Provisional Peer-Reviewed Toxicity Values for

Methyl Acetate
(CASRN 79-20-9)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
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TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS

BMC	Benchmark Concentration
BMD	Benchmark Dose
BMCL	Benchmark Concentration Lower bound 95% confidence interval
BMDL	Benchmark Dose Lower bound 95% confidence interval
HEC	Human Equivalent Concentration
HED	Human Equivalent 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 reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure (oral)
RfC	reference concentration (inhalation)
RfD	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
WOE	weight of evidence

**PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR
METHYL ACETATE (CASRN 79-20-9)**

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency'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) EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) 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 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 a panel of 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 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 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.

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INTRODUCTION

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Methyl acetate appears as a colorless liquid with a fruity or sweet ester odor. It can be used as a solvent in fast drying paints such as lacquers, a solvent for waste film in the production of cellulosic adhesives, and is a perfume solvent. Additionally, it is a reaction solvent in dye production. The empirical formula for methyl acetate is $C_3H_6O_2$ (see Figure 1). A table of chemico-physical properties is provided below (see Table 1).

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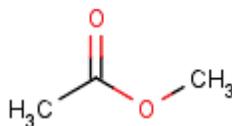
Figure 1. Chemical Structure of Methyl Acetate

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Table 1. Physical Properties Table (Methyl Acetate)[a]	
Property (unit)	**Value**
Boiling point (ºC)	55.8
Melting point (ºC)	-98
Density (g/cm^3)	0.9342
Vapor pressure (mm Hg)	216
pH (unitless)	-
Solubility in water (g/L at 20 ºC)	2.43×10^5
Molecular weight (g/mol)	74.08
Octanol/water partition coefficient (unitless)	0.18

[a]Hazardous Substances Data Bank (HSDB, 2005)

No RfD, RfC, or carcinogenicity assessment for methyl acetate (see Figure 1 for chemical structure of methyl acetate) is available on IRIS (U.S. EPA, 2010) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The HEAST (U.S. EPA, 1997) lists subchronic and chronic RfDs of 10 and 1 mg/kg-day, respectively, derived in a Health and Environmental Effects Profile (HEEP) for methyl acetate (U.S. EPA, 1986). These RfDs were derived by analogy to methanol based on in vivo evidence for metabolic hydrolysis of methyl acetate to methanol and acetic acid in rabbits (Tambo, 1973) and humans (Tada et al., 1974). The adjustment across chemicals was made by multiplying the EPA RfD for methanol (0.5 mg/kg-day) by the ratio of molecular weights for methanol and methyl acetate. The RfD for methanol, which is currently available on the IRIS database (U.S. EPA, 1993, 2010) but is currently undergoing reassessment, was based on a NOEL of 500 mg/kg-day as a point of departure (POD) for serum chemistry and decreased brain weight in rats given gavage doses for 90 days (Toxicity Research Laboratory, 1986) and adjusted by a composite uncertainty factor (UF) of 1000, including a factor of 10 for extrapolation from subchronic–to-chronic duration. The LOAEL is 2500 mg/kg-day. The HEEP did not include derivation of RfC values for methyl acetate.

The Chemical Assessment and Related Activities (CARA) list (U.S. EPA, 1994a, 1991) includes no other documents for methyl acetate except for the previously mentioned HEEP (U.S. EPA, 1986). No Environmental Health Criteria document (WHO, 2009) is available. The chronic toxicity and carcinogenicity of methyl acetate have not been assessed by the International Agency for Research on Cancer (IARC, 2009), the National Toxicology Program (NTP, 2009, 2005), ATSDR (2009), or Cal EPA (2009a,b,c). The American Conference of Governmental Industrial Hygienists (ACGIH, 2008, 2001) recommends a Threshold Limit Value of 200 ppm (606 mg/m^3) derived by analogy to methanol. The National Institute for Occupational Safety and Health (NIOSH, 2009) Recommended Exposure Limit and Occupational Safety and Health Administration (OSHA, 2009) Permissible Exposure Limit are also 200 ppm (606 mg/m^3).

Literature searches were conducted from 1960s through August 2010 for studies relevant to the derivation of provisional toxicity values for methyl acetate. The databases searched include MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents (previous 6 months).

REVIEW OF PERTINENT DATA

HUMAN STUDIES
No oral or inhalation studies of methyl acetate in humans were located.

ANIMAL STUDIES
Oral Exposure
No oral studies of subchronic or chronic toxicity of methyl acetate in animals were located.

Inhalation Exposure

Groups of Sprague-Dawley rats (10/sex/group) were subjected to nose-only inhalation exposures of 0, 75, 350, or 2000-ppm methyl acetate (>99.5% pure) for 6 hours/day, 5 days/week, for 28 days (Hofmann, 1999). These exposures equate to 0, 227, 1060, or 6060 mg/m^3. Clinical observations were performed daily, while body weights and food consumption were measured twice weekly. Hematological (counts of red blood cells [RBCs], white blood cells [WBCs, differential], platelets, reticulocytes, and Heinz bodies; hemoglobin [Hgb] and hematocrit [Hct] levels; mean corpuscular volume, corpuscular hemoglobin, and corpuscular hemoglobin concentration; and coagulation time), clinical chemistry (serum levels of sodium, potassium, inorganic phosphorus, uric acid, bilirubin, creatinine, glucose, urea, calcium, chloride, triglycerides, albumin, total lipids, and proteins, and activity levels of aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], and gamma-glutamyltranspeptidase [GGT]), and urinalysis (appearance, color, volume, specific weight, pH, hemoglobin, protein, glucose, bilirubin, ketone bodies, and sediment) were performed at the end of the study. After sacrifice, organ weights were measured, observations were made for gross abnormalities, and histopathological examinations were performed on the following tissues: adrenal glands; brain; diaphragm; esophagus; ileum; knee joint; iliac and mandibular lymph nodes; sciatic nerve; pancreas; rectum; skeletal muscle; cervical, lumbar, and thoracic spinal cord; spleen; thymus; trachea; larynx; aorta; cecum; duodenum; eye and optic nerve; jejunum; liver; nasoturbinates and nasopharynx; pituitary glands; salivary glands; skin (with mammary glands); stomach; thyroid (with parathyroid); urinary bladder; sternal bone marrow; colon; epididymides; heart; kidneys; lung; medulla oblongata; ovaries; prostate gland; seminal vesicles; vagina; testes; tongue; and uteri. Statistical comparisons were performed on observed endpoints.

No deaths or exposure-related clinical signs were observed. Statistically significant (*t*-test; $p < 0.05$) changes in the following endpoints were generally seen only at the high exposure level of 2000 ppm (see Table 2). Daily average food consumption was statistically significantly decreased ($p < 0.05$) in males (-17%) and females (-9%) relative to controls. In both sexes, body weights were reduced throughout most of the study. Terminal body weight was statistically significantly reduced by 10% in males ($p < 0.05$). In females, the decrease in terminal body weight (-3%) was not statistically significant. Small, statistically significant increases ($p < 0.05$) in RBC counts (+5%), Hgb (+5–6%), and Hct (+4–5%) were observed in both sexes, possibly due to hemoconcentration. Statistically significant larger decreases ($p < 0.05$) in WBC counts (-25–33%) were also observed in both sexes at the highest dose, although with no significant changes in WBC differential in either sex in lower doses. Serum chemistry changes were generally unremarkable; the only consistent, dose-related changes observed in both sexes were increases in serum calcium (+2–3%) and decreases in serum cholesterol (-19–22%). Although decreases in serum cholesterol were also statistically significant ($p < 0.05$) in low- and mid-level females, the researchers reported that the observed cholesterol levels in these groups were similar to contemporary female control groups. Urinalysis revealed no marked treatment-related effects.

Table 2. Selected Changes in Sprague Dawley Rats Exposed to Methyl Acetate by Nose-Only Inhalation for 6 Hours/Day, 5 Days/Week, for 28 Days				
	Exposure in ppm (mg/m^3)			
	Control	**75 (227)**	**350 (1060)**	**2000 (6060)**
Males				
Number of animals examined	10	10	10	10
Terminal body weight (g)	277.7 ± 18.3[a]	275.3 ± 16.9	280.3 ± 19.0 (9)	249.5 ± 16.3[b]
Average daily food intake (g)	20.2 ± 1.44 (80)	20.0 ± 1.51 (80)	20.5 ± 1.63 (79)	16.7 ± 1.75 (80)[c]
Hematology				
RBC (10^{12}/L)	8.39 ± 0.21	8.37 ± 0.26 (9)	8.29 ± 0.35 (8)	8.87 ± 0.27 (8)[b]
Hemoglobin (g/L)	158 ± 4	161 ± 4 (9)	160 ± 7 (8)	169 ± 5 (8)[b]
Hematocrit (fraction)	0.46 ± 0.01	0.46 ± 0.01 (9)	0.46 ± 0.02 (8)	0.48 ± 0.01 (8)[b]
WBC (10^9/L)	11.6 ± 1.7	9.9 ± 1.6 (9)	11.3 ± 2.9 (8)	7.7 ± 2.2 (8)[b]
Clinical chemistry				
Calcium (mmol/L)	2.46 ± 0.07	2.48 ± 0.06	2.43 ± 0.05	2.53 ± 0.06[b]
Cholesterol (mmol/L)	2.36 ± 0.15	2.31 ± 0.23	2.29 ± 0.24	1.90 ± 0.18[b]
Organ weights				
Adrenal, absolute (g)	0.0428 ± 0.0079	0.0384 ± 0.0052	0.0400 ± 0.0052 (9)	0.0508 ± 0.0081 (9)[b]
Adrenal, relative (%)	0.016 ± 0.003	0.014 ± 0.002	0.014 ± 0.002 (9)	0.020 ± 0.003 (9)[b]
Nonneoplastic lesions				
Degeneration of olfactory epithelium (incidence)	0/10[d]	0/10	0/10	10/10[b,e]
Females				
Number of animals examined	10	10	10	10
Terminal body weight (g)	204.6 ± 10.6[a]	204.9 ± 10.4	204.6 ± 9.9	198.9 ± 8.5
Average daily food intake (g)	15.0 ± 0.81 (80)	15.3 ± 1.03 (80)	15.2 ± 0.85 (80)	13.6 ± 1.13 (80)[b,c]
Hematology				
RBC (10^{12}/L)	7.87 ± 0.23	8.04 ± 0.20	7.85 ± 0.20	8.29 ± 0.34[b]
Hemoglobin (g/L)	148 ± 3	152 ± 4	149 ± 4	156 ± 4[b]
Hematocrit (fraction)	0.42 ± 0.01	0.43 ± 0.02	0.42 ± 0.01	0.44±0.01[b]
WBC (10^9/L)	9.6 ± 1.6	9.9 ± 1.8	8.9 ± 1.4	7.2 ± 1.5[b]
Clinical chemistry				
Calcium (mmol/L)	2.52 ± 0.05	2.53 ± 0.05	2.49 ± 0.05	2.56 ± 0.06[b]
Cholesterol (mmol/L)	2.22 ± 0.09	2.07 ± 0.23[b]	2.01 ± 0.11[b]	1.73 ± 0.32[b]
Organ weights				
Adrenal, absolute (g)	0.0530 ± 0.0065	0.0537 ± 0.0094	0.0611 ± 0.0080[b]	0.0640 ± 0.0063[b]
Adrenal, relative (%)	0.2600 ± 0.0373	0.2624 ± 0.0454	0.2993 ± 0.0428[b]	0.3222 ± 0.0337[b]
Thymus, absolute (g)	0.288 ± 0.067	0.266 ± 0.087	0.247 ± 0.085	0.212 ± 0.080[b]
Thymus, relative (%)	0.140 ± 0.032	0.130 ± 0.038	0.120 ± 0.040	0.108 ± 0.041[b]
Nonneoplastic lesions				
Degeneration of olfactory epithelium (incidence)	0/10[d]	0/10	0/10	9/10[b,e]

[a]Mean ± standard deviation (*n*, if different from group size).
[b]Significantly different from control at $p < 0.05$.
[c]Statistical analysis performed for this review (*t*-test at $p < 0.05$).
[d]Number affected/number examined.
[e]Statistical analysis performed for this review (Fisher exact test at $p < 0.05$).

Source: Hofmann (1999).

Methyl acetate

Organ weight changes were generally consistent with the observed decrease in body weight (small, scattered decreases in absolute weight and/or increases in relative weight in a number of organs), except for larger (approximately 20%) increases in absolute and relative adrenal weights in both sexes (mid-dose and high-dose in females) and decreases in absolute and relative thymus weight in females. The researchers considered it likely that the increased adrenal weights reflected stress in the exposed animals. No gross pathology was observed. Histopathological examination revealed no marked changes in the adrenals, thymus, or other tissues, except for degeneration of the olfactory epithelium (Grade 3 indicating moderate change), which was observed in nearly all high-dose animals in both sexes but not in lower-dose animals (see Table 2). For this study, a LOAEL of 2000 ppm (6060 mg/m^3) and a NOAEL of 350 ppm (1060 mg/m^3) are identified for reduced body weight and food consumption, changes in organ weights, hematology and clinical chemistries, and olfactory epithelial degeneration in rats.

Toxicokinetics

There are very few data available describing the absorption, distribution, metabolism, or elimination of methyl acetate in humans or animals. None of the available data are sufficient for estimating rates of chemical uptake or elimination (via excretion or metabolism), or extent of hydrolysis. Methyl acetate is hydrolyzed to methanol, as was shown for glycol ether acetates that are hydrolyzed to their parent alcohols in aqueous solution (Miller et al., 1984, 1983; Nagano et al., 1979). In vitro hydrolysis of methyl acetate is a reversible reaction; two products are methanol and acetic acid as follows (Mizunuma et al., 1992):

$$\text{MeAc} + \text{H}_2\text{O} \;\leftrightarrow\; \text{HAc} + \text{MeOH} \qquad \text{(aq.)}$$

Henderson and Haggard (1943; also cited in ACGIH, 2001) suggested that the methanol formed by hydrolysis of methyl acetate in the human body might be responsible for its toxicity: "Methyl acetate is the most soluble of the series [of esters of organic acids]. Its hydrolysis in the body yields methyl alcohol. The concentration inhaled for prolonged periods should, therefore, be regulated with the toxicity of methyl alcohol in mind." Acute physiological action includes mild irritation and some anesthetic effects. The authors claimed that the "vapors on absorption, and probably to some extent on surface tissues as well, are largely hydrolyzed, with the liberation of the acid and the primary alcohol. Any anesthetic effects developed are due to the alcohol."

Two studies in humans and rabbits, respectively, indicate that methanol is produced in both species (human and rabbit) following exposure to methyl acetate. Tada et al. (1974, also cited in U.S. EPA, 1986) exposed two volunteers (33 and 48 years old) to 200 ppm (606 mg/m^3) methyl acetate for 2 hours twice daily for 4 days. Urine samples were collected throughout the 4-day study and analyzed for methanol. Urinary methanol, measured in the two subjects for 27 days prior to exposure, ranged from approximately 0.5 to 4.5 mg/L. Peak urinary methanol levels occurred each day following the second exposure, ranging from 10 to 15 mg/L. In rabbits, oral administration (dose unknown, article in Japanese) of methyl acetate resulted in hydrolysis to methanol and acetic acid (Tambo, 1973, also cited in U.S. EPA, 1986). Tambo (1973) concluded, "Occurrence of alcohol became cause of [t]hinner drunkenness. Occurrence of acetic acid in blood became cause of acidosis." They also stated that paint thinner, which contains methyl acetate, "evaporates at mean temperature and is readily absorbed into the lung." However, acidosis is only of concern by acetic acid at very high doses, and the half-life of acetic acid is short at low doses.

Genotoxicity

Zimmerman et al. (1985) reported that methyl acetate induces chromosomal aneuploidy, but not recombination or point mutations, in the diploid yeast, *Saccharomyces cerevisiae*. No other studies are identified for in vitro or in vivo genotoxic effects of methyl acetate in animal or humans.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RFD VALUES FOR METHYL ACETATE

Due to a lack of data, no chronic or subchronic p-RfDs are developed. However, the appendix of this document contains a screening p-RfD based on an analog treatment, which may be useful in certain instances. Please see Appendix A for details.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RFC VALUES FOR METHYL ACETATE

Because the toxicity data based on a Toxic Substances Control Act (TSCA) study (Hofmann, 1999) are not peer reviewed, no chronic or subchronic p-RfCs are developed. However, the appendix of this document contains a screening subchronic p-RfC that may be useful in certain instances. Please see Appendix A for details.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR METHYL ACETATE

WEIGHT-OF-EVIDENCE DESCRIPTOR (WOE)

No human or animal data are available to inform on the carcinogenicity of methyl acetate. The database for methyl acetate does not contain a chronic bioassay sufficient for derivation of an oral cancer slope factor or inhalation unit cancer risk. In addition, the 1993 IRIS summary for methanol (U.S. EPA, 1993) did not conduct a qualitative cancer assessment. According to the EPA (2005) *Guidelines for Carcinogen Risk Assessment*, there is "*Inadequate Information to Assess Carcinogenic Potential*" for methyl acetate.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for methyl acetate is precluded by the lack of available data. In addition, because the 1993 IRIS summary for methanol (U.S. EPA, 1993) did not provide a quantitative cancer assessment, a screening p-OSF cannot be derived based on analogy to methanol for methyl acetate.

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APPENDIX A. DERIVATION OF A SCREENING VALUE
FOR METHYL ACETATE

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for methyl acetate. However, information is available for this chemical, which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center (STSC) summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the STSC.

ORAL STUDIES
Screening Provisional Reference Dose (p-RfD)
No oral data are available for subchronic or chronic exposure of animals or humans to methyl acetate. However, methyl acetate can be extensively hydrolyzed to methanol in the body (in aqueous phase). Formation of methanol from methyl acetate has been observed in humans (Tada et al., 1974) and in rabbits (Tambo, 1973). Oral data for methanol are available and have been used previously by EPA to develop an assessment for methyl acetate. Previously, EPA (1986) derived a chronic RfD of 1 mg/kg-day for methyl acetate by analogy to methanol. This was accomplished by multiplying an RfD of 0.5 mg/kg-day for methanol by the methyl acetate-to-methanol molecular weight ratio of 74.08 g/mol ÷ 32.04 g/mol = 2.312 (U.S. EPA, 1986). The critical effect is based on increased serum alkaline phosphatase (SAP) and serum glutamic pyruvic transaminase (SGPT), and decreased brain weight (U.S. EPA, 1993).

In the 1993 IRIS summary for methanol, the POD (500 mg/kg-day) was divided by a composite UF of 1000, which includes a 10-fold UF for interspecies extrapolation, a 10-fold UF for intraspecies variability, and a 10-fold UF for extrapolation from subchronic-to-chronic duration, and the chronic RfD (0.5 mg/kg-day) for methanol was derived (U.S. EPA, 1993). Because of the similar toxicity profiles between methyl acetate and methanol as shown in occupational and in vivo studies (e.g., Tada et al., 1974; Tambo, 1973; Henderson and Haggard, 1943) and by hydrolysis reaction (1 mol of methyl acetate plus 1 mol of water can be converted into one mol of methanol and 1 mol of acetic acid), a screening chronic p-RfD for methyl acetate can be derived by analogy to methanol by molecular weight adjustment as follows:

$$
\begin{aligned}
\textbf{Screening Chronic p-RfD} \quad &= \quad \text{IRIS RfD (methanol)} \times (\text{MW}_{\text{methyl acetate}} \div \text{MW}_{\text{methanol}}) \\
\text{(methyl acetate)} \quad &= \quad 0.5 \text{ mg/kg-day} \times (74.08 \text{ g/mol} \div 32.04 \text{ g/mol}) \\
&= \quad 0.5 \text{ mg/kg-day} \times 2.312 \\
&= \quad \textbf{1 mg/kg-day}
\end{aligned}
$$

Because the screening chronic p-RfD for methyl acetate was derived explicitly from those of methanol, the uncertainties associated with the POD for methanol and confidence in the principal study and database for methanol all contribute to uncertainty for methyl acetate as well. For methanol, the confidence in the study, database, and RfD are medium, low, and medium, respectively. According to EPA (1993):

> *The principal study was well-designed and provided adequate toxicological endpoints, but the method of administration was not ideal. The overall database is weak, lacking data on reproductive, developmental, or other toxicological endpoints. The RfD is given a medium confidence rating because of the strengths of the principal study.*

Notably, a UF for database deficiency was not applied at time. For methyl acetate, based on the 1993 IRIS summary, there is additional uncertainty due to the reliance on data for methanol to obtain an assessment. Therefore, the overall confidence in the screening chronic p-RfD for methyl acetate is low.

INHALATION STUDIES
Screening Provisional Reference Concentration (p-RfC)
No human toxicity studies of methyl acetate are available. The only available animal study is for nose-only inhalation exposure of rats to 0, 75, 350, or 2000 ppm (0, 227, 1060, or 6060 mg/m^3) for 6 hours/day, 5 days/week, for 28 days (Hofmann, 1999) (see Table 2). This study was submitted to TSCA and has not been peer-reviewed. In this study, no toxicologically relevant changes were seen at ≤350 ppm (1060 mg/m^3). Systemic effects, including changes in body weight, food consumption, hematology, clinical chemistries, and organ weights, occurred at 2000 ppm (6060 mg/m^3). In this report, body-weight decrease is considered both biologically and statistically significant ($p < 0.05$) with a 10% decrease at the highest dose in male rats (6060 mg/m^3). Degeneration of the nasal epithelium was seen in 10/10 males and 9/10 females at this same exposure level.

Unlike the systemic effects, changes to the nasal epithelium are considered portal-of-entry effects. For this reason, human equivalent concentrations (HECs) were calculated differently for nasal epithelium degeneration versus systemic effects, as described by EPA (1994b). Table A-1 shows the HECs for both the nasal and systemic effects.

Table A-1. Summary of Inhalation Study of Methyl Acetate in Animals					
Species and Study Type (*n*/sex/group)	**Exposure**	**NOAEL**	**LOAEL**	**Responses at the LOAEL**	**Reference**
Rats Subacute Nose-only Inhalation	Groups of male and female Sprague-Dawley rats (10/sex/group) exposed to 0, 75, 350, or 2000 ppm, 6 hrs/d, 5 d/wk, for 4 wks	350 ppm (1060 mg/m^3) HEC: 189 mg/m^3 (for systemic effects) HEC: 31 mg/m^3 (for nasal effects)	2000 ppm (6060 mg/m^3) HEC: 1082 mg/m^3 (for systemic effects) HEC: 180 mg/m^3 (for nasal effects)	Reduced body-weight gain and food consumption, and changes in organ weights and hematology and clinical chemistry endpoints at 2000 ppm. Degeneration of the olfactory epithelium at 2000 ppm.	Hofmann, 1999

HEC for systemic effects derived using EPA (1994b) equations for a Category 3 gas:

$NOAEL_{HEC} = NOAEL_{ADJ} \times [(H_{b/g})_A \div (H_{b/g})_H]$,

where $NOAEL_{ADJ} = NOAEL \times (6 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days})$ and

$(H_{b/g})_A \div (H_{b/g})_H$, the ratio of animal to human blood:air partition coefficients, is set to 1 by default (see text).

HEC for respiratory effects derived using EPA (1994b) equations for a Category 1 gas:

$NOAEL_{HEC} = NOAEL_{ADJ} \times [(V_E/SA_{ET})_A \div (V_E/SA_{ET})_H]$,

where $NOAEL_{ADJ} = NOAEL \times (6 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days})$ and

$(V_E/SA_{ET})_A \div (V_E/SA_{ET})_H$, the ratio of animal and human inhalation minute volumes (V_E in L/min), normalized to tissue surface area of the extrathoracic region (SA_{ET}, cm^2), is 0.166 (see text for calculation).

For degeneration of the nasal epithelium,

$$\text{NOAEL}_{\text{ADJ}} = \text{NOAEL} \times (6 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days})$$
$$\text{NOAEL}_{\text{HEC,CAT1}} = \text{NOAEL}_{\text{ADJ}} \times [(V_E \div SA_{ET})_A \div (V_E \div SA_{ET})_H]$$

where $\text{NOAEL}_{\text{HEC,CAT1}}$ was calculated as the dosimetric adjustment from the $\text{NOAEL}_{\text{ADJ}}$ in animals (189 mg/m^3) to a NOAEL in humans based on treatment of methyl acetate as a Category 1 gas exhibiting extrathoracic effects. This was accomplished by multiplying the $\text{NOAEL}_{\text{ADJ}}$ by the ratio of animal and human inhalation minute volumes (V_E in L/minute), normalized to tissue surface area of the extrathoracic region (SA_{ET} in cm^2) (U.S. EPA, 1994b). The minute volume used for humans was 13.8 L/minute (U.S. EPA, 1994b). For rats, the minute volume was calculated as

$$\ln(V_E) = b_0 + b_1 \ln(BW)$$

For rats, b_0 equals -0.578, b_1 equals 0.821, and a reference body weight of 0.236 kg (average for male and female Sprague-Dawley rats in a subchronic study; U.S. EPA, 1988) was used, resulting in a V_E value of 0.171 L/minute. The values used for surface area for extrathoracic tissues of rats and humans were 15 and 200 cm^2, respectively (U.S. EPA, 1994b). Thus, using a NOAEL of 6060 mg/m^3, the $\text{NOAEL}_{\text{HEC,CAT1}}$ is calculated as follows:

$$\text{NOAEL}_{\text{HEC,CAT1}} = 189 \text{ mg/m}^3 \times [(0.171 \text{ mg/m}^3 \div 15) \div (13.8 \div 200)]$$
$$\text{NOAEL}_{\text{HEC,CAT1}} = 31 \text{ mg/m}^3$$

Similarly, for systemic effects:

$$\text{NOAEL}_{\text{HEC,CAT3}} = \text{NOAEL}_{\text{ADJ}} \times [(H_{b/g})_A \div (H_{b/g})_H]$$

where $\text{NOAEL}_{\text{HEC,CAT3}}$ is calculated as the dosimetric adjustment from the $\text{NOAEL}_{\text{ADJ}}$ in animals to a NOAEL in humans based on treatment of methyl acetate as a Category 3 gas exhibiting remote, extrarespiratory effects. This was accomplished by multiplying the $\text{NOAEL}_{\text{ADJ}}$ by the ratio of animal and human blood:gas (air) partition coefficients ($H_{b/g}$) (U.S. EPA, 1994b). Blood:air partition coefficients were measured by Kaneko et al. (1994) for methyl acetate in humans (90.1) and rats (100). Because the ratio of rat and human blood:air partition coefficients is $100 \div 90.1 \geq 1.0$, the default value of 1 is applied to the $\text{NOAEL}_{\text{ADJ}}$. Thus, the $\text{NOAEL}_{\text{HEC,CAT3}}$ is equal to the $\text{NOAEL}_{\text{ADJ}}$ of 189 mg/m^3.

The $\text{NOAEL}_{\text{HEC,CAT1}}$ for nasal lesions of 31 mg/m^3 is approximately 7-fold lower than the $\text{NOAEL}_{\text{HEC,CAT3}}$ of 189 mg/m^3 for systemic effects. In addition, examination of the data on body-weight decrease in male rats (see Table 2) shows that the change rises deeply from 0.8% at 227 mg/m^3 to 0.9% at 1060 mg/m^3 to 10% at 6060 mg/m^3 (LOAEL). Because there is a lack of dose-response at lower doses and only a biological response at 10% at the highest dose, benchmark dose (BMD) modeling was not conducted on this data set. Therefore, degeneration of nasal epithelium from the 28-day exposure in rats (Hofmann, 1999) was selected as the critical effect for inhaled methyl acetate.

Similarly, examination of the data on nasal lesions in rats (see Table 2) shows that the incidence rises steeply from 0/10 in the control, low-, and mid-dose groups to 9/10 or 10/10 for females and males, respectively at the LOAEL. Because there is no exposure level at which the

incidence of this effect is significantly less than 100% (lack of dose-response at lower doses), BMD modeling was not conducted on this data set. Thus, a LOAEL/NOAEL approach was used to derive the screening subchronic p-RfC for methyl acetate, using the $NOAEL_{HEC,CAT1}$ of 31 mg/m³ for nasal lesions in rats as the POD.

The **screening subchronic p-RfC** for methyl acetate is derived as follows:

Screening Subchronic p-RfC	=	$NOAEL_{HEC} \div UF$
	=	31 mg/m³ ÷ 300
	=	**0.1 or 1×10^{-1} mg/m³**

The composite UF of 300 is composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 3 is applied to account for interspecies extrapolation (toxicodynamic portion only) because a dosimetric adjustment was made.
- UF_D: A factor of 10 is applied for database deficiencies because data for inhalation developmental and multigeneration reproduction studies are not available. The database also lacks any neurotoxicological studies for potential neurotoxicity.
- UF_L: A factor of 1 is applied for use of a $NOAEL_{HEC}$ as the POD for derivation of the RfC.
- UF_S: A factor of 1 is applied for subchronic-to-chronic extrapolation because a short-term study was used for deriving a subchronic p-RfC.

Confidence in the principal study is medium. The study of Hofmann (1999) is a well-designed toxicity study in which data for multiple endpoints of toxicity, including histological examination of a variety of tissues, were provided for rats. However, the study was only 4 weeks in duration. Confidence in the database is low. The 28-day study of Hofmann (1999) is the only inhalation toxicity study available. The rat is the only species for which inhalation toxicity data exist. No subchronic, chronic, reproductive, or developmental toxicity data in animals are available. Given medium confidence in the principal study and low confidence in the database, confidence in the screening subchronic p-RfC is low.

A screening chronic p-RfC for methyl acetate is not derived due to lack of subchronic or chronic inhalation data.