Nomination: Naphthalene

Review committee: NTP Executive Committee Working Group for the Report on Carcinogens - RG2

Review Date: 10/02/02

Application of criteria

- **Exposure**
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The RG2 felt that there was sufficient evidence of human exposure to naphthalene in the United States. Naphthalene is an intermediate in the production of phthalic anhydride, 1-naphthyl-N-methylcarbamate insecticides, beta-naphthol, synthetic leather tanning chemicals and surfactants. Crystalline naphthalene is used as a moth repellent and a toilet bowl deodorant. Production of naphthalene in the US in 2000 was 235 million pounds. There is documented worker exposure to naphthalene and data that shows naphthalene enters the environment through discharge into the air or in the fugitive emissions and exhaust from the combustion of wood and fossil fuels.

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Carcinogenicity

Animal Data:

The NTP conducted two 2-year inhalation bioassays, one in $B6C3F_1$ mice and one in F344/N rats. Mice were treated with 10 or 30 ppm six hours/day, five days/week for 104 weeks. Rats were treated with 10, 30, or 60ppm six hours/day, five days /week for 105 weeks. The RG2 felt both studies were adequate in terms of protocol.

In the mouse study, there was no significant increased incidence of neoplasms in male mice. There was a significant increased incidence of alveolar/bronchiolar adenomas in the high dose female mice (30ppm) as well as one alveolar/bronchiolar carcinoma in this group. No carcinomas were seen in the control or low dose female mice. In addition to the neoplastic lesions, naphthalene exposure increased the incidences and severity of chronic inflammation of the nose and lungs, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium in the nose. The NTP concluded that there was "some evidence of carcinogenicity" in female mice.

In the rat study, the incidences of neuroblastoma of the olfactory epithelium, a rare neoplasm, occurred with positive trends in males and females. It did not occur in controls or the 10ppm treatment group. In males, the incidences of adenoma of the respiratory epithelium of the nose, another rare neoplasm, occurred with a positive trend and were significantly increased in all exposed groups; none occurred in the chamber controls. In females, these neoplasms occurred in the 30 and 60ppm groups but not in the controls or 10ppm group. The NTP concluded that there was clear evidence of carcinogenicity in male and female F344/N rats.

The RG2 review of the animal data centered on the issue of whether the results of the two bioassays meet the RoC criteria for listing as *reasonably anticipated to be a human carcinogen*.

The committee's discussion concentrated on the evidence of carcinogenicity from the inhalation studies and if their results showed "an increased incidence of malignant and/or a combination of malignant and benign tumors in multiple species, or at multiple tissue sites; --- or to an unusual degree with regard to incidence, site or type of tumor or age at onset."

RG2 considered whether the results of the mouse study qualified as a positive response in one species. It was pointed out that all but one of the neoplasms observed in the female mice were benign. An argument was made that the one carcinoma indicated there was progression from benign to malignant tumors and this then should be considered evidence for a positive response for one species since there was an increased incidence of a "combination of malignant and benign tumors"? This issue was not resolved. Also considered was whether the rat study alone could constitute sufficient evidence on the basis that the tumors are "unusual … with regard to type of tumor"? The discussion of the results of the bioassay emphasized that both the neuroblastomas and the adenomas of the respiratory epithelium were rare tumors that were not seen in the chamber controls or the historical controls. An argument was made that the rarity of the nasal tumors in rats as well as the unusual occurrence of tumors at this site in humans suggested this response was of questionable relevance for humans. This issue was also not resolved.

It was pointed out by several RG2 members that that the International Agency for Research on Cancer (IARC) had recently reviewed the carcinogenicity data for naphthalene and reported there was sufficient evidence of carcinogenicity in animals and will list naphthalene as a possible human carcinogen (Group 2B) in an upcoming IARC Monograph (Vol 82).

Human Data:

There are two case series studies of cancer occurring in individuals exposed to naphthalene that have been reported- one investigating laryngeal and other cancers occurring in naphthalene-exposed workers in Germany and the other studying colorectal carcinoma occurring among individuals in Africa who used a naphthalene compound for medicinal purposes. The RG2 felt that it was difficult to draw any conclusions from these human epidemiology studies as the data from these two series are insufficient for evaluation of the carcinogenicity of naphthalene.

Other Scientific Concerns

Genotoxicity and Mechanistic Data:

The majority of the genotoxicity tests have shown naphthalene not to be mutagenic in vitro. Naphthalene is rapidly absorbed and metabolized when inhaled or administered dermally or orally to animals. Naphthalene-induced oxidative damage and DNA breakage, which have been observed in rat liver and brain tissue, may contribute to the toxicity and carcinogenicity of naphthalene. Mice appear to be more susceptible to induction of lung neoplasia by epoxides and epoxide-forming chemicals than are rats. Differences between rats and mice in the metabolism of naphthalene by nasal epithelia and in nasal anatomy may contribute to the species differences in susceptibility to these tumors.

Recommendation

Motions

First motion: Recommend that naphthalene be listed in the RoC as *reasonably anticipated to be a human carcinogen* based on sufficient evidence in animals of an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in multiple species.

Vote on the motion: 4 yes votes to 4 no votes

Reason for dissenting votes: members felt the results of the mouse study were not sufficient to say it is positive in this species and also believed that the nasal tumors observed in the rat study, although rare, were insufficient to meet the criteria for listing in the RoC, without supporting evidence in mice.

Second motion: Recommend that naphthalene not be listed in the RoC because the relevant data are insufficient to list as *reasonably anticipated to be a human carcinogen*

Vote on the motion: 4 yes votes to 4 no votes

Reason for dissenting votes: members felt the results of the inhalation bioassay studies in rats and mice were sufficient to list naphthalene in the RoC as *reasonably anticipated to be a human carcinogen.*

The chairman felt the results of the voting on these two motions reflected the difficulty the RG2 had with this nomination and chose to abstain from casting a tie-breaking vote. He stated that the Director NTP will be informed that the RG2 could not make a majority recommendation for either listing or not listing naphthalene in the RoC.