National Toxicology Program
U.S. Department of Health and Human Services

Center For The Evaluation Of Risks To Human Reproduction

DRAFT

NTP-CERHR EXPERT PANEL REPORT on REPRODUCTIVE and DEVELOPMENTAL TOXICITY of METHANOL

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2.4 Carcinogenicity

Kavet and Nauss (*2*) and IPCS (*1*) reviewed methanol studies by the Japanese New Energy Development Organization (NEDO). Rats and mice were exposed to 10, 100, or 1,000 ppm methanol vapors for 20 hours/day for 24 and 18 months, respectively. A non-statistically significant increased incidence of papillary adenomas and adrenal pheochromocytomas were observed at the highest dose, but NEDO concluded that there was no evidence of cancer. NEDO also exposed 8 female *Macaca fascicularis* monkeys/group to 10, 100, or 1,000 ppm methanol vapors for 22 hours/day for up to or to 29 months and reported a non-dose- and time-related hyperplasia of "reactive astrocytes" in the nervous system. Methanol exposure had no effect on bodyweight or hematological or pathological parameters. Kavet and Nauss (*2*) noted that a critical review of the NEDO studies and results was not possible because the reports did not contain sufficient amounts of technical data and histopathological results.

2.5 Summary of General Toxicological and Biological Parameters

Toxicokinetics

Methanol is not foreign to the bodies of mammals including man as it occurs naturally as a product of endogenous biochemical processes. As described in Section 1 methanol is consumed as a natural part of the human diet and is also found in different aspartame-sweetened and fermented beverages. Thus, methanol is present in human blood; background blood levels are somewhat variable and may range from 0.6 (*21*) to 1.8 mg/L (*24, 28*). At least one study has reported higher baseline blood levels of methanol in females than males (*25*).

The absorption, distribution, metabolism and excretion of methanol are generally understood in humans, monkeys, rats, and mice (*1, 2*). There are sufficient data from human studies and those of other species to demonstrate rapid absorption following exposure by inhalation, dermal and oral routes. Following absorption, methanol distributes rapidly and uniformly to all organs and tissues in direct relation to their water content. Methanol elimination, in expired air and urine, are somewhat proportional to methanol concentration in blood, but account for a minor portion, 3.1%, of the dose at concentrations that do not saturate metabolic pathways. At saturating doses these routes may become more significant (*34*).

In mammals methanol is eliminated primarily by metabolism through a series of oxidation steps to sequentially form formaldehyde, formate and carbon dioxide. At high methanol doses, increased formate concentration and resulting acidosis is thought to account for most of the toxicity (*1*). While metabolism of methanol to formaldehyde utilizes different enzymatic pathways this step occurs at similar rates in primates and rodents (*1*). Formaldehyde is rapidly oxidized (half-life of ~1 minute) to formate in all species. It is the rate at which formate is oxidized to CO_2 that accounts for the pronounced species difference in the toxicity of methanol. In rodents the catalase-peroxide system and enzymes utilizing folate as a co-enzyme provide considerable capacity to catalyze this reaction whereas primates depend heavily on the pathway involving folate. Since primates appear to have less catalase and naturally have lower folate concentrations than do rodents they have considerably less capacity to metabolize methanol. Formate is oxidized to CO_2 in rodents at twice the rate seen in primates. As a result, the rate of formate oxidation in rats exceeds the maximal rate at which methanol is converted to formate - 1.6 vs. 0.9 mmol/kg/hr, respectively (*2*). In contrast, when primates receive moderately high doses of methanol the formation of formate can exceed the oxidation of formate - ~1.5 vs. 0.75

6.0 REFERENCES

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