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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

METHYL ISOBUTYL KETONE

1. Exposure Data

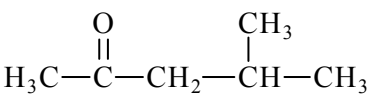
1.1 Chemical and physical data

From IPCS (1990, 1997), Toxicological Index (2005), and HSDB (2008) unless otherwise specified.

1.1.1 Nomenclature

Chem. Abstr. Services Reg. No.: 108-10-1
Chem. Abstr. Name: 4-Methylpentan-2-one
Synonyms: Hexone; isobutyl methyl ketone; isopropylacetone; ketone, isobutyl methyl; methyl *i*-butyl ketone; methyl-2-oxopentane; methylpentan-2-one; 2-methyl-4-pentanone; 4-methyl-2-pentanone; 4-methylpentan-2-one; 2-methylpropyl methyl ketone; MIBK; MIK; 2-pentanone, 4-methyl-
RTECS No.: SA9275000
EINECS No.: 203-550-1
United Nations TDG number: 1245

1.1.2 Structural and molecular formulae and relative molecular mass



$C_6H_{12}O$
Relative molecular mass: 100.16

1.1.3 Chemical and physical properties of the pure substance

Description: Colourless liquid with a sweet odour
Boiling-point: 117–118 °C
Melting-point: -84 °C (Lide, 2005); -80.26 °C
Relative density (water = 1): 0.80 at 20 °C (Lewis, 2001)
Vapour pressure: 19.9 mm Hg at 25 °C
Solubility: Soluble in water (1.91 g/100 mL at 20 °C); miscible with most organic solvents; soluble in chloroform
Relative vapour density (air = 1): 3.45
Flash-point: 14 °C
Autoignition: 460 °C
Octanol/water partition coefficient: log P, 1.31 (LOGKOW, 2010)
Water/air partition coefficient: 79 (Sato & Nakajima, 1979)
Blood/air partition coefficient: 90 (Sato & Nakajima, 1979)
Oil/air partition coefficient: 926 (Sato & Nakajima, 1979)
Henry's law constant: 1.38×10^{-4} atm.m^3/mol at 25 °C
Conversion factor at 25°C and 760 mm/Hg: 1 ppm = 4.09 mg/m^3; 1 mg/m^3 = 0.245 ppm

1.1.4 Technical products and impurities

No data were available to the Working Group.

1.1.5 Analysis

More than 15 methods to measure methyl isobutyl ketone in different environments are available. Although sampling and extraction techniques differ, all methods involve gas chromatography.

The Environmental Protection Agency of the United States of America (US EPA) has published at least three different methods for the analysis of waste material (EPA methods 8015, 8015A and 8240A), two methods for water (EPA-NERL 524.2 and EPA-OSW 8015C) and one method for different environmental matrices (EPA-OSW 8260B).

The National Institute of Occupational Safety and Health (NIOSH) has also developed methods for the analysis of methyl isobutyl ketone in air. Both methods (1300, Issue 2 and 2555, Issue 1) use gas chromatography with a flame ionization detector. The American Society for Testing and Materials (ASTM D5790) uses gas chromatography/mass spectrometry to measure methyl isobutyl ketone in water (HSDB, 2008).

1.2 Production and use

1.2.1 Production

More than 60% of methyl isobutyl ketone is produced by aldol condensation of acetone and its derivative intermediates, diacetone alcohol and mesityl oxide. Acetone is treated with barium hydroxide to yield diacetone alcohol, which is dehydrated to mesityl oxide, which in turn is hydrogenated to saturate the double bond and produce methyl isobutyl ketone. Another method is the hydrogenation of mesityl oxide over nickel at 160–190 °C. Methyl isobutyl ketone can also be prepared by reacting sodium acetoacetic ester with isopropyl bromide and treating the resulting 2-isopropyl acetoacetic ester with diluted acid to saponify the ester and decarboxylate the resulting keto acid (NTP, 2007).

In 1995 and 1996, the USA produced 80 000 tonnes of methyl isobutyl ketone (NTP, 2007). In 2003, the industrial production capacity in the USA was 195 million pounds [88 000 tonnes] per year (HSDB, 2008). Sources indicate that methyl isobutyl ketone was produced by three companies in the USA (HSDB, 2008). According to IUCLID (2000), nine companies in Europe produced methyl isobutyl ketone in 2002: three in France, two in the Netherlands, and one each in Belgium, Germany, Denmark, and the United Kingdom.

1.2.2 Use

Methyl isobutyl ketone is used primarily as a denaturant and solvent in cosmetic products, in denatured alcohol, and as an excipient in drugs. It is also used as a component of synthetic flavouring substances and adjuvants, and as a component of adhesives that are present in articles intended for use in packaging, transporting or holding food (HSDB, 2008).

Methyl isobutyl ketone is also considered to be an excellent solvent for resins used in the production of surface coating and is widely used in rubber chemicals for the production of tyres. (HSDB, 2008). Methyl isobutyl ketone is also used as a solvent in paint and lacquers (IPCS, 1990).

1.3 Occurrence and exposure

1.3.1 Natural occurrence

Methyl isobutyl ketone occurs naturally in food (see Section 1.3.3).

1.3.2 Occupational exposure

The most probable routes of exposure in the workplace are by inhalation of vapours and by skin and eye contact during the production and use of methyl isobutyl ketone and products in which it is a constituent. In the National

Occupational Exposure Survey (NIOSH, 1990) conducted from 1981 to 1983, the number of workers potentially exposed to methyl isobutyl ketone in the USA was estimated as 48 000.

Exposure to methyl isobutyl ketone during spray painting was found to be 0.6 ppm (time-weighted average; TWA) (Whitehead *et al.*, 1984). Concentrations of methyl isobutyl ketone at three locations in a poly(vinyl) chloride plastic waste recycling plant in Taiwan, China, ranged from 1517 to 11 324 μg/m^3. In the same study, concentrations at nine locations in polyethylene-polypropylene recycling plants ranged from 12 to 72 μg/m^3 (Tsai *et al.*, 2009). In a study of workers in two factories in Taipei, mean concentrations of methyl isobutyl ketone in the air samples of solvent-exposed workers were 2 ppm (range, 0–68 ppm), while the mean exposure of spray painters in painting booths was 76 ppm (range, 8–369 ppm) (Chen *et al.*, 1991). In a study among solvent-exposed workers, a mean exposure of 16.7 ppm was noted in an unidentified factory (Ogata *et al.*, 1995). Among a group of 27 furniture-makers exposed to a mixture of methyl isobutyl ketone, methyl ethyl ketone, acetone, toluene, xylene, ethylbenzene, butyl acetate, and isobutyl acetate, the TWA concentration of each solvent was below the corresponding occupational exposure limit. Arithmetic mean exposure to methyl isobutyl ketone was 1.8 ppm (range, 0.1–15.1 ppm). A linear relationship between exposure and urinary concentration was found (Kawai *et al.*, 2003). Hänninen *et al.* (1976) reported a mean TWA concentration of 7 mg/m^3 (range, 4–160 mg/m^3) [1.7 ppm; range, 1–39 ppm] in the breathing zone of spray painters in car repair shops.

Methyl isobutyl ketone may occur as a contaminant in environments near spacecraft, where it has been detected at levels of < 0.005–0.02 mg/m^3 (IPCS, 1990). It has been identified as a volatile degradation product of polypropylene at temperatures of 220–280 °C and under reduced pressure (Frostling *et al.*, 1984).

1.3.3 Occurrence in food and dietary exposure

The most probable routes of exposure to methyl isobutyl ketone by the general population are ingestion of contaminated drinking-water and dermal contact with consumer products of which it is a constituent (Johnson, 2004).

Dietary sources of exposure are: natural occurrence in food, addition to food as a flavouring, and migration into food from food packaging. Methyl isobutyl ketone has also been detected in human breast milk (Pellizzari *et al.*, 1982), and traces have also been detected in tap-water in the USA (IPCS, 1990).

(a) Natural occurrence in food

Methyl isobutyl ketone was reported to occur naturally in orange and lemon juice, grapes, vinegar, baked potatoes, papaya, ginger, wheat bread, cheeses, milk, cooked eggs, roast chicken, cooked beef, lamb fat, pork liver, hop oil, beer, cognac, coffee, tea, plumcot, plum brandy, mushrooms, trassi, sesame seed, buckwheat, wort, elder flowers, Bourbon vanilla, clary and red sage, crabs, clams, and Chinese quince (Burdock, 2005). The following levels have been reported (IPCS, 1990): papaya, 8 μg/kg; beer, 10–120 μg/kg; and coffee, 6.5 mg/kg.

(b) Flavouring agent

Methyl isobutyl ketone is permitted as a flavouring agent in the USA, where it is considered as safe at current levels of intake. Usual reported levels ranged from 2.6 mg/kg in meat products to 12.3 mg/kg in soft candy; maximum reported levels were 25 mg/kg in frozen dairy and non-alcoholic beverages; other reported uses are in baked goods, gelatines and puddings (Burdock, 2005).

The Council of Europe reported maximum levels of 11 mg/kg in beverages and 1 mg/kg foods in general (Council of Europe, 2000).

Table 1.1 International limit values for methyl isobutyl ketone

	Limit value –8 h		Limit value – short-term	
	ppm	mg/m³	ppm	mg/m³
Austria	20	83	50	208
Belgium	20	83	50	208
Canada – Québec	50	205	75	307
Denmark	20	83	40	166
European Union	**20**	**83**	**50**	**208**
France	**20**	**83**	**50**	**208**
Germany (AGS)	20	83	40 (1)	166 (1)
Germany (DFG)	20	83	40	166
Hungary		83		208
Italy	20	83	50	208
Japan	50			
the Netherlands		104		208
Poland		83		200
Spain	20	83	50	208
Sweden	25	100	50	200
Switzerland	20	82	40	164
USA – NIOSH	50	205	75 (1)	300 (1)
USA – OSHA	100	410		
United Kingdom	50	208	100	416
Remarks				
European Union	Bold type: indicative occupational exposure limit values and limit values for occupational exposure			
France	Bold type: restrictive statutory limit values			
Germany (AGS)	(1) 15 min average value			
Germany (DFG)	15 min average value			
USA – NIOSH	(1) 15 min average value			

AGS, German Committee on Hazardous Substances (Ausschuss für Gefahrstoffe); DFG, German Research Foundation (Deutsche Forschungsgemeinschaft); h, hour or hours; NIOSH, National Institute of Occupational Safety and Health; OSHA, Occupational Safety and Health Administration
From GESTIS (2011)

Per-capita exposure to methyl isobutyl ketone, estimated by the FAO/WHO Expert Committee on Food Additives based on poundage data provided by industry, is 7 μg per capita per day in Europe (based on a reported volume of 50 kg/year) and 2 μg per capita per day in the USA (based on a reported production volume of 8 kg/year) (FAO/WHO, 1999). More recently, individual intake was estimated at 0.02 μg/kg per day (Burdock, 2005).

(c) Migration from food packaging

Methyl isobutyl ketone is used in packaging materials that come into contact with food. Levels reported in foods from packaging are: baked goods, 10.9 mg/kg; frozen dairy products, 11.5 mg/kg; meat products, 2.6 mg/kg; soft candy, 12.3 mg/kg; gelatins and puddings, 10.9 mg/kg; and beverages, 10.2 mg/kg (IPCS, 1990).

1.3.4 Environmental occurrence

Methyl isobutyl ketone may be released into the environment in effluent and emissions from its manufacture and use, in exhaust gas from motor vehicles (Hoshika & Takata, 1976) and from land disposal of waste that contains this compound (Verschueren, 2009). Release of methyl isobutyl ketone into the atmosphere may occur during its production through fugitive emissions and incomplete removal of vapours from reaction gases before they are vented or disposed of in a scrubber. In addition, methyl isobutyl ketone has frequently been identified in leakages from landfills and could potentially contaminate groundwater (Francis *et al.*, 1980; IPCS, 1990). Another source of environmental contamination is the release of methyl isobutyl ketone during the discharge of spent scrubbing water from industrial production processes (IPCS, 1990).

1.4 Regulations and guidelines

Methyl isobutyl ketone has been listed by the Council of Europe in category B (flavouring substances for which further information is required before the Committee of Experts is able to offer a firm opinion on the safety of their use; these substances can be used provisionally in foodstuff) (Council of Europe, 2000). Methyl isobutyl ketone is listed in the European register of chemically defined flavourings (FLAVIS number 07.017), and no further evaluation is needed from a legal point of view according to the European Union (EU) evaluation programme (European Comission, 2009). Methyl isobutyl ketone is listed in the EU database for cosmetic ingredients with the following functions: denaturant, solvent and perfume (European Commission, online). Based on the Commission Regulation (EC) No 3199/93, methyl isobutyl ketone is permitted for use to denature alcohol in all EU countries (European Commission, 1993).

Short-term and 8-hour limit values for methyl isobutyl ketone are given in Table 1.1. Both the American Conference of Governmental Industrial Hygienists (ACGIH) in the USA and the Maximale Arbeitsplatz-Konzentrations Commission in Germany provide guidelines for methyl isobutyl ketone in the workplace environment (Table 1.1).

2. Studies in Humans

No data were available to the Working Group

3. Cancer in Experimental Animals

The carcinogenicity studies reviewed below are limited to those of inhalation exposure of mice and rats to methyl isobutyl ketone that were adequately conducted by the National Toxicology Program (NTP, 2007; Stout *et al.*, 2008), the results of which are summarized in Table 3.1.

3.1 Inhalation

3.1.1 Mouse

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed by whole-body inhalation to methyl isobutyl ketone (> 99% pure) at concentrations of 0, 450, 900 and 1800 ppm for 6 hours plus T_{90} (time required to reach 90% of the target concentration within the exposure chamber; 12 minutes) per day on 5 days a week for 105 weeks. Treatment-related increases in the incidence of liver tumours (hepatocellular adenoma and carcinoma combined) were observed in males and females, together with concurrent treatment-related increases in the incidence of eosinophilic foci in the liver.

Table 3.1 Carcinogenicity studies of inhalation exposure to methyl isobutyl ketone (> 99% pure) in experimental animals

Species, strain (sex) Duration	Dosing regimen Animals/group at start	Incidence of tumours	Significance (poly-3 test)	Comments
Mouse, B6C3F$_1$ (M) 105 wk	0, 450, 900 or 1 800 ppm, 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Liver (hepatocellular adenoma or carcinoma)[a]: 27/50, 34/50, 28/50, 37/50 Liver (hepatocellular adenoma)[a]: 17/50, 25/50, 23/50, 34/50 Liver (hepatocellular carcinoma)[a]: 12/50, 12/50, 10/50, 9/50	$P = 0.019$ (high dose) $P = 0.028$ (trend) $P < 0.001$ (high dose) $P < 0.001$ (trend) NS	Survival: 40/50, 42/50, 35/50, 37/50 Liver (eosinophilic foci): 3/50, 4/50, 5/50, 8/50
Mouse, B6C3F$_1$ (F) 105 wk	0, 450, 900 or 1 800 ppm, 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Liver (hepatocellular adenoma or carcinoma)[b]: 17/50, 17/50, 22/50, 27/50 Liver (hepatocellular adenoma)[b]: 13/50, 15/50, 20/50, 23/50 Liver (hepatocellular carcinoma)[b]: 6/50, 5/50, 6/50, 11/50	$P = 0.035$ (high dose) $P = 0.013$ (trend) $P = 0.033$ (high dose) $P = 0.016$ (trend) NS	Survival: 35/50, 37/50, 39/50, 38/50 Liver (eosinophilic foci): 4/50, 11/50[g] 10/50, 14/50[f]
Rat, F344/N (M) 104 wk	0, 450, 900 or 1 800 ppm, 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Kidney (renal tubule adenoma or carcinoma)[c, d]: 2/50, 4/50, 3/50, 11/50 Kidney (renal tubule adenoma)[d]: 2/50, 3/50, 3/50, 10/50 Kidney (renal tubule carcinoma)[c,d]: 0/50, 1/50, 0/50, 2/50 *Single section alone* Kidney (renal tubule adenoma): 0/50, 0/50, 2/50, 3/50 Kidney (renal tubule carcinoma): 0/50, 1/50, 0/50, 2/50 *Step section evaluation alone (3–4 sections per kidney):* Kidney (renal tubule adenoma): 2/50, 3/50, 1/50, 7/50	$P = 0.004$ (high dose) $P < 0.001$ (trend) $P = 0.009$ (high dose) $P = 0.002$ (trend) NS	Survival: 32/50, 28/50, 25/50, 19/50 Kidney (renal tubule hyperplasia)[e]: 1/50 (2.0), 14/50[f] (2.9), 7/50[f] (2.0), 21/50[g] (2.5)[h] Kidney (nephropathy): 42/50 (2.0), 45/50 (2.6), 47/50 (2.4), 50/50[f] (3.1) Kidney (papilla, mineralization): 1/50 (1.0), 6/50[f] (1.2), 22/50[g] (1.6), 29/50[g] (1.5) Kidney (pelvis, transitional epithelium hyperplasia): 1/50 (1.0), 5/50 (1.8), 6/50[f] (1.2), 19/50[g] (1.4)

Table 3.1 (continued)

Species, strain (sex) Duration	Dosing regimen Animals/group at start	Incidence of tumours	Significance (poly-3 test)	Comments
Rat, F344/N (F) 104 wk	0, 450, 900 or 1 800 ppm, 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Kidney (malignant mesenchymal tumour[i]): 0/50, 0/50, 0/50, 2/50	$P = 0.043$ (trend)	Survival: 35/50, 34/50, 26/50, 32/50 Kidney (nephropathy): 19/50 (1.4), 35/50[f] (1.5), 38/50[f] (1.5), 44/50[f] (1.9)

[a] Historical incidence in male B6C3F$_1$ mice for 2-year inhalation studies with chamber controls given NTP-2000 diet (mean ± standard deviation): hepatocellular adenoma or carcinoma, 196/350 (56.0 ± 6.2%), range 50–68%; hepatocellular adenoma, 134/350 (38.3 ± 6.3%), range 30–46%; hepatocellular carcinoma, 85/350 (24.3 ± 4.8%), range 18–32%

[b] Historical incidence in female B6C3F$_1$ mice for 2-year inhalation studies with chamber controls given NTP-2000 diet (mean ± standard deviation): hepatocellular adenoma or carcinoma, 108/347 (31.1 ± 6.8%), range 22–39%; hepatocellular adenoma, 78/347 (22.5 ± 8.1%), range 12–35%; hepatocellular carcinoma, 37/347 (10.7 ± 1.8%), range 8–12%

[c] No additional renal tubule carcinomas were identified in the step section evaluation.

[d] Historical incidence in male F344/N rats for 2-year inhalation studies with chamber controls given NTP-2000 diet for single section evaluations (mean ± standard deviation): renal tubule adenoma, 3/399 (0.8 ± 1.0%), range 0–2%; renal tubule carcinoma, 1/399 (0.3 ± 0.7%), range 0–2%; renal tubule adenoma or carcinoma, 4/399 (1.0 ± 1.1%), range 0–2%

[e] Based on combined single section and step section evaluations. Single sections alone: 1/50 (2.0), 11/50[f] (3.2), 3/50 (2.0), 18/50[f] (2.7); Step section evaluation alone: 0/50, 3/50 (2.0), 4/50 (2.0), 6/50[g] (2.3)

[f] Significantly different ($P \leq 0.05$) from the chamber control group by the poly-3 test

[g] $P \leq 0.01$

[h] Numbers in parentheses indicate average grade of severity of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

[i] Historical incidence in female F344/N rats for 2-year inhalation studies with chamber controls given NTP-2000 diet: 0/396

d, day or days; F, female; h, hour or hours; M, male; min, minute or minutes; NS, not significant; wk, week or weeks

From NTP (2007), Stout *et al.* (2008)

3.1.2 Rat

Groups of 50 male and 50 female F344/N rats were exposed by whole-body inhalation to methyl isobutyl ketone (> 99% pure) at concentrations of 0, 450, 900 and 1800 ppm for 6 hours plus T_{90} (12 minutes) per day on 5 days a week for 104 weeks. Treatment-related increases in the incidence of kidney tumours were observed in males and females (renal tubule adenoma and carcinoma combined in males and two malignant mesenchymal tumours in high-dose females), together with concurrent treatment-related increases in the incidence of renal tubule hyperplasia and papillary mineralization (which had a linear pattern) in males.

[The Working Group noted that kidney tumours are rare spontaneous neoplasms in experimental animals.]

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

Johnson (2004) reviewed the available pharmacokinetic data for methyl isobutyl ketone. Primary data in humans were described for eight male volunteers (18–35 years of age) exposed to 2.4, 24.4 or 48.8 ppm (10, 100 or 200 mg/m^3) for 2 hours on three different occasions during light physical exercise (Hjelm *et al.*, 1990). The relative pulmonary uptake was ~60%, which increased with increasing dose (0.2 mmol at 10 mg/m^3, 1.7 mmol at 100 mg/m^3 and 3.2 mmol at 200 mg/m^3). Levels in the blood rose rapidly after the onset of exposure, levelled off and did not reach a plateau for 2 hours. At the end of the exposure, blood concentrations increased linearly with dose, with no tendency for saturation kinetics. The terminal elimination half-life was increased with dose, but exposure concentration did not impact the apparent rate of blood clearance (1.6 L/h/kg). Blood concentrations measured at the end of the exposures indicated linear kinetics (dose-proportional blood concentration) of methyl isobutyl ketone at the three doses tested. Only 0.04% of the total dose was eliminated unchanged in the urine within 3 hours after dosing, but the concentration in the urine was higher than that in arterial blood at 0.5 and 3 hours after the end of exposure.

After exposure, methyl isobutyl ketone was reported to be eliminated via a rapid and slow phase. Saghir & Rick (2008) cited another study that reported biphasic urinary elimination of methyl isobutyl ketone from human volunteers (Ogata *et al.*, 1995). However, the major route of elimination was exhalation.

Human volunteers (98 men and women) were exposed to 100 ppm (410 mg/m^3) methyl isobutyl ketone for 4 hours in an environmental chamber (Dick *et al.*, 1990). Steady-state blood concentrations of methyl isobutyl ketone were attained after 2 hours of exposure. Blood and breath samples collected 90 minutes after exposure indicated that most of the absorbed compound had been eliminated from the body.

Bellanca *et al.* (1982) reported that methyl isobutyl ketone was detected in the brain, liver, lung, vitreous fluid, kidney, and blood in two workers who died after exposure to several organic solvents during spray painting. One died from a fall and the other died of cerebral oedema 9 hours later. Tissue concentrations (mg/100 g) were reported to be: case 1 — brain, 0.25; liver, 0.49; lung, 0.43; vitreous fluid, 0.52; kidney, 0.24; and femoral blood, 0.14; and case 2 — brain, 0.06; liver, 0.22; lung, 0.11; vitreous fluid, 0.02; kidney, 0.08; and heart blood, 0.04.

Dowty *et al.* (1976) reported methyl isobutyl ketone in human maternal blood samples collected immediately after delivery, indicating the potential for the compound to enter the umbilical cord and cross the placenta. Methyl

isobutyl ketone is readily soluble in blood and has a high affinity for fat. In-vitro partition coefficients of 70–90 between blood and air and 926 between water and oil were reported (Sato & Nakajima, 1979).

Saghir and Rick (2008) used the data of Hjelm *et al.* (1990) on single-dose inhalation exposure to simulate the repeated-dose kinetics of methyl isobutyl ketone in humans. The physiologically based pharmacokinetic model predicted the kinetics and accumulation of methyl isobutyl ketone after repeated exposures for 8, 12 and 24 hours per day for 7 days to the current ACGIH exposure threshold limit value-TWA of 50 ppm, and followed a two-compartment model using inhalation-chamber data. Elimination of methyl isobutyl ketone was assumed to occur primarily through exhalation, because only 0.04% of the total dose was reported to be eliminated through the urine (Hjelm *et al.*, 1990). The model did not account for elimination from the blood/body via other routes of elimination, e.g. as carbon dioxide, or metabolic incorporation into tissues. Measured blood concentrations were used to derive kinetic parameters that were then used to predict blood concentrations following different exposure scenarios at 50 ppm. [The model was not validated using an independent data set.] The model output was then used to assess the probable effects of various conditions of blood concentration, potential for accumulation and TWA blood concentrations. Kinetic rates were calculated using the methodology of Hjelm *et al.* (1990). Berkeley-Madonna modelling software was used that can simulate a simple one- or two-compartment situation. The model made no attempt to predict the levels of exhaled methyl isobutyl ketone. Therefore, the amount exhaled was not fed back into the exposure concentration and the exposure concentration defined in the model was fixed over a defined exposure period. The model was optimized by fitting all three blood concentration time-course concentrations of methyl isobutyl ketone. The model (Saghir & Rick, 2008) correctly simulated the experimental data measured after single exposures and demonstrated a rapid rise in blood concentration to 1.06 µg/mL within 1 hour, which approached steady-state levels of 1.37 µg/mL at 4 hours of exposure and 1.47 µg/mL at the end of exposure. Methyl isobutyl ketone was predicted to be rapidly eliminated from blood after cessation of exposure, reaching 0.53 µg/mL and 0.13 µg/mL within 0.5 and 2 hours after cessation, respectively. It was concluded that methyl isobutyl ketone is not likely to accumulate in workers exposed to 50 ppm.

4.1.2 Experimental systems

Methyl isobutyl ketone was rapidly absorbed following oral administration to or inhalation exposure of male Sprague-Dawley rats (Duguay & Plaa, 1995). The compound was rapidly absorbed and was detected in the lung, liver and plasma after inhalation or within 1 hour after an oral dose. In CD-1 mice, an intraperitoneal injection was quickly distributed and eliminated (Granvil *et al.*, 1994). Clearance time was 6 hours and the half-life in serum was 66 minutes in guinea-pigs that received a single intraperitoneal dose of methyl isobutyl ketone (DiVincenzo *et al.*, 1976).

Male Sprague-Dawley rats were exposed to methyl isobutyl ketone orally (0.5, 3 or 6 mmol/kg body weight (bw)) or by inhalation (200, 400 or 600 ppm) (Duguay & Plaa, 1995). The parent compound and two products — 4-hydroxymethyl isobutyl ketone and 4-methyl-2-pentanol — were identified in the plasma, liver and lung following inhalation. After oral administration, the parent compound and the hydroxylated product were detected in these tissues, but not 4-methyl-2-pentanol. These results were consistent with the metabolism of methyl isobutyl ketone via alcohol dehydrogenase and cytochrome P450 (CYP) mono-oxygenases (Vézina *et al.*, 1990). In CD-1 mice that received an intraperitoneal injection of

5 mmol/kg bw methyl isobutyl ketone (Granvil *et al.*, 1994), the major metabolites detected in the blood and brain were 4-methyl-2-pentanol and 4-hydroxy-4 methyl-2-pentanone.

In a review, Stout *et al.* (2008) indicated that the metabolism of methyl isobutyl ketone in guinea-pigs entails the 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-hydrodroxymethyl isobutyl ketone, also known as diacetone alcohol). 4-Methyl-2-pentanol may be further conjugated with sulfate or glucuronic acid, may undergo intermediary metabolism and be eliminated as carbon dioxide or may be incorporated into tissues.

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

Johnson (2004) reviewed the genetic toxicology of methyl isobutyl ketone and found that it is generally not genotoxic in a variety of systems. An effort was made to test this volatile compound in closed systems in some of the assays, including *Salmonella* and the mouse lymphoma thymidine kinase locus $Tk^{+/-}$, but the compound still gave either negative or equivocal results. In studies in *Salmonella* (Brooks *et al.*, 1988; Zeiger *et al.*, 1992), methyl isobutyl ketone was not mutagenic in the presence or absence of metabolic activation in a variety of strains (TA98, TA100, TA1535, TA1537 and TA1538) in the pre-incubation assay in closed tubes. Similar negative results were also observed in the *S. typhimurium* assay with TA102 and TA104 (Zeiger *et al.*, 1992). Equivocal results were found in the L5178Y mouse lymphoma $Tk^{+/-}$ assay which was also performed in closed tubes (O'Donoghue *et al.*, 1988).

Methyl isobutyl ketone gave negative results for unscheduled DNA synthesis in rat hepatocytes, for micronuclei in the bone marrow of CD-1 mice (after intraperitoneal injection), for cell transformation in BALB/3T3 mouse embryo cells (O'Donoghue *et al.*, 1988), for mitotic gene conversion (Brooks *et al.*, 1988) and mitotic chromosome loss (Zimmermann *et al.*, 1989) in yeast and for chromosome damage in rat liver cells *in vitro* (Brooks *et al.*, 1988).

4.3 Toxic effects

4.3.1 Humans

No data were available to the Working Group.

4.3.2 Experimental systems

(a) Liver and kidney

Methyl isobutyl ketone, its metabolites and other ketones are known to potentiate liver necrosis induced by haloalkanes (e.g. carbon tetrachloride and chloroform (Vézina *et al.*, 1990)), and cholestasis induced by cholestatic agents (e.g. taurolithocholate (Plaa & Ayotte, 1985; Dahlström-King *et al.*, 1990; Duguay & Plaa, 1997) or manganese-bilirubin (Vézina & Plaa, 1987; Duguay & Plaa, 1997)). There is no evidence, however, that methyl isobutyl ketone or its metabolites have adverse effects on the liver when administered alone either orally (up to 7.5 mmol/kg) or by inhalation (up to 600 ppm) under conditions of a single or repeated (3 days) exposure (Joseph *et al.*, 1992; Duguay & Plaa, 1997).

Although methyl isobutyl ketone showed no toxic effect on the liver in acute or subacute exposures, it has been shown (Vézina *et al.*, 1990) to increase the total amount of CYP in the rat liver 24 hours after a single dose (lowest effective dose tested, 7.5 mmol/kg bw in corn oil vehicle

by gavage) or after a 5-day treatment regime (lowest effective dose, 5 mmol/kg bw). While no individual CYP enzymes were evaluated in this study, the authors tested for the activity of aniline hydroxylase (CYP2E activity), ethoxycoumarin *O*-deethylase (CYP1A and –2E activity) and aminopyrine *N*-demethylase (CYP2B activity) and reported increased activity after treatment with methyl isobutyl ketone for all three enzymes at both time-points with minimal effective doses identical to that required to increase total CYP content.

The induction of liver CYPs has been associated with the 'potentiating' effect of methyl isobutyl ketone on prior hepatotoxic treatments (Vézina *et al.*, 1990). However, this mechanism does not appear to be exclusive because it also affects the toxicity of bile acid, and it has been suggested that methyl isobutyl ketone may also reduce the bile salt pool and/or affect hepatic secretion of bile acids (Joseph *et al.*, 1992).

A similar effect on the induction of total CYP, as well as aniline hydroxylase (CYP2E activity) and aminopyrine *N*-demethylase (CYP2B activity), was observed in the rat kidney after oral (3 days; minimal effective dose, 13.6 mmol/kg bw) administration of methyl isobutyl ketone (Raymond & Plaa, 1995a). Interestingly, while total CYP, CYP2E and –2B activities in the liver were much greater than those in the kidney, the induction of total CYP was 2–3 times greater in the kidney than in the liver. In the same study, covalent binding of [^{14}C]carbon tetrachloride to renal proteins was potentiated by methyl isobutyl ketone, similarly to the observation in the liver. It was also shown that methyl isobutyl ketone potentiates chloroform-induced kidney toxicity, albeit to a lesser degree than that of carbon tetrachloride (Raymond & Plaa, 1995b). Both studies concluded that enzyme induction by methyl isobutyl ketone played a major role in the potentiation of toxicity of the two nephrotoxicants which are known to require metabolic activation.

Subchronic (≥ 90 days) exposure to methyl isobutyl ketone by inhalation was shown to increase liver weights, characterized by hepatocellular hypertrophy, in both rats and mice (Phillips *et al.*, 1987; Nemec *et al.*, 2004). A comparison of the effects of exposure by inhalation to 410 mg/m^3 methyl isobutyl ketone for 90 days in male rats, beagle dogs and *Macaca mulatta* monkeys (MacEwen *et al.*, 1971) revealed no pathological effects in dogs or monkeys in any of the major organs examined at necropsy. Statistically significant increases in liver and kidney weights were observed only in male rats. Hyaline droplets were detected in the proximal tubules of all exposed male rats within 15 days of exposure (some rats were necropsied after 2, 3, 4, 10, or 12 weeks). A study that investigated oral administration of methyl isobutyl ketone (1.04 g/kg per day in the drinking-water for 120 days) to female rats found a significant increase in absolute and relative kidney (but not liver or other organ) weight, and one of five rats tested had renal tubule-cell hyperplasia (US EPA, 2003). Another subchronic toxicity study compared male and female rats administered methyl isobutyl ketone daily by oral gavage (59, 250 or 1000 mg/kg bw) for 13 weeks (IPCS, 1990). Nephrotoxicity and increased liver and kidney weights were observed in both males and females at the highest dose. The no-adverse-effect dose was 50 mg/kg bw.

(b) Other studies of toxicity

Rats, mice, guinea-pigs, cats and dogs were studied for the acute toxicity of methyl isobutyl ketone after oral, dermal, inhalational, intravenous or intraperitoneal administration. These studies have been reviewed extensively (Johnson, 2004). No species differences in acute toxic effects were observed. Methyl isobutyl ketone was shown to be neurotoxic and irritating (to the upper respiratory tract and lungs after inhalation) at the highest concentrations tested. Little evidence of hepatic or renal toxicity was reported even at doses that were lethal.

Two studies of the reproductive and developmental toxicity of methyl isobutyl ketone were available. Tyl *et al.* (1987) exposed F344 rats and CD-1 mice to methyl isobutyl ketone (up to 3000 ppm) by inhalation on gestational days 6–15. Maternal toxicity (death, increases in absolute and relative liver weights) were observed in the 3000-ppm groups of rats and mice. Fetal toxicity (decrease in body weight, retardation of ossification) was observed in the offspring of both rats and mice in the 3000-ppm group. Nemec *et al.* (2004) exposed Sprague-Dawley rats to up to 2000 ppm methyl isobutyl ketone (whole-body inhalation) for 70 days before mating. F0 and F1 females were exposed from mating to gestational day 20 and then from postnatal day 5; F2 litters were maintained through postnatal day 21. Most adverse effects were observed only in the 2000-ppm group. Specifically, a sedative effect (central nervous system depression) was observed in the pups. Increased liver weight was observed in the F0 and F1 generation males and females. In F0 generation males, increased kidney (in the 500- and 1000-ppm groups) and seminal vesicle weights were observed. In F0 females, an increase in the weight of ovaries and adrenal glands was observed. Nephropathy, characterized by basophilic tubules with variable inflammation and thickening of the tubular basement membrane, was reported in F0 and F1 males exposed to 1000 or 2000 ppm methyl isobutyl ketone. No effects on sexual maturation or reproductive end-points were observed at any dose tested.

4.4 Mechanistic considerations

4.4.1 Tumours of the kidney

The development of kidney tumours in male rats in association with chemically induced α2u-globulin nephropathy is mechanism that is not considered to be a predictor of carcinogenic risk to humans by the IARC or the US EPA (US EPA, 1991; Swenberg & Lehman-McKeeman, 1999). The lack of relevance of the α2u-globulin mechanism for the evaluation of carcinogenic risk is based on the absence of the production of an analogous protein in humans. Strict scientific criteria have been outlined to establish the role of α2u-globulin-associated nephropathy in renal carcinogenesis in male rats (Swenberg & Lehman-McKeeman, 1999), and were used to determine the plausibility of an α2u-globulin-associated nephropathy based on a limited number of studies that have been carried out with subchronic and chronic exposures to methyl isobutyl ketone.

Criterion 1 is evidence of a lack of genotoxic activity (agent and/or metabolite) based on an overall evaluation of in-vitro and in-vivo data. As reviewed in Section 4.2, there was little, if any evidence that methyl isobutyl ketone was genotoxic. Two of its metabolites — 4-hydroxymethyl isobutyl ketone and 4-methyl-2-pentanol — that are found in male Sprague-Dawley rat liver, serum and lung after exposure to methyl isobutyl ketone have not been evaluated for genotoxicity. Thus, this criterion appears to be met.

Criterion 2 is the specificity in male rats for nephropathy and renal tumorigenicity; criterion 6 is the induction of sustained increased cell proliferation in the renal cortex; and criterion 7 mentions the observed similarities in the dose–response relationship of the tumour outcome with the histopathological end-points (protein droplets, α2u-globulin accumulation and cell proliferation). Stout *et al.* (2008) evaluated the potential of methyl isobutyl ketone to induce toxic and carcinogenic effects following chronic exposure. Groups of 50 male and 50 female F344 rats were exposed to concentrations of 0, 450, 900 or 1800 ppm by inhalation for 6 hours per day on 5 days a week for 2 years. Survival was decreased in 1800-ppm males, and body weight gains were decreased in 900- and 1800-ppm males. In males, but not females, increased mineralization of the renal papilla was observed at all exposure concentrations. The incidence of chronic progressive

nephropathy was increased at 1800 ppm and its severity was increased in all exposed groups of males. The incidence of chronic progressive nephropathy was increased in all treated groups of females, the severity of which was increased with the highest dose. In male, but not females, increases in incidence of renal tubule hyperplasia were observed at all exposure concentrations, and in that of adenoma and adenoma or carcinoma (combined) at 1800-ppm. α2u-Globulin levels were not evaluated in this study. This chronic study provided dose–response consistency and male specificity of mineralization, sustained increases in cell proliferation in the renal cortex and the induction of combined adenomas and carcinomas in the kidney. However, the study found that chronic progressive nephropathy was not male-specific.

Criterion 3 is the induction of the characteristic sequence of histopathological changes in shorter-term studies, of which protein droplet accumulation is obligatory. The Bushy Run Research Center (1982) exposed three groups of F344 rats (six males and six females) to methyl isobutyl ketone at concentrations of 101 ppm [413 mg/m^3], 501 ppm [2050 mg/m^3] and 1996 ppm [8180 mg/m^3] for 6 hours per day for 9 days. A fourth group served as the untreated control. The first 5 days and the remaining 4 days of exposure were separated by a 2-day non-treatment period. In the highest-dose group (1996 ppm), a significant increase in both absolute and relative kidney weights was noted in male and female rats. Epithelial regeneration of the proximal convoluted tubules was also noted at 1996 ppm [male and female specificity was indicated in the summary]. In the 501-ppm exposure group, a non-significant increase in kidney weight was observed in male but not female rats. In both 501- and 1996-ppm exposure groups, hyaline droplet formation was observed in the kidneys of male rats. No microscopic abnormalities were noted in rats exposed to 101 ppm methyl isobutyl ketone (Bushy Run Research Center, 1982, cited by US EPA, 2003).

Male and Female F344 rats and B6C3F$_1$ mice were exposed to 0, 100, 500 or 2000 ppm methyl isobutyl ketone for 6 hours per day for 2 weeks. At 2000 ppm, a slight increase in male rat liver weight (absolute and relative)was observed. The only changes observed histologically were increases in regenerative tubular epithelia and hyaline droplets in the kidneys of male but not female rats exposed to 500 or 2000 ppm Phillips *et al.* (1987). Exposure levels for a subchronic study were 0, 50, 250 or 1000 ppm methyl isobutyl ketone vapour for 6 hours per day on 5 days a week for 14 weeks. The 14-week exposure had no adverse effect on the clinical health or growth of the rats. The only microscopic change observed was an increase in the incidence and extent of hyaline droplets within the proximal tubular cells of the kidneys of male but not female rats exposed to 250 and l000 ppm. These two studies indicate the induction of hyaline protein droplets in shorter-term studies. Protein droplets were also identified and characterized further in the study described below (Borghoff *et al.*, 2009).

Another criterion is the identification of protein accumulation in tubule cells as α2u-globulin. Borghoff *et al.* (2009) administered corn oil (vehicle control), *d*-limonene (positive control, 300 mg/kg bw) or methyl isobutyl ketone (1000 mg/kg bw) to male and corn oil (vehicle control) or methyl isobutyl ketone to female F344 rats by oral gavage for 10 consecutive days. Methyl isobutyl ketone caused an increase in protein droplets, accumulation of α2u-globulin and renal cell proliferation in male but not female rats. It produced histopathological changes in the male rat kidney identical to those of *d*-limonene, an acknowledged inducer of α2u-globulin-mediated nephropathy, except that the grade of severity tended to be slightly lower with methyl isobutyl ketone. Methyl isobutyl ketone did not induce any effects in female rats. The authors found α2u-globulin

accumulation in tubule cells after exposure in males. However, the experimental design did not allow for the evaluation of a dose–response relationship in the increases in α2u-globulin accumulation; moreover, treatment-related increases in the incidence and average severity of chronic progressive nephropathy were observed in both males and females, which suggests that an alternative mechanism may also be involved. Renal tubule neoplasms probably arose via the male rat-specific α2u-globulin-mediated mechanism (NTP, 2007).

The last criterion is the reversible binding of the chemical or metabolite to α2u-globulin, which was not shown direct in any of the studies. One study showed reversibility of the adverse effects in the kidney after withdrawal of methyl isobutyl ketone. The Wright-Patterson Air Force Base Aerospace Medical Research Laboratory (MacEwen *et al.*, 1971) conducted a subchronic inhalation toxicity study in male Wistar albino rats that were exposed to 410 mg/m^3 methyl isobutyl ketone vapour [100 ppm] for 90 days in an altitude chamber. The untreated control group was maintained in a separate altitude chamber. Statistically significant increases in liver and kidney weights and organ-to-body weight ratios for these tissues were noted in exposed rats. Microscopic examination of the kidneys revealed hyaline droplet degeneration of the proximal tubules (with occasional foci of tubular necrosis) in all of the exposed rats, including those that were removed from the inhalation chamber after 15, 22, 28, 71 and 85 days. The authors noted a trend towards a linear progression of hyaline droplet degeneration during exposure, but this pattern was not seen in all treatment groups. Moreover, the hyaline droplets appeared to increase in size with time. This observation was thought to have resulted from the coalescence of smaller droplets. Microscopic examination of rat kidneys removed after 15 days of exposure indicated a gradual reversion of tubular damage with time. Kidney damage was completely reversed in rats observed up to 60 days after exposure. Recovery from methyl isobutyl ketone-induced kidney lesions was also noted in rats that were serially killed to study reversibility after 90 days of exposure. However, recovery was not as rapid as that noted in animals exposed for shorter periods. A weakness of the study was the exclusion of female rats. The study showed the reversibility of effects that could be attributed to α2u-globulin nephropathy.

Kidney tumours were induced in male but not female rats. Mechanistic studies provide evidence that some of the criteria that denote an α2u-globulin mode of action were met. [These include male rat-specific nephropathy, dose–response associations of end-points and dose-related increases in cell proliferation.] However, in a review of the linkages between end-points that are typically considered to support an α2u-globulin mode of action (Doi *et al.*, 2007), recent NTP studies demonstrated inconsistencies with this proposed mechanism, including, in some cases, kidney tumour responses that were far weaker than expected based on the extent of α2u-globulin nephropathy. The review revealed no, or at best weak, associations between tumour responses and renal α2u-globulin concentrations, indices of cell turnover or microscopic evidence of α2u-globulin nephropathy in pre-chronic studies. While tumour responses corresponded to some extent with a measure of cumulative α2u-globulin nephropathy (linear mineralization of the papilla) at the end of the 2-year studies, the severity of chronic nephropathy generally correlated best with the pattern of tumour response. These results suggest that, while α2u-globulin nephropathy may contribute to the renal tumour response, the critical component(s) of the nephropathy most closely associated with the development of tumours has not been identified. Thus, the strength of the evidence that male rat kidney tumours arose through a α2u-globulin nephropathy mechanism is weak. The relevance

of the tumour response to humans cannot be excluded.

4.4.2 Other sites

There is little, if any, evidence that rodent tumours arose through a genotoxic mechanism. However, two metabolites — 4-hydroxymethyl isobutyl ketone and 4-methyl-2-pentanol — found in male Sprague-Dawley rat liver, serum and lung after exposure to methyl isobutyl ketone have not been evaluated for genotoxicity. Methyl isobutyl ketone induced liver tumours in male and female mice, but there was no evidence that the tumours arose from a cytotoxic-regenerative cell proliferation mechanism as no overt toxicity occurred in the livers of exposed mice. Only weak evidence exists that the tumours arose through a receptor-mediated mechanism, resulting from the induction of enzymes (CYP1A1 and CYP2B) that have been considered to be typical targets of the aryl hydrocarbon receptor and the constitutive activated receptor, respectively (Nebert *et al.*, 2000; Zelko & Negishi, 2000). The strength of evidence that male and female liver tumours arose through a nuclear receptor mechanism is weak. The relevance of the tumour response to humans cannot be excluded.

5. Summary of Data Reported

5.1 Exposure data

Methyl isobutyl ketone is used as an industrial solvent, a fragrance, denaturant or solvent in cosmetic products, to denature alcohol and as an excipient in drugs. Methyl isobutyl ketone is naturally present in food and may be added as a flavouring ingredient. It may be released into the environment as emissions from its manufacture and use, and from leakage from landfills. Exposure in the workplace occurs by inhalation of the vapours and skin contact. Routes of exposure to methyl isobutyl ketone by the general population are ingestion through food and dermal contact with consumer products.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

In a 2-year inhalation study in male and female mice and rats, methyl isobutyl ketone increased the incidence of hepatocellular adenoma and hepatocellular adenoma and carcinoma combined in male and female mice, and that of renal tubule adenoma and renal tubule adenoma and carcinoma combined in male rats, and caused two rare renal malignant mesenchymal tumours in high-dose female rats.

Kidney tumours are rare spontaneous neoplasms in experimental animals.

5.4 Other relevant data

Toxicokinetic data for methyl isobutyl ketone indicate that pulmonary uptake and blood concentrations of this chemical increase linearly with the dose in human volunteers who were exposed via inhalation. Steady-state blood levels were attained after 2 hours of exposure. The major route of elimination was exhalation, and only a tiny fraction was excreted in the urine. Analysis of blood and breath samples collected after exposure indicated that most of the absorbed methyl isobutyl ketone had been eliminated from the body within 2 hours. The compound was detected in the brain, liver, lung, vitreous fluid, kidney and blood in autopsy samples of two workers who had been exposed to organic solvents. There is evidence that methyl isobutyl ketone may enter the umbilical cord and cross the placenta.

Data from single-dose inhalation exposure studies were used to simulate the repeated-dose kinetics of methyl isobutyl ketone in humans. The two-compartment pharmacologically based pharmacokinetic model predicted the kinetics and accumulation for repeated exposures. It correctly simulated the experimental data measured after single exposures and demonstrated a rapid rise in blood concentration within 1 hour and rapid elimination from the blood after cessation of exposure. On the basis of these results, methyl isobutyl ketone is not likely to accumulate in workers exposed to 50 ppm. Methyl isobutyl ketone was rapidly absorbed after oral administration to or inhalation exposure of male rats. It was detected in the lung, liver and plasma within 1 hour after an oral dose. In mice, methyl isobutyl ketone administered by intravenous injection was quickly distributed and eliminated. A clearance time of 6 hours and a half-life in serum of about 1 hour were measured in guinea-pigs after a single intraperitoneal dose of methyl isobutyl ketone.

No data were available on the metabolism of methyl isobutyl ketone in humans. In rats, the parent compound and two metabolites — 4-hydroxymethyl isobutyl ketone and 4-methyl-2-pentanol — were identified in the plasma, liver and lung following inhalation. After an oral dose, the parent compound and the hydroxylated product were detected in these tissues, but not 4-methyl-2-pentanol. These data are consistent with metabolism that involves alcohol dehydrogenase and cytochrome P450 mono-oxygenases. Similar patterns of metabolism were seen in mice and guinea-pigs.

Methyl isobutyl ketone was generally not genotoxic in a variety of systems. Also, when this volatile compound was tested in closed systems, no indication of genotoxicity was found. Methyl isobutyl ketone was not mutagenic in bacterial assays. It did not induce unscheduled DNA synthesis in rat hepatocytes, micronuclei mouse bone marrow, cell transformation in BALB/3T3 mouse embryo cells, mitotic gene conversion or mitotic chromosome loss in yeast or chromosome damage in rat liver cells *in vitro*. There is little, if any, evidence that methyl isobutyl ketone-induced tumours in rodents arise through a genotoxic mechanism, although its two metabolites (4-hydroxymethyl isobutyl ketone and 4-methyl-2-pentanol) have not been evaluated for genotoxicity.

Methyl isobutyl ketone and its metabolites potentiate liver necrosis induced by haloalkanes and enhance cholestasis induced by cholestatic agents or manganese-bilirubin. There is no evidence that acute administration of methyl isobutyl ketone or its metabolites has adverse effects on the liver when given alone, either orally or via inhalation. It increased the total activity of cytochrome P450s 1A, 2B and 2E in the liver and kidney of rats. The induction of these isozymes by methyl isobutyl ketone has been associated with the potentiating effect mentioned above. It has been suggested that methyl isobutyl ketone also reduces the bile-salt pool and affects the secretion of bile acids by the liver.

Subchronic inhalation exposure to methyl isobutyl ketone was shown in one study to result in increased liver weight, characterized by hepatocellular hypertrophy, in both rats and mice, but statistically significant increases in both liver and kidney weights were observed only in male rats. Hyaline droplets were detected in the proximal tubules of all exposed male rats. However, another subchronic toxicity study that compared male and female rats demonstrated nephrotoxicity and increased liver and kidney weights in both male and female rats.

In various animal species, methyl isobutyl ketone was shown to be neurotoxic and irritating to the upper respiratory tract and lungs after inhalation at high concentrations.

The IARC scientific criteria to determine the plausibility of α2u-globulin-associated nephropathy as the underlying mechanism of kidney tumorigenesis were considered based on the

limited number of studies on subchronic and chronic exposure to methyl isobutyl ketone, and were not completely fulfilled. The strength of the evidence that the kidney tumours in male rats arise through an α2u-nephropathy-associated mechanism is weak.

There is no evidence that liver tumours in mice arise from a cytotoxic-regenerative cell-proliferation mechanism, because no overt liver toxicity has been demonstrated. There is only weak evidence that the tumours arise through a receptor-mediated mechanism.

The relevance of the tumour response in mice and rats to humans cannot be excluded.

6. Evaluation

6.1 Cancer in humans

No data were available to the Working Group.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of methyl isobutyl ketone.

6.3 Overall evaluation

Methyl isobutyl ketone is *possibly carcinogenic to humans (Group 2B).*

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