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 diasone (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*

- 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*
- 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 females*
  - *No treatment-related tumor findings in males*
- 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
  - Two-year feeding studies (78 week exposure) in male and female $B6C3F_1$ mice: NCI (1977)
    - *No treatment-related tumor findings in males or females*
  - 104-week studies, with *in utero*, lactational and post-weaning gavage exposure, in male and female C_7BL mice: Griciute and Tomatis, (1980)
    - *No treatment-related tumor findings in males*
    - *Increase in numbers of tumors per animal in females*
  - 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
  - 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
    - 104-week studies in male and female C_7BL 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:
    - 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)*
    - 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
    - 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[1]

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

Brinton LA, Hoover R, Jacobson RR, Fraumeni JF (1984). Cancer mortality among patients with Hansen's disease. *JNCI*, **72**:109-114.

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.

Goodman DG, Ward JM, Reichardt WD (1984). Splenic fibrosis and sarcomas in F344 rats fed diets containing aniline hydrochloride, p-chloroaniline, azobenzene, o-toluidine hydrochloride, 4,4'-sulfonyldianiline, or D & C red No. 9. *J Natl Cancer Inst* 73(1):265-73

Griciute L, Tomatis L (1980). Carcinogenicity of dapsone in mice and rats. *Int J Cancer* **25**:123-129.

Hironaka K, Mizushima M, Tsuzi C, Makina H (1997). Urinary tract carcinoma in leprosy patients treated with dapsone for a long period. *Nephron* **76**:358-359.

International Agency for Research on Cancer (IARC, 1980). *IARC Monographs on the evaluation of carcinogenic risks to humans.* Volume 24. IARC, Lyon, France. pp. 59-76.

National Cancer Institute (NCI, 1977). Bioassay of Dapsone for Possible Carcinogenicity. (Technical Report Series No. 20), DHEW Publication No. (NIH) 77-820, Washington, DC, US Department of Health, Education, and Welfare.

Roy B, Das RK (1988). Cytogenetic effect of dapsone, an antileprotic drug, in the mouse in vivo system,.*Int J Lepr Other Mycobact Dis* **56**(4):574-9.

Stoner GD, Shimkin MB, Kniazeff AJ, Weisburger JH, Weisburger EK, Gori GB (1973). Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in Strain A mice. *Cancer Res* **33**:3069-3085.

[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.