

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
 - Mesothelioma in a 9-year-old child with prenatal exposure to isoniazid: Tuman *et al.* (1980), as cited in IARC (1987)

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*
 - 290- and 355-day drinking water studies in Albino rats: Loscalzo (1964) as cited in IARC (1974, p. 164)

- *No treatment-related tumor findings*
 - 87-week dietary studies in male Sprague-Dawley rats: Gershbein and Rao (1992) as reviewed in CCRIS (1996)
 - *No treatment-related tumor findings*
 - 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
 - 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
 - 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)
 - *Salmonella typhimurium* mutagenicity assays (*positive and negative*)
 - *Escherichia coli* mutagenicity assays (*negative*)
 - Gene conversion in yeast (*negative*)
 - Chromosomal aberrations (CA) (*positive*) and sister chromatid exchanges (SCEs) in rodent cells *in vitro* (*positive*)
 - DNA damage in rodent cells *in vitro* (*negative*)
 - Malignant transformation of Syrian hamster embryo cells (*negative*)
 - CA (*inconclusive*), SCEs (*inconclusive*), and unscheduled DNA synthesis (*negative*) in human cells *in vitro*
 - CA (*negative*), SCEs (*negative*) and DNA damage (*negative*) in rodents *in vivo*
 - Dominant lethal mutations in mice (*negative*)
 - CA in lymphocytes of exposed humans (*negative*)
- Carcinogenic metabolite
 - 1-Acetyl-2-isonicotinoylhydrazine, a major metabolite of isoniazid, induces lung tumors in Swiss mice: Toth and Shimizu (1973)
- Structure activity considerations
 - Isoniazid is a hydrazine compound: Toth and Shimizu (1973)
 - 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)

References¹

Chemical Carcinogenesis Research Information System (CCRIS, 1996)
<http://toxnet.nlm.nih.gov> (accessed on January 12, 2009).

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.

International Agency for Research on Cancer (IARC, 1987). *IARC Monographs on the evaluation of the carcinogenic risks to humans, Overall evaluations of carcinogenicity: An updating of IARC Monograph Volume 1 to 42. Supplement 7*, pp. 227-228. IARC, Lyon, France.

Maru G, Bhide SV (1982). Effect of antioxidants and antitoxicants of isoniazid on the formation of lung tumours in mice by isoniazid and hydrazine sulphate. *Cancer Letters* **17**:75-80.

Menon MM, Bhide SV (1983). Perinatal carcinogenicity of isoniazid (INH) in Swiss mice. *J Cancer Res Clin Oncol* **105**:258-261.

Severi L, Biancifiori C (1968). Hepatic carcinogenesis in CBA/Cb/Se mice and Cb/Se rats by isonicotinic acid hydrazide and hydrazine sulfate. *J National Cancer Institute* **41**:331-340.

Toth B, Shimizu H (1973). Lung carcinogenesis with 1-acetyl-2-isonicotinoylhydrazine, the major metabolite of isoniazid. *Eur J Cancer* **9**:285-9.

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.