Review Summary of the NTP Executive Committee Working Group for the Report on Carcinogens (RG2)

Nomination: 4,4'-Thiodianiline

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

Meeting Date: 5/01/2002

Application of the criteria:

- Exposure

  4, 4' Thiodianiline (TDA) has been used almost exclusively as an intermediate in the preparation of several dyes; one of which, C.I. mordant yellow 16, has been used in the United States. However, TDA is no longer used in the U.S. to produce C.I. mordant yellow 16. C.I. Mordant yellow 16 has also been used to dye fabric and previously as an indicator in the U.S. government's nerve gas detector program. There is documentation that the U.S. produced TDA in the past but the U.S. dye manufacturers estimate only a few hundred pounds are currently imported. Several members of RG2 expressed concern that the exposure criterion of "a significant number of individuals in the United States" had not been met. Most members felt that the exposure criteria was fulfilled by past exposure, for which a precedent has already been established. However, some members felt that for previous nominations the past exposure had been well documented whereas the evidence for past exposure for TDA is implied and based on the potential for exposure. Other members felt that the criteria allowed for a broad definition of both past and present exposure. They felt that the past production data and its use in C.I. mordant yellow 16 were evidence of significant past exposure.

- Carcinogenicity

  RG2 felt that there was sufficient evidence of carcinogenicity of TDA in experimental animals based on significant increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites (liver, thyroid, uterus, and ear canal) in multiple species of experimental animals (mice and rats. The evidence in experimental animals was from NCI feeding studies in $B6C3F_1$ mice and F344 rats. In mice, dietary administration of TDA induced significant increased incidences of malignant liver (hepatocellular carcinoma) and thyroid (follicular cell carcinoma) tumors. In rats, TDA induced significant increased incidences of malignant tumors of the thyroid (follicular cell carcinoma) and uterus (adenocarcinoma) in females and significant increased incidences of malignant tumors of the liver, thyroid, and tumors of the ear canal (Zymbal gland tumors) in males. Marginal increases in adenocarcinoma of the colon in male rats and in tumors of the ear canal (Zymbal's glands) in female rats were thought to be exposure-related.

Other Scientific Concerns

- Human Studies

  No human cancer studies on exposure to TDA were available.

- Genotoxicity and Mechanism

  TDA was mutagenic in some but not all strains of bacteria and caused DNA damage in the brains, liver, urinary bladder and lungs of mice. The mechanism of carcinogenicity is not known. There is no information for TDA on metabolism or formation of intermediates, which some members felt would be helpful in determining whether TDA may currently persist in the environment due to past exposures.

Recommendation:

- Motion

  Recommend 4,4'-thiodianiline to be listed as *reasonably anticipated to be a human carcinogen* based on sufficient evidence in animals which 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

  6 yes votes to 3 no votes.

  Reason for the dissenting votes: inadequate evidence of present exposure or inadequate documentation of past exposure.