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Provisional Peer Reviewed Toxicity Values for
2-Methylnaphthalene
(CASRN 91-57-6)

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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
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
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
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

PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2-METHYLNAPHTHALENE (CASRN 91-57-6)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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. EPA's Integrated Risk Information System (IRIS).
2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in 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 EPA's Integrated Risk Information System (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 EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all 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 five-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 manuscripts 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 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 manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) (U.S. EPA, 2003) for 2-Methylnaphthalene (2-MN) included an RfD of 4×10^{-3} mg/kg-day based on a BMDL₀₅ of 3.5 mg/kg-day and an uncertainty factor of 1000. IRIS also included a carcinogenicity assessment that concluded data were inadequate to assess human carcinogenic potential. ATSDR (2005) derived a chronic MRL of 4×10^{-2} mg/kg-day based on a BMDL₀₅ of 4.3 mg/kg-day in mice (Murata et al., 1997) and an uncertainty factor of 100. ATSDR also had derived an MRL of 7×10^{-2} mg/kg-day for chronic duration oral exposure to 1-MN based on a LOAEL of 71.6 mg/kg-day for increased incidence of alveolar proteinosis in mice (Murata et al., 1993) and an uncertainty factor of 1000.

Updated literature searches for oral noncancer data were conducted from 1983 to 2007. The databases searched were TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No relevant human studies were found in the literature.

Animal Studies

Lifetime Exposure

The chronic toxicity of 2-MN was investigated in mice by Murata et al. (1997). Groups of 50 male and 50 female B6C3F1 mice were given diets containing 0, 0.075, or 0.15% 2-MN for 81 weeks. Food consumption and body weight were recorded throughout the experimental period. At necropsy organ weights were recorded for brain, liver, kidney, heart, spleen, lungs, testes, pancreas, thymus, and salivary glands. Gross pathology and histopathology were conducted for these tissues and for adrenals, trachea, stomach, large and small intestines, seminal vesicles, ovaries, uterus, vagina, mammary glands, skeletal muscle, eye, Harderian glands, spinal cord, bone, skin, and other tissues with abnormal appearance. A complete clinical chemistry examination was performed, including hematology, serology, and enzyme analysis. Incidence data were statistically evaluated using a Fisher's exact test and analysis of variance. Continuous endpoints (organ weights, blood, and serum parameters) were evaluated using a multiple comparison post-test with the Dunnett procedure.

Average 2-MN intakes of 50.3 (males) and 54.3 (females) mg/kg-day were calculated from food consumption data reported in Murata et al. (1997) for the 0.075% 2-MN dose group. Similarly, 2-MN intakes for the 0.15% 2-MN dose group were 107.6 (males) and 113.8 (females) mg/kg-day.

Animals at the high dose exhibited slight growth retardation over the entire experimental period. Compared with control animals, final body weights were reduced by 4.5% for females and 7.5% for males. Only the male body weight reductions were statistically significant ($p < 0.01$). Survival was not affected by 2-MN treatment. Pulmonary alveolar proteinosis (PAP) was reported in both treatment groups. PAP was characterized by the appearance of foamy cells in the alveoli and the accumulation of protein and lipid in the lungs. On gross examination, the protenosis appeared as white nodules, 1-5 mm in diameter. Microscopically, the alveolar lumens contained acidophilic amorphous material, foamy cells, and cholesterol crystals. The incidence of PAP was 42.9% among males at 50.3 mg/kg-day and 55.1% among females at 54.3 mg/kg-day; in the high-dose group, the incidence was 46.9% for males and 45.8% for females. The fraction of lung volume affected for individual treated or control animals was not reported. Incidence of this effect in the control animals was 8.2% for males and 10% for females; the effects in control animals were less pronounced than those in the treatment groups. The authors stated that this effect had not been observed previously in more than 5000 B6C3F1 mice housed in the same room and speculated that the control mice may have been exposed to volatilized 1-MN and 2-MN from the treatment groups housed in the same room for this experiment. The authors also concluded that 2-MN was not carcinogenic in this study, although some results were equivocal. In particular, there appeared to be an increase in the incidence of lung tumors. Incidence of lung adenomas and adenocarcinomas, combined, was significantly increased (10/49 vs. 2/49 controls; $p < 0.05$) in male mice at 50.3 mg/kg-day; the increase (6/49) was not significant at the 107.6 mg/kg-day dose. Because they noted association between tumorigenesis and PAP, the authors concluded that PAP was not a risk factor for carcinogenesis in the mouse.

A study by the same group (Murata et al., 1993) investigated the effect of 1-MN in the same strain of mice. Although the study results were published four years apart, the two studies were conducted at the same time and utilized the same control group. The nominal dose groups and endpoints were the same in both studies. The actual exposure levels were somewhat higher for 1-MN (approximately 73 mg/kg-day at 0.075% and 142 mg/kg-day at 0.15%). Results for 1-MN were similar to those for 2-MN, with PAP occurring in both treatment groups. The incidence, however, was slightly lower in the 1-MN treated mice (46% in both males and females at 0.075% 1-MN, and 38 and 35% in males and females, respectively, at 0.15% 1-MN). Unlike 2-MN, this study concluded 1-MN was a lung carcinogen (adenomas and adenocarcinomas) for B6C3F1 mice.

Less-than-Lifetime Exposure

A subchronic 2-MN dietary study in B6C3F1 mice was briefly reported in Murata et al. (1997). This study was preliminary to the chronic study to determine the chronic dosing regimen. Groups of ten mice of each sex each were fed 2-MN for 13 weeks at dietary concentrations of 0, 0.0163, 0.049, 0.147, 0.44, or 1.33%. Estimated doses were: 0, 29.4, 88.4, 265, 794, or 2400 mg/kg-day for males and 0, 31.8, 95.6, 287, 859, or 2600 mg/kg-day for females, respectively. Approximate average doses (across genders) were 0, 31, 92, 276, 827, or 2500 mg/kg-day, respectively (U.S. EPA, 2003). Growth retardation was reported at the three highest dose levels, but was attributed to food refusal. The authors reported no histopathological lesions in any organs of the control or treated animals, although it was unclear whether the lungs were examined. Based on this study, a subchronic NOAEL of 2500 mg/kg-day could be established, because growth retardation accompanied by reduced food consumption in the absence of other effects was not considered an adverse effect.

In a number of studies (Reid et al., 1973; Mahvi et al., 1977; Tong et al., 1981; Griffin et al., 1981, 1982; Warren et al., 1982), intraperitoneal (IP) injection of 2-MN or naphthalene resulted in lung lesions (Clara cell necrosis) similar to those observed in the long-term dietary studies of Murata et al. (1993, 1997).

PAP also was observed in mice following dermal exposure to a mixture of 1-MN and 2-MN for 30 weeks (Murata et al., 1992). A 100% incidence of PAP was observed in 15 B6C3F1 female mice treated dermally with 119 mg MN/kg twice a week. No lesions were observed in the control animals, which were exposed to the acetone vehicle only.

Developmental/Reproductive

No relevant reproductive or developmental data were found in the literature.

Toxicokinetics and Toxicodynamics

Some evidence suggested that mice may be a sensitive species for the type of lung toxicity induced by the methylnaphthalenes. Mice were far more sensitive than rats to acute lung effects arising from exposure to dichloroethylene (Chieco et al., 1981; Krijgheld et al., 1984), bromobenzene (Reid et al., 1973), butylated hydroxytoluene (Kehrer & Witschi, 1980),

naphthalene (Reid et al., 1973; O'Brien et al., 1985), and 2-MN (Griffin et al., 1982). For naphthalene, Buckpitt and Franklin (1989) suggested that the selective lung cytotoxicity in mice may be a result of the high degree of stereoselectivity with which naphthalene is epoxidated in the mouse lung (in vitro microsomal incubations). Rats and humans did not show the same stereoselectivity (Buckpitt and Bahnsen, 1986). Together, these data suggested that mice exposed to naphthalene might be more sensitive than humans for this particular endpoint. This conclusion should be considered somewhat speculative, however, particularly because subchronic oral naphthalene studies in mice did not produce lung effects at dose levels producing other adverse effects (142 mg/kg-day for decreased body weight, 286 mg/kg-day for mortality [BCL, 1980b]; 133 mg/kg-day for decreased organ weights [Shopp et al., 1984]). There was, however, a suggestion that tolerance could be developed for this effect in mice (Shopp et al., 1984). Also, the role of metabolic activation in the toxicity of the methylnaphthalenes was less clear than for naphthalene (Griffin and Franklin, 1982; Buckpitt et al., 1984; Buckpitt and Franklin, 1989). Much less was known about species differences in the metabolism of methylnaphthalenes, so no firm conclusions could be made regarding the potential for unique susceptibility mouse to 2-MN-induced lung toxicity. More extensive discussions of the metabolism of naphthalene and the methylnaphthalenes were found in the Toxicological Review of Naphthalene on IRIS (U.S. EPA, 2003) and in Buckpitt and Franklin (1989).

DERIVATION OF PROVISIONAL SUBCHRONIC OR CHRONIC ORAL RfD VALUES FOR 2-METHYLNAPHTHALENE

Fitzhugh and Buschke (1949) evaluated the ability of 2-methylnaphthalene to induce cataract formation in rats. While no cataracts were found in a group of 5 weanling F344 rats fed a diet of 2% 2-MN (equivalent to 2000 mg/kg-day) for at least 2 months, cataracts were detected in rats fed an equivalent concentration of naphthalene. Evaluation of this study was limited by the lack of experimental details. In this study, 2000 mg/kg-day was an apparent NOAEL for cataract formation.

Evaluation of the Murata et al. (1997) subchronic data was limited by inadequate reporting of study results. It appeared that very few potential endpoints were considered. In its evaluation of these data, IRIS (U.S. EPA, 2003) concluded that 92 mg/kg-day and 276 mg/kg-day (averaged between genders) were the NOAEL and LOAEL, respectively, for reduced weight gain in rats, apparently rejecting the study authors' attribution of these effects to food refusal. However, the study report did not clearly identify what organs were examined or other potential effects were considered. This raised the possibility that other effects might have resulted from subchronic dosing that were not observed. Because very few details of the data or methods for the subchronic study were reported by Murata et al. (1997) and because it was unclear whether the reduced weight gain resulted from treatment with 2-MN, these data were considered inadequate for derivation of a subchronic p-RfD. As a result, the chronic RfD of 4×10^{-3} mg/kg-day on IRIS was selected as the subchronic p-RfD.

The IRIS chronic RfD (U.S. EPA, 2003) was based on a BMDL₀₅ of 3.5 mg/kg-day for 5% extra risk of pulmonary alveolar proteinosis in male and female mice exposed to 2-MN in the diet for 81 weeks (Murata et al., 1997). A total UF of 1000 was applied to this effect level: 10

for interspecies differences (UF_A : animal to human); 10 for intraspecies variation (UF_H : human variability); and 10 for deficiencies in the database (UF_D).

The subchronic p-RfD for 2-MN was calculated using the same factors as follows:

$$\begin{aligned}\text{subchronic p-RfD} &= \text{BMDL}_{05} \div UF \\ &= 3.5 \text{ mg/kg-day} \div 1000 \\ &= 0.004 \text{ mg/kg-day} = 4 \times 10^{-3} \text{ mg/kg-day}\end{aligned}$$

In the derivation of the chronic RfD, IRIS (U.S. EPA, 2003) noted that, in addition to the uncertainties noted above, there was model uncertainty owing to the lack of actual dose-response information or mode of action information near a dose where the point of departure was estimated. The responses in 2-MN exposed animals suggested a continuation of the plateau into the lower exposure region, so using a linear model might have provided a higher benchmark dose than was appropriate. In addition, while BMDS was used to generate a lower bound on the estimated benchmark dose, the lower bound probably described too narrow a confidence limit on the benchmark dose. This was because the uncertainty in the data set could not be adequately described without the high dose responses.

CONFIDENCE IN THE SUBCHRONIC ORAL RFD

The principal study for the p-RfD (Murata et al., 1997) examined a comprehensive number of endpoints, including extensive histopathology, and tested two dietary dose levels using sufficient numbers (50/gender/group) of B6C3F1 mice. Confidence in the study was medium because there was potential confounding from possible inhalation exposure of controls to volatilized 2-MN and 1-MN. This added some uncertainty to the dose-response relationship between oral exposure to 2-MN and pulmonary alveolar proteinosis described by the results. Confidence in the oral toxicity database was low. No epidemiology studies or case reports were located which examined the potential effects of human exposure to 2-MN. Only mice had been examined in adequate animal studies on toxicity from repeated exposure to 2-MN. No assays of developmental toxicity, reproductive toxicity, or neurotoxicity following oral exposure to 2-MN were available. Confidence in the oral RfD was low, principally due to the low confidence in the database.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC OR CHRONIC INHALATION RfC VALUES FOR 2-METHYLNAPHTHALENE

A provisional inhalation RfC could not be derived for 2-MN because data on adverse health effects following inhalation exposure were lacking for humans and animals. Without sufficient pharmacokinetic data and information to rule out portal-of-entry effects, there was no basis to support a route-to-route extrapolation from the oral data, even if they otherwise were considered sufficient.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2-METHYLNAPHTHALENE

Weight-of-Evidence Descriptor

Using the draft revised guidelines for carcinogen risk assessment (U.S. EPA, 1999), the IRIS assessment (U.S. EPA, 2003) concluded the data were inadequate for an assessment of human carcinogenic potential of 2-MN. This conclusion was based on the absence of data concerning the carcinogenic potential of 2-MN in humans, by any route of exposure, and limited, equivocal oral evidence in animals. Updated literature searches for this assessment identified no relevant data other than those already considered for the IRIS assessment. Based on the revised guidelines for carcinogen risk assessment (U.S. EPA, 2005), the equivalent carcinogenicity descriptor would be “*Inadequate Information to Assess Carcinogenic Potential.*”

Quantitative Estimates of Carcinogenic Risk

Quantitative estimates of cancer risk for 2-MN could not be derived because no data demonstrating carcinogenicity associated with 2-MN exposure were identified.

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