Nomination: Diazoaminobenzene (DAAB)

Review Committee: RG1

Review Date: 11/22/2002

Major Issues Discussed

General:
DAAB is being considered for listing in the Report on Carcinogens due to its metabolism to benzene, a known human carcinogen, and to aniline, an agent that induced tumors in animals. In oral studies on the absorption, distribution, metabolism, and excretion of DAAB in mice and rats, benzene and aniline were detected in blood, benzene was measured in exhaled breath, and metabolites of aniline and benzene were excreted in urine. Exhalation of benzene implies that there is systemic exposure to benzene. Reductive metabolism of DAAB to benzene, aniline and nitrogen likely occurs in the GI tract. Metabolism may also occur in liver; in vitro studies indicate cytochrome P450 reductase will catalyze the reductive cleavage. In vitro studies with human hepatocytes indicate that DAAB can be reduced to aniline and benzene in humans. In vivo ESR studies show that phenyl radicals are produced as intermediates in the metabolism of DAAB to benzene. In addition, DAAB and benzene induced micronuclei in mice; however, the effect of DAAB was greater than a mixture containing equivalent doses of benzene plus aniline.

Human Studies:
No data are available for DAAB; however, is quantitatively metabolized to benzene, a known human carcinogen.

Experimental animal studies:
The carcinogenicity of DAAB following dermal application was reported in the 1940s. There is some confusion as to whether DAAB was the chemical being studied as it is referred to as "p-diazoaminobenzene" as well as "DAAB". While p-diazoaminobenzene is listed as a synonym for DAAB there are no para substituents in diazoaminobenzene. From the text, the statement that DAAB is readily rearranged to the azo dye, p-aminoazobenzene, indicates that the chemical used in the study was diazoaminobenzene as this is a well-known reaction of DAAB. The dermal study began with daily administration of a 0.5% solution (volume not given) which was increased to 1, 2 and finally 5% over approximately 2 years. Treatment resulted in a squamous carcinoma in one mouse of the sixteen treated.

The micronucleus test conducted as part of the NTP toxicity studies provides compelling evidence that DAAB is genotoxic. DAAB was a very strong inducer of micronuclei, stronger than the equivalent dose of benzene or aniline. DAAB is also mutagenic in Salmonella with metabolic activation, whereas benzene and aniline are not. The difference in mutagenicity between the parent chemical and its metabolites may be due to the phenyl radical formed during DAAB metabolism.

Human Exposure:
There are no data available on US production of DAAB or on environmental or occupational exposures. DAAB is allowed as an impurity in dyes permitted for use in drugs and cosmetics.

Recommendation: RG1 recommend by a vote of 5 yes to 0 no that DAAB be listed as *reasonably anticipated to be a human carcinogen* based on its metabolism to benzene, a known human carcinogen, and induction of micronuclei.