After uptake and distribution, most of the methanol is metabolized in the liver to carbon dioxide (96.9%), while a small fraction is excreted directly to the urine (0.6%) and through the lung. In all mammalian species studied, methanol is metabolized in the liver by sequential oxidative steps to form formaldehyde, formic acid and CO_2 (Fig. 1). However, there are profound differences in the rate of formate oxidation in different species which determine the sensitivity to methanol (Rietbrock, 1969; Palese & Tephly, 1975; McMartin et al., 1977; Eells et al., 1981a, 1983).

Two enzymes are important in the oxidation of methanol to formaldehyde, alcohol dehydrogenase and catalase. In non-human primates and humans, alcohol dehydrogenase mediates this reaction (Makar et al., 1968; Röe, 1982). In rats and other non-primate species this reaction is mediated by catalase. Definitive evidence of these differences has been provided by studies of methanol oxidation *in vivo* using alternative substrates (ethanol, 1-butanol) and selective inhibitors of catalase (3-amino-1,2,4-triazole) and alcohol dehydrogenase (4-amino-pyrazole). The hepatic microsomal mixed-function oxidase system (P_{450}IIE1) has also been implicated in the conversion of methanol to formaldehyde, but there is no definitive information on its role *in vivo* (Rietbrock et al., 1966; Teschke et al., 1975). Despite the difference in enzyme mediation, the conversion from methanol to formate occurs at similar rates in non-human primates and in rats (Tephly et al., 1964; Makar et al., 1968; Noker et al., 1980; Eells et al., 1981a, 1983). The metabolism of methanol can be significantly inhibited by co-exposure to ethanol, which acts as a competing substrate for alcohol dehydrogenase (Jones, 1987).

The elimination of formaldehyde in many species including primates is extremely rapid with a half-life of approximately 1 min (Rietbrock, 1965; McMartin et al., 1979). Malorny et al. (1965) found that equimolar infusions of formaldehyde, formic acid and sodium formate in dogs produced equivalent peak concentrations of formic acid, indicating that formaldehyde was rapidly metabolized to formic acid. In a human case of formaldehyde poisoning, toxic concentrations of formate (7-8 mm) were detected within 30 min of ingestion, confirming rapid metabolism of formaldehyde to formate in humans (Eells et al., 1981b). Formaldehyde has not been detected in body fluids or tissues following toxic methanol exposures (Makar & Tephly, 1977, McMartin et al., 1977, McMartin et al., 1980a).

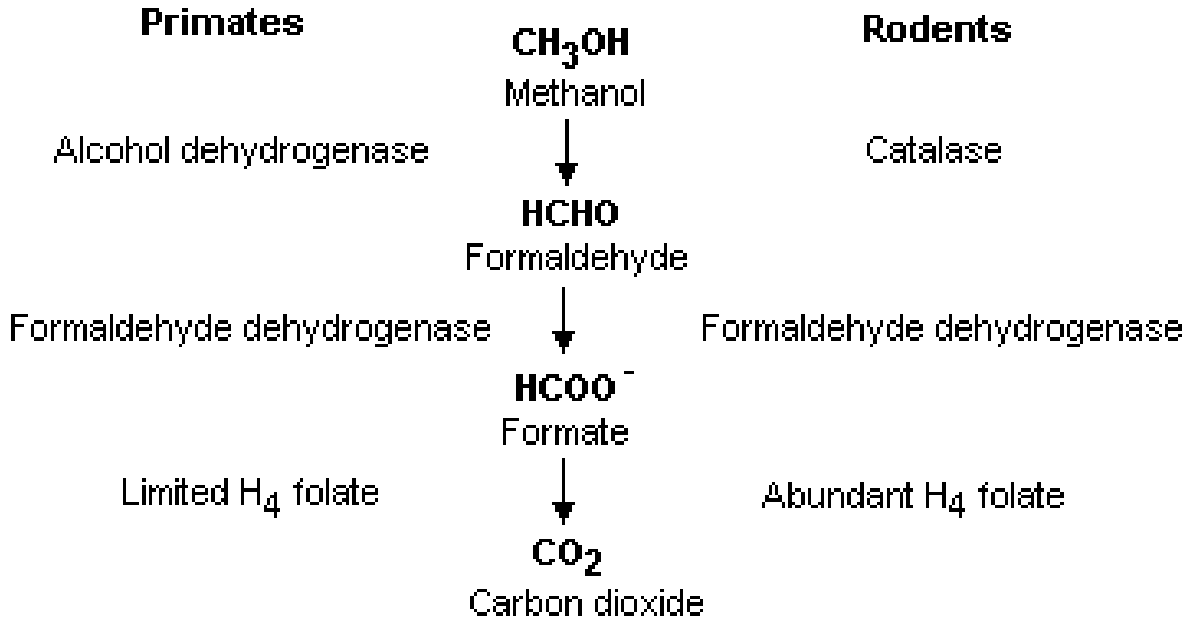

Fig. 2. Scheme for the metabolism of methanol. Major enzymes for primates (left) and rodents (right) are noted. Species differences in methanol toxicity are due primarily to the metabolic conversion of formate to carbon dioxide, which is rapid in rodents but slow in primates (from: Medinsky & Dorman, 1994).

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Chronic maternal methanol inhalation in nonhuman primates (Macaca fascicularis): reproductive performance and birth outcome.

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The present study was designed to characterize maternal reproductive performance and early offspring effects following exposure to methanol (MeOH) vapor in a nonhuman primate model. The two-cohort study design used 48 adult female Macaca fascicularis (24/cohort) monkeys exposed to 0, 200, 600, or 1800 ppm MeOH vapor for approximately 2.5 h/day, 7 days/week prior to breeding and throughout pregnancy. Maternal body weight measurement, clinical observations and health assessments were conducted routinely throughout the study. Menstrual cyclicity was monitored during the pre-breeding and breeding periods and timed matings were conducted with nonexposed males. Females were monitored closely during the last month of pregnancy. At birth, infant physical characteristics were measured and a newborn health assessment was conducted. Methanol exposure did not alter menstrual cycles, the number of breedings to conception or conception rate. A total of 34 live-born infants were delivered (control=8, 200 ppm=9, 600 ppm=8, 1800 ppm=9). One female each in the control and 600-ppm group delivered a stillborn infant and a cesarean section (C-section) was required to deliver a hydrocephalic infant who died in utero in the maternal 1800-ppm group. Although not statistically significant, five MeOH-exposed females were C-sectioned due to pregnancy complications such as uterine bleeding and prolonged unproductive labor. These complications were not observed in the control group. The mean length of pregnancy in the MeOH-exposed groups was significantly decreased by 6 to 8 days when compared to controls. There were no MeOH-related effects on offspring birthweight or newborn health status. The consistent reduction in length of pregnancy observed in the MeOH females may reflect a treatment effect on the fetal neuroendocrine system. Given that the fetal hypothalamic--pituitary-adrenal axis controls pregnancy length in most species, these results suggest a modest but significant effect of MeOH on the biochemical events that control the timing of birth.