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Provisional Peer-Reviewed Toxicity Values for

Methylcyclopentane
(CASRN 96-37-7)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR METHYLCYCLOPENTANE (CASRN 96-37-7)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Methylcyclopentane is a normal constituent of gasoline and other petroleum distillates. It is also a constituent (approximately 15%) of commercial hexane. There is a paucity of toxicity data associated with the chemical. No RfD, RfC, or carcinogenicity assessment is available on IRIS (U.S. EPA, 2008). Methylcyclopentane is not included on the HEAST (U.S. EPA, 1997), the Drinking Water Standards and Health Advisory list (U.S. EPA, 2006) or the CARA list (U.S. EPA, 1991, 1994). ATSDR (2008) has not produced a Toxicological Profile for methylcyclopentane, and no Environmental Health Criteria Document is available (WHO, 2008). The carcinogenicity has not been assessed by IARC (2008) or NTP (2005, 2008). ACGIH (2007), OSHA (2008), and NIOSH (2005) have not established occupational health standards for methylcyclopentane. CalEPA (2002, 2005a, 2005b) has also not derived risk values for methylcyclopentane.

Literature searches were conducted from 1960s through May 2008, and updated in April 2009 for studies relevant to the derivation of provisional toxicity values for methylcyclopentane. Databases searched included: MEDLINE, TOXLINE (Special), BIOSIS, TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents.

REVIEW OF PERTINENT LITERATURE

Human Oral Studies

The literature search did not identify any studies related to oral dosing of humans.

Animal Oral Studies

The literature search identified two animal studies of oral exposure to methylcyclopentane, a 4-week nephrotoxicity screening study in rats (Borriston Laboratories, 1985; Halder et al., 1985) that is used as the critical study, and an 8 week peripheral neuropathy study in rats (Ono et al., 1981).

In a nephrotoxicity screening study of unleaded gasoline components, groups of 10 male Fischer 344 rats were administered 0.5 or 2.0 g/kg (500 or 2000 mg/kg) of undiluted methylcyclopentane (98% purity) by gavage, once daily, 5 days/week, for 4 weeks (Borriston Laboratories, 1985; Halder et al., 1985). A negative control group received isotonic saline at a dose of 2.0 g/kg-day (2000 mg/kg-day). Animals were observed twice daily for mortality and clinical signs of toxicity. Body weights were measured prior to dosing on Day 1, and at the time of the scheduled sacrifices. Gross necropsies were performed on all animals following moribund condition, death, or terminal sacrifice. Only the kidney was evaluated histopathologically.

In the high dose group, 4/10 rats died. One of the 10 low dose rats died; no clinical signs were observed in the surviving low dose rats. No deaths or clinical signs were reported among control rats. Terminal body weight was significantly reduced 16% in the high dose group and 8% in the low dose group. Absolute kidney weight was similar to controls in both groups. Gross necropsy findings not observed in controls included, in the high dose group, prominent lobular liver patterns in 2/10, speckled patterns on the kidney cortex in 2/10, and a raised pale area in a nonglandular section of stomach in 1/10 animals, and in both low and high dose groups, spotted lung in 1/10 from each group, and discolored pancreas in 1/10 animals from each group. Histological examinations of the kidney did not indicate any significant methylcyclopentane-related nephropathy. Stomach irritation (observed during gross necropsy) or other portal-of-entry effects were not verified since these tissues were not examined histologically. For the purposes of this review, the 500 mg/kg dose is considered a NOAEL and the 2000 mg/kg dose a LOAEL for the body weight endpoint.

Ono et al. (1981) conducted a comparative neurotoxicity study of commercial hexane components (each >99% pure) in which a group of 5–7 male Wistar rats was treated with methylcyclopentane by daily gavage in olive oil for 8 weeks at doses of 0.4 mL for the first 4 weeks, 0.6 mL for the next 2 weeks, and 1.2 mL for the final 2 weeks of the study. Taking into account the average increase in body weight over the 8 weeks of the study, methylcyclopentane doses can be estimated as 800, 1050, and 2020 mg/kg-day for Weeks 1–4, 5–6, and 7–8, respectively. A group of 5–7 control animals was administered olive oil alone. Peripheral nerve activity was measured in the tail of unanesthetized animals. Motor nerve conduction velocity, motor distal latency, and mixed nerve conduction velocity were measured. Body weights and conduction velocities were measured at the start of the experiment, and then every 2 weeks until termination.

No mortality or clinical signs of toxicity were observed. Body weight gain in treated animals was similar to controls. Motor nerve conduction velocity and mixed nerve conduction velocity (proximal, but not distal, portion of tail nerve) were significantly reduced in treated rats at 8 weeks. Distal latency was not affected at any time. The researchers characterized these proximal effects as a slight, though significant, difference from control ($p < 0.05$) in the impairment of peripheral nerve function by methylcyclopentane.

Human Inhalation Studies

In a study by Lehmann et al., 2002, investigators passively sampled the air in the homes of newborns as part of a larger German Lifestyle-Immune System-Allergy (LISA) study. A random sample of 85 newborns (43 boys, 42 girls) was selected from the pool of 976 in the larger study. Umbilical cord-blood samples were taken at delivery, and T-cell function was assayed using intracellular cytokine staining. In vitro stimulated cells were fixed and stained with monoclonal antibodies against T-cell surface antigen CD-3, the cytokines INF-gamma, TNF-alpha, IL-2 and IL-4. Fluorescent-labeled cells were analyzed by flow cytometry. Volatile organics were sampled passively in the homes for 4 weeks after birth using 3M monitors, and adsorbed compounds were extracted and analyzed by GC-MS. Statistic associations were determined using STATISTICA 5.1. For the logistic regression model, T-cell functions were categorized by quartiles, where percentages of cytokine-producing cells below the 25th percentile were categorized as reduced, while those over the 75th percentile were considered enhanced.

Indoor concentrations of VOCs differed widely among the children's dwellings. Significant associations between elevated VOC levels in homes and changes in cytokine-producing T-cells were observed for 10 chemicals (including methylcyclopentane). In the regression model, significant associations were found with only naphthalene, methylcyclopentane and tetrachloroethylene. Of the children in the group most exposed to methylcyclopentane, 40.9% of the children had an increased amount of IL-4 producing T-cells, compared to 19.3% in the least exposed group. The *p*-value for the association was $p < 0.03$. The most prominent risk factor was new carpeting in the infants' bedroom (Odds Ratio 4.6; Confidence Interval 1.11–19.3).

It is not known if the changed cytokine or T-lymphocyte levels are of any clinical significance, therefore it is difficult to call theses effects adverse. The interpretational issue with the complex chemical mixtures found in the various homes remains problematic.

Animal Inhalation Studies

No studies investigating the effects of subchronic or chronic inhalation exposure to methylcyclopentane in animals was identified.

Genotoxicity Studies

The results with the Ames test with methylcyclopentane were uniformly negative in strains TA100, TA98, TA135, TA1535, and TA97, with or without metabolic activation.

Neurotoxicity Studies

The Ono et al. study (1981) cited previously, points to a neurological endpoint for methylcyclopentane. Concern exists because of the theoretical possibility that metabolism may lead to ring-opening of methylcyclopentane to form *n*-hexane, a known neurotoxin, or other branched hexanes. In the case of *n*-hexane, further metabolic activation is required which generates the ultimate toxicant 2,5-hexanedione. This diketone reacts with protein amino groups to form an imine in an initial reversible step, and then to cyclize irreversibly to form a pyrole. This leads to a retrograde distal axonopathy presenting initially as peripheral parasthesias (U.S. EPA, 2008). There is, however, no direct evidence that the cyclopentane ring of methylcyclopentane is cleaved in vivo, and the neuropathy observed by methylcyclohexane was not an exact mimic of *n*-hexane.

DERIVATION OF A PROVISIONAL SUBCHRONIC RfD FOR METHYLCYCLOPENTANE

The reduction in body weight gain in subchronic exposures Halder et al., 1985 remains a plausible subchronic endpoint, with reductions of 8% at 500 mg/kg and 16% at 2000 mg/kg compared to controls. The reduction in body weight gain at the low dose was considered to be minimal, therefore, the low dose was considered a NOAEL. The NOAEL was first adjusted to continuous exposure from the 5 days/week dosing schedule. The $NOAEL_{ADJ}$ was calculated as the study NOAEL × 5/7 (500 mg/kg-day × 5/7 = 357 mg/kg-day). The $NOAEL_{ADJ}$ was used as the POD to derive a provisional sRfD for methylcyclopentane of **0.4 mg/kg-day** as follows:

Subchronic p-RfD = $NOAEL_{ADJ} \div UF$
= 357 mg/kg/day ÷ 1000
= **0.4 or 4×10^{-1} mg/kg-day**

The composite uncertainty factor of 1000 is composed of the following:

- A full UF of 10 was applied for inter-species extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- A full UF of 10 for intra-species differences was used to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A database UF of 10 was employed. The toxicological database for oral exposure to methylcyclopentane is composed of two subchronic studies. The database lacks developmental toxicity studies and a multigeneration reproduction study.
- An uncertainty factor for LOAEL to NOAEL extrapolation was not needed as a NOAEL was used to derive the subchronic p-RfD.

Confidence in the study is low. Dosimetry is suspect, given the potential volatilization of the test chemical; however, this would result in a conservative value for toxicity. Confidence in the database is low, since there were no chronic studies, no two-generational reproductive studies and no developmental studies. Consequently, the confidence in the value is also low.

DERIVATION OF A PROVISIONAL CHRONIC RfD FOR METHYLCYCLOPENTANE

The studies by Borriston Laboratories (1985; Halder et al., 1985) are considered inappropriate for deriving a chronic RfD because of the short duration of the dosing regimens. Additionally, based on data from Ono et al. and Krasavage et al., the overt neurological endpoint identified in Ono et al. may require significantly more than 4 weeks of exposure before it becomes apparent in rodents. Thus, extension of the subchronic results to chronic exposures (even with an additional uncertainty factor) may not be warranted.

DERIVATION OF A PROVISIONAL RfC FOR METHYLCYCLOPENTANE

The study by Lehmann et al., 2002 is inappropriate for use in defining an RfC because of limited dose-response information (only the data from the lowest and highest quartiles was published), the lack of clear clinical significance for the potential endpoint, and the problem of varying chemical mixtures with no controls.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR METHYLCYCLOPENTANE

Because of a lack of carcinogenic data in humans or animals, under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), this review classifies methylcyclopentane as having "Inadequate Information to Assess the Carcinogenic Potential."

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR OR INHALATION UNIT RISK FOR METHYLCYCLOPENTANE

Neither a provisional oral slope factor nor a provisional inhalation unit risk could be derived for methylcyclopentane because of the lack of suitable human or animal, oral or inhalation data.

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