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Toxicity and carcinogenicity of methyl isobutyl ketone in F344N rats and B6C3F1 mice following 2-year inhalation exposure

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Abstract

Methyl isobutyl ketone (MIBK) is primarily used as a denaturant for rubbing alcohol, as a solvent and in the manufacture of methyl amyl alcohol. Inhalation of vapors is the most likely route of exposure in the work place. In order to evaluate the potential of MIBK to induce toxic and carcinogenic effects following chronic exposure, groups of 50 male and 50 female F344/N rats and B6C3F1 mice were exposed to MIBK at concentrations of 0, 450, 900, or 1800 ppm by inhalation, 6 h/day, 5 days per week for 2 years. Survival was decreased in male rats at 1800 ppm. Body weight gains were decreased in male rats at 900 and 1800 ppm and in female mice at 1800 ppm. The primary targets of MIBK toxicity and carcinogenicity were the kidney in rats and the liver in mice. In male rats, there was increased mineralization of the renal papilla at all exposure concentrations. The incidence of chronic progressive nephropathy (CPN) was increased at 1800 ppm and the severity was increased in all exposed groups. There were also increases in renal tubule hyperplasia at all exposure concentrations, and in adenoma and adenoma or carcinoma (combined) at 1800 ppm; these lesions are thought to represent a continuum in the progression of proliferative lesions in renal tubule epithelium. These increases may have resulted from the increased severity of CPN, either through α2μ-globulin-dependent or -independent mechanisms. An increase in mononuclear cell leukemia at 1800 ppm was an uncertain finding. Adrenal medulla hyperplasia was increased at 1800 ppm, and there was a positive trend for increases in benign or malignant pheochromocytomas (combined). In female rats, there were increases in the incidence of CPN in all exposure concentrations and in the severity at 1800 ppm, indicating that CPN was increased by mechanisms in addition to those related to α2μ-globulin. There were renal mesenchymal tumors, which have not been observed in historical control animals, in two female rats at 1800 ppm.

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The relationship of these tumors to exposure to MIBK was uncertain. Hepatocellular adenomas, and adenoma or carcinoma (combined) were increased in male and female mice exposed to 1800 ppm. There were also treatment-related increases in multiple adenomas in both sexes.
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Keywords: Methyl isobutyl ketone; Carcinogenicity; National Toxicology Program; Inhalation; Kidney; Liver

1. Introduction

Methyl isobutyl ketone (MIBK), an important industrial chemical, is classified as a volatile organic compound, with a vapor pressure of 15 mmHg at 20 °C. In 1995 and 1996, the United States production of MIBK was 80,000 metric tonnes (CMA, 1997), and the projected demand for 2006 has been calculated at 147 million pounds (CMR, 2004). Primarily, MIBK is used as a denaturant for rubbing alcohol, as a solvent for paints, varnishes, nitrocellulose, and lacquers and in the manufacture of methyl amyl alcohol (IPCS, 1990). Methyl isobutyl ketone is also used in industrial extraction processes, as a solvent for protective coatings and in rare metals extraction and in dewaxing of mineral oils, in drycleaning preparations and in the synthesis of methyl isobutyl carbinol. The most likely exposures in the work place are primarily by inhalation of the vapors, although exposures by contact with the skin and eyes also occur. Time-weighted average (205 mg/m^3; 50 ppm) and short-term exposure limit (307 mg/m^3; 75 ppm) values have been recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2005).

MIBK is readily absorbed into the bloodstream after inhalation exposure and is likely to be widely distributed in the body (Duguay and Plaa, 1995). Metabolism occurs by reduction of the carbonyl group to a secondary alcohol, 4-methyl-2-pentanol and oxidation at the ω-1 carbon atom to form a hydroxylated ketone, 4-hydroxymethyl isobutyl ketone, also known as diacetone alcohol (DiVincenzo et al., 1976). 4-Methyl-2-pentanol may be further conjugated with sulphate or glucuronic acid, or may enter intermediary metabolism to be eliminated as CO_2, or may be incorporated into tissues. These metabolites have been measured in the tissues of rats following MIBK exposure (Duguay and Plaa, 1995; Granvil et al., 1994). Induction of P450 enzyme activities by MIBK (Lapadula et al., 1991; Raymond and Plaa, 1995a) and potentiation of the toxic effects produced by other chemicals, by MIBK or metabolites of MIBK, have been reported (Abou-Donia et al., 1985; Plaa and Ayotte, 1985; Raymond and Plaa, 1995a,b; Vezina et al., 1990; Vezina and Plaa, 1988).

The toxicity of MIBK in short-term inhalation studies has been characterized. Groups of 6 male and female F344 rats and B6C3F1 mice were exposed by inhalation to 100, 500, or 2000 ppm MIBK, 6 h/day; there were nine exposures over 11 days (Phillips et al., 1987). Lethargy and lacrimation were observed in high dose animals, but no ophthalmologic lesions or changes in body weight were found. There were increases in absolute and relative liver and kidney weights in both rats and mice at various exposure concentrations. The primary microscopic findings were hyaline droplet formation (500 or 2000 ppm) and epithelial regeneration of the proximal convoluted tubule cells (2000 ppm) in the male rat kidney. In the liver, there were increased mitotic figures (qualitative assessment) in one female rat and two male rats, hepatic mitosis in one female mouse, and glycogen depletion in four female mice.

Groups of 14 male and female F344 rats and B6C3F1 mice were exposed by inhalation to 50, 250, or 1000 ppm methyl isobutyl ketone for 14 weeks (Phillips et al., 1987). One male mouse exposed to 1000 ppm died near the end of the study of an unknown cause. Terminal body weights of dosed rats and mice were similar to controls, except for slight but significant increases in females at 250 and 1000 ppm. Changes in organ weights included increases in absolute liver weight (male rats at 50 or 1000 ppm, male mice at 250 or 1000 ppm), relative liver weight (male mice at 1000 ppm), and absolute kidney weight (female rats at 250 ppm). There were increases in serum cholesterol levels in male rats exposed to 250 or 1000 ppm, in urinary glucose excretion in male rats exposed to 250 ppm and in male and female rats exposed to 1000 ppm, and in urinary total protein excretion in male rats exposed to 1000 ppm. There was an increase in both the incidences and extent of hyaline droplets in the kidneys of male rats exposed to 250 or 1000 ppm. There were no changes in serum or urine biomarkers of injury or in histopathology in mice.

Male and female 7-week-old Sprague–Dawley rats were exposed to 0, 500, 1000 or 2000 by inhalation for at least 70 days as part of a two-generation reproductive study (Nemec et al., 2004). There were increases in both absolute and relative kidney weights in males. Histologic changes suggestive of CPN were clearly present in Sprague–Dawley rats exposed to 1000 or 2000 ppm