

METHYL ISOAMYL KETONE
CAS # 110-12-3
ORAL RISK ASSESSMENT DOCUMENT



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EXECUTIVE SUMMARY

Methyl Isoamyl Ketone – Oral Risk Assessment CAS # 110-12-3			
PARAMETER	LEVEL	UNITS	CALCULATED:
NOAEL (no-observed-adverse-effect level)	25	mg/kg-day	From a 13-week rat inhalation study.
Oral RfD (oral reference dose)	0.008	mg/kg-day	From a 13-week rat inhalation study.
TAC (total allowable concentration)	0.06	mg/L	For a 70 kg adult drinking 2 L/day with a 20% Relative Source Contribution for drinking water.
SPAC (single product allowable concentration)	0.006	mg/L	For a 70 kg adult drinking 2 L/day.
STEL (short term exposure level)	0.8	mg/L	For a 10 kg child drinking 1 L/day.
KEY STUDIES	Katz, G.V., E.R. Renner Jr., and C.J. Terhaar. 1986. Subchronic inhalation toxicity of methyl isoamyl ketone in rats. <i>Fund. Appl. Toxicol.</i> 6:498-505. Katz, G.V. 1983. Two week and 90-day inhalation studies of methyl isoamyl ketone in rats. Health and Environment Laboratories, Eastman Kodak Company.		
CRITICAL EFFECT	Hepatocyte hypertrophy in both sexes and minimal necrosis of the liver in males.		
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD: • 3x for interspecies extrapolation • 10x for intraspecies extrapolation • 10x for subchronic to chronic extrapolation • 1x for extrapolation from LOAEL to NOAEL • 10x for database deficiencies The total uncertainty factor is therefore 3,000x.		
TOXICITY SUMMARY	Toxicology evaluations of methyl isoamyl ketone include acute, subacute, subchronic, and genotoxicity studies. Developmental and neurotoxicity studies are available for structurally related ketones. The gavage studies located for methyl isoamyl ketone contained deficiencies considered to impact the risk assessment. A 13-week study evaluated only one dose level in male rats only, and a three-week study evaluated only male rats and did not include complete clinical chemistry or histological evaluation. The critical study was a 13-week rat inhalation study, which identified a NOAEL of 212 ppm (human equivalent oral dose of 25 mg/kg-day) based on increased mean absolute and relative liver weight and hepatocyte hypertrophy in both sexes. The changes in liver weight and liver pathology were also observed in the subchronic gavage study. Histopathological changes noted in the kidneys of males were associated with alpha-2μ-globulin nephropathy, thus were not relevant to human health. Based on a rat hepatic peroxisome proliferation study, the liver changes are not likely attributable to hepatic peroxisome proliferation, thus were considered relevant for this risk assessment. A human equivalent oral RfD of 0.01 mg/kg-day was derived from the 13-week rat NOAEL, using appropriate dose conversion factors and an inhalation absorption factor of 50%, based on absorption data for methyl ethyl ketone, since oral or inhalation kinetic, dynamic, or metabolic data for methyl isoamyl ketone were unavailable. Methyl isoamyl ketone was not mutagenic in <i>Salmonella typhimurium</i> over a range of doses in the presence and absence of metabolic activation, and was negative in a 3T3 cell transformation assay. The evidence of chromosomal aberrations observed at high concentrations was discounted since these concentrations were greater than 10 mM and cytotoxicity was observed.		
CONCLUSIONS	Subacute and subchronic toxicity data exist to characterize the magnitude and duration of methyl isoamyl ketone exposure required to induce hepatotoxicity in rats. Although the weight of evidence of genotoxicity data suggests that methyl isoamyl ketone is not genotoxic, no chronic animal or human epidemiological studies were identified for methyl isoamyl ketone. Thus the cancer risk to humans from exposure to methyl isoamyl ketone <i>cannot be determined</i> . Taking into account the uncertainty factors used, the drinking water action levels established for methyl isoamyl ketone are considered to be protective of public health.		

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **methyl isoamyl ketone** in drinking water, as an extractant from one or more drinking water system components evaluated under NSF/ANSI 61 (2002), or as a contaminant in a drinking water treatment chemical evaluated under NSF/ANSI 60 (2002). Both non-cancer and cancer endpoints have been considered, and risk assessment methodology developed by the U.S. Environmental Protection Agency (U.S. EPA) has been used.

Non-cancer endpoints are evaluated using the reference dose (RfD) approach (Barnes and Dourson, 1988; Dourson, 1994; U.S. EPA, 1993a), which assumes that there is a threshold for these endpoints that will not be exceeded if appropriate uncertainty factors (Dourson et al., 1996) are applied to the highest dose showing no significant effects. This highest dose is derived from human exposure data when available, but more often is derived from studies in laboratory animals. Either the no-observed-adverse-effect level (NOAEL) taken directly from the dose-response data, or the calculated lower 95% confidence limit on the dose resulting in an estimated 10% increase in response (the LED₁₀ or BMDL from benchmark dose programs) can be used (U.S. EPA, 2001). The lowest-observed-adverse-effect level (LOAEL) can also be used, with an additional uncertainty factor, although the benchmark dose approach is preferred in this case. The RfD is expressed in mg/kg-day. It is defined by the U.S. EPA as “an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime” (Barnes and Dourson, 1988; U.S. EPA, 1993a; U.S. EPA, 1999a).

NSF uses the RfD to derive three product evaluation criteria for non-cancer endpoints. The total allowable concentration (TAC), generally used to evaluate the results of extraction testing normalized to static at-the-tap conditions, is defined as the RfD multiplied by the 70 kg weight of an average adult assumed to drink two liters of water per day. A relative source contribution (RSC), to ensure that the RfD is not exceeded when food and other non-water sources of exposure to the chemical are considered, is also applied in calculating the TAC. The relative source contribution should be data derived, if possible. Alternately, a 20% default contribution for water can be used (U.S. EPA, 1991a). The TAC calculation is then as follows:

$$\text{TAC (mg/L)} = \frac{[\text{RfD (mg/kg-day)} \times 70 \text{ kg}] - [\text{total contribution of other sources (mg/day)}]}{2\text{L/day}}$$

or

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-day)} \times 70 \text{ kg}}{2\text{L/day}} \times 0.2 \text{ (RSC)}$$

The single product allowable concentration (SPAC), used for water treatment chemicals and for water contact materials normalized to flowing at-the-tap conditions, is the TAC divided by the estimated total number of sources of the substance in the drinking water treatment and distribution system. In the absence of source data, a default multiple source factor of 10 is used.

This accounts for the possibility that more than one product in the water and/or its distribution system could contribute the contaminant in question to drinking water.

Finally, a short-term exposure level (STEL), at a higher level than the TAC, may be calculated for contaminants such as solvents expected to extract at higher levels from new product, but also expected to decay rapidly over time. The STEL is calculated from the NOAEL or the LED₁₀ of an animal study of 14- to 90-days duration, with uncertainty factors appropriate to the duration of the study. The contaminant level must decay to the TAC or below under static conditions, or to the SPAC or below under flowing conditions within 90 days, based on the contaminant decay curve generated from over-time laboratory extraction data.

Endpoints related to cancer are evaluated using modeling to fit a curve to the appropriate dose-response data (U.S. EPA, 1996a; U.S. EPA, 1999b). If there is sufficient evidence to use a non-linear model, the LED₁₀ or BMDL, divided by the anticipated exposure, is calculated to give a margin of exposure. If there is insufficient evidence to document non-linearity, a linear model drawing a straight line from the LED₁₀ or BMDL to zero is used as a default. If a linear model (generally reflecting a genotoxic carcinogen) is used, a target risk range of 10^{-6} to 10^{-4} is considered by the U.S. EPA to be safe and protective of public health (U.S. EPA, 1991a). For the purposes of NSF/ANSI 60 (2002) and 61 (2002), the TAC is set at the 10^{-5} risk level, and the SPAC is set at the 10^{-6} risk level. Use of a higher risk level is not ruled out but would generally require documentation of a benefit to counteract the additional risk.

The RfD, TAC, SPAC, and STEL values derived in this document are based on available health effects data and are intended for use in determining compliance of products with the requirements of NSF/ANSI 60 (2002) and 61 (2002). Application of these values to other exposure scenarios should be done with care and with a full understanding of the derivation of the values and of the comparative magnitude and duration of the exposures. These values do not have the rigor of regulatory values, as data gaps are generally filled by industry or government studies prior to regulation. Data gaps introduce uncertainty into an evaluation and require the use of additional uncertainty factors to protect public health.

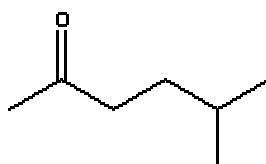
The general guidelines for this risk assessment include those from the National Research Council (1983) and from The Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a, 1997b). Other guidelines used in the development of this assessment may include the following: Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a), Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), draft revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999b), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991b), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b), Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1998), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), and Health Effects Testing Guidelines (U.S. EPA 1996c, OPPTS series 870; U.S. EPA, 2002a, 40 CFR Part 798).

The literature search strategy employed for this compound was based on the Chemical Abstract Service Registry Number (CASRN) and at least one common name. As a minimum, the following data banks were searched:

- ChemID Plus
- Registry of Toxic Effects of Chemical Substances (RTECS)
- Hazardous Substances Data Bank (HSDB)
- GENE-TOX
- Environmental Mutagen Information Center (EMIC)
- Developmental and Reproductive Toxicology (DART/ETIC)
- TOXLINE
- Toxicology Literature from Special Sources (TOXLIT)
- CANCERLIT
- Chemical Carcinogenesis Research Information System (CCRIS)
- Medline (via PubMed)
- Integrated Risk Information System (IRIS)
- Syracuse Research Corporation Online Toxic Substance Control Act Database (TSCATS)

2.0 PHYSICAL AND CHEMICAL PROPERTIES

Methyl isoamyl ketone is an aliphatic, alkylated ketone with the following chemical structure:



It has synonyms of 5-methyl-2-hexanone; 5-methylhexan-2-one; isoamyl methyl ketone; and isopentyl methyl ketone.

The physical and chemical properties of methyl isoamyl ketone are listed in Table 1.

2.1 Organoleptic Properties

The odor threshold for methyl isoamyl ketone detection in water was reported as 0.01 mg/L, which is defined as “the concentration of a substance in water which will generate the air odor threshold concentration in the headspace of a stoppered flask” (Amoore and Hautala, 1983). The odor threshold for methyl isoamyl ketone detection in air is 0.012 ppm (0.06 mg/m³), which is defined as “the minimum physical intensity detection by a subject where he is not required to identify the stimulus, but just detect the existence of a stimulus”. The recognition threshold is 0.049 ppm (0.23 mg/m³), and is defined as “the minimum physical intensity detection by a subject where he is required to identify the stimulus in some manner” (Fazzalari, 1978). In each case, the purity of the test compound was not reported.

Table 1. Physical and chemical properties of methyl isoamyl ketone

Property	Data	Reference
Empirical Formula	C ₇ H ₁₄ O	Lewis, 1997
CAS#	110-12-3	Lewis, 1997
Molecular Weight	114.2	Lewis, 1997
Physical State and Color	Clear, colorless liquid at room temperature	Acros, 1998
Melting Point	-73.9 °C	Lewis, 1993
Boiling Point	144 °C	Lewis, 1997
Density	0.888 g/mL at 20 °C	Lide, 1996
Vapor Pressure	5.77 mm Hg at 25 °C (experimental)	Alarie et al. 1995
Water Solubility	5.4 g/L at 20 °C	Acros, 1998
Dissociation Constant (pK _a)	Not located	
n-Octanol/Water Partition Coefficient (log K _{ow})	1.88 (experimental) 1.72 (estimated) 1.66 (estimated)	Hansch et al., 1995 http://esc.syrres.com
Henry's Law Constant (air/water partition)	1.6X10 ⁻⁴ atm-m ³ /mol	HSDB, 2001

3.0 PRODUCTION AND USE

3.1 Production

In 1990 and 1994, methyl isoamyl ketone was listed on the U.S. EPA High Production Volume (HPV) chemical list, indicating that it was produced in or imported to the United States in amounts over 1 million pounds per year (U.S. EPA, 2002b). Methyl isoamyl ketone is also listed as a HPV chemical by the European Union, indicating that it is produced or imported at levels greater than 1,000 tons per year in at least one member country of the European Union (OECD, 2000).

3.2 Use

Methyl isoamyl ketone is used as an industrial solvent (ACGIH, 1991) and as a solvent for high-solids coatings, nitrocellulose, cellulose acetate, acrylics, and vinyl copolymers (Seigel and Eggersdorfer, 1990; Lewis, 1993). Methyl isoamyl ketone has also been detected as an extractant from drinking water system components tested under NSF/ANSI 61 (2002), Section 6: Joining and Sealing Materials.

4.0 ANALYTICAL METHODS

4.1 Analysis in Water

NSF International uses U.S. EPA Method 502.2, which is a purge and trap gas chromatographic method with photo ionization detection, to quantitate methyl isoamyl ketone in water to a detection limit of 0.005 mg/L.

4.2 Analysis in Biological Matrices

No reports regarding the analysis of methyl isoamyl ketone in biological matrices in laboratory animals or humans were located.

5.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

5.1 Sources of Human Exposure

The general population is exposed to methyl isoamyl ketone through the ingestion of food (HSDB, 2001). It has been reported that small amounts of methyl isoamyl ketone are found as volatile components of roasted filberts and fried bacon, but the exact concentrations were not reported (Ho et al., 1983; Kinlin et al., 1972). Using 1981-1983 survey data, NIOSH estimated that 12,600 workers are potentially exposed to methyl isoamyl ketone in the United States (NIOSH, 1983). Occupational exposure is primarily through inhalation and/or dermal contact in establishments where methyl isoamyl ketone is produced or used (HSDB, 2001).

5.2 Sources of Environmental Exposure

The production and use of methyl isoamyl ketone as a solvent for high solids coatings, nitrocellulose, cellulose acetate, acrylics, and vinyl copolymers may result in the release of methyl isoamyl ketone to the environment through various waste streams (HSDB, 2001).

6.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS

Several kinetic parameters in the rat were similar after oral or inhalation exposure to methyl isoamyl ketone. These included the peak blood concentration, the area under the concentration-versus-time curve, and first-order elimination kinetics. However, a marked difference in the elimination half-life was observed, in that methyl isoamyl ketone was more rapidly cleared after inhalation than after oral exposure. In the dog, methyl isoamyl ketone is absorbed through the skin after topical application and excreted in the urine after dermal and intravenous administration. A quantitative comparison between the kinetics and metabolism of methyl isoamyl ketone between humans and laboratory animals could not be made due to the lack of data specifically for methyl isoamyl ketone.

6.1 Absorption

6.1.1 Oral

The uptake of methyl isoamyl ketone (99.1% purity) after a single gavage dose of 1,830 mg/kg in three male Sprague Dawley rats was investigated by Katz et al. (1986). Heparinized blood samples were collected 1, 2, 4, 6, 7, 8, 10, 14, 16, 22, and 32 hours after dosing by tail bleeding. All blood samples were quantitatively analyzed via gas chromatography. Food and water were available *ad libitum*.

Large animal-to-animal variation was observed, but the raw data were not reported. Between one and 22 hours after dosing, the concentration versus time curve displayed first-order kinetics, based on a mono-exponential regression correlation coefficient of 0.944. The total area under the concentration-versus-time curve was 862 units. Methyl isoamyl ketone blood concentrations peaked at 94 ± 13 µg/mL one hour after administration.

6.1.2 Inhalation

The uptake of methyl isoamyl ketone (99.1% purity) after inhalation of methyl isoamyl ketone vapors at 1,950 ppm ($\sim 9,100$ mg/m³; Appendix) for six hours in three male Sprague Dawley rats was investigated by Katz et al. (1986). Heparinized blood samples were collected from the tail at 1, 2, 4, and 6 hours during inhalation, and 1, 2, 4, 8, 10, 16, 26, and 32 hours post exposure. All blood samples were quantitatively analyzed via gas chromatography. Food and water were available *ad libitum*, except during exposure.

Large animal-to-animal variation was observed, but the raw data were not reported. The concentration versus time curve displayed first-order kinetics, based on a monoexponential regression correlation coefficient of 0.998. The total area under the concentration versus time curve was 829 units. Methyl isoamyl ketone blood concentrations peaked at 138 ± 11 µg/mL four hours after the start of exposure.

6.1.3 Dermal

The percutaneous absorption of [2-¹⁴C]-methyl isoamyl ketone (purity unspecified) was investigated in four male beagle dogs (DiVincenzo and Hamilton, 1982). Twenty µCi of [2-¹⁴C]-methyl isoamyl ketone with 15 mL unlabelled methyl isoamyl ketone (> 98%) was placed in an all-glass absorption cell containing cotton gauze for uniform solvent distribution. The cell was affixed to the surface of the clipped skin of the thorax with adhesive and tape and allowed to remain for either 20, 40, or 60 minutes. The amount of [2-¹⁴C]-methyl isoamyl ketone detected in the urine was measured after eight hours. No further analyses were performed.

Eight hours after each exposure period, [2-¹⁴C]-methyl isoamyl ketone was detected in the urine, indicating that it was absorbed through the skin (refer to section 6.4 for additional details). The authors concluded that methyl isoamyl ketone was absorbed through canine skin, and thus likely to be absorbed through human skin.

6.2 Distribution

There were no reports regarding the distribution of methyl isoamyl ketone in laboratory animals or humans in the available literature.

6.3 Metabolism

There were no reports regarding the metabolism of methyl isoamyl ketone in laboratory animals or humans in the available literature. It has been reported that methyl isoamyl ketone is

metabolized by the hepatic microsomal mixed function oxidase system, but the results of the study were not published (DiVincenzo and Hamilton, 1982).

6.4 Elimination/Excretion

6.4.1 Oral

The clearance of methyl isoamyl ketone after a single gavage dose of 1,830 mg/kg in three male Sprague Dawley rats was investigated by Katz et al. (1986). Heparinized blood samples were collected 1, 2, 4, 6, 7, 8, 10, 14, 16, 22, and 32 hours after dosing by tail bleeding. All blood samples were quantitatively analyzed by gas chromatography. Food and water were available *ad libitum*. Concentrations of methyl isoamyl ketone versus time were plotted to calculate the first-order rate constant, which was used to determine a 5.3-hour elimination half-life in blood.

6.4.2 Inhalation

The clearance of methyl isoamyl ketone after a single inhalation of methyl isoamyl ketone vapor at 1,950 ppm ($\sim 9,100 \text{ mg/m}^3$; Appendix) in three male Sprague Dawley rats was investigated by Katz et al. (1986). Heparinized blood samples were collected from the tail at 1, 2, 4, 8, 10, 16, 26, and 32 hours post-treatment. All blood samples were quantitatively analyzed via gas chromatography. Food and water were available *ad libitum*, except during exposure. Blood concentrations of methyl isoamyl ketone versus time were plotted to determine the first-order rate constant, which was used to determine a 0.7-hour elimination half-life of methyl isoamyl ketone in the blood.

6.4.3 Intravenous

Four young male beagle dogs (unspecified age and body weight) were administered single intravenous doses of 1 mg/kg $[2\text{-}^{14}\text{C}]$ -methyl isoamyl ketone ($> 97\%$, with specific activity of $0.5 \text{ } \mu\text{Ci/mg}$). Total radioactivity measured in the urine after eight hours was $0.86 \pm 0.085 \text{ mCi}$. The dogs eliminated about 12.3% of the radioactivity in the urine within eight hours (DiVincenzo and Hamilton, 1982).

6.4.4 Dermal

The elimination of $[2\text{-}^{14}\text{C}]$ -methyl isoamyl ketone ($> 97\%$, with specific activity of $0.5 \text{ } \mu\text{Ci/mg}$) was investigated in four male beagle dogs after topical exposure for 20, 40, or 60 minutes (DiVincenzo and Hamilton, 1982). Twenty, 40, and 60 minutes after dermal application, the mean quantity of $[2\text{-}^{14}\text{C}]$ -methyl isoamyl ketone measured in the urine was 90 ± 16.1 , 35 ± 10.2 , and $67 \pm 1 \text{ mg}$, respectively. No direct correlation could be made between the duration of skin contact and the quantity of methyl isoamyl ketone absorbed. The total radioactivity excreted in the urine 20, 40, and 60 minutes after dermal exposure was 17 ± 3 , 7 ± 2 , and $12 \pm 0 \text{ } \mu\text{Ci} \times 10^{-3}$, respectively.