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 an*d fem*ale 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*
        - *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)

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