Isophosphamide

Isophosphamide, also called ifosfamide, is an anti-neoplastic and immune suppressive drug that is widely used in pediatric oncology. Human exposure occurs when patients take this prescription drug.

Isophosphamide 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

- Intraperitoneal (i.p.) injection studies in mice
  - Male and female B6C3F1 mice (i.p. injections three times per week for 52 weeks and additional 28-week observation): NCI (1977)
    - Increase in malignant lymphoma (by pairwise comparison and trend) in females
    - No treatment-related tumor findings in males
  - Male and female Strain A/He mice (i.p. injections three times per week for eight weeks and additional 16-week observation): Stoner et al. (1973) as reviewed in IARC (1981)
    - Increase in lung adenomas (by pairwise comparison)

- Subcutaneous (s.c.) injection studies in mice
  - Female New Zealand Black/White hybrid mice (s.c. injections either once per week or five times per week beginning at either 120 or 180 days of age until 21 months of age): Mitrou et al. (1979a) as reviewed in IARC (1981)
    - Increase in animals with tumors in each treatment group (all sites combined) compared to controls. IARC noted that poor survival in controls precluded direct comparison with treated mice.
  - Female New Zealand Black/White hybrid mice (s.c. injections five times per week beginning at six, seven, eight, or 12 weeks of age for seven or eight months of treatment): Mitrou et al. (1979b) as reviewed in IARC (1981)
    - No treatment-related tumor findings
I.p. injection studies in rats
  o Male and female Sprague-Dawley rats (i.p. injections three times per week for 52 weeks and additional 31-week observation): NCI (1977)
    ▪ Increases in mammary fibroadenomas (by pairwise comparison and time-adjusted trend analysis) and uterine leiomyosarcomas with metastasis to other organs (by pairwise comparison) in females
    ▪ No treatment-related tumor findings in males

Other relevant data

  • Genotoxicity
    o Individual test evaluation compiled by CCRIS (1996) and as reviewed in IARC (1981)
      ▪ Salmonella typhimurium mutagenicity assay with metabolic activation (positive and negative)
      ▪ Chromosomal aberrations in Chinese hamster bone-marrow in vivo (positive)
    o Sister chromatid exchange in chicken embryo B lymphocytes (positive): Wilmer et al. (1992)

  • Metabolism
    o Metabolites include acrolein and probably also isophosphoramide mustard (IARC, 1981). Isophosphoramide mustard is a nitrogen mustard, and induced sister chromatid exchange in chicken embryo B lymphocytes: Wilmer et al. (1992)

  • Structure activity considerations
    o Structurally similar to cyclophosphamide, which is an IARC Group 1 carcinogen: IARC (1987)
    o Isophosphamide, cyclophosphamide, and isophosphoramide mustard (structures shown below) are bifunctional alkylating agents that induce sister chromatid exchange in chicken embryo B lymphocytes: Wilmer et al. (1992)
Isophosphamide:

Cyclophosphamide (IARC Group 1 carcinogen):

Isophosphoramide mustard

Reviews

- IARC (1981)
References

Chemical Carcinogenesis Research Information System (CCRIS, 1996)  

International Agency for Research on Cancer (IARC, 1981).  IARC monographs  
on the evaluation of carcinogenic risk of chemicals to humans; Some  
antineoplastic and immunosuppressive agents.  Volume 26, pp. 237-247.  IARC,  
Lyon, France.

International Agency for Research on Cancer (IARC, 1987).  IARC monographs  
on the evaluation of the carcinogenic risk of chemicals to humans. Overall  
evaluations of carcinogenicity: An updating of IARC monographs Volumes 1 to  
IARC, Lyon, France.

National Cancer Institute (NCI, 1977).  Bioassay of isophosphamide for possible  
Health Service, National Institute of Health.  National Cancer Institute, DHEW  
Publication No. (NIH) 77-832.

selective toxicity of cyclophosphamide analogs and metabolites towards avian  
embryonic B lymphocytes in vivo.  Mutat Res 268: 115-130.

---

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.