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. Fund. Appl. Toxicol. 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 *Salmonella typhimurium* 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 *cannot be determined*. 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 LED_{10} 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.