Isoniazid

Isoniazid (isonicotinic acid hydrazide) is a widely used drug for the treatment of tuberculosis.

Isoniazid 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

- Cohort studies in tuberculosis patients (*inconclusive or no evidence of risk*) as reviewed in IARC (1987)
  - Cancer mortality (bronchus, lung, pleura): Stott et al. (1976)
  - Cancer mortality: Boice and Fraumeni (1980)
  - Cancer incidence and mortality: Howe et al. (1979)
  - Lung cancer mortality: Clemmesen et al. (1979)

- Cohort studies in recipients of isoniazid preventive therapy (*no evidence of risk*) as reviewed in IARC (1987)
  - Cancer mortality: Glassroth et al. (1977)
  - Cancer incidence: Costello and Snider (1980)

- Case-control studies (*no conclusive evidence of risk*) as reviewed in IARC (1987)
  - Bladder and kidney cancer: Glassroth et al. (1977)
  - Bladder cancer: Miller et al. (1978); Kantor et al. (1985)
  - Childhood cancer: Sanders and Draper (1979)

- Case report

Animal carcinogenicity data

- Oral administration studies in mice
  - Gavage studies (daily gavage for 36 weeks, followed by observation for life) in male and female CBA/Cb/Se mice: Severi and Biancifiori (1968)
    - *Increases in lung tumors in males and females (by pairwise comparison)*
  - 25-month gavage studies (five days per week) in Swiss mice: Maru and Bhide (1982)
    - *Increase in lung tumors (by pairwise comparison)*
Lifetime gavage studies (five days per week) across three generations in Swiss mice: Menon and Bhide (1983)
F₀ exposed from day 1 of pregnancy till death
F₁ exposed in utero from day 1 of gestation, from birth to ~day 20 via milk, and post-weaning till death via gavage
F₂ exposed in utero from day 1 of gestation and from birth to ~day 20 via milk
- Increases in lung adenocarcinoma in F₀, F₁, F₂ mice (by pairwise comparisons)

Multiple additional oral administration studies in mice: as reviewed in IARC (1974, pp. 163-164)
- Increases in lung tumors

Subcutaneous (s.c.) injection studies in mice
- ‘dd’ mice received s.c. injections once every two days for 18 weeks, followed by observation for seven months: Mori et al. (1960) as cited in IARC (1974, pp. 164-165)
  - Increase in lung tumors (by pairwise comparison)
- Male and female Strong A and BALB/c mice received s.c. injections once every two days for 18 weeks: Jones et al. (1971) as cited in IARC (1974, p. 165)
  - Increases in lung tumors in males and females in both strains (by pairwise comparisons)

Intraperitoneal (i.p.) injection studies in mice
- White mice received 30 i.p. injections during three months, followed by observation for 7.5 months: Jahász et al. (1957) as cited in IARC (1974, p. 165)
  - Increases in leukemia and lung adenoma (by pairwise comparison)
- White mice received i.p. injections and were observed for thirteen months: Jahász et al. (1963) as cited in IARC (1974, p. 165)
  - Increases in lymphosarcoma and myeloid leukemia (by pairwise comparison)
- R₃-strain mice received 87 daily i.p. injections: Schwan (1962) as cited in IARC (1974, p. 165)
  - Increase in lung tumors (by pairwise comparison)

Oral administration studies in rats
- Drinking water studies in male and female Cb/Se rats (exposed for 48 weeks, and then observed for life): Severi and Biancifio (1968)
  - Increase in fibroadenoma of the mammary gland in females (by pairwise comparison)
  - No treatment-related tumor findings in males
No treatment-related tumor findings
    • No treatment-related tumor findings
  o Multiple additional oral administration studies in rats: as reviewed in IARC (1974, p. 164)
    • No treatment-related tumor findings

S.C. injection studies in rats
  o Male Sprague-Dawley rats (injected once per week for 87 weeks): Gershbein and Rao (1992) as reviewed in CCRIS (1996)
    • No treatment-related tumor findings

Oral administration studies in hamsters
  o Multiple drinking water studies: as reviewed in IARC (1974, p. 164)
    • No treatment-related tumor findings

Other relevant data

Genotoxicity as reviewed in IARC (1987) and CCRIS (1996)
  o *Salmonella typhimurium* mutagenicity assays (*positive and negative*)
  o *Escherichia coli* mutagenicity assays (*negative*)
  o Gene conversion in yeast (*negative*)
  o Chromosomal aberrations (CA) (*positive*) and sister chromatid exchanges (SCEs) in rodent cells *in vitro* (*positive*)
  o DNA damage in rodent cells *in vitro* (*negative*)
  o Malignant transformation of Syrian hamster embryo cells (*negative*)
  o CA (*inconclusive*), SCEs (*inconclusive*), and unscheduled DNA synthesis (*negative*) in human cells *in vitro*
  o CA (*negative*), SCEs (*negative*) and DNA damage (*negative*) in rodents *in vivo*
  o Dominant lethal mutations in mice (*negative*)
  o CA in lymphocytes of exposed humans (*negative*)

Carcinogenic metabolite
  o 1-Acetyl-2-isonicotinoylhydrazine, a major metabolite of isoniazid, induces lung tumors in Swiss mice: Toth and Shimizu (1973)

Structure activity considerations
  o Isoniazid is a hydrazine compound: Toth and Shimizu (1973)
  o Hydrazine compounds listed as Proposition 65 carcinogens include:
    • Hydrazine
    • Hydrazine sulfate
    • Methylhydrazine and its salts
    • Phenylhydrazine and its salts
• 1,2-Diethylhydrazine
• 1,1-Dimethylhydrazine
• 1,2-Dimethylhydrazine
• 1,2-Diphenylhydrazine

Reviews

• IARC (1974; 1987)

References


International Agency for Research on Cancer (IARC, 1974). IARC Monographs on the evaluation of the carcinogenic risk of chemicals to man: Some aromatic amines, hydrazine and related substances, N-nitroso compounds and miscellaneous alkylating agents. IARC Monographs Volume 4, pp. 159-172. IARC, Lyon, France.


