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 benzenedizonium (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 ± 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**
    - 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**


Hiramoto K, Kaku M, Sueyoshi A, Fujise M, Kikugawa K (1995a). DNA base and deoxyribose modification by the carbon-centered radical generated from...


