Nomination: Nitrobenzene

Review committee: NTP Executive Committee Working Group for the Report on Carcinogens - RG2
Review Date: 10/02/02

Application of criteria

- **Exposure**

  The RG2 agreed that nitrobenzene met the "significant human exposure" criteria for possible listing in the RoC based primarily on production estimates which have increased more than four fold since 1975. According to public comments provided by the Nitrobenzene Association, the recent demand for aniline has caused marked annual increases in nitrobenzene consumption for aniline production. The National Occupational Exposure Survey in 1981-1983 estimated 5080 workers had potential exposure.

Carcinogenicity

Animal Data:

The RG2 agreed that the CIIT 2-year inhalation bioassay conducted in both sexes of B6C3F1 mice and F344 rats, and male CD rats, resulted in increased tumor incidences in multiple tissue sites in both species, and provided sufficient evidence for carcinogenicity of nitrobenzene in experimental animals. Male mice demonstrated significant increases in alveolar/bronchiolar tumors and thyroid follicular cell adenomas. Female mice showed significant increases in mammary gland adenocarcinomas and marginal increases in hepatocellular adenomas. Both strains of male rats showed significant increases in hepatocellular neoplasms, adenomas and adenomas and carcinomas combined. The male F344 rats also showed significant increases in kidney tubule cell tumors and marginal increases in thyroid follicular cell tumors. Since both sexes of rats and mice and a second strain of rat all developed histologic renal lesions, the nephropathy and renal tubule tumor development observed in the male F344 rat is not likely due to alpha 2u globulin accumulation. In female rats, the incidence of endometrial stromal polyps was significantly increased, and there were also marginal increases in the incidence of hepatocellular neoplasms. Although the committee noted that the incidences of malignant tumors were relatively low, the members all agreed that the induction of tumors in numerous tissue sites was sufficient to clearly establish the carcinogenicity of nitrobenzene in rats and mice.

Human data:

The RG2 determined that the extremely limited human data, a single published case control study, was insufficient to draw any conclusions concerning nitrobenzene. This one study reported paternal exposure to nitrobenzene was associated with a 1.6 odds ratio of childhood brain cancer. No other human studies were found in the published literature that looked at the possible relationship between human cancer and exposure to nitrobenzene.

Other Scientific Concerns

The RG2 noted that nitrobenzene is structurally related to other aromatic nitro and amino compounds that are considered by the NTP and/or IARC to be "reasonably anticipated" or "possible" human carcinogens. The committee also noted that some of the nitrobenzene active intermediate metabolites are the likely putative agents in the carcinogenicity of the parent compound, and that nitrobenzene biotransformation is qualitatively similar in humans and animals producing the same urinary end products. The nitrobenzene reduction biometabolite, aniline, is a carcinogen. Both nitrobenzene and aniline can generate nitroxide intermediates and associated free radicals. The committee also recognized that little data exists supporting genotoxicity for nitrobenzene, and thus the compound may not act through a mutagenic mode of action.

Recommendation

Motion:

Recommend that nitrobenzene be listed in the RoC as *reasonably anticipated to be a human carcinogen* based on sufficient evidence in animals that indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in multiple species of experimental animals

Vote on the motion: 7 yes votes to 0 no votes