in males and females*
- I.P./dietary studies
  - Pre-weanling male and female Wistar rats received carbadox by i.p. injection for 8-20 days, followed by carbadox in the diet until study termination 12 months after administration of the first dose: WHO (1991a, p. 5)
    - *Liver tumors in males and females*

#### *Desoxycarbadox*

- Two-year dietary studies
  - Male and female Charles River C-D rats: WHO (2003; p. 5); WHO (1991a, p. 5); FDA (1998, p. 3)
    - *Mammary tumors in females and liver tumors, hemangiomas, and subcutaneous fibromas in males and females combined (by pairwise comparison and trend)*
- 10-month dietary studies
  - Male and female rats: WHO (2003, p. 5); WHO (1991a, p. 5); FDA (1998, p. 2)
    - *Liver tumors in males and females combined (by pairwise comparison)*

#### *Olaquinox*

- Drinking water studies in rats
  - BR 46 rats (males and females combined) received olaquinox in drinking water five days per week for life: WHO (1991b, p. 10)
    - *Increases in mammary fibroadenoma (by pairwise comparison and trend) (Comment: sex not specified)*
- Lifetime dietary studies in mice
  - Male and female NMRI mice: WHO (1991b, pp. 9-10)

- *Increases in pulmonary and adrenal cortical adenomas in males (by pairwise comparison and trend)*
  - *Increases in pulmonary adenomas (by trend) and ovarian benign granulosa cell tumors in females (by pairwise comparison and trend)*
- Gavage studies in rats
  - Male and female Wistar rats received olaquinox once per week for 80 weeks, followed by observation for life: WHO (1991b, p. 10)
    - *No treatment-related tumor findings*
- Lifetime (including exposure *in utero*) dietary studies in rats
  - Male and female BR 46 rats: WHO (1991b, pp. 10-12)
    - *No treatment-related tumor findings (Comment: anomalies/errors in reporting of tumor findings in one set of studies, and inadequate number of animals surviving long enough for assessment of carcinogenicity potential in another set of studies)*
- 90-week drinking water studies in mice
  - Male and female NMRI mice (20 animals/sex/dose): WHO (1991b, p. 9)
    - *No treatment-related tumor findings*

#### Quinoxin

- 18-month dietary studies
  - Male and female Wistar rats: Tucker (1975)
    - *Increases in nasal cavity and liver tumors in males and females (by pairwise comparison and trend)*

#### Other relevant data

- *Genotoxicity*
  - *Carbadox*: FDA (1998, pp. 1-2); WHO (1991a, pp. 6-7); Beutin *et al.* (1981); Chen *et al.* (2009)
    - *Mutagenicity in *S. typhimurium* (positive and negative), *E. coli*, *Klebsiella pneumonia*, and *Saccharomyces cerevisiae* D4 (positive)*
    - *DNA repair in *Bacillus subtilis* (positive)*
    - *Micronuclei in monkey kidney epithelial Vero cells *in vitro* (positive)*
    - *DNA damage in monkey kidney epithelial Vero cells (positive)*
    - *Chromosome aberrations in human lymphocytes *in vitro* (positive and negative)*
    - *Micronuclei in rat bone marrow *in vivo* (positive)*

- Chromosome aberrations in mouse and rat bone marrow *in vivo* (positive and negative)
    - Dominant lethal assay in mice (negative)
  - Desoxycarbadox: FDA (1998, p. 3); WHO (2003, p. 4)
    - Mutagenicity in *S. typhimurium* (with rat microsomes) (positive)
    - Chromosomal aberrations in rat bone marrow *in vivo* (positive and negative)
    - Cell transformation in BALB/C Swiss 3T3 mice (positive)
    - Chromosome aberrations in human lymphocytes *in vitro* (negative)
  - Olaquinox: WHO (1991b, pp. 14-18); Beutin *et al.* (1981); Hao *et al.* (2006); Chen *et al.* (2009); Zou *et al.* (2009)
    - Reverse mutations in *S. typhimurium* (positive)
    - Forward mutations in *E. coli* (positive)
    - Gene mutation in the shuttle vector pSP189/mammalian cell system (positive)
    - DNA damage (SOS chromotest) in bacteria (positive)
    - Clastogenic activity in cultured human lymphocytes *in vitro* (positive)
    - Clastogenic activity in mouse bone marrow and in Chinese hamster spermatogonia *in vivo* (positive)
    - Micronucleus in monkey kidney epithelial Vero cells (positive)
    - Micronucleus in mice and rats *in vivo* (positive and negative)
    - Sister chromatid exchange in Chinese hamster V79 cells (positive)
    - DNA damage in human hepatoma G2 cells and in monkey kidney epithelial Vero cells (positive)
    - Dominant lethal mutations in mice (positive and negative)
    - DNA binding in rats *in vivo* (negative)
  - Quinoxin: WHO (1991b, p. 18); Beutin *et al.* (1981); Ganley *et al.* (2001)
    - Reverse mutations in *S. typhimurium* (positive)
    - DNA damage in a plasmid-based *in vitro* system (positive)
    - DNA binding (negative)
- Metabolism
  - Carbadox is metabolized to desoxycarbadox, hydrazine, quinoxaline-2-carboxylic acid, and methyl carbazate: WHO (1991a, p. 4-8)
    - Hydrazine is a genotoxic carcinogen (WHO, 2003) listed under Proposition 65
  - Quinoxin is metabolized to quinoxaline-n-oxide: Beutin *et al.* (1981)
    - Quinoxaline-n-oxide is mutagenic in *S. typhimurium*

## References<sup>1</sup>

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<sup>1</sup> 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.