

HEI Statement

Synopsis of Research Report 89

Effects of Prenatal Exposure to Inhaled Methanol on Nonhuman Primates and Their Infant Offspring

INTRODUCTION

In an effort to improve air quality and decrease dependence on petroleum, the federal government, industry, and other groups have encouraged development of alternative fuels such as methanol to substitute for gasoline or diesel fuel. Methanol is also a candidate to provide the hydrogen for fuel cells, which are being developed for a variety of power sources (including motor vehicle engines). Before people are exposed to increased concentrations of methanol, the potential health effects of such exposures require study.

Methanol, a simple alcohol containing one carbon atom, occurs naturally in plants and animals and participates in human metabolism. People regularly consume low doses of methanol in fruits, vegetables, and fermented beverages as well as soft drinks and foods sweetened with aspartame (which breaks down to methanol in the gastrointestinal tract). Despite its ubiquitous presence, methanol can be highly toxic if sufficient quantities are consumed. Ingestion of methanol (usually in the form of wood alcohol or tainted alcoholic beverages) can result in metabolic acidosis, blindness, and even death. Although the body has the capacity to metabolize the low doses of methanol to which people are regularly exposed, it cannot handle high doses because too much methanol overwhelms the body's ability to remove a toxic metabolite (formate). When formate accumulates, methanol poisoning occurs. One factor that regulates the rate at which formate is removed is the liver level of a derivative of the vitamin folic acid. People who are deficient in folic acid (including 15% to 30% of pregnant women) may be particularly susceptible to the toxic effects of methanol.

If methanol were to be widely adopted as a fuel, environmental exposures would increase through ingestion of contaminated drinking water, inhalation of vapors from evaporative and other emissions, and dermal contact. Current concentrations of methanol in ambient air are very low, 1 to 30 parts per billion (ppb). If all motor vehicles in the United States were converted to 100% methanol fuel, methanol levels in ambient air are estimated to increase approximately 1,000-fold (to 1 to 10 ppm in cities) and in a worst-case situation could occasionally reach concentrations as high as 200 ppm in enclosed spaces (HEI 1987). Inhaling these concentrations of methanol for short periods of time is not predicted to affect formate production and thus should not present a health risk. However, little is known about the consequences of long-term inhalation of methanol vapors, especially in susceptible populations of pregnant women and developing fetuses. HEI, therefore, developed a research program to address this information gap.

APPROACH

Dr. Thomas Burbacher and colleagues of the University of Washington studied the effects of long-term exposure to methanol vapors on metabolism and reproduction in adult female monkeys (*Macaca fascicularis*) and developmental effects in their offspring, who were exposed prenatally to methanol.

The investigators exposed adult female monkeys (11 to 12 animals/group) to one of four concentrations of methanol vapors (0, 200, 600, and 1,800 ppm) for 2.5 hours a day, seven days a week during the following periods: (1) before breeding, (2) during breeding, and (3) during pregnancy. They collected blood from the adults at regular intervals to monitor methanol levels (which served as a marker of internal dose) and formate concentrations. They also conducted pharmacokinetic studies to determine whether methanol disposition (which includes absorption, distribution, metabolism, and excretion) was altered as a result of

repeated methanol exposures and to assess pregnancy-related changes. Because high doses of methanol damage the central nervous system, the infants (8 to 9 animals/group) were examined at regular intervals during the first nine months of life to assess their growth and neurobehavioral development.

RESULTS

Exposure to methanol vapors did not affect the health of the adult monkeys prior to or during pregnancy. Single 2.5-hour exposures to methanol vapors caused short-term elevations in blood methanol concentrations of approximately 0- to 2-fold in the 200 ppm exposure group, 3- to 4-fold in the 600 ppm group, and 13- to 16-fold in the 1,800 ppm group. After long-term exposures, peak blood methanol concentrations declined slightly over the first month and remained constant thereafter. The concentrations of plasma formate (the toxic intermediate) remained at baseline levels during the entire course of the study in all exposure groups. Pregnancy had no effect on methanol disposition. Serum folate concentrations were not affected by pregnancy and methanol exposure.

Methanol exposure had no effect on most measures of reproductive performance, including menstrual cycles, conception rate, and live-birth delivery rate. However, all methanol-exposed animals had a decrease of about six to eight days in the duration of pregnancy compared to the control animals. It is not clear whether this decrease was related to methanol exposure as there was no dose response and no differences among offspring groups in body weight or other physical parameters. Prenatal exposure to methanol had no effect on infant growth and physical development for the first year of life. An unexplained wasting syndrome, characterized by growth retardation, malnutrition, and gastroenteritis, occurred after one year of age in two female offspring exposed in utero to 1,800 ppm methanol.

The investigators reported no systematic effects of prenatal methanol exposure on most of the measures used to test infant neurobehavioral development (neonatal behavior, early reflex responses, infant gross motor development, spatial memory, and social behavior). The investigators reported two possible methanol-related effects, one on visually directed reaching in male infants (a test of sensorimotor development), and one on novelty preference (a test of memory and cognitive function). Care must be taken in interpreting these results because a large number of neurobehavioral endpoints were analyzed and these results were based on a small number of subjects. Random fluctuations in the data may have appeared to be statistically significant. At the same time, however, both observations warrant further investigation as these central nervous system functions are complex perceptual processes that take time to develop and may be subject to latent neurotoxic effects.

CONCLUSIONS

This study adds substantially to our understanding of the effects of long-term exposure to inhaled methanol vapors. Because of the high quality of the study, the relevance of the animal model, the opportunities for dose-response analyses, and the availability of a marker of internal methanol dose, the results are appropriate for use in risk assessment. They can be readily used to predict the response of nutritionally competent people; they do not necessarily apply to women who are folate deficient.

The investigators' findings suggest that repeated inhalation exposure to concentrations of methanol vapors as high as 1,800 ppm would not result in accumulation of blood formate above baseline levels. With the exception of an unexplained shortening of gestation, methanol exposure had no effect on reproductive performance. The most significant result to emerge from this study was the wasting observed in two monkeys exposed in utero to 1,800 ppm methanol. Although this observation raises concern for prenatal exposures of this magnitude, pregnant women are unlikely to be exposed to such extremely high concentrations of methanol for prolonged periods of time.

Overall, the results provide no evidence of a robust effect of prenatal methanol exposure on the neurobehavioral development of nonhuman primate infants during the first nine months of life. However, improved understanding of methanol neurobehavioral toxicity will result from evaluation at later stages of development when more sophisticated tests of cognitive performance can be conducted and when latent effects may emerge. Such studies are now under way in the same monkeys at 4 to 5 years of age.

REFERENCE

Health Effects Institute. 1987. Automotive Methanol Vapors and Human Health: An Evaluation of Existing Scientific Information and Issues for Future Research. A Special Report of the Institute's Health Research Committee. Health Effects Institute, Cambridge, MA.