United States Environmental Protection Agency

EPA/690/R-11/002F
Final
06-15-2011

Provisional Peer-Reviewed Toxicity Values for

Acetophenone
(CASRN 98-86-2)

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

Harlal Choudhury, DVM, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

ICF International
9300 Lee Highway
Fairfax, VA 22031

PRIMARY INTERNAL REVIEWERS

Ambuja Bale, PhD, DABT
National Center for Environmental Assessment, Washington, DC

Martin W. Gehlhaus, III, MHS
National Center for Environmental Assessment, Washington, DC

Geniece M. Lehmann, PhD
National Center for Environmental Assessment, Research Triangle Park, NC

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).

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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
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
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 ACETOPHENONE (CASRN 98-86-2)

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

Acetophenone is made from benzene and acetylchoride in the presence of aluminum chloride or catalytically from acetic and benzoic acids (ACGIH, 2001). It is used in perfume to yield an orange blossom-like odor (ACGIH, 2001) and as a food flavoring agent (WHO, 2001). The empirical formula for acetophenone is C_8H_8O (see Figure 1). A table of physicochemical properties is provided below (see Table 1). In this document, "statistically significant" denotes a *p*-value of <0.05.

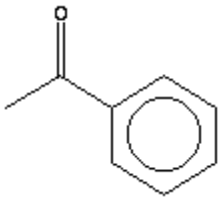

Figure 1. Acetophenone Structure

Table 1. Physicochemical Properties Table for Acetophenone (CASRN 98-86-2)[a]

Property (unit)	Value
Boiling point (ºC)	201.7
Melting point (ºC)	20.5
Density (g/cm^3)	1.0296
Vapor pressure (mm Hg at 25ºC)	0.372
pH (unitless)	Not available
Solubility in water (g/L at 25ºC)	5.5
Relative vapor density (air = 1)	4.1
Molecular weight (g/mol)	120.15
Flash point (°C)	82 (closed cup); 93 (open cup)
Octanol/water partition coefficient (unitless)	1.58

[a]Values from ACGIH (2001) and EPA (1987).

No reference dose (RfD), reference concentration (RfC), or cancer assessment for acetophenone is included on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). IRIS (U.S. EPA, 1989) reports an RfD for acetophenone of 0.1 mg/kg-day based on general toxicity from a subchronic-duration rat toxicity study but does not report an RfC. No RfC is reported in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2010), but a subchronic RfD of 1 mg/kg-day, based on the same subchronic-duration rat study used in the IRIS assessment, is reported. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) does not include a Health and Environmental Effects Profile (HEEP) for acetophenone (U.S. EPA, 2009). The toxicity of acetophenone has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2011). The World

Health Organization (WHO) evaluated the toxicity of acetophenone and determined that there was no safety concern (WHO, 2001), estimating a daily intake of 170 µg/day or 3 µg/kg-day. CalEPA (2008) has not derived toxicity values for exposure to acetophenone. An occupational exposure limit (TLV-TWA) of 10 ppm for acetophenone was derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2001), but no occupational exposure limit has been developed by the National Institute of Occupational Safety and Health (NIOSH, 2009) or the Occupational Safety and Health Administration (OSHA, 2009).

IRIS (U.S. EPA, 1989) reported an EPA (1986) cancer weight-of-evidence classification of Group D (*Not Classifiable as to Human Carcinogenicity*) for acetophenone based on the lack of carcinogenicity studies in humans or animals. The International Agency for Research on Cancer (IARC, 2009) has not reviewed the carcinogenic potential of acetophenone nor was acetophenone included in the National Toxicology Program's *11th Report on Carcinogens* (NTP, 2005). CalEPA (2008) has not prepared a quantitative estimate for the carcinogenic potential of acetophenone.

Literature searches were conducted on sources published from 1900 through February 3, 2011. for studies relevant to the derivation of provisional toxicity values for acetophenone, CAS No. 98-86-2. Searches were conducted using 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, Multidatabase 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 risk assessment values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides information for all of the potentially relevant acute, subchronic, and chronic toxicity studies. NOAELs, LOAELs, and BMDL/BMCLs are provided in HED/HEC units for comparison except that oral noncancer values are not converted to HEDs and are identified in parentheses as (adjusted) rather than HED/HECs. Entries for the principal studies are bolded and identified by the marking "PS." Following the table, important aspects of all the

studies in the table are provided in the same order as the table. The phrase "statistical significance", used throughout the document, indicates a *p*-value of <0.05.

Table 2. Summary of Potentially Relevant Data for Acetophenone (CASRN 98-86-2)

Notes[a]	Category	Number of Male/Female, Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
Human								
				1. Oral (mg/kg-d)[b]				
	Subchronic	Not reported	1.4−8.6	Weaker and slower pulse rate, increased frequency of urination, and a slight, transient decrease in hemoglobin levels	4.3	NA	6.4	BIBRA (1991)
	Chronic	None						
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						
				2. Inhalation (mg/m^3)[b]				
	Acute	Number and sex were not reported, acute, single exposure	Not reported	Malaise, headache, stomach pain, dizziness, and sleepiness	None	NA	None	BIBRA (1991)
		3 odor-sensitive volunteers, no other details provided	0.007−0.02	Decreased eye-sensitivity to light	0.007	NA	0.01	Imasheva (1966)
		5 normal volunteers, sex not reported, inhalation, 40−50 min	0.003 or 0.007	Decreased energy assimilation in the brain as measured by electrical brain activity	0.003	NA	0.007	Imasheva (1966)
	Subchronic	None						
	Chronic	None						
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						

Table 2. Summary of Potentially Relevant Data for Acetophenone (CASRN 98-86-2)

Notes[a]	Category	Number of Male/Female, Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
Animal								
			1. Oral (mg/kg-d)[b]					
IRIS (1989)	**Subchronic**	**10/10, Osborne-Mendel rat, diet, 7 d/wk, 17 wks**	**0, 42, 106, or 423 (adjusted)[d]**	**No critical effect**	**423**	**NA**	**None**	**Hagan et al. (1967)**
PS, NPR		**10/5, Sprague-Dawley rat, gavage, 7 d/wk, 33 d in males and 34 d in females**	**0, 75, 225, or 750 (adjusted)**	**Neurological: decreased mean forelimb grip strength and motor activity** **Systemic: pre and postsalivation; increased liver and kidney weight in females**	**225** **75**	NA	**750** **225**	**ATF (2003)**
	Chronic	None						
PS, NPR	**Developmental**	**10/10, Sprague-Dawley rat, gavage, 7 d/wk, Gestational Day (GD) 0 to Lactation Day (LD) 4 (dams and offspring)**	**0, 75, 225, or 750 (adjusted)**	**Decreased pup survival and pup body weight during lactation**	**225**	**NA**	**750**	**ATF (2003)**
PS, NPR	**Reproductive**	**10/10, Sprague-Dawley rat, gavage, 7 d/wk, 28−42 d beginning 14 d prior to mating**	**0, 75, 225, or 750 (adjusted)**	**Decreased live birth index**	**225**	**NA**	**750**	**ATF (2003)**
	Carcinogenic	None						
			2. Inhalation (mg/m^3)[b]					
	Subchronic	15 males, white rat, inhalation, continuous, 70 d	0.007 or 0.076[e]	Changes in muscle antagonist, decreased cholinesterase activity, increased incidence of cardiovascular plethora, and acute liver dystrophy	0.007	NA	0.076	Imasheva (1966)
		4 (sex not specified), Wistar rat, inhalation, continuous, 1 or 5 wk or 2 mo	1.2[f]	Degeneration of mitral cells in the olfactory bulb	None	NA	1.2	Pinching and Døving (1974)

Table 2. Summary of Potentially Relevant Data for Acetophenone (CASRN 98-86-2)

Notes[a]	Category	Number of Male/Female, Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
		6−12 males, Wistar rat, inhalation, continuous, 33−230 d	0.04 or 2.2[g]	Histopathological changes of the olfactory bulb	None	NA	0.04	Dalland and Døving (1981)
	Chronic	None						
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						

[a]Notes: IRIS = Utilized by IRIS, date of last update; PS = Principal study, NPR = Not peer reviewed.

[b]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to human equivalent dose (HED in mg/kg-day) or human equivalent concentration (HEC in mg/m^3) units. All exposure values of long-term exposure (4 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values for inhalation (cancer and noncancer) and oral (cancer only) are further converted to an HEC/D. Values from animal developmental studies are not adjusted to a continuous exposure.

[c]Not reported by the study author but determined from data.

[d]The adjusted daily doses were calculated by EPA (1989) as follows: 10,000 ppm × 0.845, based on 15.5% volatilization = 8450 ppm; assuming a rat consumed 5% of its body weight, 8450 ppm (mg/kg food) × 0.05 kg food/kg body weight/day = 423 mg/kg-day.

[e]HEC_{EXRESP} was calculated as follows: dose × hours treated ÷ 24 hours × days treated ÷ 7 days × ratio of blood/gas partition coefficient = $0.007\ mg/m^3 \times 24 \div 24 \times 7 \div 7 \times 1 = 0.007\ mg/m^3$.

[f]HEC_{RESP} was calculated as follows: 7.4×10^{-8} moles/L × 120.15 g/mole × 1000 mg/g × 1000 $L/m^3 = 8.9\ mg/m^3 \times 24 \div 24 \times 7 \div 7 \times$ Regional Gas Deposition Ratio (RGDR) of 0.136 = $1.2\ mg/m^3$.

[g]HEC_{RESP} was calculated as follows: 2.0×10^{-9} moles/L × 120.15 g/mole × 1000 mg/g × 1000 $L/m^3 = 0.24\ mg/m^3 \times 24 \div 24 \times 7 \div 7 \times$ RGDR of 0.154 = $0.04\ mg/m^3$.

HUMAN STUDIES

Oral Exposure

No studies investigating the effects of subchronic or chronic-duration oral exposure to acetophenone in humans were identified. BIBRA (1991) provides details on a study by Mairet and Combemale (1886), which was published in a foreign language and reported no clinical effects with oral doses of 100−300 mg/day (stated to be equivalent to 1.4−4.3 mg/kg-day) for an unspecified amount of time in healthy subjects. Healthy subjects exposed to doses of 450 to 600 mg/day (equivalent to 6.4−8.6 mg/kg-day) had weaker and slower pulse rates, increased frequency of urination, and slight, transient decreases in hemoglobin levels. The compound, reportedly used as an anticonvulsant and hypnotic, was apparently being tested for therapeutic use. The authors reported that the doses of acetophenone in mentally abnormal or epileptic patients did not cause muscular excitement, although there was some evidence of a tranquilizing effect, and some patients complained of a burning sensation in the stomach.

Inhalation Exposure

Little information is available regarding inhalation exposure to acetophenone in humans. Malaise, headache, stomach pain, dizziness, and sleepiness have been reported after a single exposure to an unspecified amount of vapor (BIBRA, 1991). The original source of this information (Laborde, 1885) was unavailable for review. Imasheva (1966), translation provided by Levine (BIBRA, 1991), reported an odor perception threshold of 0.01 mg/m^3 in 18 "odor-sensitive" volunteers. Acetophenone-induced "eye sensitivity" (not further defined or explained) to light was tested in 3 of the 18 volunteers. All three volunteers reported a decrease in eye sensitivity to light when exposed to 0.015-mg/m^3 acetophenone—but to a lesser degree than when exposed to 0.02 mg/m^3. At 0.01-mg/m^3 acetophenone, one of the three volunteers reported a decreased sensitivity to light; no changes were observed at 0.007 mg/m^3. Imasheva (1966) also tested the electrical brain activity of five presumably normal volunteers (18−35 years old) during a 40−50-minute test. A lowering (35−40%) in the total amount of energy assimilated by the brain (stated as statistically reliable by the study authors) was noted in all volunteers between Minutes 2 and 6 of exposure to 0.007-mg/m^3 acetophenone, but there were no recordable changes at 0.003 mg/m^3.

ANIMAL STUDIES

Oral Exposure

The effects of oral exposure of animals to acetophenone have been evaluated in two subchronic-duration (Hagan et al., 1967) studies and a reproductive/developmental screening (ATF, 2003) toxicity study. There are currently no chronic-duration oral studies with acetophenone in animals. The subchronic-duration study and reproductive/developmental screening study was a single study performed concurrently but conducted in two parts and reported as proprietary data (ATF, 2003). Because the reproductive/developmental screening study is a single study and is not written up as separate components, it will only be referenced as a single study (i.e., ATF, 2003).

Subchronic-duration Studies

Male and female (10/sex/dose) Osborne-Mendel rats (husbandry not reported) were administered 0-, 1000-, 2500-, or 10,000-ppm acetophenone (purity not reported) daily via the diet for 17 weeks (Hagan et al., 1967). These doses correspond to adjusted daily doses (ADDs) of 0, 42, 106, or 423 mg/kg-day (as calculated by U.S. EPA, 1989). The study does not provide

details on the controls (i.e., untreated or concurrent vehicle). Diets were prepared weekly, but it was determined that 31% of the test compound was lost from the diet during the 7 days. This loss could be attributed to volatility (15.5%) and stability of the compound at room temperature (U.S. EPA, 1989). Body weight, food consumption, and general condition were evaluated weekly. Hematology (including white blood cells [WBCs], erythrocyte counts, hematocrit, and hemoglobin) was measured at study termination. At termination, animals were sacrificed, grossly examined, and organs were weighed (including liver, kidneys, spleen, heart, and testes). These same organs, as well as abdominal and thoracic viscera and one hind leg (to provide bone, bone marrow, and muscle), were preserved for histopathological examination from three or four rats per sex from the control and high-dose groups. No treatment-related effects were observed. There is no GLP (Good Laboratory Practice) statement provided. The authors did not provide a NOAEL. However, IRIS provides a NOAEL of 423 mg/kg-day (U.S. EPA, 1989). This NOAEL is the highest dose tested in the study at which no effects were observed (Hagan et al., 1967).

The study by ATF (2003) is selected as the principal study for deriving the screening subchronic p-RfD. The ATF (2003) study was provided as a proprietary study with only the text available for review (no data summary tables were available). The study was stated to be a repeated dose toxicity test combined with a reproductive/developmental screening test conducted according to the Organization for Economic Co-operation and Development (OECD) Guideline No. 422 and was GLP compliant. Acetophenone (98.8% pure) was administered daily via gavage at adjusted doses of 0, 75, 225, or 750 mg/kg-day in corn oil to male and female Sprague-Dawley rats from Charles River Laboratories, Inc. in Raleigh, North Carolina (10 male and 5 female rats/treatment group for the repeated dose toxicity portion of the test). Dose formulations were tested for homogeneity, stability, and analytical concentration. All were found to be within acceptable ranges, and the dose formulation was determined to be stable for at least 10 days at room temperature. All rats were treated for a minimum of 28 days during the toxicity phase. Males from the toxicity phase were mated with females in the reproduction phase. Animals were checked twice per day for mortality and general health. Cage-side observations for clinical signs of toxicity were conducted daily within 2 hours of dosing. Detailed clinical observations were conducted weekly. An abbreviated functional observational battery (FOB) test (including home cage observation, removal from home cage observation, open field observation, manipulative tests, and motor activity assessments) was conducted weekly. Body weight and food consumption were measured every 3−5 days. Blood was collected from five animals/sex/treatment and hematology (including erythrocyte count, hematocrit, hemoglobin, mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], mean corpuscular volume [MCV], platelet count, total and differential WBC count, prothrombin time, and activated partial prothrombin time) and clinical chemistry (including alanine aminotransferase [ALT], albumin, globulin, albumin/globulin ratio, alkaline phosphatase, aspartate aminotransferase [AST], calcium, cholesterol, creatinine, glucose, sodium, potassium, chloride, phosphorus, total bilirubin, total serum protein, triglycerides, and urea nitrogen) tests were performed. All animals were necropsied at sacrifice. The adrenals, epididymides, brain, heart, kidneys, liver, spleen, testes, and thymus were weighed. All OECD guideline-recommended tissues/organs were processed for histopathology in five animals/sex/treatment group. The study authors used appropriate statistical analyses including one-way analysis of variance (ANOVA), Tukey-Kramer test, Fisher's exact test,

Levene's test for homogeneity of variance, Kruskal Wallis nonparametric ANOVA followed by Dunn's test, and Chi-square test followed by Fischer's exact test.

No mortality occurred in this study (ATF, 2003). Clinical signs included pre and postdose salivation in the mid- and high-dose groups and postdose wobbly gait and urine staining (low incidence) in the high-dose group. Some high-dose females also exhibited hair loss. High-dose animals had a statistically significant mean lower body weight and food consumption compared with the controls early in the study, but it appeared to rebound in the second half of the study. However, the mean body weights of the high-dose males were 5−10% lower than the controls from Treatment Days 3−30. High-dose males had a statistically significant decrease in mean forelimb grip strength and motor activity on Day 29. There were no treatment-related effects on hematology. Clinical chemistry data indicated a statistically significant increase in the cholesterol levels of high-dose males and females (750 mg/kg-day) and increased total protein and calcium levels in high-dose males. Although the biological significance of this is not clear, the study authors stated that these numbers were outside the historical control range observed in the test laboratory. Values in the 225-mg/kg-day group were within the historical control range even if they were statistically different from the controls; however, there appeared to be a dose-related increase in total protein, albumin, and globulin that appeared to be related to increased liver weights. There were no abnormal findings at necropsy. There was a statistically significant increase in the relative liver weight in high-dose males compared with the control. In females, there was a statistically significant increase in absolute and relative liver weight and relative kidney weight in the mid- and high-dose groups. Mild-to-moderate hyaline droplet nephropathy was observed in all of the male treatment groups. The results were not dose related and were not considered toxicologically relevant to humans. There were no other histopathological changes related to treatment. The systemic NOAEL was stated to be 75 mg/kg-day, with a neurological NOAEL of 225 mg/kg-day. The study authors did not report a LOAEL, but a LOAEL of 225 mg/kg-day can be derived for systemic effects, based on pre and postdose salivation, and increases in liver and kidney weight in females. The neurological LOAEL is 750 mg/kg-day, based on decreased mean forelimb grip strength and motor activity in male rats.

Chronic-duration Studies

No chronic-duration oral studies with acetophenone are available.

Developmental and Reproduction Studies

For the reproductive/developmental phase of the ATF (2003) study, male and female rats were treated for a minimum of 14 days before mating, and female rats were treated through Lactation Day (LD) 3. Males from the toxicity phase were mated with females in the reproduction phase. The F0 generation was checked twice per day for mortality and general health. Cage-side observations were conducted once per day within 2 hours of dosing. Detailed clinical observations were conducted at least weekly until evidence of mating, and then females were checked daily through gestation and lactation. Males were processed as part of the repeated dose toxicity study detailed above. Body weights of the F0 females were measured on Days 0, 3, 7, and 12 prior to mating. After evidence of mating was detected, females were weighed on Gestational Days (GDs) 0, 7, 14, and 20 and on LDs 1 and 4. Food consumption was measured on the same days as the body weight. After at least 14 days of treatment, a single male was cohabitated with a single female for a maximum of 14 days. Mating was considered to have

occurred if the presence of a sperm-positive vaginal smear or copulary plug was detected. The day copulation was detected was designated as GD 0, and the female was returned to its cage. Females were observed for abnormal nesting, parturition, and nursing behaviors. Females with no evidence of mating were sacrificed 19 days after mating began, females that failed to deliver were sacrificed on GD 25, and F0 females and their offspring were sacrificed on LD 4. All females were sacrificed and necropsied. Uterine contents were examined, and the number of implants and the number of corpora lutea were recorded. Although all OECD guideline-specified tissues were collected from F0 females, routine histopathology was not conducted. In F1 pups, viability, sex, external examinations, and body weights were evaluated. Stillborn or dead pups were examined for abnormalities. On LD 4, all live pups were sacrificed and examined for external abnormalities. The study authors used appropriate methods of statistical analysis, which included ANOVA, Tukey-Kramer test, Fisher's exact test, Levene's test for homogeneity of variance, Kruskal Wallis nonparametric ANOVA followed by Dunn's test, and Chi-square test followed by Fisher's exact test.

No parental mortality occurred in this study (ATF, 2003). The details of the repeated-dose portion of the study are provided above. Clinical signs in the dams primarily occurred in the mid- and high-dose groups and included a low incidence of urine staining, pre- and postdose salivation, and postdose feces small in size. Decreased activity, pale skin, unkempt appearance, rough coat, and a postdose wobbly gait were observed in the high-dose group, though at a low incidence. There was a slight (6%), but statistically nonsignificant, lower body weight in high-dose dams that was related to a statistically significant lower body-weight gain during GDs 0−7 due to decreased food consumption. There were no treatment-related effects on the mating index, fertility index, mean gestation length, or ability to deliver. However, there was an increase in the number of litters with stillborn pups in the treated groups (2/7, 4/9, 3/10, and 7/9 females delivered stillborn pups in the control, 75-, 225-, and 750-mg/kg-day groups, respectively). This translated into a statistically significant decrease in the live birth index (number of liveborn pups/number of pups delivered) in the high-dose group. In addition, six of the high-dose litters with liveborn pups had no pups surviving to LD 4. The number of pups surviving to sacrifice on LD 4 were 99 in the control, 131 in the 75-mg/kg-day group, 137 in the 225-mg/kg-day group, and only 25 in the 750-mg/kg-day group. These translated into viability indexes of 94.3%, 96.3%, 94.5%, and 22.9%, respectively, which were statistically significant in the high-dose group compared with the control. The study report did not report any abnormalities in the stillborn or dying pups. The mean pup body weight was statistically lower in the high-dose group compared with the control group on LDs 1 and 4 and was outside of the historical control range. The reproductive/developmental NOAEL was stated to be 225 mg/kg-day. The reproductive/developmental LOAEL is considered to be 750 mg/kg-day, based on the decreased live birth index, pup survival, and body weight of pups during lactation.

Inhalation Exposure

The only available inhalation toxicity studies with acetophenone are subchronic. However, the endpoints are questionable, and the study details are lacking. Imasheva (1966) examined the most endpoints, but the reporting of the study details is inadequate. Pinching and Døving (1974) and Dalland and Døving (1981) examined only the olfactory bulb histopathology and/or avoidance reactions in acetophenone-exposed rats.

Subchronic-duration Studies

Imasheva (1966) exposed 15 white male rats (60−70 g) to continuous acetophenone (97% pure) at concentrations of 0.007 or 0.076 mg/m^3 or clean air for 70 days (15 animals/treatment group). Clinical signs, body weight (measured every 10 days), dynamics, muscle antagonist "chronaxie ratio" (measured every 10 days), whole blood cholinesterase (five animals/group), blood serum protein fractions (five animals/group), and gross necropsy and histopathology were evaluated. The study author described in detail measured differences in the motor chronaxie ratios, cholinesterase levels, and serum protein fractions.

Every 10 days, Imasheva (1966) used an electronic impulse stimulator to measure the motor chronaxie of the extensor and flexor muscles.[1] The flexor and extensor muscle chronaxie ratio was similar between the controls and the 0.007-mg/m^3 group. However, in rats administered 0.076 mg/m^3, there was a change in the ratio (stated as a reverse character) at the end of the second month. Whole blood cholinesterase was determined using the Pokrovskii colorimetric assay.[2] Again, at the end of the second month, shifts in cholinesterase activity occurred in the 0.076-mg/m^3 group. In three of the rats, there was a decrease (average of 22%) in activity, while in one rat, there was a 45% increase in activity. Fractions of albumin and globulins, as well as total protein levels, were also examined every 20 days. While there was no change in the total protein levels, transient changes were noted in all fractions. Albumin decreased by 38.7−48.9% of initial levels by the end of the first month, while globulin levels demonstrated a corresponding increase. The study author stated that original levels were obtained after 20 days of recuperation. At the end of treatment, some animals (exact number not provided) were sacrificed for gross and histopathological examinations. The effects that were reported were conditions referred to, but not defined, as cardiovascular plethora[3] and acute liver dystrophy in rats administered 0.076 mg/m^3. The study authors did not report a NOAEL. However, a NOAEL of 0.007 mg/m^3 can be determined from the data. The LOAEL is 0.076 mg/m^3, based on changes in chronaxie ratios, shifts in cholinesterase activity, transient changes in protein fractions, and histopathology; however, the toxicological significance of any of the endpoints is not clear.

Pinching and Døving (1974) tested the effects of inhalation exposure of several odorous compounds including acetophenone on the olfactory tissues of four weanling Wistar rats (sex ratios not reported). Animals (28−39 g, approximately 2 weeks old) were continuously exposed to 7.4×10^{-8}-M (molar) acetophenone (purity not reported) for varying durations of exposure ranging from 1 week to 3 months. According to tabulated data, rats were exposed to acetophenone for 1-week or 5-week exposure periods. Data were also presented for animals exposed for 2 months, but the study report did not discuss 3-month exposures to acetophenone. Controls received filtered room air only. The focus of the study was limited to histopathological examination of the mitral cells in the olfactory bulb. There was moderate degeneration of these cells observed in rats exposed to acetophenone; results were similar between paired animals in the 1-month and 2-month exposure groups. It is assumed that this effect is respiratory (i.e.,

[1]According to the author, changes in muscle chronaxie ratios could be used as an indicator of central nervous system damage. Chronaxie, along with rheobase, are points along the strength duration curve for electrical stimulus of an excitable tissue such as nerve or muscle.

[2]This assay measures changes in cholinesterase activity as color changes in a pH indicator resulting from hydrolyzation of acetylcholine.

[3]This term was not defined or clarified and is not elsewhere in the existing medical literature.

including the olfactory epithelium) because the study lacks any data to indicate that there was systemic toxicity and the HEC was calculated as a respiratory effect. The study authors did not report a NOAEL. No NOAEL can be established from the data as presented. The LOAEL, however, is 1.2 mg/m^3, based on moderate degeneration in the mitral cells of the olfactory bulb observed at a single concentration.

Dalland and Døving (1981) exposed 14-day-old male Wistar rats to control air or continuous exposure to acetophenone (purity not reported) for 33, 50, or 230 days in a study focused on alterations in tissues and cell types of the olfactory bulb in the brain (this is assumed to be a respiratory effect including the respiratory epithelium lacking any indication of systemic toxicity in the study). The study report stated that the concentrations in the two cages of acetophenone were 2.0×10^{-9} and 1.2×10^{-7} M (HEC of 0.04 and 2.2 mg/m^3, respectively, based on the assumption that this is a respiratory effect including the olfactory epithelium). There were three exposure groups in this study. In Group 1, rats were exposed for 50 days (6 rats per treatment group), then sacrificed for histological examination. In Group 2, rats were exposed for 33 days (12 rats per treatment group), then transferred to laboratory cages. Forty days later, the animals were tested for avoidance reaction. These 12 animals were separated into three groups for conditioned stimulus testing (control air, acetophenone, or 4-methylvaleric acid). Three weeks after avoidance-reaction tests, they were sacrificed for histological examination. In Group 3, rats were exposed for 230 days (9 rats per treatment group). One rat each from the control and acetophenone groups was tested for avoidance reaction 200 days later, and the rest were sacrificed 150 days after testing. Response to a conditioned stimulus was tested with a 20-second presentation of acetophenone at concentrations of 3.6 or 7.2×10^{-9} M when rats were drinking. The unconditioned stimulus was a 1-second scrambled electrical shock of 0.4 mA (milliampere) given through the grid floor of the box immediately after the conditioned stimulus.

Rats sacrificed immediately after 50 days of exposure exhibited shrinkage and cytoplasmic darkening of the mitral cells in distinct patterns (Dalland and Døving, 1981). The histopathology of the olfactory bulb was still altered following removal from acetophenone, but the patterns were different in the three groups. All rats developed an avoidance reaction to the strongest conditioned stimulus within 3 days with no differences between the groups. Results indicate that rats still respond to the odor even after having been exposed to it for long periods of time; morphological changes in the olfactory bulb did not alter the behavior. The study authors did not provide a NOAEL. No NOAEL can be established from the data. Based on the histopathology of the olfactory bulb, the LOAEL is 0.04 mg/m^3.

Chronic-duration Studies

There are no chronic-duration inhalation studies available for acetophenone.

Developmental and Reproduction Studies

No studies could be located regarding the effects of inhaled acetophenone on reproduction or fetal development.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Acetophenone is rapidly absorbed from the gut, metabolized efficiently by the liver to benzoic acid or mandelic acid, and excreted primarily in the urine and, to a very small extent, in the feces (WHO, 2001).

The genotoxicity of acetophenone has been tested in numerous studies using various in vitro test systems (see Table 3). These tests indicate that acetophenone is not mutagenic but may be clastogenic. Studies investigating the genotoxic potential of acetophenone in vivo were not identified.

Table 3. Other Studies for Acetophenone (CASRN 98-86-2)

Tests	Materials and Methods	Results	Conclusions	References
Genotoxicity	Tested for reverse mutation in *Salmonella typhimurium* (Ames assay, strains TA100, TA98, and TA1537), with and without metabolic activation at concentrations up to 3000 nmoles/plate.	No increase in mutagenic activity.	Acetophenone was not mutagenic in *Salmonella typhimurium*.	Elliger et al. (1984)
Genotoxicity	Tested for reverse mutation in *Salmonella typhimurium* (Ames assay, strains TA100, TA2637, TA98), with and without metabolic activation at concentrations ranging from 0.05 to 5.0 mg/plate.	No increase in mutagenic activity.	Acetophenone was not mutagenic in *Salmonella typhimurium*.	Nohmi et al. (1985)
Genotoxicity	Tested for reverse mutation in *Salmonella typhimurium* (Ames assay, strains TA100, TA98), with and without metabolic activation (concentrations not reported).	No increase in mutagenic activity was observed with any of the cigarette smoke condensate including the one containing acetophenone.	Acetophenone was not mutagenic in *Salmonella typhimurium*.	Curvall et al. (1985)
Genotoxicity	Tested for the induction of sister chromatid exchanges (SCEs) in a fraction of cigarette smoke condensate (≤100 µg/ml) known to contain acetophenones, benzonitriles, indoles, methyl alkylketones, and esters of fatty acids.	There was a statistically significant increase in SCE ($p < 0.01$) with the cigarette smoke condensate fraction containing acetophenone.	There can be no definitive conclusion on the effect of acetophenone on SCE induction because it was only one constituent in the mixture that was tested.	Curvall et al. (1985)
Genotoxicity	Chromosomal aberrations in hamster lung cells. Concentrations of 0.8−1.2 mg/plate in the absence of S9 and 0.6−1.0 mg/mL in the presence of S9.	Acetophenone caused chromosomal aberrations in hamster lung cells in the presence of metabolic activation but not in the absence.	Metabolic activation is needed to cause chromosomal aberrations.	Sofuni et al. (1985)

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present a summary of noncancer and cancer reference values, respectively. IRIS data are indicated in the table, if available.

DERIVATION OF ORAL REFERENCE DOSE

Derivation of Subchronic p-RfD

No subchronic p-RfD values can be derived because no adequate, well-described studies are available.

There are two studies available that examine the subchronic effects of acetophenone by the oral route of exposure in animals. The Hagan et al. (1967) study was used by IRIS to develop a chronic RfD; however, the study report is lacking in its presentation of the data, and no effects were found, even at the highest dose tested. The study did not examine neurological or reproductive/developmental effects. ATF (2003) conducted a combined repeated dose toxicity, screening reproductive/developmental study. In this study, neurological tests and reproductive/developmental screening were conducted, and effects were observed. However, the ATF (2003) study was a proprietary study that was not peer reviewed, and only the text without summary or individual data tables was available for review. The ATF (2003) study provides a lower POD for endpoints not tested in the Hagan et al. (1967) study. At the highest dose tested (423 mg/kg-day), no effects were observed (Hagan et al., 1967). However, because the ATF (2003) study was not peer reviewed and the data were not available for review, the subchronic p-RfD derived from the study is relegated to a screening value and is provided in Appendix A.

Table 4. Summary of Noncancer Reference Values for Acetophenone (CASRN 98-86-2)

Toxicity Type (Units)[a]	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-day)	Rat/M+F	Neurotoxicity, reproductive and developmental toxicity	8×10^{-1}	NOAEL	225	300	ATF (2003)
Chronic RfD (mg/kg-day) (IRIS, 1989)	Rat/M+F	Absence of general toxicity	1×10^{-1}	NOAEL	423	3000	Hagan et al. (1967)
Subchronic p-RfC (mg/m^3)	None	None	None	None	None	None	None
Chronic p-RfC (mg/m^3)	None	None	None	None	None	None	None

[a]All the reference values obtained from IRIS are indicated with latest review date.

Table 5. Summary of Cancer Values for Acetophenone (CASRN 98-86-2)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None	None	None	None
p-IUR	None	None	None	None

Derivation of Chronic RfD

IRIS (U.S. EPA, 1989) reported an RfD of 0.1 mg/kg-day, based on the lack of effects on growth, hematology, or macroscopic tissue changes in male and female Osborne-Mendel rats exposed to 0-, 1000-, 2500-, or 10,000-ppm acetophenone (equivalent to 0, 42, 106, and 423 mg/kg-day, respectively) in the diet for 17 weeks (Hagan et al., 1967) and an uncertainty factor of 3000. Subsequent to the IRIS posting, additional relevant studies have been reported. These studies are summarized in this PPRTV document.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No subchronic or chronic p-RfC values can be derived because no adequate, well-described studies are available.

Limited information is available regarding the effects of acetophenone by the inhalation route of exposure in humans or animals. The only human studies available were acute exposure study and were not adequately described. Limited information such as histopathology of the olfactory bulb and avoidance reactions in rats is reported in the Dalland and Døving (1981). Similarly, the Pinching and Døving (1974) study includes only the histopathology of the olfactory bulb. While the study by Imasheva (1966) measured more endpoints, including clinical signs and body weight, no data were provided for these endpoints. The lack of experimental details, specifics of the protocol used, and description of instrumentation of the study by Imasheva (1966) precludes the use of this study for the derivation of inhalation toxicity values. Although chronaxie, the principal endpoint reported in this study, was used to estimate the relative excitability of muscles in the clinical setting, results from the method are acknowledged to be difficult to reproduce for technical reasons (Oka and Miyajima, 2002; Geddes, 2004). The strength-duration curves of the muscle response used to estimate chronaxie and the chronaxie ratio are difficult to generate primarily due to the individual characteristics of the test subjects and, historically, to the subjective visual detection of the start of muscle vibration. Other deficiencies within the study are the lack of any descriptions of the standardization of response judging, as well as no indication that the measurements were made in an unbiased manner. These may be substantial confounding factors for any dose-response relationship and are considered sufficient to preclude the use of this study for the purposes of deriving a provisional value. In addition, the findings of altered levels of cholinesterase activity are limited in their interpretation only as a biomarker of exposure (criteria stated in *Guidelines for Neurotoxicity Risk Assessment*, U.S. EPA, 1998). Although an oral study (ATF, 2003) did report alterations in salivation, which may be an autonomic effect mediated by cholinesterase activity, it was transient in nature and occurred at a low incidence at doses much higher than the concentration used by Imasheva (1966).

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

IRIS provides a cancer WOE descriptor of Classification D (i.e., "*Inadequate Information to Assess Carcinogenic Potential*") (U.S. EPA, 1989).

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The available data do not support derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A: PROVISIONAL SCREENING VALUES

For the reasons noted in the main document, it is inappropriate to derive a provisional subchronic p-RfD for acetophenone. However, information is available 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 summarizes available information in a supplement and develops a screening value. Appendices receive the same level of internal and external scientific peer review as the main document to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in a supplement to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of a supplement 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 Superfund Heath Risk Technical Support Center.

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCE DOSES

The study by ATF (2003) is selected as the principal study for derivation of the screening subchronic p-RfD. The critical endpoints are decreased mean forelimb grip strength and motor activity in male rats, decreased live birth index (i.e., increase in the number of stillborn pups), decreased number of F1 pups surviving to LD 4, and decreased pup body weight. All these effects occurred at the same dose (i.e., 750 mg/kg-day), but because the individual data were not available, BMD modeling could not be conducted; as such the critical effects are grouped together with a POD of 750 mg/kg-day. This study is a proprietary study (ATF, 2003) and has not been peer reviewed, but appears to follow OECD Guideline No. 422, meets the standards of study design and performance, and was GLP compliant. Details are provided in the "Review of Potentially Relevant Data" section. Benchmark dose (BMD) analysis is not possible because no summary or individual data are available for review. Among the available, acceptable studies, this study represents the lowest POD for developing a subchronic p-RfD.

The POD in this study is a NOAEL of 225 mg/kg-day.

No dosimetric adjustments are made because the doses in the principal study were administered via gavage in mg/kg-day, 7 days a week, for the study duration, and no animal-to-human body-weight adjustment is used for oral noncancer assessments.

The screening subchronic p-RfD for acetophenone, based on a POD of 225 mg/kg-day in male and female rats, is derived as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= NOAEL_{ADJ} \div UF \\ &= 225 \text{ mg/kg-day} \div 300 \\ &= \mathbf{8 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

Table A.1 summarizes the uncertainty factors for the screening subchronic p-RfD for acetophenone.

Table A.1. Uncertainty Factors for Screening Subchronic p-RfD of Acetophenone[a]

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to the general toxicity of acetophenone.
UF_D	3	A UF_D of 3 is selected because the database includes one acceptable developmental study in rats (ATF, 2003) but no acceptable two-generation reproduction studies.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied because the POD has been developed using a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study (ATF, 2003) was utilized as the principal study.
UF_C $\leq$3000	300	

[a]ATF (2003).

APPENDIX B: DATA TABLES

There are no data available from the principal studies to present in tables.

APPENDIX C: BMD MODELING OUTPUTS FOR ACETOPHENONE

There are no BMD modeling outputs for acetophenone.

APPENDIX D: REFERENCES

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