

## 4-Hydroxymethyl, 4-Methyl and 4-Hydroxy Benzenediazonium and Their Salts

- 4-Hydroxymethyl benzenediazonium (4-HMBD) is naturally present in the commonly cultivated edible mushroom *Agaricus bisporus*.
- 4-Methyl benzenediazonium (4-MBD) may form from 4-HMBD.
- 4-Hydroxy benzenediazonium (4-HBD) is naturally present in *Agaricus xanthodermus*, a wild inedible mushroom that may be mistaken for *Agaricus bisporus*.

Consumption of *Agaricus bisporus* mushrooms may result in exposure to 4-HMBD and its salts, and possibly, to 4-MBD and its salts. If *Agaricus xanthodermus* mushrooms are mistakenly ingested, exposure to 4-HBD and its salts may occur.

These benzenediazonium compounds and their salts each 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 on these benzenediazonium compounds were identified.

### Animal carcinogenicity data

#### 4-HMBD

- Subcutaneous injection studies of 4-HMBD tetrafluoroborate
  - Male and female Swiss mice (injected once per week for 26 weeks, observed for life): Toth *et al.* (1981)
    - *Increases in tumors of the subcutis and skin in females and males (by pairwise comparisons)*
- Gavage studies of 4-HMBD tetrafluoroborate
  - Male and female Swiss mice (single gavage, observed for life): Toth *et al.* (1982)
    - *Increases in tumors of the glandular stomach in females and males (by pairwise comparisons)*

- Subcutaneous injection studies of 4-HMBD sulfate
  - Male and female Swiss mice (injected once per week for 26 weeks, observed for life): Toth (1987)
    - *Increases in tumors of the subcutis and skin in females and males (by pairwise comparisons)*

#### 4-MBD

- Subcutaneous injection studies of 4-MBD sulfate
  - Male and female Swiss mice (injected once per week for 16 to 19 weeks, observed for life): Toth *et al.* (1989b)
    - *Increases in tumors of the subcutis and skin in females (by pairwise comparisons) and of the subcutis in males (by pairwise comparison)*

#### 4-HBD

- Subcutaneous injection studies of 4-HBD sulfate
  - Male and female Swiss mice (injected once per week for 36 weeks, observed for life): Toth *et al.* (1989a)
    - *Increases in tumors of the subcutis in females and males (by pairwise comparisons)*
  - Male and female Swiss mice (injected once per week for 2 weeks, observed for life): Toth *et al.* (1989a)
    - *No treatment-related tumor findings*
- Five-week skin painting study of 4-HBD
  - Male Wistar rats  $\pm$  magnesium-deficient diet: Quintero *et al.* (2006)
    - *Increase in incipient fibrosarcoma in treated magnesium-deficient vs. untreated magnesium-deficient animals (and vs. treated magnesium-sufficient animals)*

#### Other relevant data

- Genotoxicity
  - 4-HMBD
    - *In vitro* DNA damage/base modification, single strand breaks (*positive*): Lawson *et al.* (1995); Hiramoto *et al.* (1995a, 1995b)
    - *In vivo* mouse liver DNA adduct formation (*positive*): Hiramoto *et al.* (1998)
    - Mutations in *Salmonella* (*positive*): Lawson *et al.* (1995)
    - Mutations in V79 cells (*weakly positive*): Lawson *et al.* (1995)
    - DNA cross-links in V79 cells (*positive*): Lawson *et al.* (1995)

- *In vivo* mouse peripheral reticulocyte micronuclei (*positive*): Hiramoto *et al.* (1995b)
  - 4-MBD
    - *In vitro* DNA damage/base modification, single strand breaks (*positive*): Lawson *et al.* (1995)
    - Mutations in *Salmonella* (*positive*): Lawson *et al.* (1995)
    - Mutations in V79 cells (*weakly positive*): Lawson *et al.* (1995)
    - DNA cross-links in V79 cells (*negative*): Lawson *et al.* (1995)
    - DNA adduct formation in the mouse C50 keratinocyte cell line and mouse primary keratinocytes (*positive*): Gannett *et al.* (1996)
- Mechanistic considerations
  - 4-MBD activation of transcription factor AP-1 in a mouse cell line and in mice *in vivo* (*positive*): Gannett *et al.* (2000)
  - Review of mechanistic information on arenediazonium ion carcinogenicity: Powell and Gannett (2002)
- Structure activity considerations
  - 4-HMBD, 4-HBD, and 4-MBD are structurally similar to each other, and all three induce skin and subcutaneous tumors in male and female mice
  - A fourth structurally related compound, benzenediazonium sulphate, also induces skin and subcutaneous tumors in male and female mice: Toth *et al.* (1999)

## 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.

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