Dapsone

*(4,4'-Diaminodiphenyl sulfone; 4,4'-Sulfonyldianiline)*

Dapsone is a sulfone used in the treatment of leprosy, alone or in combination with other drugs, and also as a primary treatment for Dermatitis herpetiformis. Dapsone has also been used to treat coccidiosis in cattle.

Dapsone passed the human and animal data screens, 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**

- Cohort study in leprosy patients
  - Dapsone and dapsone (metabolized to dapsone) use: Brinton et al. (1984, p. 112)
    - *Increased mortality from bladder and kidney cancer in users of less than 10 years. These cancers not elevated in non-user patients or those with more than 10 years drug use.*

- Case series in dermatitis herpetiformis patients treated with dapsone: IARC (1980, p. 69)
  - Adenocarcinoma of the caecum, lung carcinomas (2 cases), renal carcinoma, prostate cancer, Hodgkin’s disease, anaplastic tumor of uncertain histology

- Case series in leprosy patients treated with dapsone or dapsone derivatives: Hironaka et al. (1997)
  - Urinary tract carcinomas in male patients (10 cases) significantly higher than general population (Okayama Prefecture)

**Animal carcinogenicity data**

- Studies in rats
  - Two-year feeding studies (78-week exposure) in male and female F344 rats: NCI (1977)
    - *Increase in spleen fibroma (by pairwise comparison and trend), and spleen fibroma, fibrosarcoma and sarcoma (combined) (by pairwise comparison and trend) in males*
    - *Increase in peritoneum fibrosarcoma and sarcoma (combined) (by pairwise comparison and trend) in males*
    - *No treatment-related tumor findings in females*
o 104-week studies, with *in utero*, lactational and post-weaning gavage exposure, in male and female BDIV rats: Griciute and Tomatis (1980)
   ▪ *Increase in spleen mesenchymal malignancies* (fibrosarcoma and angiosarcoma) *(by pairwise comparison)* in males
   ▪ *Increase in thyroid C-cell carcinoma* *(by pairwise comparison)* in males and females

o 104-week studies with adult only gavage exposure in male and female BDIV rats: Griciute and Tomatis (1980)
   ▪ *Increase in thyroid C-cell carcinoma* *(by pairwise comparison)* in males and females
   ▪ *No treatment-related tumor findings in males*

o 17-25 month diet study in male Wistar rats: Bergel (1973) as reviewed by IARC (1980, p. 65)
   ▪ 9 tumors detected in 8 of 12 rats – spleen fibrosarcoma, spleen fibroadenoma, three thyroid follicular adenocarcinoma, retroperitoneum fibrosarcoma, mesentery fibrosarcoma, intestinal reticulosarcoma, liver angioma *(compared to one subcutaneous fibroma in 13 controls)*

• Studies in mice
  o Two-year feeding studies (78 week exposure) in male and female B6C3F1 mice: NCI (1977)
    ▪ *No treatment-related tumor findings in males or females*
  o 104-week studies, with *in utero*, lactational and post-weaning gavage exposure, in male and female C7BL mice: Griciute and Tomatis, (1980)
    ▪ *No treatment-related tumor findings in males*
    ▪ *Increase in numbers of tumors per animal in females*
  o 24-week intraperitoneal injection study (8-week exposure) in Strain A/He mice: Stoner *et al.* (1973)
    ▪ *Increase in number of lung tumors per animal in mid-dose, but not high-dose mice*
    ▪ *No increase in number of animals with lung tumors*

• Co-carcinogenicity studies in rats
  o 104-week studies in male and female BDIV rats administered a single intratracheal dose of benzo[a]pyrene, with or without dapsone gavage (five times per week): Griciute and Tomatis (1980)
    ▪ *Increase in malignant pulmonary tumors with dapsone* *(by pairwise comparison with benzo[a]pyrene only group)* in males
    ▪ *No co-carcinogenic effect observed in females*
• Co-carcinogenicity studies in mice
  o 104-week studies in male and female C57BL administered urethane by intraperitoneal injection, with or without in utero and lactational dapsone gavage exposure: Griciute and Tomatis (1980)
    ▪ No co-carcinogenic effect observed in males or females

Other relevant data

• Genotoxicity:
  o Mutagenicity assays as reviewed in IARC (1980, p. 68) and compiled in CCRIS (2010 update):
    ▪ Salmonella typhimurium mutagenicity assays with and without activation (negative)
    ▪ E. Coli with and without activation (negative)
  o Clastogenicity
    ▪ Aneuploidy and achromatic gaps in human leukocytes in vitro (positive): Beiguelman et al. (1975)
    ▪ In vivo mouse chromosome aberrations (bone marrow and spermatocytes) and micronuclei (bone marrow) (positive): Roy and Das (1988)

• Structure activity considerations
  o Several structurally similar aniline compounds and compounds that are metabolized to anilines are listed under Proposition 65 and also induce mesenchymal spleen tumors in rats (see for example Goodman et al., 1984), including:
    ▪ Aniline
    ▪ Aniline hydrochloride
    ▪ Azobenzene
    ▪ p-Chloroaniline
    ▪ p-Chloroaniline hydrochloride
    ▪ D & C Red No. 9
    ▪ o-Toluidine
    ▪ o-Toluidine hydrochloride

Reviews

• IARC (1980)
References

Beiguelman B, Pisani RCB, El-Guindy MM (1975) In vitro effects of dapsone of human chromosomes. *Int J Lepr* **43:**41-44


Chemical Carcinogenesis Research Information System (CCRIS), Dapsone database, last updated June 2, 2010, available through the National Library of Medicine, at http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+80-08-0.


---

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.