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 B6C3F_1 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
    - 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*

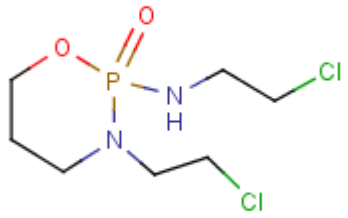
Other relevant data

- Genotoxicity
    - 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)*
    - Sister chromatid exchange in chicken embryo B lymphocytes *(positive):* Wilmer *et al.* (1992)

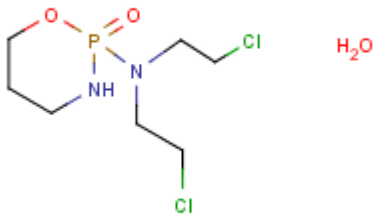
- Metabolism
    - Metabolites include acrolein and probably also isophosphoramide mustard (IARC, 1981). Isophosphoramide mustard is a nitrogen mustard, and induced sister chromatid exchange in chicken embryo B lymphocytes: Wilmer *et al.* (1992)

- Structure activity considerations
    - Structurally similar to cyclophosphamide, which is an IARC Group 1 carcinogen: IARC (1987)
    - 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)

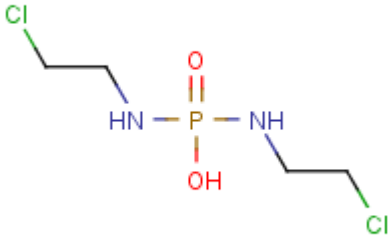
Isophosphamide:



Cyclophosphamide (IARC Group 1 carcinogen):



Isophosphoramide mustard



Reviews

- IARC (1981)

References[1]

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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 42.* Supplement 7. p. 65 (Isophosphamide) & p. 182-184 (cyclophosphamide). IARC, Lyon, France.

National Cancer Institute (NCI, 1977). Bioassay of isophosphamide for possible carcinogenicity. US Department of Health, Education, and Welfare, Public Health Service, National Institute of Health. National Cancer Institute, DHEW Publication No. (NIH) 77-832.

Wilmer JL, Colvin OM, Bloom SE (1992). Cytogenetic mechanisms in the 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.