of Methanol NTP-CERHR Monograph on the
Potential Human Reproductive
and Developmental Effects
of Methanol

September 2003 NIH Publication No. 03-4478
NTP (National Toxicology Program)
CERHR (Center For The Evaluation Of Risks To Human Reproduction)
U.S. Department of Health and Human Services
ntp.niehs.nih.gov/ntp/ohat/methanol/methanol_monograph.pdf

NTP Brief on Methanol

What is Methanol?

Methanol is a clear, colorless liquid with the chemical formula CH3OH.

Most of the methanol manufactured worldwide is used in the production of chemicals such as formaldehyde, methyl tertiary butyl ether (MTBE), acetic acid, methyl methacrylate, and dimethyl terephthalate. It also is used in the treatment of wastewater and sewage. Methanol is used in a variety of consumer products including varnishes, paints, antifreeze, adhesives, and window washer fluid. Methanol occurs naturally in a variety of fresh fruits and vegetables. It also occurs in alcoholic beverages and cigarette smoke.

Methanol is primarily made from natural gas and carbon dioxide. It is also produced from biomass, especially plant materials. Reports used by the expert panel indicate the United States (U.S.) produced approximately 2.2 billion gallons (14 billion pounds) of methanol in 1998. The most recent information available indicates U.S. production capacity totaled over 1.5 billion gallons of methanol in 2001. Domestic production meets about one-half of the US methanol demand with the remaining supply imported from Trinidad, Chile, Venezuela, and Canada. (Methanol Institute, 2003).

Are People Exposed to Methanol?

Yes. Methanol is a naturally occurring chemical produced in the human body and found in expired air and body fluids. Human methanol exposure from external sources can occur through the use of consumer products containing methanol, the presence of methanol in the environment, and the manufacture and use of methanol and chemicals that use methanol in their production.

Environmental exposures can occur through air, water, or food. Food is the primary source of human methanol exposure. Methanol occurs naturally in fresh fruits and vegetables. People also are exposed to methanol through two direct food additives, aspartame and dimethyl dicarbonate (DMDC), which are metabolized to produce methanol. Exposure also may occur through the consumption of alcoholic beverages and smoking tobacco products. Motor vehicle fuels may represent another important source of exposure through inhalation or contact with the skin. Studies to determine the extent of methanol exposures due to motor vehicle fuels have not been conducted.

The expert panel cited studies showing the U.S. general population has a background blood methanol concentration of less than 3 mg/L blood (milligrams per liter blood). Occupational exposures typically occur through inhalation of fumes during methanol production or use. The expert panel estimated that, at permissible exposure limits, exposures were below 25 mg/ kg body weight/day. In controlled studies, humans breathing air containing 200 ppm methanol had blood levels below 10 mg/L.

While it is possible that certain occupations, hobbies, or other activities may lead to higher exposures to methanol, no data were available on such exposures.

Can Methanol Affect Human Development or Reproduction?

Possibly. There is no direct evidence that exposure of people to methanol adversely affects reproduction or development. Laboratory animal studies reviewed by the expert panel, and an additional published study using cultured mouse embryos, show that methanol can adversely affect development (Figure 2). Based on recent data regarding the extent to which humans absorb, metabolize, and excrete methanol, the NTP believes it is reasonable and prudent to conclude that the results reported in laboratory animals indicate a potential for adverse effects in humans.

Scienti c decisions concerning health risks are generally based on what is known as “weight-of-evidence” approach. In this case, recognizing the lack of human data and the clear evidence of laboratory animal effects (Figure 2), the NTP judges the scientific evidence sufficient to conclude that methanol may adversely affect human development if exposures are sufficiently high.

Supporting Evidence

As presented in the expert panel report (see report for details and literature citations), the panel concluded that developmental toxicity was the most sensitive endpoint of concern.

The critical developmental toxicity study in animals showed inhalation exposure of pregnant mice to 1,000 ppm methanol resulted in no developmental effects while exposure to 2,000 ppm resulted in a significant increase in cervical ribs in the fetuses. Higher exposures significantly increased the incidence of cleft palates, exencephaly, and skeletal malformations.

Reproductive toxicity studies showed exposure of sexually mature male rats to methanol vapors at up to 800 ppm did not affect the structure of the male reproductive system. Another study showed methanol exposures up to 1,500 ppm did not consistently alter male rat sex hormone levels.

Primates (Macaca fascicularis) exposed to 200 to 1,800 ppm showed no effects on menstrual cycles or conception rates. Variations in the gestation length and a non-dose related increase in Caesarean section deliveries in treated animals were noted. In addition, the study provided some evidence of subtle neurobehavioral effects in offspring. However, some limitations in the study reduced the usefulness of the data in assessing human health effects.

Figure 2. (omitted) The weight of evidence that methanol causes adverse developmental or reproductive effects in laboratory animals

Species differences in methanol metabolism were noted and considered by the expert panel. In primates, including humans, methanol is converted to formaldehyde by the enzyme alcohol dehydrogenase. In rodents this conversion is made by catalase. Metabolism of methanol to formaldehyde and then to formate occurs at similar rates in rodents and primates. However, conversion of formate to carbon dioxide in primates proceeds at half the rate observed in rats. This indicates that primates accumulate formate at lower doses of methanol than some other species. Studies indicate that formate is the methanol metabolite responsible for methanol

toxicity resulting in systemic clinical signs, metabolic acidosis, and ophthalmic effects in primates. Kinetic studies in methanol poisoned patients showed that the half-life of formate in blood is 3.4 hours *(Kerns et al., 2002)*.

While formate is responsible for the acute toxicity of methanol, it appears that methanol itself results in the developmental toxicity observed in rodents. The panel noted that the maternal blood concentration at which developmental effects were observed in mice, approximately 500 mg/L, has been observed in humans suffering acute methanol poisoning. Therefore, there may be overlap between methanol doses that result in clinical signs of methanol toxicity in humans and doses that result in developmental toxicity in rodents.

The expert panel concluded that there was insufficient evidence to determine if a human fetus is more or less sensitive than rodents to the adverse effects of methanol. Additionally, it was noted that other factors such as certain genetic conditions or low maternal folate levels might predispose some humans to developmental toxicity at lower methanol levels.

The expert panel noted that there were limited data on the effects of methanol on male reproduction. Studies in pregnant rats showed that extended exposure to methanol vapors at 800 ppm did not adversely affect the structure of the male offspring's reproductive systems. Several rodent studies indicated that adult exposures resulting in blood methanol levels up to approximately 1,500 mg/L did not consistently alter levels of male sex hormones.

An *in vitro* study not available to the panel was conducted to determine if methanol could alter methylation of mouse embryonal (GD 8) DNA (Huang et al., 2001). Studies showed that culturing cells in methanol increased methylation of DNA at 4 mg/mL, but not at 8 mg/mL. The authors hypothesized that the lack of effect at the higher concentration might be due to embryo growth retardation. This study further showed that methanol exposure did not alter overall mouse embryonic protein levels or synthesis, but was specifically incorporated into life-stagespecific embryonal proteins. The authors noted that the concentrations used in the study correlated with peak serum methanol concentrations found in pregnant mice following inhalation exposures to 10,000 and 15,000 ppm methanol for 7 hours. This study provides further evidence that methanol could adversely affect embryo development at high concentrations. However, the use of only higher concentrations in the study limits the utility of the study in assessing possible human health effects.

A recent study evaluated the role of folic acid on rat pups exposed to methanol through nursing *(Aziz et al., 2002)*. Female mice were maintained on a folate sufficient (FS) or folate deficient (FD) diet beginning prior to mating. Following birth of the pups, mothers had access to water containing methanol and pups were assumed to be exposed to methanol through breast milk from PND1 to PND21. Results indicated that lactational exposure to methanol decreased body weight and altered behavior in pups from FS and FD mothers. These effects were greater in the pups of FD mothers. The authors conclude that folate status of the mother can play a role in the severity of methanol-induced neurotoxicity in lactationally exposed rats.

Are Current Exposures to Methanol High Enough to Cause Concern?

Probably Not. The general U.S. population presently appears to be exposed to methanol at levels that are not of immediate concern for causing adverse reproductive or developmental effects. However, there are studies to suggest that maternal exposure to acutely toxic doses of methanol may produce developmental effects in children. Data are not available to permit conclusions regarding the possibility of effects in various age groups, occupations, and socioeconomic strata. Thus, the NTP offers the following conclusions (see also Figure 3):

The NTP concurs with the CERHR Methanol Expert Panel that there is concern for adverse developmental effects in fetuses if pregnant women are exposed to methanol at levels that result in high blood methanol concentrations.

This conclusion is based on evidence that blood methanol levels in humans suffering acute methanol poisoning are similar to maternal blood methanol levels resulting in developmental toxicity in rodents. Further, evidence suggests that methanol, rather than one of its metabolites, results in developmental toxicity.

The NTP concurs with the CERHR Methanol Expert Panel that there is minimal concern for adverse developmental effects when humans are exposed to methanol levels that result in low blood methanol concentrations, i.e., < 10 mg/L blood.

Blood methanol levels of 10 mg/L or greater are not expected to result from normal dietary or occupational exposures. NTP does not intend this value to represent the highest "safe" blood concentration. It is possible that substantially higher blood levels would not result in developmental toxicity.

The NTP concurs with the CERHR Methanol Expert Panel that there is negligible concern for adverse male reproductive effects when exposed to methanol levels that result in a low blood methanol level (< 10 mg/L blood).

Data available to the expert panel were not sufficient to rule out the possibility of male reproductive effects at toxic exposure levels.

The NTP concurs with the CERHR Methanol Expert Panel that there is insufficient evidence to assess the effects of methanol on female reproduction.

> **These conclusions are based on the information available at the time this brief was prepared. As new information on toxicity and exposure accumulate, it may form the basis for either lowering or raising the levels of concern ex- pressed in the conclusions.**

References

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