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Provisional Peer-Reviewed Toxicity Values for

Ethyl Acetate
(CASRN 141-78-6)

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

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Carrie R. Fleming, PhD
National Center for Environmental Assessment, Cincinnati, OH

CONTRIBUTOR

Jason C. Lambert, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

ICF International
9300 Lee Highway
Fairfax, VA 22031

PRIMARY INTERNAL REVIEWERS

Audrey Galizia, DrPH
National Center for Environmental Assessment, Washington, DC

Suryanarayana V. Vulimiri, BVSc, PhD, DABT
National Center for Environmental Assessment, Washington, DC

This document was externally peer reviewed under contract to
Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document 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).

CONTENTS

COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
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
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
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 ETHYL ACETATE (CASRN 141-78-6)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

Ethyl acetate (CASRN 141-78-6)—also known as acetic acid, ethyl ester—is a clear, volatile, flammable liquid having a characteristic fruity odor and a reportedly pleasant taste when diluted. Ethyl acetate is a naturally occurring constituent of plants and is found in a wide variety of commonly consumed fruits, such as apples, bananas, and nectarines. It is used industrially as a solvent for lacquers, paints, and inks, and as an inert ingredient in pesticides as a solvent, cosolvent, or attractant. It is also used by the pharmaceutical industry as a flavoring agent. Ethyl acetate is included in 21 CFR 182.60 (U.S. FDA, 2010) as a "substance generally recognized as safe." The structure of ethyl acetate is shown in Figure 1, and selected physicochemical properties of ethyl acetate are provided in Table 1.

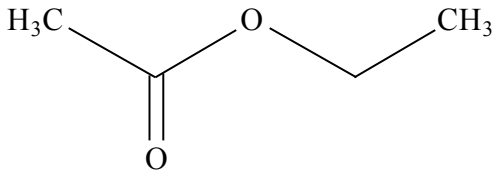

Figure 1. Ethyl Acetate Structure

Table 1. Physicochemical Properties of Ethyl Acetate (CASRN 141-78-6)

Property (unit)	Value
Molecular formula	$C_4H_8O_2$[a]
Boiling point (ºC)	77.1[a]
Melting point (ºC)	−83.6[a]
Density (g/cm^3 at 20°C)	0.902[b]
Vapor pressure (mm Hg at 25ºC)	93.2[a]
pH (unitless)	ND
Solubility in water (mg/L at 25ºC)	8.0×10^4[a]
Relative vapor density (air = 1)	3.04[b]
Molecular weight (g/mol)	88.11[b]

[a]NLM (2011).
[b]U.S. EPA (2006).

ND = no data.

A summary of available health-related values for ethyl acetate from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Ethyl Acetate (CASRN 141-78-6)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Noncancer				
ACGIH	TLV-TWA: 1440 mg/m^3 (400 ppm)	To provide "an occupational exposure value with a significant safety factor from the standpoint of adverse health effects."	ACGIH, 1991	9-26-2012
ATSDR	NV	NA	ATSDR, 2011	9-26-2012
CalEPA	NV	NA	CalEPA, 2008, 2009a	9-26-2012
NIOSH	REL-TWA: 1440 mg/m^3 (400 ppm) IDLH: 10,000 ppm (35,963 mg/m^3)	NA	NIOSH, 2005	9-26-2012
OSHA	PEL-TWA: 1440 mg/m^3 (400 ppm)	NA	OSHA, 2011	9-26-2012
IRIS	RfD: 9×10^{-1} mg/kg-d	Based on mortality and body-weight loss	U.S. EPA, 1988	9-26-2012
Drinking water	NV	NA	U.S. EPA, 2011a	9-26-2012
HEAST	Subchronic RfD: 9×10^{0} mg/kg-d	NA	U.S. EPA, 2003	9-26-2012
CARA HEEP	NV	A profile was available in an earlier version of HEEP (U.S. EPA, 1986a)	U.S. EPA, 1994a	9-26-2012
WHO	NV	NA	WHO, 2011	9-26-2012
Cancer				
IRIS	NV	NA	U.S. EPA, 1988	9-26-2012
HEAST	NV	NA	U.S. EPA, 2003	9-26-2012
IARC	NV	NA	IARC, 2011	9-26-2012
NTP	NV	NA	NTP, 2011	9-26-2012
CalEPA	NV	NA	CalEPA (2009b)	9-26-2012

[a]Sources: Integrated Risk Information System (IRIS) database; Health Effects Assessment Summary Tables (HEAST); International Agency for Research on Cancer (IARC); National Toxicology Program (NTP); California Environmental Protection Agency (CalEPA); American Conference of Governmental Industrial Hygienists (ACGIH); Agency for Toxic Substances and Disease Registry (ATSDR); National Institute for Occupational Safety and Health (NIOSH); Occupational Safety and Health Administration (OSHA); Chemical Assessments and Related Activities (CARA) list; Health and Environmental Effects Profile (HEEP); World Health Organization (WHO).

IDLH= immediately dangerous to life or health; NA = not applicable; NV = not available; PEL-TWA = permissible exposure level-time weighted average; REL-TWA = recommended exposure level-time weighted average; TLV-TWA = threshold limit value-time weighted average.

Literature searches were conducted on sources published from 1900 through September 2012, for studies relevant to the derivation of provisional toxicity values for ethyl acetate, CASRN 141-78-6. Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications (NSCEP) and National Environmental Publications Internet Site (NEPIS) database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for health-related values: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 3 provides an overview of the relevant database for ethyl acetate and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. The term "significance" used throughout the document indicates a p-value of <0.05, unless otherwise indicated.

Table 3. Summary of Potentially Relevant Data for Ethyl Acetate (CASRN 141-78-6)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-d)[a]								
Acute[c]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
2. Inhalation (mg/m^3)[a]								
Acute[c]	1 male, 39-yr-old, case study, duration unknown	NDr	Mortality	NDr	NDr	NDr	Coopman et al. (2005)	PR
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
Animal								
1. Oral (mg/kg-d)[a]								
Subchronic	**30/30 S-D rats, gavage (7d/wk), 93 d Interim sacrifice of 10/10 rats at 44–45 d**	**0, 300, 900, or 3600 mg/kg-d (Adjusted)**	**Clinical signs, including increased salivation, irregular breathing, and lethargy in both sexes**	**900**	**DU**	**3600**	**American Biogenics Corp. (1986)**	**PS, IRIS, NPR**
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

Table 3. Summary of Potentially Relevant Data for Ethyl Acetate (CASRN 141-78-6)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
2. Inhalation (mg/m^3)[a]								
Short-term	10/5 CD rat, whole-body inhalation, 6 h/d, 5 d/wk, 2 wk	0, 959, 1973, or 3877 mg/m^3	Decreased food consumption (both sexes)	NDr	DU	959	Burleigh-Flayer et al. (1995)	NPR
Subchronic	**12 or 18 S-D rats/sex, 6 h/d, 5 d/wk, 13 wk, with a 4-wk recovery period**	**0, 209, 448, or 896 mg/m^3**	**Decreased body weights, body-weight gains, food efficiency, and startle response (both sexes), and decreased food consumption (males)**	**209**	**DU**	**448**	**Christoph et al. (2003)**	**PS, PR**
Subchronic	10/0 S-D rats, whole-body inhalation, 6 h/d, 5 d/wk, 89 d for a total of 65 exposures	0, 225, 483, or 965 mg/m^3	Animals were evaluated specifically for alterations in operant behavior. Changes in operant testing results were not clearly treatment related	965	DU	NDr	Christoph (1997) and Christoph et al. (2003)	PR
Subchronic	3 Guinea pigs (number/sex not specified), 4 h/d, 6−7 d/wk, duration not reported (total of 65 exposures)	1030 mg/m^3	None	1030	DU	NDr	Smyth and Smyth (1928)	PR
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood:air partition coefficient.
[b]Notes: IRIS = Utilized by IRIS, 1988; PS = principal study, PR = peer reviewed, NPR = not peer reviewed.
[c]Acute = Exposure for 24 hours or less (U.S. EPA, 2002).
[d]Short-term = Repeated exposure for >24 h ≤30 d (U.S. EPA, 2002).
[e]Long-term = Repeated exposure for >30 d ≤10% lifespan (based on 70 years typical lifespan) (U.S. EPA, 2002).
[f]Chronic = Repeated exposure for ≥10% lifespan (U.S. EPA, 2002).

DU = data unsuitable, NA = not applicable, NV = not available, ND = no data, NDr = not determinable, NI = not identified, NP = not provided, NR = not reported, NR/Dr = not reported but determined from data, NS = not selected, S-D = Sprague-Dawley.

HUMAN STUDIES

Oral Exposures

No studies were identified.

Inhalation Exposures

No inhalation exposure studies were found on the short-term, long-term, or chronic toxicity of ethyl acetate in humans. An acute study was presented by Coopman et al. (2005).

Acute Exposure

Coopman et al., 2005

Coopman et al. (2005) presented a case study of the distribution of ethyl acetate and ethanol in the tissues of a 39-year-old man following an acute fatal intoxication. The victim was found dead lying on his abdomen in the interior of a tank containing ethyl acetate. Atmospheric concentrations of ethyl acetate were not reported. Low ratios of ethyl acetate concentration to ethanol concentration in tissue samples suggested rapid in vivo hydrolysis of ethyl acetate to ethanol; a police investigation indicated that the victim had not consumed alcohol within 24 hours of his death. Results regarding tissue distribution of ethyl acetate were confounded by postmortem penetration through the body surface and possible redistribution.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to ethyl acetate were evaluated in one subchronic-duration study (American Biogenics Corp., 1986).

Subchronic-duration Studies

American Biogenics Corp., 1986

The study by American Biogenics Corp. (1986) is selected as the principal study for the derivation of the subchronic p-RfD value; it is also the principal study for the chronic RfD available from IRIS (U.S. EPA, 1988). The original American Biogenics Corp. (1986) study report could not be obtained; however, study summaries are available in both IRIS (U.S. EPA, 1988) and HEEP (U.S. EPA, 1986a). Peer-review status of the original study report is unknown. Tabular data could not be obtained, and standard deviations were not provided. The following information was indicated in the more detailed HEEP study summary (U.S. EPA, 1986a). The study authors administered ethyl acetate (99.9% purity) in corn oil to 30 Sprague-Dawley rats/sex/group by daily gavage at doses of 0, 300, 900, or 3600 mg/kg-day for up to 93 days. An interim sacrifice of 10 rats/sex/group was performed on Days 44−45; the remaining rats were euthanized on Days 91−93. Systemic evaluations including mortality, clinical signs of toxicity, body-weight gain, food consumption, hematology, clinical chemistry, urinalysis, and ophthalmoscopic examinations were performed before the interim and terminal sacrifices. All rats were subjected to a gross necropsy, and major organs (not specified) were weighed. Comprehensive histological examinations were performed on all control and 3600-mg/kg-day rats that died or were euthanized at study termination. Histological examinations of the 300- and 900-mg/kg-day rats that died or were euthanized at study termination were limited to the heart, kidneys, liver, and gross lesions.

Prior to scheduled termination, 2/30 rats died at 900 mg/kg-day, and 7/30 rats died at 3600 mg/kg-day (sex not specified). It was stated that "the deaths of several high-dose rats were due to pulmonary accident or gavaging trauma" (U.S. EPA, 1986a); therefore, the reported

mortalities are not considered treatment related. At 3600 mg/kg-day, significantly increased incidences of salivation, irregular breathing, and lethargy were observed in both sexes, and significantly reduced body-weight gains were noted in the males. Additionally at this dose, significant organ-weight changes were observed as follows: in males, decreased absolute spleen weight, decreased absolute and relative (to brain) kidney weights, decreased absolute and relative (to body and brain) liver weights, and increased relative (to body) testes weight; and in females, decreased relative (to body) liver weight. It cannot be determined from the information available whether the observed decreases in organ and body weights were treatment related or attributable to the early accidental deaths (for which body and organ weights were recorded at the time of death). No other changes were described in the available summaries (U.S. EPA, 1986a, 1988).

A LOAEL of 3600 mg/kg-day and a corresponding NOAEL of 900 mg/kg-day is identified based on clinical observations of toxicity, including increased salivation, irregular breathing, and lethargy in both sexes.

Chronic-duration Studies
No studies were identified.

Developmental Studies
No studies were identified.

Reproductive Studies
No studies were identified.

Carcinogenicity Studies
No studies were identified.

Inhalation Exposures

The effects of inhalation exposure of animals to ethyl acetate have been evaluated in one short-term study (Burleigh-Flayer et al., 1995) and two subchronic-duration studies (Christoph et al., 2003; Smyth and Smyth, 1928).

Short-term Studies

Burleigh-Flayer et al., 1995

In a nonpeer-reviewed study, Burleigh-Flayer et al. (1995) exposed groups of CD rats (10 males/5 females per group) to ethyl acetate (>99% purity) by whole-body inhalation at nominal concentrations of 0, 1500, 3000, or 6000 ppm (analytical concentrations: 0, 1491, 3066, and 6024 ppm) for 6 hours/day, 5 days/week for 2 weeks. Analytical concentrations have been converted to human equivalent concentrations (HECs) based on the following equation: $CONC_{HEC} = CONC_{ppm} \times$ (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × Blood:Air Partition Coefficient Ratio. The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied. The applied concentrations of 0, 1491, 3066, and 6024 ppm correspond to HECs of 0, 959, 1973, and 3877 mg/m^3, respectively. The male rats were further subdivided into two groups of five rats each to undergo separate feeding regimens: either ad libitum or on a restricted basis to maintain their body weight at approximately 300 g. All females were fed ad libitum. The results presented below are from the animals fed ad libitum only. A functional observational battery (FOB) and motor activity testing were performed prior to the start of exposure and at the end of

the first and second weeks of exposure. Clinical signs, body weights, food consumption, and water consumption were reported at several time points during the exposure period. All rats received a complete necropsy at study termination, and absolute and relative (to body) organ weights were reported for liver, kidneys, lungs, heart, spleen, brain, adrenal glands, testes, and ovaries.

All animals survived to scheduled termination (Burleigh-Flayer et al., 1995). Clinical signs were observed at 1973 and 3877 mg/m^3; they included hypoactivity, blepharospasm (abnormal contraction or twitch of the eye), and a lack of a startle reflex. In males, body weights were decreased in a concentration-dependent manner but were only statistically significant on Day 12 at 1973 (8% change) and 3877 (12% change) mg/m^3. In females, no statistically significant effect was observed on body weights. Significant decreases in food consumption were observed at all concentrations in males and females; average daily food consumption over the duration of the study was decreased by 11−22% in males and 16−21% in females. Increased water consumption was noted in males at 3877 mg/m^3 throughout the study but was only statistically significant during Days 12−13; there appeared to be a concentration-related trend toward increased water consumption with increased concentration. In the males, absolute spleen weights were significantly decreased at 1973 and 3877 mg/m^3, and absolute liver weights were significantly decreased at 3877 mg/m^3; however, there were no statistically significant changes in relative (to body) weights for these organs. In the females, absolute and relative ovary weights were significantly decreased at 3877 mg/m^3 (21% change in relative ovary weight), and relative brain weights were increased (8−11%) at all concentrations. Motor activity was also decreased in females in a concentration-dependent trend, with a statistically significant decrease at the high-exposure concentration (3877 mg/m^3). No statistically significant changes in mean motor activity were noted in the males, and the data suggested a trend toward increased activity at the low concentration rather than decreased. The study authors indicated an increased incidence of several of the endpoints from the FOB. However, these changes were not statistically significant; importantly, the small sample size may have limited the ability to detect changes in incidence of observations from the FOB. No treatment-related gross lesions were noted at necropsy.

A $LOAEL_{HEC}$ of 959 mg/m^3 is identified based on decreased food consumption in both sexes. A NOAEL cannot be determined under the conditions of this study. Due to the limited exposure period (10 days), this study is not considered adequate for derivation of a subchronic p-RfC.

Subchronic-duration Studies

Christoph et al., 2003

The study by Christoph et al. (2003) is selected as the principal study for the derivation of the subchronic and chronic p-RfC values. In this peer-reviewed study, Christoph et al. (2003) exposed Sprague-Dawley rats (Crl:CD®BR; Charles River Laboratories, Raleigh, NC) to ethyl acetate (99.9% purity) by whole-body inhalation at concentrations of 0 (*n* = 18/sex), 350 (*n* = 12/sex), 750 (*n* = 12/sex), or 1500 (*n* = 18/sex) ppm for 6 hours/day, 5 days/week for 13 weeks (0, 225, 483, and 965 mg/m^3 HEC, respectively). This exposure pattern was interrupted for neurobehavioral testing as detailed below; however, rats were exposed into Week 14 as necessary to ensure that each rat received 65 exposures. Performing duration adjustment based on 65 doses in 14 weeks instead of 13 weeks results in the following conservative estimates of the HEC: 0, 209, 448, and 896 mg/m^3. Mean analytical concentrations

were equivalent to nominal values when expressed to two significant figures. Three 0.75-m^3 stainless steel and glass chambers (209, 448, and 896 mg/m^3) and one 1.0-m^3 chamber (0 mg/m^3) were used for the exposures. Test compound concentrations were determined every 30 minutes by gas chromatography, and homogeneity of the test atmospheres was confirmed by sampling at nine locations in the exposure chambers.

Christoph et al. (2003) recorded body weights, food consumption, and food efficiency (body-weight gain per amount of food consumed) at least once per week throughout exposure. During each exposure session, startle responses to a sharp sound were scored every 2 hours. An observer (not blinded to treatment group) made a visual judgment of the vigor of the group response (excessive, normal, diminished, or no response). Additionally, standard clinical observations were recorded immediately after each exposure and at weekly intervals prior to exposure to identify any enduring signs. Neurobehavioral testing was performed prior to study initiation and during Weeks 4, 8, and 13. The animals were not exposed on the day of neurobehavioral testing, but at least one exposure day always preceded a neurobehavioral testing day. Neurobehavioral testing included an FOB, which included subjectively scored observations made while the rat was inside a cage, being handled, and in an open field arena, and a motor activity test in which the number of movements and time spent in motion was recorded for each rat. After the final exposure, six randomly selected rats from each group were prepared for neuropathological examination of the brain (forebrain, cerebrum, midbrain, pons, medulla, and cerebellum), spinal cord (cervical and lumbar), sciatic nerve, tibial nerve, gasserian ganglia, cervical and lumbar dorsal root fibers and ganglia, cervical and lumbar ventral root fibers, and gastrocnemius muscle. Remaining rats from the 209- and 448-mg/m^3 groups were euthanized, while 12 rats/sex from the control and 896-mg/m^3 groups were monitored for an additional 4-week recovery period; neurobehavioral testing was performed on these animals at the end of this period (Week 18). No necropsies were performed. A separate experiment involving operant behavioral training and testing was performed and is discussed below.

Body weights, body-weight gains, food consumption, and food efficiency were analyzed with Bartlett's test for homogeneity of variance, followed by an analysis of variance (ANOVA) and a post hoc Dunnett's test to identify treatment groups that differed significantly from the controls. Although it was not stated whether this study was conducted in compliance with good laboratory practice (GLP) standards, a separate report detailing the operant behavioral training and testing only was GLP-compliant (Christoph, 1997).

Body weights were decreased in a concentration-dependent manner and were statistically significantly lower than controls at ≥448 mg/m^3 in both sexes (Christoph et al., 2003). Body weights were presented only graphically, but data were digitized from the graph using GetData Graph Digitizer. The estimated body weights from this digitization are presented in Table B.1. Body weights at the end of dosing were 6, 8, and 15% lower than controls in the 209-, 448-, and 896-mg/m^3 males, respectively. In females, 4, 10, and 10% reductions were observed. Over the entire treatment period, body-weight gains were significantly reduced in all treatment groups in both sexes (decreased 12, 17, and 28% in the males, and 11, 25, and 30% in the females, respectively; presented by the study authors in text only) compared to the controls. Food consumption and food efficiency were reported in text only as percent change from control. Overall (Weeks 0−13) food consumption was significantly decreased by 9 and 13% in the 448- and 896-mg/m^3 males, respectively, and by 8% in the 896-mg/m^3 females. Similarly, food efficiency was significantly decreased by 9, 8, and 17% in the males at 209, 448, and 896 mg/m^3,

respectively, and by 20 and 25% in the females at 448 and 896 mg/m^3, respectively. The study authors stated that some evidence of recovery was noted in these parameters in the 896 mg/m^3 rats during the 4-week postexposure period.

Exposure to 448 and 896 mg/m^3 resulted in diminished startle responses to unexpected auditory stimuli during the exposure period, suggesting an acute sedative effect. No signs of acute intoxication were observed during clinical observations 30 minutes after the exposures ended. In the neurobehavioral testing performed on nonexposure days, the principal behavioral effect was reduced motor activity in the 896-mg/m^3 females; this effect was no longer present after a 4-week recovery period. During Week 13, the mean total duration of movements for the 896-mg/m^3 females was decreased by 22% (statistically significant) compared to controls, and the number of movements was decreased (not statistically significant, magnitude of decrease not reported). All other neurobehavioral parameters and motor activity measurements were similar to controls, and no nervous system lesions were observed during the neuropathological examinations.

The small decreases in body-weight gain and food efficiency at 209 mg/m^3 are not considered biologically significant. The $LOAEL_{HEC}$ is 448 mg/m^3, based on decreased body weights, food efficiency, and startle response in both sexes, and decreased food consumption in the males. The $NOAEL_{HEC}$ is 209 mg/m^3.

Christoph et al. also performed operant behavior testing on groups of male Sprague-Dawley rats in a subchronic-duration inhalation study Christoph (1997) and Christoph et al. (2003). Ten male rats/concentration received training to press a lever on a multiple fixed ratio-fixed interval schedule of reinforcement for 8 weeks, with the fixed ratio and fixed interval portions of the schedule being indicated by an illuminated light and a continuous tone, respectively. In order to motivate the rats to perform the behavioral task, these animals had limited access to food with a target weight range of 280−313 g. The rats were exposed by whole-body inhalation to ethyl acetate concentrations of 0, 350, 750, or 1500 ppm (0, 225, 483, or 965 mg/m^3 HEC) for 6 hours/day, 5 days/week, over a period of 89 days for a total of 65 exposures. Operant testing was performed in the morning prior to each exposure session and continued during a 2-week postexposure evaluation period. The only difference noted between treated and control groups in the operant testing was a change in the fixed interval response rate; the response rate drifted down over time in control animals and up over time in all the treated groups, and results in all three treated groups were similar. Comparison of the 1500-ppm group to laboratory historical controls revealed that the pattern of increasing fixed interval response rate over time was typical of control animals from this laboratory. Results for controls and treated animals were similar for all other endpoints measured in the operant testing. The study authors concluded that there was no evidence that subchronic-duration exposure to ethyl acetate at concentrations of up to 1500 ppm (965 mg/m^3 HEC) caused any persistent neurotoxic effects in rats.

Smyth and Smyth (1928)

In a peer-reviewed study, Smyth and Smyth (1928) exposed three guinea pigs (strain not provided) to ethyl acetate (purity not specified) by inhalation at a concentration of 2000 ppm (1030 mg/m^3 HEC) for a total of 65 exposures in "gassing jars" (additional details not provided). It was stated that during the first 2 weeks, the animals were exposed daily, and then "almost always for 4-hour periods each day for 6 days a week." As the majority of the exposures were

performed in this fashion, the HEC is calculated using a 4-hour per day, 6-days per week paradigm. Body weights were recorded at approximately weekly intervals, and blood counts (erythrocyte count, hematocrit, and absolute and differential lymphocyte counts reported) and urine examinations (specific gravity reported) were performed every 2 weeks. It was stated that all three animals "continued in good condition and showed no definite evidence of harm for a period of 65 exposures." A LOAEL was not observed; the $NOAEL_{HEC}$ was 1030 mg/m^3. This study was not considered adequate for derivation of a subchronic p-RfC due to deficiencies in study design and reporting, especially the insufficient description of dosing techniques.

Chronic-duration Studies
No studies were identified.

Developmental Studies
No studies were identified.

Reproductive Studies
No studies were identified.

Carcinogenicity Studies
No studies were identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Other studies that are not appropriate for selection of a point of departure (POD) for ethyl acetate and the determination of p-RfD, p-RfC, provisional oral slope factor (p-OSF), or provisional inhalation unit risk (p-IUR) values may provide supportive data for hazard identification or dose-response analysis. These studies may include genotoxicity (see Table 4A), as well as metabolism and mechanistic studies (see Table 4B).

Table 4A. Summary of Ethyl Acetate Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 were preincubated with ethyl acetate in the presence of Kanechlor KC-400-induced Fischer rat S9 liver microsomes, plated, and incubated overnight.	5 mg/plate	NA	−	Ethyl acetate was not mutagenic in this test system.	Ishidate et al. (1984)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	ND					
Recombination induction	ND					
Chromosomal abberation	ND					
Chromosomal malsegregation	Ethyl acetate was evaluated in *Saccharomyces cerevisiae* D61.M yeast cells. The cells were exposed to the test compound while culturing at 28°C for 4 h, then incubating in an ice bath for 17 h, and finally growing at 28°C again.	2.44%	+	NA	Ethyl acetate induced mitotic aneuploidy. There was no change in the frequency of point mutation or mitotic recombination.	Zimmermann et al. (1985)
Mitotic arrest	ND					

Table 4A. Summary of Ethyl Acetate Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in mammalian cells—in vitro						
Mutation	ND					
Chromosomal aberrations	Ethyl acetate was evaluated using a Chinese hamster fibroblast cell line. The cells were exposed to the test compound at three different doses for 24 and 48 h, with no metabolic activation.	9.0 mg/mL maximum	NA	+, 11% at 48 h (equivocal at 24 h)	D_{20} (calculated dose at which structural aberrations, including gaps, were detected in 20% of the metaphases observed) = 15.8; translocation (TR) value (indicates the frequency of cells with exchange-type aberrations per unit dose in mg/mL) = 0.3.	Ishidate et al. (1984)
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations	Ten male and female Chinese hamsters (number/sex not specified) were administered ethyl acetate in corn oil by intraperitoneal injection. The number of micronucleated erythrocytes was counted. An additional 10 animals were administered ethyl acetate by gavage, and the number of micronucleated erythrocytes was counted.	473 mg/kg intraperitoneal injection 2500 mg/kg gavage	−	NA	Ethyl acetate did not induce micronuclei in the bone marrow cells of treated hamsters by either route of administration.	Basler (1986)
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					

Table 4A. Summary of Ethyl Acetate Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	ND					
Genotoxicity studies in subcellular systems						
DNA binding	ND					

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive, ± = equivocal or weakly positive, − = negative, T = cytotoxicity, DU = data unsuitable, NA = not applicable, NV = not available, ND = no data, NDr = not determinable, NI = not identified, NP = not provided, NR = not reported, NR/Dr = not reported but determined from data, NS = not selected.

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Carcinogenicity—intraperitoneal (i.p.) administration	A/He mice were dosed i.p. with 24 doses of 150 or 750 mg/kg ethyl acetate in tricaprylin (3 doses/wk for 8 wk). Mice were killed 24 wk after the first injection. The lungs were removed, fixed, and examined grossly and microscopically; liver, kidney, spleen, thymus, intestine, salivary gland, and endocrine glands were examined grossly.	There was no increase in pulmonary tumors.	Ethyl acetate is not carcinogenic in this assay system.	Stoner et al. (1973)
Carcinogenicity—dermal application	Female CD-1 mice (n = 8) were exposed to ethyl acetate as solvent controls in an initiation/promotion carcinogenicity study. Mice were initiated by applying a single 0.2 mL dose of test compound to shaved dorsal skin. Four days later, mice were exposed to promoter chemicals twice weekly for 22 wk. In this case, ethyl acetate was applied in place of the initiator and the promoter.	Ethyl acetate-treated mice did not develop papillomas after 22 wk of treatment.	Ethyl acetate is not carcinogenic in this assay system.	Lindenfelser et al. (1974)
Metabolism/ toxicokinetic	In a metabolism study, male S-D rats were dosed with [^{14}C]-ethyl acetate to determine the rate of hydrolysis. Rats were given intravenous bolus doses of either 10 or 100 mg/kg; radiolabeled metabolites were measured in blood and brain samples from 30−540 seconds after dosing. An in vitro blood kinetic study was also performed.	Intravenously administered ethyl acetate was rapidly distributed and equilibrated and then very rapidly eliminated from blood and brain tissue, primarily by hydrolysis to ethanol and acetate. The in vitro blood hydrolysis proceeded at a significantly slower rate indicating that systemic organ carboxyesterase activity was predominant in the in vivo hydrolysis of ethyl acetate	Ethyl acetate is rapidly converted to ethanol and acetate following in vivo administration to rats.	Deisinger and English (1998)
Metabolism/ toxicokinetic	In a metabolism study, male S-D rats were used to determine the hydrolysis of ethyl acetate by whole blood in vitro, in vivo by rats injected intraperitoneally with ethyl acetate in corn oil, and in vivo by rats exposed to ethyl acetate by inhalation.	Whole blood hydrolyzed ethyl acetate with a half-life of 65−70 min, producing ethanol. Intraperitoneal injection of ethyl acetate resulted in high ethanol blood concentrations within 5 min. Animals exposed to over 2000 ppm ethyl acetate by inhalation steadily accumulated ethanol in the blood during exposure.	Ethyl acetate is hydrolyzed to ethanol more rapidly by in vivo exposure than in vitro.	Gallaher and Loomis (1975)

S-D = Sprague-Dawley.

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

The genotoxicity of ethyl acetate has been investigated in various studies including Ishidate et al. (1984a,b), Zimmermann et al. (1985), and Basler (1986). Ishidate et al. (1984) preincubated *Salmonella typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 with ethyl acetate in the presence of an S9 liver fraction from Fischer rats pretreated with a polychlorinated biphenyl mixture (Kanechlor KC-400). Ethyl acetate was not mutagenic up to a concentration of 5 mg/plate.

Zimmermann et al. (1985) investigated the induction of mitotic chromosomal malsegregation by ethyl acetate in *Saccharomyces cerevisiae* D61.M yeast cells. Efficient induction of aneuploid cells was only observed when growing cells were exposed to ethyl acetate during a growth period of 4 hours at 28°C followed by incubation in ice for 17 hours and then another growth period at 28°C for at least 1 hour. At an exposure concentration of 2.44% ethyl acetate, mitotic aneuploidy was observed, but the frequency of point mutation or mitotic recombination was not increased. The study authors suggested that the most likely target producing the malsegregation was the spindle apparatus.

Ishidate et al. (1984) evaluated the potential of ethyl acetate to induce chromosomal aberrations in a Chinese hamster fibroblast cell line using methodology typical of these assays. The cells were exposed to the test compound at three different doses for 24 and 48 hours, with no metabolic activation. At the maximum dose of 9.0 mg/mL, ethyl acetate was weakly genotoxic, with an 11% total incidence of cells with structural aberrations at 48 hours (equivocal at 24 hours). A positive result was designated by a value of 10% or above. The D_{20} (the calculated dose at which structural aberrations, including gaps, would be detected in 20% of the metaphases observed) was 15.8, while the translocation (TR) value (indicates the frequency of cells with exchange-type aberrations per unit dose in mg/mL) was 0.3. The study authors stated that TR values for chemicals that show carcinogenic potential in animals are relatively high; the value for ethyl acetate was low.

Basler (1986) investigated the genotoxic potential of ethyl acetate in Chinese hamsters. Animals were dosed with ethyl acetate in corn oil either by gavage at a dose level of 2500 mg/kg or by intraperitoneal injection at a dose level of 473 mg/kg. Micronucleus tests counting the number of micronucleated erythrocytes were negative for both routes of exposure.

Carcinogenicity—Intraperitoneal Administration

Stoner et al. (1973) administered ethyl acetate in purified tricaprylin by intraperitoneal injection to groups of male and female A/He mice (15/sex/dose group) at dose levels of either 150 or 750 mg/kg three times per week for 8 weeks. The study was terminated 24 weeks after the first injection. At necropsy, the liver, kidney, spleen, thymus, intestine, salivary gland, and endocrine glands were examined grossly for abnormalities, and suspicious tissues were examined microscopically. The lungs were removed and fixed in Tellyesniczky's fluid. After fixation, any nodules on the lung surface were counted, and some were examined microscopically. The lungs themselves were examined grossly and microscopically. One male and 2 females dosed at 150 mg/kg and 2 females dosed at 750 mg/kg died prior to study termination; these deaths were considered incidental to treatment. At 150 mg/kg, 1 male and 1 female were observed to have one lung tumor each; at 750 mg/kg, 4/15 males and 3/13 females were observed to have at least one lung tumor each (one of the males had two lung tumors). These results were not significantly different from untreated mice (in which incidence of mice with lung tumors was

22% in males and 17% in females); therefore, the study authors did not consider ethyl acetate to be a carcinogen under these study conditions.

Carcinogenicity—Dermal Application

Lindenfelser et al. (1974) treated eight female CD-1 mice with ethyl acetate by dermal application according to a standard initiation/promotion protocol, in which ethyl acetate was used as a solvent control. For initiation, a single administration of 0.2 mL of ethyl acetate was applied to shaved dorsal skin. After 4 days, the mice were treated twice weekly for 22 weeks; the number of papillomas were recorded weekly, and body weights were recorded every 2 weeks. None of the eight mice treated with ethyl acetate developed papillomas; therefore, the study author did not consider ethyl acetate to be a carcinogen under these study conditions.

Metabolism/Toxicokinetic Studies

Deisinger and English (1998) investigated the rate of hydrolysis of ethyl acetate both in vivo and in vitro. Groups of five male Sprague-Dawley rats were dosed with [^{14}C]-ethyl acetate (>99% chemical and radiochemical purity) in saline (3.75 mL/kg) at 10 or 100 mg/kg via a femoral vein cannula for an in vivo blood kinetics study. Serial blood samples were collected from a jugular vein cannula at eight time points ranging from 30−540 seconds postdosing and deproteinized. Groups of four male Sprague-Dawley rats were dosed with [^{14}C]-ethyl acetate in saline (3.75 mL/kg) at 100 mg/kg via a femoral vein cannula for an in vivo brain kinetics study. The rats were euthanized by exsanguination under CO_2 anesthesia at each of four time points from approximately 30−300 seconds postdosing, and the brain was excised, homogenized, and deproteinized. For both studies, concentrations of [^{14}C]-ethyl acetate, [^{14}C]-ethanol, [^{14}C]-acetaldehyde, and [^{14}C]-acetic acid in deproteinized blood and/or brain homogenates were determined by high-performance liquid chromatography (HPLC) using a radiochemical flow-through detector. Total [^{14}C] concentrations in whole and deproteinized blood and whole and deproteinized brain homogenates were determined by liquid scintillation counting (LSC). In an in vitro blood kinetics study, untreated Sprague-Dawley rat whole blood samples were spiked with [^{14}C]-ethyl acetate in saline at approximately the highest concentration (400 µg/g) seen in the blood after administration of the 100-mg/kg dose in the in vivo blood kinetics study. The spiked samples were incubated at 37°C, and aliquots were removed from 2−120 minutes after spiking. Concentrations of [^{14}C]-ethyl acetate, [^{14}C]-ethanol, and [^{14}C]-acetic acid in deproteinized and whole blood were determined by HPLC; total [^{14}C] concentrations in whole and deproteinized blood were determined by LSC. In the in vivo blood kinetics study, distribution and equilibration of the doses was rapid, followed by very rapid elimination of ethyl acetate. First-order elimination rate constants of 0.0208/second and 0.0188/second, and elimination half-lives of 33.4 seconds and 36.9 seconds were estimated for the 10 and 100 mg/kg doses, respectively. The similar rates indicated that the elimination pathway (carboxyesterase) was not saturated at 100 mg/kg. In the in vivo brain kinetics study, total brain [^{14}C] concentrations were approximately 75% of those seen in the blood following the 100-mg/kg dose. Ethyl acetate in the brain was rapidly hydrolyzed, with an elimination rate constant of 0.0285/second, and the resulting ethanol was rapidly eliminated. In the in vitro blood kinetics study, the estimated elimination rate constant was 0.0005/second, indicating that systemic organ carboxyesterase activity is the predominant pathway for in vivo hydrolysis of ethyl acetate.

Gallaher and Loomis (1975) investigated the hydrolysis of ethyl acetate both in vivo and in vitro using male Sprague-Dawley rats. For the in vitro analysis, an aqueous solution of ethyl acetate was mixed with whole blood to yield an initial concentration of 0.20 g/100 mL and then

incubated at 37°C for 5 hours. Aliquots were withdrawn at regular intervals, and ethyl acetate and ethanol concentrations were measured. Hydrolysis of ethyl acetate in whole blood produced ethanol, with a calculated half-life of 65−70 minutes. In a separate in vivo experiment, four rats were given intraperitoneal injections of a 25% solution of ethyl acetate in corn oil at a dose level of 1.6 mL/kg (calculated to produce an approximate blood concentration of 0.20 g/100 mL). Blood samples were obtained at regular intervals and analyzed as above. High concentrations of ethanol were detected in the blood within 5 minutes of dosing, while concentrations of ethyl acetate were low (<0.02 g/100 mL) for the first 20 minutes and undetectable thereafter (measurements were taken up to 5 hours after dosing). The half-life in vivo was estimated to be approximately 5−10 minutes. A third kinetic study examined ethyl acetate metabolism following inhalation exposure. Rats were exposed to ethyl acetate vapor via endotracheal tube at concentrations of 500−10,000 ppm. Blood samples were obtained at regular intervals and analyzed as above. Accumulation of ethanol occurred only when the rats were exposed to concentrations above 2000-ppm ethyl acetate. At 5000 ppm, there was a steady accumulation of ethanol in the blood throughout the exposure period, while at 10,000 ppm, ethanol accumulated more rapidly (to over 100 mg/100 mL 4−5 hours after dosing), resulting in severe respiratory depression. No appreciable accumulation of ethyl acetate was observed (<0.01 g/100 mL). The study authors concluded that because ethyl acetate is hydrolyzed to ethanol more rapidly in vivo than in vitro, it was doubtful that blood enzymes were solely responsible for the hydrolysis. Additionally, blood ethanol accumulation could be expected to occur in humans if the ambient concentration of inhaled ethyl acetate was high enough.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present a summary of noncancer and cancer reference values, respectively. IRIS data are indicated in the table, if available.

Table 5. Summary of Noncancer Reference Values for Ethyl Acetate (CASRN 141-78-6)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	$POD_{HED/HEC}$	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/M+F	Clinical signs, including increased salivation, irregular breathing, and lethargy in both sexes	7×10^{-1}	NOAEL	216	300	American Biogenics Corp. (1986)
Chronic RfD (mg/kg-d) IRIS (U.S. EPA, 1988)	Rat/M+F	Mortality and body-weight loss	9×10^{-1}	NOAEL	900 (unadjusted by IRIS)	1000	American Biogenics Corp. (1986)
Subchronic p-RfC (mg/m^3)	Rat/M+F	Decreased body weights, body-weight gains, food efficiency, and startle response (both sexes), and decreased food consumption (males)	7×10^{-1}	NOAEL	209	300	Christoph et al. (2003)
Chronic p-RfC (mg/m^3)	Rat/M+F	Decreased body weights, body-weight gains, food efficiency, and startle response (both sexes), and decreased food consumption (males)	7×10^{-2}	NOAEL	209	3000	Christoph et al. (2003)

Table 6. Summary of Cancer Values for Ethyl Acetate (CASRN 141-78-6)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	ND			
p-IUR	ND			

ND = no data.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The study by American Biogenics Corp. (1986) is selected as the principal study for the derivation of the subchronic p-RfD value. This is the only available study of subchronic duration by the oral route of exposure. The original study report was not obtainable; however, study summaries are available in both IRIS (U.S. EPA, 1988) and HEEP (U.S. EPA, 1986a). Although it could not be determined if this study was performed according to GLP regulations, this study did meet standards of design and performance with respect to inclusion of an adequate number of animals and examination of a variety of endpoints. Systemic parameters evaluated included mortality, morbidity, clinical signs of toxicity, body-weight gain, food consumption, hematology, clinical chemistry, urinalysis, ophthalmoscopic examinations, gross necropsy, organ weights, and histological examinations. This study was selected for development of an RfD by IRIS (U.S. EPA, 1988) and is deemed adequate for development of a subchronic p-RfD.

As detailed in the section "Review of Potentially Relevant Data," clinical signs, including increased salivation, irregular breathing, and lethargy, in rats of both sexes occurred at the highest dose level of 3600 mg/kg-day. Tabular data could not be obtained, and standard deviations were not provided; therefore, benchmark dose (BMD) modeling was not possible, and the POD is selected using the NOAEL/LOAEL method. The POD selected is a NOAEL of 900 mg/kg-day based on the above-mentioned clinical signs at a LOAEL of 3600 mg/kg-day. No dosimetric adjustment was necessary because this was a continuous exposure.

In EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite but not for portal-of-entry effects or developmental endpoints.

A validated human physiologically based pharmacokinetic (PBPK) model for ethyl acetate is not available for use in extrapolating doses from animals to humans. The selected critical effect of clinical signs, including increased salivation, irregular breathing, and lethargy (in both sexes) was associated with the parent compound or a stable metabolite. Furthermore, these aforementioned clinical signs are not portal-of-entry or developmental effects. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for these effects.

Following U.S. EPA (2011b) guidance, the POD for clinical signs in adult animals is converted to an HED through application of a dosimetric adjustment factor (DAF)[1] derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a BW_a of 0.25 kg for rats and a BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.24. Applying this DAF to the NOAEL identified for the critical effect in mature rats yields a $NOAEL_{HED}$ as follows:

$$\begin{aligned} NOAEL_{HED} &= \text{NOAEL (mg/kg-day)} \times DAF \\ &= 900 \text{ (mg/kg-day)} \times 0.24 \\ &= 216 \text{ mg/kg-day} \end{aligned}$$

The subchronic p-RfD for ethyl acetate, based on the $NOAEL_{HED}$ of 216 mg/kg-day for clinical signs, including salivation, irregular breathing, and lethargy, in male and female Sprague-Dawley rats (American Biogenics Corp., 1986), is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \mathbf{NOAEL_{HED} \div UF_C} \\ &= 216 \text{ mg/kg-day} \div 300 \\ &= \mathbf{7 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

[1]As described in detail in *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011), rate-related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and allometric scaling ($BW^{3/4}$) aspects such that $BW^{3/4} \div BW^{1/1} = BW^{-1/4}$, converted to a $DAF = BW_a^{1/4} \div BW_h^{1/4}$.

Tables 7 and 8, respectively, summarize the UFs and the confidence descriptors for the subchronic p-RfD for ethyl acetate.

Table 7. Uncertainty Factors for Subchronic p-RfD of Ethyl Acetate

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) has been applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following oral ethyl acetate exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011).
UF_D	10	A UF_D of 10 has been applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of ethyl acetate in humans.
UF_L	1	A UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 has been applied because a subchronic-duration study was selected as the principal study.
UF_C	300	

The confidence of the subchronic p-RfD for ethyl acetate is low, as explained in Table 8.

Table 8. Confidence Descriptors for Subchronic p-RfD for Ethyl Acetate

Confidence Categories	Designation[a]	Discussion
Confidence in study	L	The study is given low confidence. It was well designed and well conducted, and several appropriate parameters were evaluated; however, the original study could not be obtained for review, limiting interpretation.
Confidence in database	L	The database is given a low confidence because there are no additional subchronic-duration studies, and no developmental or reproductive studies are available.
Confidence in subchronic p-RfD[b]	L	The overall confidence in the subchronic p-RfD is low because there are no oral developmental or reproductive toxicity studies available, and there are no studies in a second species.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

Derivation of Chronic RfD (Chronic RfD)

A chronic RfD of 9×10^{-1} mg/kg-day is available in IRIS (U.S. EPA, 1988), based on an oral subchronic-duration study in the rat (American Biogenics Corp., 1986). This chronic RfD was derived based on a NOAEL of 900 mg/kg-day for mortality and body-weight loss in rats and included a UF_C of 1000. The IRIS database should be checked to determine if any changes have been made.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

The Christoph et al. (2003) study is selected as the critical study for the derivation of a subchronic p-RfC. This study is published and peer-reviewed. It was limited in scope to examination of body weights, food and water consumption, behavioral endpoints, and neuropathology, and did not examine other endpoints. Christoph et al. also examined operant behavior in male rats exposed by inhalation to ethyl acetate but found no association between subchronic whole-body exposure and alterations in operant behavior (Christoph, 1997; Christoph et al., 2003). There was only one other subchronic-duration study identified (Smyth and Smyth, 1928) and it did not provide sufficient information to determine the average daily dose administered and is, therefore, not suitable for derivation of toxicity values. The database also contains one short-term (2-week) study (Burleigh-Flayer et al., 1995), which, although not of sufficient duration to support derivation of a subchronic p-RfC, was more comprehensive than the study by Christoph et al. (2003) and provides support for the findings in that study.

As detailed in the section "Review of Potentially Relevant Data," statistically significant changes in the study by Christoph et al. (2003) included decreased body weights, body-weight gains, food efficiency, and startle response in both sexes, and decreased food consumption in the males at 448 mg/m^3 and above. This decreased food consumption is not thought to be related to palatability as dosing was performed by inhalation, but may be a result of irritation; however, appropriate tissues were not examined to verify this. In support of these findings, the most sensitive effect in a 2-week inhalation study (Burleigh-Flayer et al., 1995) was decreased food consumption, with decreased motor activity also observed at higher doses. Tabular data could not be obtained for the effects at the LOAEL in the Christoph et al. (2003) study, and standard deviations were not provided; therefore, BMD modeling was not possible, and the POD was selected using the NOAEL/LOAEL method. The POD selected is a $NOAEL_{HEC}$ of 209 mg/m^3 for changes including decreased body weights, body-weight gains, food efficiency, and startle response in both sexes and decreased food consumption in males occurring at a $LOAEL_{HEC}$ of 448 mg/m^3.

The metabolism study by Gallaher and Loomis (1975) demonstrated that Sprague-Dawley rats inhaling ethyl acetate vapors rapidly hydrolyzed the test compound to ethanol, and that ethyl acetate concentrations of 5000 ppm caused an accumulation of ethanol in the blood. As humans appear to hydrolyze ethyl acetate in a similar fashion (Coopman et al., 2005), ethyl acetate is considered a Category 3 gas and, thus, has effects peripheral to the respiratory system (U.S. EPA, 2009). Because Category 3 gases cause extrarespiratory effects, the concentrations in the study were converted to adjusted doses (to account for continuous exposure) and then to HEC concentrations utilizing a default blood:air partition coefficient of 1 because the actual value is unknown.

The following dosimetric adjustments were made for all inhalation exposure doses in adjusting for continuous exposure and then HECs. As described in the "Review of Potentially Relevant Data" section, this study dosed for 6 hours/day on an interrupted schedule, resulting in 65 doses applied over 13 to 14 weeks. The dosimetric adjustments for continuous exposure were performed with the assumption that 65 doses were applied over 14 weeks. The dosimetric adjustment for 350 ppm is presented below.

1) Exposure concentration adjustment for continuous exposure

$$\begin{aligned} \mathbf{CONC_{ADJ}} &= \mathbf{CONC \times (molecular\ weight \div 24.45) \times} \\ &\quad \mathbf{(hours\ exposed \div 24\ hours) \times (days\ exposed \div 98\ days)} \\ &= 350\ \text{ppm} \times (88.11\ \text{g/mol} \div 24.45) \times (6\ \text{h} \div 24\ \text{h}) \times (65\ \text{d} \div 98\ \text{d}) \\ &= 350 \times 3.60 \times 0.25 \times 0.66 \\ &= \mathbf{209\ mg/m^3} \end{aligned}$$

2) HEC conversion

$$\begin{aligned} \mathbf{CONC_{HEC}} &= \mathbf{CONC_{ADJ} \times Blood{:}Air\ Partition\ Coefficient} \\ &= 209\ \text{mg/m}^3 \times 1 \\ &= 209\ \text{mg/m}^3 \end{aligned}$$

The subchronic p-RfC for ethyl acetate, based on the rat $NOAEL_{HEC}$, is derived as follows:

$$\begin{aligned} \mathbf{Subchronic\ p\text{-}RfC} &= \mathbf{NOAEL_{HEC} \div UF_C} \\ &= 209\ \text{mg/m}^3 \div 300 \\ &= \mathbf{7 \times 10^{-1}\ mg/m^3} \end{aligned}$$

Table 9 summarizes the UFs for the subchronic p-RfC for ethyl acetate.

Table 9. Uncertainty Factors for Subchronic p-RfC of Ethyl Acetate		
UF	**Value**	**Justification**
UF_A	3	A UF_A of 3 ($10^{0.5}$) has been applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following inhalation exposure to ethyl acetate. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent concentration (HEC) as described in the RfC methodology (U.S. EPA, 1994b).
UF_D	10	A UF_D of 10 has been applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of ethyl acetate in humans.
UF_L	1	A UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 has been applied because a subchronic-duration study was selected as the principal study.
UF_C	300	

The confidence in the subchronic p-RfC for ethyl acetate is low, as explained in Table 10 below.

Table 10. Confidence Descriptors for Subchronic p-RfC for Ethyl Acetate		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in study	L	The study is given low confidence. It was well designed and well conducted; however, it was not comprehensive and only examined neurological effects, body weight, and food and water intake.
Confidence in database	L	The database is given a low confidence because no developmental or reproductive studies are available.
Confidence in subchronic p-RfC[b]	L	The overall confidence in the subchronic p-RfC is low because no inhalation developmental or reproductive toxicity studies are available and because the critical study only examined one organ system.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

The Christoph et al. (2003) study is selected as the critical study for the derivation of a chronic p-RfC. There are no available studies of chronic duration by the inhalation route of exposure. As discussed above in the "Derivation of a Subchronic Provisional RfC (Subchronic p-RfC)" section, the study by Christoph et al. (2003) is the only suitable study of subchronic

duration by the inhalation route of exposure. It is supported by a short-term (2 week) study by Burleigh-Flayer et al. (1995).

The POD selected is a $NOAEL_{HEC}$ of 209 mg/m^3 for changes including decreased body weights, body-weight gains, food efficiency, and startle response in both sexes, and decreased food consumption in males occurring at the $LOAEL_{HEC}$ of 448 mg/m^3. Further discussion of the selection of this critical effect is provided in the "Derivation of a Subchronic Provisional RfC (Subchronic p-RfC)" section.

As previously stated, ethyl acetate is considered a Category 3 gas and, thus, has effects peripheral to the respiratory system (U.S. EPA, 2009). Because Category 3 gases cause extrarespiratory effects, the concentrations in the study were converted to adjusted doses (to account for continuous exposure) and then to HEC concentrations utilizing a default blood:air partition coefficient of 1 because the actual value is unknown.

Identically to that presented above for derivation of the subchronic p-RfC, the following dosimetric adjustments were made for all inhalation exposure doses in adjusting for continuous exposure and then HECs.

1) Exposure concentration adjustment for continuous exposure

$$\begin{aligned} \mathbf{CONC_{ADJ}} &= \mathbf{CONC \times (molecular\ weight \div 24.45) \times} \\ &\quad \mathbf{(hours\ exposed \div 24\ hours) \times (days\ exposed \div 98\ days)} \\ &= 350\ \text{ppm} \times (88.11\ \text{g/mol} \div 24.45) \times (6\ \text{h} \div 24\ \text{h}) \times (65\ \text{d} \div 98\ \text{d}) \\ &= 350 \times 3.60 \times 0.25 \times 0.66 \\ &= \mathbf{209\ mg/m^3} \end{aligned}$$

2) HEC conversion

$$\begin{aligned} \mathbf{CONC_{HEC}} &= \mathbf{CONC_{ADJ} \times Blood{:}Air\ Partition\ Coefficient} \\ &= 209\ \text{mg/m}^3 \times 1 \\ &= 209\ \text{mg/m}^3 \end{aligned}$$

The chronic p-RfC for ethyl acetate, based on the rat $NOAEL_{HEC}$, is derived as follows:

$$\begin{aligned} \mathbf{Chronic\ p\text{-}RfC} &= \mathbf{NOAEL_{HEC} \div UF_C} \\ &= 209\ \text{mg/m}^3 \div 3000 \\ &= \mathbf{7 \times 10^{-2}\ mg/m^3} \end{aligned}$$

Table 11 summarizes the UFs for the chronic p-RfC for ethyl acetate.

Table 11. Uncertainty Factors for Chronic p-RfC of Ethyl Acetate

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) has been applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following inhalation exposure to ethyl acetate. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent concentration (HEC) as described in the RfC methodology (U.S. EPA, 1994b).
UF_D	10	A UF_D of 10 has been applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of ethyl acetate in humans.
UF_L	1	A UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	10	A UF_S of 10 has been applied because a subchronic-duration study was selected as the principal study.
UF_C	3000	

The confidence in the chronic p-RfC for ethyl acetate is low, as explained in Table 12 below.

Table 12. Confidence Descriptors for Chronic p-RfC for Ethyl Acetate

Confidence Categories	Designation[a]	Discussion
Confidence in study	L	The study is given low confidence. It was well designed and well conducted; however it was not comprehensive and only examined neurological effects, body weight, and food and water intake.
Confidence in database	L	The database is given a low confidence because no developmental or reproductive studies are available.
Confidence in chronic p-RfC[b]	L	The overall confidence in the chronic p-RfC is low because no inhalation chronic, developmental, or reproductive toxicity studies are available and because the critical study only examined one organ system.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 13 identifies the cancer WOE descriptor for ethyl acetate. No carcinogenicity studies in animals by the oral or inhalation routes have been found. The carcinogenicity of ethyl acetate was investigated in a mouse dermal application study (Lindenfelser et al., 1974) and in a mouse pulmonary tumor study (Stoner et al., 1973) using intraperitoneal injection as the route of exposure. No evidence of carcinogenic potential was observed in either of these studies; however, these studies were not by the inhalation or oral route of administration, and animals were not treated for the majority of their life spans. These studies do not provide sufficient data to designate a cancer WOE descriptor other than "*Inadequate Information to Assess Carcinogenic Potential*."

Table 13. Cancer WOE Descriptor for Ethyl Acetate

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NA	NA	No human cancer studies are available.
"Likely to Be Carcinogenic to Humans"	NA	NA	No animal cancer studies are available.
"Suggestive Evidence of Carcinogenic Potential"	NA	NA	There are no data available to suggest that there is a carcinogenic potential.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**There is not adequate information available to assess carcinogenic potential.**
"Not Likely to Be Carcinogenic to Humans"	NA	NA	No strong evidence of noncarcinogenicity in humans is available

NA = not applicable.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

No human or animal studies evaluating the carcinogenicity of ethyl acetate following oral exposure have been located. Therefore, derivation of a p-OSF is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No human or animal studies examining the carcinogenicity of ethyl acetate following inhalation exposure have been located. Therefore, derivation of a p-IUR is precluded.

APPENDIX A. PROVISIONAL SCREENING VALUES

There are no provisional screening values for ethyl acetate.

APPENDIX B. DATA TABLES

Table B.1. Estimated Body Weight[a] (g) of Sprague-Dawley Rats Exposed to Ethyl Acetate by Inhalation for 13−14 Weeks and Then Allowed to Recover for 4 Weeks

Day	0 ppm		350 ppm (209 mg/m^3)		750 ppm (448 mg/m^3)		1500 ppm (896 mg/m^3)	
	Male	Female	Male	Female	Male	Female	Male	Female
2	303	192	296	192	296	187	287	192
5	323	201	316	196	309	192	298	196
9	348	212	339	208	330	203	318	205
12	366	219	359	215	345	208	327	212
19	404	235	391	228	382	221	361	224
26	431	242	415	230	406	228	384	233
33	458	253	440	239	429	235	404	242
40	479	262	458	248	447	242	420	244
47	497	266	476	251	465	246	438	247
54	517	271	492	257	481	251	454	255
61	531	278	508	262	490	253	463	260
68	546	282	519	266	504	260	474	264
75	555	289	528	271	510	262	481	264
82	574	291	540	278	526	266	492	266
89	585	296	549	278	535	269	501	269
96	592	300	555	287	544	271	506	269
103	614	298	NM[b]	NM	NM	NM	517	273
110	628	300	NM	NM	NM	NM	544	278
117	639	303	NM	NM	NM	NM	558	289
124	646	305	NM	NM	NM	NM	562	294

[a]Body weights are estimated based on digitization of Figure 1 from Christoph et al. (2003).
[b]NM = not measured. Body weights after exposures ended (week 96) were only measured in the 0- and 1500-ppm exposure groups.

APPENDIX C. BMD OUTPUTS

There are no BMD modeling outputs for ethyl acetate.

APPENDIX D. REFERENCES

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