2,4,6-Trimethylaniline and Its Salts

2,4,6-Trimethylaniline is used to produce commercial quantities of Acid Blue 129 dye, which is used in histochemistry studies. 2,4,6-Trimethylaniline has been detected among the volatile compounds in the smoke distillates from one type of tobacco (Latakia); thus it can be present in tobacco smoke. 2,4,6-Trimethylaniline is produced by microbes and mammals, including humans, during the metabolism of certain azo dyes. The general public may be exposed through tobacco smoke. Workers can be exposed in manufacturing processes that use the compound.

2,4,6-Trimethylaniline and its salts 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

- Long-term feeding studies in mice
  - 18-month dietary exposure and additional three month observation in male and female albino CD-1 mice: Weisburger *et al.* (1978)
    - *Increases in hepatocellular carcinoma and vascular tumors (by pairwise comparison) in males*
    - *Increase in hepatocellular carcinoma (by pairwise comparison) in females*

- Long-term feeding studies in rats
  - 18-month dietary exposure and additional six month observation in male and female Charles River CD rats: Weisburger *et al.* (1978)
    - *Increases in combined hepatocellular carcinoma and cholangiocarcinoma, combined lung adenoma and adenocarcinoma, and stomach tumors (by pairwise comparison) in males*
    - *No treatment-related tumor findings in females*
  - 18-month study in female Buffalo strain rats: Kovi and Morris (1976); Kovi *et al*. (1977)
    - *Occurrence of pituitary tumor and hepatoma*

- Two-year study in male Charles River Sprague-Dawley rats : Russfield *et al*. (1973)
  - *Increases in rare liver cholangiocarcinoma (by pairwise comparison) and hepatoma*

Other relevant data

- Genotoxicity
  - DNA damage tests by alkaline Comet assay in liver and bone marrow cells of $B6C3F_1$ mice *in vivo (positive)*: Przybojewska (1997; 1999)
  - DNA repair test with primary cultured rat hepatocytes *(positive)* : Yoshimi *et al*. (1988)
  - A number of short-term genotoxicity tests: Kugler-Steigmeier *et al*. (1989)
    - *Salmonella typhimurium strain* reverse mutation assay *(weakly positive)*
    - *Drosophila melanogaster* wing spot mutation test *(positive)*
    - Mutagenicity in cultured rat fibroblasts *(positive)*
  - Review: IARC (1982, pp. 185)
    - *Salmonella typhimurium strain TA100* reverse mutation assay *(negative)*
    - DNA breaks in Chinese hamster lung fibroblast V79 cells *(positive)*

- Formation of active metabolites
  - 2,4,6-Trimethylaniline can be metabolited to N-hydroxylated metabolites, including 3,5-dimethyl, 2- and 4-amino benzoic acids, 2,6-dimethyl quinone and hydroquinone, and conjugates (Lindstrom *et al.*, 1969). Formation of N-hydroxylated metabolites and conjugates is considered to be an important step in the activation of various carcinogenic aromatic amines.

  - 2,4,6-Trimethylaniline induced methemoglobinemia and anaemia in rats. Both syndromes are indicators of the formation of N-hydroxylated metabolites: IARC (1882).

- Structure activity considerations
  - A close structural analogue, 2,4,5-trimethylaniline (and its strong acid salts), has also been shown to induce liver tumors in mice and rats, and is listed under Proposition 65.
  - Other substituted anilines have also been shown to induce tumors in animals and are listed under Proposition 65, including:

- Aniline
- Aniline hydrochloride
- *o*-Anisidine
- *o*-Anisidine hydrochloride
- *p*-Chloroaniline
- *p*-Chloroaniline hydrochloride
- *p*-Chloro-*o*-toluidine
- *p*-Chloro-*o*-toluidine, strong acid salts of
- 5-Chloro-*o*-toluidine and its strong acid salts
- *o*-Toluidine (2-methylaniline)
- *o*-Toluidine hydrochloride
- 2,6-Xylidine (2,6-dimethylaniline)

Reviews

- IARC (1982)

References[1]

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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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