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Provisional Peer-Reviewed Toxicity Values for

Acenaphthene
(CASRN 83-32-9)

Superfund Health Risk Technical Support Center
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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 ACENAPHTHENE (CASRN 83-32-9)

BACKGROUND

HISTORY

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

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

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

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

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVS

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

INTRODUCTION

Acenaphthene (1,2-dihydroacenaphthylene), a white-to-light yellowish solid, is an ethylene-bridged, three-ring unsaturated hydrocarbon derived from naphthalene. Acenaphthene is a polycyclic aromatic hydrocarbon (PAH), a compound having two or more single or fused aromatic rings. It is one of the simplest PAHs in structure and is generally grouped with up to 16 other PAHs (acenaphthylene, anthracene, benz[a]anthracene, benzo[a]pyrene, benzo[e]pyrene, benzo[b]fluoranthene, benzo[g,h,i]perylene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, fluoranthene, fluorene, indeno[1,2,3-c,d]pyrene, phenanthrene, and pyrene). These PAHs occur at the highest concentrations at National Priorities List (NPL) hazardous waste sites and are the PAHs to which the general public is most likely to be exposed (ATSDR, 1995). Acenaphthene is one of the few PAHs, along with naphthalene, acenaphthylene, and anthracene, produced commercially in the United States. It is used as an intermediate for naphthalic acids, naphthalic anhydride (intermediate for pigments), and acenaphthylene (intermediate for resins). Acenaphthene is also used as an intermediate in the production of soaps and pharmaceuticals, as an insecticide, fungicide, and herbicide; in plastics manufacturing; and as an agent for inducing polyploidy (U.S. EPA, 1982; ATSDR, 1995). Exposure to PAHs is common throughout the environment, and generally occurs through incomplete fuel combustion (coal, gas, oil, wood, and other organic substances such as food and tobacco). Outside of manufacturing, exposure generally involves a mixture of PAHs instead of individual compounds. Exposure can occur by inhalation, oral (eating and drinking), placental, transfer via breast milk, and dermal routes, and the route and magnitude of exposure are dependent on a variety of factors such as geography, occupation, and culture. Acenaphthene can be a constituent of tar, coal tar creosote oil, and asphalt (U.S. EPA, 1982; ATSDR, 1995), and occupational exposure to acenaphthene and other PAHs has been documented (Ares, 1993; Omland et al., 1994; Petry et al., 1996; Brandt et al., 2000; Bieniek et al., 2004; Campo et al., 2006). Benzo[a]pyrene, a common PAH, is a known carcinogen. However, acenaphthene is categorized as Group 3, "*Unclassifiable as to Carcinogenicity to Humans*" (IARC, 2010 [Vol. 92]), and Group D, "*Not Classified as to Human*

Carcinogenicity" (U.S. EPA, 1987). In this document, "statistically significant" denotes a *p*-value of <0.05, unless otherwise noted.

The empirical formula for acenaphthene is $C_{12}H_{10}$ (see Figure 1). Table 1 provides a list of physicochemical properties.

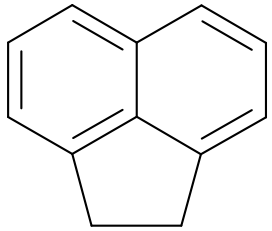

Figure 1. Acenaphthene Structure

Table 1. Physicochemical Properties Table—Acenapthene[a,b,c] (CASRN 83-32-9)

Property (unit)	Value
Boiling point (ºC)	278−280[c]
Melting point (ºC)	90−94[a], 95−97[c]
Density (g/cm^3)	1.06[a]
Vapor pressure (Pa at 25ºC)	0.59595[a]
pH (unitless)	NA[a]
Solubility in water (g/L at 25ºC)	0.00347−0.00388[a]
Relative vapor density (air = 1)	5.32[a]
Molecular weight (g/mol)	154.21[b]
Log Octanol/water partition coefficient	3.92[b]

[a]Chemical Book(2010) .
[b]U.S. EPA (1987).
[c]Sittig (1980).
NA = Not available.

A chronic RfD of 0.06 mg/kg-day for acenaphthene is included in the EPA's IRIS database (U.S. EPA, 1994a). This RfD value is based on increased liver weights accompanied by cellular hypertrophy and increased cholesterol levels observed in the 350- and 700-mg/kg-day dose groups of male and female CD-1 mice administered acenaphthene by gavage. An uncertainty factor (UF) of 3000 has been applied to the NOAEL of 175 mg/kg-day from this study to derive the RfD value. No RfC or cancer assessment for acenaphthene is included in the IRIS database (U.S. EPA, 1994a).

The Drinking Water Standards and Health Advisories List (U.S. EPA, 2009) reports an RfD of 0.06 mg/kg-day for acenaphthene, and a drinking water equivalent level (DWEL) value for acenaphthene of 2 mg/L, which is approximately equivalent to the RfD value for a 70-kg adult drinking 2 liters of water per day (2 mg/L × 2 L = 4 mg ≈ 0.06 mg/kg-day × 70 kg = 4.2 mg). No standards, exposures for a 10-kg child, cancer risk value, or cancer descriptor are listed for acenaphthene. The HEAST (U.S. EPA, 2010) does not report RfD or RfC values. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994b) does not include a Health and Environmental Effects Profile (HEEP) for acenaphthene. The CARA lists (U.S. EPA, 1994b) include an Ambient Water Quality Criteria document (AWQCD) for acenaphthene (U.S. EPA, 1980), an AWQCD addendum (U.S. EPA, 1990), and a Health Effects Assessment (HEA) document for PAHs (U.S. EPA, 1984). In addition, a HEA document for acenaphthene (U.S. EPA, 1987) and an AWQCD document for PAHs (U.S. EPA, 1980) are available (although not listed on the CARA). These five documents report a lack of data regarding chronic-duration exposure or carcinogenicity for acenaphthene, but a lower limit of 0.02 ppm (0.02 mg/L) in drinking water was proposed based on organoleptic, not toxic, considerations. ATSDR (2008) has not reviewed the toxicity of acenaphthene individually but has included it in the review of PAHs (ATSDR, 1995). A recommended oral minimum risk level (MRL) for acenaphthene of 0.6 mg/kg-day is reported for intermediate-duration exposure (15 to 364 days); no inhalation MRL values are reported for any PAH. Although this value is based on the same study in the CD-1 mouse as cited for the chronic RfD value in the IRIS database, the ATSDR document reports the 175-mg/kg-day dose level as the LOAEL for hepatic effects. This is based on increased liver weights without the accompanying hepatocellular hypertrophy noted after administration of acenaphthene at 350 and 700 mg/kg-day. The ATSDR document also reports that acenaphthene is negative for genotoxicity in the *Salmonella typhimurium* and *Escherichia coli* SOS chromotest gene mutation screens. A World Health Organization (WHO, 1998) Environmental Health Criteria (EHC) document on PAHs reports the NOAEL and LOAEL values cited by IRIS (175 and 350 mg/kg-day, respectively); no EHC document exists for acenaphthene. CalEPA (2008a,b, 2009a) has not derived toxicity values for exposure to acenaphthene. No occupational exposure limits for acenaphthene as an individual PAH have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010), the National Institute of Occupational Safety and Health (NIOSH, 2005), or the Occupational Safety and Health Administration (OSHA, 2010). The Hazardous Substances Data Bank recognizes acenaphthene as a skin, eye, and mucous membrane irritant. Acenaphthene is a potential component of PAH mixtures (coal tar and creosote) that have a threshold limit value (TLV) level of 0.2-mg/m^3 time-weighted average (TWA) (ACGIH, 2010), a relative exposure limit (REL) value of 0.1-mg/m^3 TWA (NIOSH, 2005), and a permissible exposure limit (PEL) value of 0.2-mg/m^3 TWA (OSHA, 2010).

The HEAST (U.S. EPA, 2010) does not report an EPA (1986) cancer weight-of-evidence (WOE) classification for acenaphthene, although a HEA document (U.S. EPA, 1987) indicated that the appropriate classification for acenaphthene was in Group D ("*Not Classified as to Human Carcinogenicity"*). IARC (2010) categorizes the carcinogenic potential of acenaphthene as Group 3, "Un*classifiable as to Carcinogenicity to Humans"*. Results from two experiments in the mouse examining carcinogenicity by dermal application are inadequate for evaluation because of poor survival and/or the lack of a control group. Acenaphthene is not included as an individual PAH in the *11th Report on Carcinogens* (NTP, 2005). CalEPA (2009b) has not prepared a quantitative estimate of carcinogenic potential for acenaphthene.

Literature searches were conducted on sources published from 1900 through December 2010 for studies relevant to the derivation of provisional toxicity values for acenaphthene, CAS No. 83-32-9. 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, 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 toxicity information: 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 an overview of the relevant database for acenaphthene and includes all potentially relevant 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 as adjusted (ADJ) rather than HED/HECs. Principal studies are identified. Entries for the principal studies (PS) are bolded.

HUMAN STUDIES

No data on the effects of acenaphthene in humans following inhalation or oral exposure have been located in the literature searches.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to acenaphthene have been evaluated in two subchronic-duration studies (i.e., U.S. EPA, 1989; Knobloch et al., 1969 [as cited in U.S. EPA, 1980]), but not in any chronic-duration, developmental, reproductive, or carcinogenicity studies.

Subchronic-duration Studies

A study submitted to the EPA (1989) is discussed in the IRIS document for acenaphthene (U.S. EPA, 1994a) and used to derive a chronic RfD value. Because this is the only study that provides suitable data for derivation of a subchronic p-RfD value, a summary of the study's methodology and results is presented in this document.

Table 2. Summary of Potentially Relevant Data for Acenaphthene (CASRN 83-32-9)

Notes[a]	Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b,c]	BMDL/ BMCL[b]	LOAEL[b, c]	Reference (Comments)
Human								
1. Oral (mg/kg-d)								
None								
2. Inhalation (mg/m^3)								
None								
Animal								
1. Oral (mg/kg-d)								
PS IRIS (U.S. EPA, 1994a)	**Subchronic**	**20/20, CD-1 mouse, daily gavage, 90 d**	**Male/Female ADJ: 0, 175, 350, or 700 mg/kg-d**	**Increased absolute and relative liver weight, increased serum total cholesterol, minimal-to-slight centrilobular hepatocellular hypertrophy**	**N/A**	**161 mg/kg-d; identified in female mice for increased relative liver weight**	**175 mg/kg-d; identified in female mice for increased absolute and relative liver weight**	**U.S. EPA (1989)**
IRIS (U.S. EPA, 1994a)	Subchronic	Number of animals not reported, rat and mouse (strain not reported), oral, 32 d	2000 mg/kg-d	Weight loss, peripheral blood changes, increased serum aminotransferase levels (alanine or aspartate not specified), mild morphological damage to liver/kidney, mild bronchitis/bronchial tissue inflammation	Not established	Not run	2000 mg/kg-d (only dose)	Knobloch et al. (1969) (in Polish, as cited in U.S. EPA, 1980)
	Chronic	None						

Table 2. Summary of Potentially Relevant Data for Acenaphthene (CASRN 83-32-9)

Notes[a]	Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b,c]	BMDL/ BMCL[b]	LOAEL[b, c]	Reference (Comments)
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						
2. Inhalation (mg/m^3)								
	Subchronic	None						
IRIS (U.S. EPA, 1994a)	Chronic	Unknown number of rats (strain not reported), inhalation, 5 mo	12 ± 1.5 mg/m^3 (4 hr/d, 6 d/wk) or HEC: 1.7 mg/m^3	Chronic aspecific pneumonia, circulatory alterations, desquamation of alveolar epithelium, focal bronchitis with hyperplasia and metaplasia	Not established	Not run	1.7 mg/m^3 (only dose)	Reshetycek et al. (1970) (in Russian, translation not available)
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						

[a]Notes: IRIS = Utilized by IRIS, date of last update; PS = Principal study, N/A = Not applicable.
[b]Dosimetry: Where appropriate, 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. Noncancer oral data are only adjusted for continuous exposure.
HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood gas partition coefficient.
[c]Not reported by the study author but determined from the data.

The nonpeer-reviewed study conducted in compliance with Good Laboratory Practice (GLP) regulations by Hazleton Laboratories America, Inc. and submitted to the EPA (1989) is selected as the principal study for deriving the subchronic p-RfD. Although this study has not been peer reviewed, it was selected for development of a chronic RfD by IRIS (U.S. EPA, 1990a) and is deemed appropriate for the development of a subchronic p-RfD value. This study examined the subchronic-duration toxicity of acenaphthene in the CD-1®(ICR)BR mouse (Charles River Breeding Laboratories). After acclimation and physical examinations, 80 mice/sex (males, 22.3−30.8 g and females, 17.8−24.6 g; 43 days old) were used. The mice were housed individually in stainless steel, hanging-wire cages. Food and tap water were available ad libitum, and a 12:12 hour light:dark cycle was maintained. Animals were randomized by weight into one of four groups (three treatment groups and a vehicle control group, 20/group/sex). The study authors conducted baseline clinical pathology measurements on nonstudy animals prior to study initiation. Dosing solutions of acenaphthene (purity not reported) were formulated in corn oil at 0, 35, 70, and 140 mg/mL (0, 175, 350, and 700 mg/kg-day, respectively, at a dose volume of 5 mL/kg), with stability determined for at least 21 days. The 175- and 350-mg/kg-day formulations were prepared as solutions, and the high-dose formulation (700 mg/kg-day) was prepared as a suspension. The mice were dosed once daily by gavage for 90 days. All animals were observed for clinical signs daily, including mortality/moribundity checks twice daily. Body weight and food consumption were recorded weekly, and ophthalmology examinations were conducted prior to treatment initiation and during the final week of the study. At the end of the study, half of the study animals/group/sex (n = 10) were bled for hematology determinations, and the remaining mice were bled for clinical chemistry analyses. All mice remaining on study were euthanized by exsanguination, and all sacrificed animals, as well as mice that died during the study, underwent a full necropsy. Selected organs (liver/gallbladder, kidneys, heart, spleen, brain/brainstem, testes/epididymides, ovaries, and adrenals) were weighed, and the terminal organ and body weights were used to calculate relative organ/body-weight ratios. Tissues were collected and prepared for histopathological examination; all tissues from the control and high-dose group mice were examined. Additionally, gross lesions, lungs, liver, and kidneys from the low- and mid-dose animals were prepared for analysis and examined.

Four unscheduled deaths occurred during the study (U.S. EPA, 1989); three high-dose female deaths were considered treatment related, but one accidental death in a high-dose male was not. No significant toxicological findings were noted in the surviving mice during the daily and weekly clinical observations. No statistically significant effects on weekly body weight, total body-weight gain, or weekly and total food consumption were observed in the study. Clinical hematology and chemistry results from blood draws at study termination indicated statistically significant elevations in total cholesterol levels in high-dose males and females (50 and 121% over control, respectively), and mid-dose females (48%), as well as a statistically significant increase in eosinophil count in the low- and high-dose females ($p < 0.05$, see Appendix B, Table B.1). Absolute and relative liver weights were increased in a dose-dependent manner in both sexes in all treatment groups at study termination (low dose, 9−13%; mid dose, 14−19%; and high dose, 28−37%; $p < 0.05$, see Appendix B, Table B.2) with the exception of absolute liver weight in low-dose males. Other statistically significant organ-weight changes included decreased absolute spleen weight (all dose groups in males), decreased relative spleen weight (mid-dose males), decreased absolute adrenal and ovary weights (mid- and high-dose females), and decreased relative adrenal and ovary weights in all treated female mice ($p < 0.05$,

see Appendix B, Table B.2). No treatment-related findings were noted in gross pathology at necropsy. Minimal-to-slight centrilobular hepatocellular hypertrophy was seen in nearly all of the high-dose animals (all terminally-sacrificed animals and three out of four unscheduled deaths) during the histopathology evaluations and was observed to a lesser degree in the mid- and low-dose groups (see Appendix B, Table B.3). Additionally, increased incidence and degree of ovarian and uterine inactivity were seen in the high-dose female but these increases were not statistically significant.

EPA (1989) noted that increased absolute and relative liver weights in female mice at all dose groups correlated with the increased incidence of hepatocellular hypertrophy and increased serum total cholesterol concentrations observed in the mid- and high-dose groups. Although the study author did not specify a NOAEL or LOAEL, a LOAEL is identified as 175 mg/kg-day for statistically and biologically significant increased absolute and relative liver weight in female mice at the lowest dose; no NOAEL is identified. Data for all statistically significant changes (e.g., organ weight changes, hepatocellular hypertrophy, etc.) observed in this study have been further evaluated, when appropriate, with the BMDS modeling program for determination of a point of departure (POD) for the subchronic p-RfD (see DERIVATION OF REFERENCE DOSES).

The study by Knobloch et al. (1969 [as cited in U.S. EPA, 1980]) is discussed in the IRIS document for acenaphthene (U.S. EPA, 1994a). Because this study is not used for the derivation of a provisional toxicity value in this document, and because an English translation of the original study written in Polish is not available, this study is not discussed further. However, this study can still be considered supporting based on a review of this study by the U.S. EPA (1980). As summarized from this review, Knobloch et al. (1969) determined that the severity of the liver effects caused by this chemical increased with repeated exposures, supporting the concern for greater sensitivity from prolonged exposure. Furthermore, acenaphthene-induced liver toxicity was observed in this study, similar to effects observed in the study by the U.S. EPA (1989), suggesting that the liver is indeed a target organ for acenaphthene toxicity. Refer to the IRIS document for acenaphthene for further study details (U.S. EPA, 1994a).

Chronic-duration Studies

IRIS (U.S. EPA, 1994a) has provided an RfD. The principal study used by IRIS (i.e., U.S. EPA, 1989) is also utilized in the derivation of a subchronic p-RfD for this document.

Inhalation Exposures

The effects of inhalation exposure of animals to acenaphthene have been evaluated in both a chronic-duration intraperitoneal and intratracheal study (Reshetycek et al., 1970)—but not in any subchronic-duration, developmental, reproductive, or carcinogenicity studies.

The inhalation study by Reshetycek et al. (1970) is discussed in the IRIS document for acenaphthene (U.S. EPA, 1994a). Because this study is not used for the derivation of a provisional toxicity value in this document, and because a translation from Russian is not available, it is not discussed further. Refer to the IRIS document for acenaphthene for further study details (U.S. EPA, 1994a).

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Various studies (see Table 3) have investigated the mutagenicity of acenaphthene including Gibson et al. (1978), Pahlman and Pelkonen (1987), Zeiger et al. (1992), Kangsadalampai et al. (1996), and Yan et al. (2004). The nonenzymatic mutagenic activation of acenaphthene and other PAHs was examined after exposure to ^{60}Co irradiation in *S. typhimurium* strains TA98, TA1535, TA1537, and TA1538 (Gibson et al., 1978). Cytotoxicity in all four *S. typhimurium* strains, and at all of the tested acenaphthene concentrations, precluded the determination of acenaphthene mutagenicity in this study. The mutagenicity of acenaphthene and other PAHs was examined in *S. typhimurium* strain TA100 in the presence of S9 prepared from mouse or rat liver after in vivo i.p. pretreatment with 3-methylcholanthrene or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (Pahlman and Pelkonen, 1987). Acenaphthene was not mutagenic in *S. typhimurium* in the absence or presence of any S9 fraction up to a toxic concentration of 324 nmol/plate. The mutagenicity of acenaphthene was investigated in *S. typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 with and without S9 activation (Zeiger et al., 1992). S9 fractions were prepared from Aroclor 1254-induced male Sprague-Dawley rat and male Syrian hamster livers. Acenaphthene demonstrated negative results in mutagenicity studies with *S. typhimurium* with S9 activation (at concentrations of 10 and 30%) and in the absence of S9. Kangsadalampai et al. (1996) investigated the mutagenicity of PAH alone or in cooked food, in the presence or absence of sodium nitrite, with *S. typhimurium* strains TA98 and TA100. Acenaphthene tested negative for mutagenicity in the absence of nitrite treatment but was positive in combination with sodium nitrite. These data support the designation that acenaphthene is not a direct mutagen.

Yan et al. (2004) investigated the photomutagenicity of acenaphthene in *S. typhimurium* strain TA102 with UVA plus visible light irradiation. Photomutagenicity tests were conducted in duplicate on separate occasions. Aroclor 1254-induced S9 activation of mutagenicity also was evaluated in *S. typhimurium* strain TA102 in separate experiments. Acenaphthene was negative for mutagenicity in the absence or presence of S9 activation, but it was weakly positive in the presence of UVA and visible light irradiation. The results of this study underscore the potential value for considering "actual" exposure conditions in risk assessment (e.g., environmental factors).

The structural basis for the genotoxicity of acenaphthene and other PAHs (as determined by induction of the SOS repair system in *E. coli* PQ37) was investigated by Mersch-Sundermann et al. (1992) with the Computer Automated Structure Evaluation (CASE) system. Experimental negative genotoxicity results for acenaphthene are supported by a CASE prediction of nongenotoxicity. The lack of genotoxicity was correlated with the chemical structure of acenaphthene (the lack of active fragments or biophores such as a bay or fjord region).

A second study by Mersch-Sundermann et al. (1993) investigated the genotoxicity of acenaphthene and other PAHs by induction of the SOS system in *E. coli* strain PQ37 with and without activation (S9 fraction prepared from Aroclor 1254-induced male rat liver). Acenaphthene was negative for genotoxicity as determined with *E. coli* strain PQ37 and S9 metabolic activation.

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Mutagenicity	Nonenzymatic mutagenic activation of acenaphthene and other PAHs was examined after exposure to ^{60}Co irradiation in *S. typhimurium* strains TA98, TA1535, TA1537, and TA1538.	Cytotoxicity in all *S. typhimurium* strains at all of the tested acenaphthene concentrations precluded determination of mutagenicity by acenaphthene.	Results inconclusive due to cytotoxicity.	Gibson et al. (1978)
Mutagenicity	Mutagenicity of acenaphthene and other PAHs was examined in *S. typhimurium* strain TA100 in the presence of S9 prepared from mouse or rat liver. Animals were pretreated (intraperitoneal [i.p.]) with corn oil (control), 3-methylcholanthrene, or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.	Acenaphthene was not mutagenic in *S. typhimurium* TA100 in the absence or presence of either S9 fraction (up to a toxic concentration of 324 nmol/plate).	Acenaphthene was nonmutagenic under the conditions examined, as were other nonbay-region PAHs.	Pahlman and Pelkonen (1987)
Mutagenicity	Mutagenicity of acenaphthene was examined in *S. typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537, with and without S9 activation (S9 prepared from Aroclor 1254-induced male Sprague-Dawley rat and male Syrian hamster livers).	Acenaphthene tested negative in all strains, with and without S9 activation (at 10% and 30% S9).	Acenaphthene was nonmutagenic under the conditions examined.	Zeiger et al. (1992)
Mutagenicity	Mutagenicity of PAHs alone or in cooked food, and with or without sodium nitrite, was investigated with *S. typhimurium* strains TA98 and TA100.	Acenaphthene tested negative for mutagenicity in *S. typhimurium* strains TA98 and TA100 in the absence of nitrite treatment but was positive in combination with sodium nitrite.	Acenaphthene was mutagenic in the presence of nitrite under the conditions examined.	Kangsadalampai et al. (1996)
Mutagenicity	Photomutagenicity of acenaphthene was examined in *S. typhimurium* strain TA102 with UVA plus visible light irradiation. Mutagenicity after Aroclor 1254-induced S9 activation also was investigated.	Acenaphthene mutagenicity in the absence or presence of S9 activation was negative. Acenaphthene mutagenicity in the presence of UVA and visible light irradiation was positive.	Acenaphthene tested positive for photomutagenicity in *S. typhimurium* strain TA102 with UVA and visible light irradiation.	Yan et al. (2004)
Genotoxicity	The structural basis for genotoxicity of acenaphthene and other PAHs with the SOS chromotest in *E. coli* PQ37 was investigated with the Computer Automated Structure Evaluation (CASE) system.	Experimental negative genotoxicity results were supported by a CASE prediction for acenaphthene of nongenotoxic.	The lack of genotoxicity by acenaphthene in the SOS chromotest was correlated with its structure.	Mersch-Sundermann et al. (1992)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Genotoxicity	The genotoxicity of acenaphthene and other PAHs was investigated with the SOS chromotest in *E. coli* PQ37 activated with S9 fractions prepared from Aroclor 1254-induced male rat liver.	Acenaphthene with S9 metabolic activation in the SOS chromotest with *E. coli* strain PQ37 was negative.	Acenaphthene was negative for genotoxicity under the conditions examined.	Mersch-Sundermann et al. (1993)
Cytotoxicity	Acute cytotoxicity of acenaphthene and other PAHs was investigated in the human hepatoma cell line (HepG2), noninduced or Arochlor-induced (3 d), and analyzed with the Neutral Red cytotoxicity assay.	Acenaphthene in noninduced and Arochlor-induced cells (25 and 50 µg/mL) was negative for cytotoxicity.	The negative cytotoxicity results for acenaphthene conflict with previous findings from this laboratory for acenaphthene and other chemicals in the presence of S9 fractions.	Babich et al. (1988)
Metabolism	Acenaphthene and other PAHs were administered to $B6C3F_1$ mice by single i.p. injection. Microsomes were prepared after animal sacrifice. Methoxyresorufin-*O*-demethylase (MROD) activity, as well as mouse hepatic cytosolic Ah receptor and 4S carcinogen-binding protein competitive binding, were evaluated.	Acenaphthene (50−400 mg/kg) statistically significantly induced MROD activity ($p < 0.05$), but did not competitively displace radioligands from the Ah receptor or the 4S carcinogen-binding protein.	Induction of hepatic CYP1A2 by acenaphthene is independent of the Ah receptor pathway.	Chaloupka et al. (1994)
Metabolism	Acenaphthene was administered to male rats (species not identified) in the diet. Urine was collected daily, filtered, and refrigerated for future analysis.	Upon numerous chemical extractions, a solid compound was isolated from rat urine. Based on its physical and chemical properties, the compound was identified to be the anhydride of naphthalene-1,8-dicarboxylic acid.	Acenaphthene is metabolized and further excreted in the urine of rats as an anhydride of naphthalene-1,8-dicarboxylic acid. Fission of the 5-membered carbon ring of acenaphthene can occur in vivo.	Chang and Young (1943)
Mitochondrial Respiration	The inhibition of bovine heart mitochondrial respiration by acenaphthene and other hydrocarbons with one or two aromatic rings was examined. The effect of the aromatic hydrocarbons on the spectra of ubiquinone also was determined.	Acenaphthene was a relatively potent inhibitor of NADH:O_2 oxidoreductase activity in a dose-dependent manner (EC_{50} = 3.9 ppm, 25.3 µM). Acenaphthene affected the spectra of ubiquinone. The inhibitory effects of the tested aromatic hydrocarbons were additive.	Acenaphthene was shown to be a potent inhibitor of mitochondrial respiration.	Beach and Harmon (1992)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Dermal Absorption	The correlation between physicochemical properties and in vitro percutaneous absorption values of various industrial chemicals, including acenaphthene and other PAHs, was investigated. Permeability coefficient ($K_{p)}$ and lag time estimates were determined, and correlations were fit with a multiple linear regression model.	Statistically significant correlations were observed for all chemicals tested between experimental values for K_p and the natural log of the octanol:water partition coefficient (ln $K_{ow)}$ values, and lag time and ln K_{ow}. Acenaphthene and other PAHs, excluding naphthalene, also correlated well between $K_{p,}$ and lag time versus solubility in water.	The multiple linear regression model was predictive of permeability and lag time estimates based on the water solubility and K_{ow} values for the chemicals examined.	Sartorelli et al. (1998)

The acute cytotoxicity of acenaphthene and other PAHs was investigated in the human hepatoma cell line (HepG2), noninduced or Arochlor-induced for 3 days (Babich et al., 1988). Cytotoxicity was determined after incubation for 3 days with individual PAHs with the Neutral Red cytotoxicity assay. Results indicated that acenaphthene was negative at concentrations of 25 and 50 µg/mL in noninduced and Arochlor-induced cells. These data conflict with previous reports from this laboratory of acenaphthene cytotoxicity determined in cell cultures with added S9 fraction.

Chaloupka et al. (1994) investigated the metabolism and intracellular binding of acenaphthene and other PAHs. B6C3F1 mice were obtained after in-laboratory breeding (C57BL/6 females and C3H males), and compounds dissolved in corn oil were administered by i.p. injection as a single dose. Microsomes were prepared after animal sacrifice, and induction potential was evaluated with a methoxyresorufin-*O*-demethylase (MROD) activity assay. Mouse hepatic cytosolic Ah receptor and 4S carcinogen-binding protein competitive binding assays were conducted with [^{3}H]TCDD and [^{3}H]benzo[a]pyrene alone or with acenaphthene or the other PAHs. Acenaphthene at concentrations of 50−400 mg/kg statistically significantly induced MROD activity ($p < 0.05$) but did not competitively displace radioligands from the Ah receptor or the 4S carcinogen-binding protein. These data indicate that induction of hepatic CYP1A2 by acenaphthene is independent of the Ah receptor pathway.

Chang and Young (1943) observed the metabolism of dietary 1% acenaphthene in rats. Urine was collected daily and then filtered and stored for future use. After analysis of urine, it was determined that acenaphthene is metabolized to an anhydride of naphthalene-1,8-dicarboxylic acid and then further excreted. Based on this observation, it was determined that fission of acenaphthene's carbon ring can occur in the body of an animal.

Beach and Harmon (1992) examined the inhibition of bovine heart mitochondrial respiration by acenaphthene and other hydrocarbons with one or two aromatic rings. Inhibition was determined individually or in various combinations as mixtures. The effect of the aromatic hydrocarbons on the spectra of ubiquinone also was determined. Acenaphthene was a relatively potent inhibitor of NADH:O_2 oxidoreductase activity in a dose-dependent manner (EC_{50} = 3.9 ppm, 25.3 µM) and affected the spectra of ubiquinone. The inhibitory effects of the tested aromatic hydrocarbons on mitochondrial respiration were additive with acenaphthene for mixtures of two, three, and all four test compounds. Acenaphthene was shown to be a potent inhibitor of mitochondrial respiration, and the potential for additive effects by acenaphthene and other hydrocarbon compounds is important because exposure to these compounds in the environment (outside of an industrial setting) would be as mixtures.

Sartorelli et al. (1998) reported the correlation between physicochemical properties and in vitro percutaneous absorption values of various industrial chemicals—including acenaphthene and other PAHs. Permeability coefficient (K_p) and lag time estimates were determined, and correlations were fit with a multiple linear regression model. Statistically significant correlations ($p < 0.001$) were observed for all chemicals tested between experimental values for K_p and the natural log of the octanol:water partition coefficient (ln K_{ow}), and between lag time and ln K_{ow}. Acenaphthene and other PAHs, excluding naphthalene, also correlated well between K_p and lag time versus solubility in water. The multiple linear regression model was predictive of permeability and lag time estimates based on the water solubility and K_{ow} values for the

chemicals examined. The study authors recognized the potential influence from different experimental systems.

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values. Table 5 presents a summary of cancer values.

Table 4. Summary of Noncancer Reference Values for Acenaphthene (CASRN 83-32-9)

Toxicity Type (Units)	Species/ Sex	Critical Effect	Reference Value	POD Method	POD (mg/kg-d)	UFc	Principal Study
Subchronic p-RfD (mg/kg-d)	Mouse/M and F	Increased relative liver weight in female mice	2×10^{-1}	BMDL	161, $BMDL_{10}$ for increased relative liver weight in female mice	1000	(U.S. EPA, 1989)
Chronic RfD (mg/kg-d)	Previously determined by IRIS (U.S. EPA, 1990a)						
Subchronic p-RfC (mg/m^3)	None						
Chronic p-RfC (mg/m^3)	None						

Table 5. Summary of Cancer Values for Acenaphthene (CASRN 83-32-9)

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

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The 90-day toxicity study in the mouse (U.S. EPA, 1989) is selected as the principal study for derivation of the subchronic p-RfD. The study was conducted according to GLP regulations and otherwise meets the standards of study design and performance, with respect to the numbers of animals and presentation of information. Although this study has not been peer reviewed, it was selected for development of a chronic RfD by IRIS (U.S. EPA, 1990a) and is deemed appropriate for the development of a subchronic p-RfD value. The number of potential toxicity endpoints that were examined includes body and organ weights, clinical hematology and chemistry measurements, and histopathology. This study provides the lowest POD from the data set for increased relative liver weight in female mice, for derivation of a subchronic p-RfD value.

The following dosimetric adjustments were made for each dose in the principal study for gavage administration. The dosimetric adjustment for 175 mg/kg-day is presented below.

$$\begin{aligned}(DOSE_{ADJ}) &= DOSE_{U.S.\ EPA,\ 1989} \times [\text{conversion to daily dose}] \\ &= 175\ \text{mg/kg-day} \times (\text{days of week dosed} \div 7) \\ &= 175\ \text{mg/kg-day} \times (7 \div 7) \\ &= 175\ \text{mg/kg-day}\end{aligned}$$

As detailed in the section "Review of Potentially Relevant Data," statistically significant changes included increased absolute and relative liver weights in female mice at all dose groups that correlated with the increased incidence of centrilobular hepatocellular hypertrophy, and statistically significant changes in serum total cholesterol, eosinophil count, spleen weight, adrenal weight, and ovary weight also occurred. However, increased serum cholesterol cannot be used for derivation of a reference value because the concentration at which this parameter is considered adverse is unknown. Also, it is unknown how cholesterol levels found in mice would compare to those of humans. The same principle applies to the data for increased eosinophil count. The level for which increased an increased eosinophil count could be toxicologically relevant is unclear. With regards to the spleen data in male mice, there is no clear dose response pattern for decreased relative or absolute spleen weights which is necessary for BMDS. Therefore, these data were not modeled by BMD. An potential POD for spleen weight changes can be determined by the NOAEL/LOAEL method as described below. The BMD modeling for liver, adrenal, and ovary weight changes and incidence of hepatocellular hypertrophy are described below.

The EPA Benchmark Dose Software (BMDS version 2.1.2) continuous data models with constant variance are fit to the data using a default BMR of 10% extra risk for increased absolute and relative liver weight. For adrenal and ovary weight changes, continuous data models with constant and model variance are fit to the data using a default BMR of one standard deviation. The dichotomous data models are fit to the increased incidence of hepatocellular hypertrophy according to the current EPA technical guidance using a default BMR of 10% extra risk (U.S. EPA, 2000). After completion of BMD modeling, the modeling output is reviewed for elimination of models that failed acceptability criteria (see Tables 6, 7, and B.1 for BMD modeling results). An adequate fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), the magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Table 8 shows the models that yielded the lowest AIC (and the associated BMDL values) after elimination of failed models. The POD was selected based on the model with the lowest AIC value because the range of remaining BMDL values was <3-fold.

Table 6. Model Predictions for Increased Relative Liver Weight in CD-1 Male Mice in a 90-Day Toxicity Study with Acenaphthene[a]

Model Name	Homogeneity Variance fit *p*-Value	Goodness of Fit *p*-Value	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Hill	0.993	0.142	-113.76	187.85	134.33
Linear	0.993	0.152	-114.15[b]	236.94	209.20
Polynomial	0.993	0.152	-114.15[b]	236.94	209.20
Power	0.993	0.152	-114.15[b]	236.94	209.20

[a]U.S. EPA (1989).
[b]Lowest AIC.

Table 7. UFs for Subchronic p-RfD for Acenaphthene

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 the mouse and humans. There are no data to determine whether humans are more or less sensitive than the mouse to acenaphthene hepatotoxicity.
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental 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 was derived by using a BMDL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study (U.S. EPA, 1989) was utilized as the principal study.
UF_C	1000	

Table 8. Selected Models and BMDL Values after Benchmark Dose Modeling of Hepatic Data from a 90-Day Acenaphthene Toxicity Study in CD-1 Mice[a]

	Lowest AIC	$BMDL_{10}$ (mg/kg-d)
Male		
Absolute Liver Wt	Linear/Polynomial/Power	211
Relative Liver Wt	Linear/Polynomial/Power	209
Female		
Absolute Liver Wt	Linear/Polynomial/Power	176
Relative Liver Wt	**Linear/Polynomial**	**161**
Hypertrophy	Log-Logistic	263

[a]U.S. EPA (1989).

As mentioned above the data for spleen weight changes cannot be modeled by BMD. Therefore, an alternate POD for splenic effects is a LOAEL of 175 mg/kg-day for decreased absolute spleen weight and a NOAEL of 175 mg/kg-day for decreased relative spleen weight, both in male mice. For adrenal weight, a potential POD is a $BMDL_{1SD}$ of 452 mg/kg-day for decreased relative adrenal weight in female mice. For ovary weight changes, the data failed to provide model fit. Thus, an alternate POD for ovarian effects is a NOAEL of 175 mg/kg-day for decreased absolute ovary weight and a LOAEL of 175 mg/kg-day for decreased relative ovary weight, both in female mice. For the increased incidence of hepatocellular hypertrophy, modeling yields a BMDL value of 155 mg/kg-day in male mice. However, the data for increased incidence of hepatocellular hypertrophy in male mice are not amenable to BMD modeling because there are no data at the low response range, which is necessary for BMD modeling. Due to the lack of dose-response data for this parameter, an alternate POD for increased incidence of hepatocellular hypertrophy in the male mice is a NOAEL of 175 m/kg-day. For liver weight changes, the most sensitive potential POD is a BMDL value of 161 mg/kg-day for increased relative liver weight in female mice. Table 9 lists the possible PODs from the principal study (U.S. EPA, 1989).

Of the toxicological effects observed in the principal study, the most sensitive POD is a BMDL value of 161 mg/kg-day for increased relative liver weight in female mice. The selection of increased relative liver weight as the critical effect is also supported by the observation that the liver appears to be a target organ of acenaphthene toxicity. Specifically, not only did acenaphthene cause hepatocellular hypertrophy in both sexes of mice but also biologically and statistically significantly increased absolute and relative liver weights in both sexes of mice as mentioned in the section "Review of Potentially Relevant Data." **Therefore, the $BMDL_{10}$ of 161 mg/kg-day based on increased relative liver weight in female mice (U.S. EPA, 1989) is chosen as the POD to derive a subchronic p-RfD.**

Table 9. Possible PODs in Mice from the U.S. EPA (1989) Study					
Effect	**Sex**	**NOAEL**	**LOAEL**	**$BMDL_{10}$**	**Comment**
Increased Absolute Liver Weight	Males	175	350	211	
Decreased Absolute Spleen Weight	Males	Not Determinable	175	Not Run	No Dose Response
Increased Relative Liver Weight	Males	Not Determinable	175	209	
Decreased Relative Spleen Weight	Males	175	350	Not Run	No Dose Response
Increased Absolute Liver Weight	Females	Not Determinable	175	176	
Decreased Absolute Adrenal Weight	Females	175	350	521	
Decreased Absolute Ovary Weight	Females	175	350	No fit	
Increased Relative Liver Weight	**Females**	**175**	**350**	**161**	**Chosen as POD**
Decreased Relative Adrenal Weight	Females	Not Determinable	175	452	
Decreased Relative Ovary Weight	Females	Not Determinable	175	No fit	
Liver Hypertrophy	Males	175	350	No fit	
Liver Hypertrophy	Females	175	350	263	

Tables B.2 (e.g., liver weights) and B.3 (e.g., incidence of hepatocellular hypertrophy) present BMD input data for these hepatic data, and Tables 6 and 10 and Appendix C present the BMD model output data for increased relative liver weight in male and female mice. Appendix C, Table C.1 provides BMD model output data for absolute liver weight and increased incidence of hepatocellular hypertrophy for both sexes of mice.

Table 10. Model Predictions for Increased Relative Liver Weight in CD-1 Female Mice in a 90-Day Toxicity Study with Acenaphthene[a]

Model Name	Homogeneity Variance fit *p*-Value	Goodness of Fit *p*-Value	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Hill	0.500	NA[b]	-55.97	197	129
Linear	**0.500**	**0.921**	**-59.81[c]**	**186**	**161**
Polynomial	**0.500**	**0.921**	**-59.81[c]**	**186**	**161**
Power	0.500	0.685	-57.81	186	161

[a]U.S. EPA (1989).
[b]NA = BMDS cannot determine a p-value.
[c]Lowest AIC.

The subchronic p-RfD for acenaphthene based on the $BMDL_{10}$ of 161 mg/kg-day from increased relative liver weight in the female mouse (U.S. EPA, 1989) is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= BMDL_{10} \div UFC \\ &= 161 \text{ mg/kg-day} \div 1000 \\ &= \mathbf{2 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

Tables 7 and 11 summarize the UFs and confidence for the subchronic p-RfD for acenaphthene, respectively.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

A chronic RfD value of 6×10^{-2} mg/kg-day is available in the IRIS database (U.S. EPA, 1994a) based on the 90-day toxicity study in the mouse (U.S. EPA, 1989). The POD for this chronic RfD was 175 mg/kg-day, identified as a LOAEL in the current PPRTV document. The critical effect for this chronic p-RfD was increased absolute and relative liver weight coupled with increased cholesterol and liver hypertrophy in male and female mice.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

No published studies investigating the effects of subchronic-duration inhalation exposure to acenaphthene in humans or animals were identified that were acceptable for use in risk assessment.

Table 11. Confidence Descriptor for Subchronic p-RfD for Acenaphthene		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	**H**	The principal study (i.e., U.S. EPA, 1989) assessed an acceptable number of endpoints including body and organ weights, hematology and clinical chemistry measurements, and histopathology. The study duration of 90 d is considered sufficient to determine subchronic toxicity.
Confidence in Database	**L**	The database does not include any developmental toxicity studies or studies in a second species, and no two-generation reproduction studies are available.
Confidence in Subchronic p-RfD[b]	**L**	The overall confidence in the subchronic p-RfD is low.

[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)

No published studies investigating the effects of chronic-duration inhalation exposure to acenaphthene in humans or animals were identified that were acceptable for use in risk assessment.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 12 identifies the cancer WOE descriptor for acenaphthene: "*Inadequate Information to Assess Carcinogenic Potential.*" No carcinogenicity studies in animals by oral or inhalation routes have been found. The carcinogenicity of acenaphthene after dermal exposure in the mouse has been investigated in two studies, but both studies were determined to be unsuitable for carcinogenicity risk determination due to a lack of control animals or poor survival in an IARC monograph evaluating some nonheterocyclic polycyclic aromatic hydrocarbons (IARC, 2010 [Vol. 92]). Two substituted acenaphthene compounds—5-aminoacenaphthene and 5-nitroacenaphthene—were reported to be carcinogenic in animals (IARC, 1998). Because there are no long-term animal studies to suggest a carcinogenic potential for acenaphthene, a discussion of the mode of action for carcinogenesis is not appropriate.

GENOTOXIC STUDIES

Acenaphthene has been shown to not be a direct mutagen in several *S. typhimurium* strains, although acenaphthene mutagenicity has been reported in the presence of nitrite (Kangsadalampai et al., 1996) and UVA and visible light irradiation (Yan et al., 2004). Additionally, the genotoxic potential for acenaphthene was reported to be negative as determined by induction of SOS repair in *E. coli* (Mersch-Sundermann et al., 1993).

Table 12. Cancer WOE Descriptor for Acenaphthene (CASRN 83-32-9)			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	No human studies are available.
"Likely to Be Carcinogenic to Humans"	N/A	N/A	
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**N/A**	**No long-term oral or inhalation studies in animals, and no epidemiological studies, are available.**
"Not Likely to Be Carcinogenic to Humans"	N/A	N/A	No strong evidence of noncarcinogenicity in humans is available.

Acenaphthene and acenaphthene derivatives have been shown to have nuclear and cytological effects in microbial and plant species (U.S. EPA, 1980, 1987, 1990; Buidin, 1975a,b, 1976). These changes involve disruption of the spindle mechanism during mitosis and induction of polyploidy. Although these effects have been demonstrated in plants, fungi, algae, and bacteria, there is no current correlation to similar effects in mammalian cells (U.S. EPA, 1980; Sittig, 1980).

The substituted compound, 5-nitroacenaphthene, and several metabolites of 5-nitroacenaphthene have been shown to be mutagenic in *S. typhimurium* TA 98 and TA100 strains (Yahagi et al., 1975; El-Bayoumy and Hecht, 1982).

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

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

APPENDIX A. PROVISIONAL SCREENING VALUES

No screening values have been derived.

APPENDIX B. DATA TABLES

Table B.1. Selected Clinical Hematology and Chemistry Parameters in CD-1 Mice After Gavage Administration of Acenaphthene in a 90-Day Subchronic-Duration Toxicity Study[a]

Sex	Parameter	Dose (mg/kg-d)			
		0	175	350	700[b]
Male	Eosinophil—(× 10^{-3}/µL, %)	0.1 ± 0.07	0.1 ± 0.08	0.1 ± 0.07	0.1 ± 0.11 (*n* = 9)
Female	Eosinophil—(× 10^{-3}/µL, %)	0.0 ± 0.03	0.1 ± 0.10* (↑)[c]	0.0 ± 0.05	0.2 ± 0.14* (↑)[c] (*n* = 8)
Male	Total cholesterol (mg/dL)	168 ± 24.9	160 ± 36.8	202 ± 42.6	252 ± 45.8* (↑50)
Female	Total cholesterol (mg/dL)	105 ± 33.2	136 ± 29.8	155 ± 28.4* (↑48)	232 ± 51.3* (↑121) (*n* = 7)

[a]Data were obtained from Tables 6 and 7 on pages 64 and 68 (U.S. EPA, 1989). Directionality of percentage difference from control is included in parentheses.
[b]*n* = 10/group except as noted for the 700-mg/kg-day group.
[c]Percentage increase over control is not calculated because the control value is zero.
*$p < 0.05$ by Fisher's Exact Test.

Table B.2. Selected Mean Absolute and Relative Organ Weights in CD-1 Mice After Gavage Administration of Acenaphthene in a 90-Day Subchronic-Duration Toxicity Study[a]

Parameter	Dose (mg/kg-d)			
	0	175	350	700[b]
Male				
Terminal mean body weight (g)	28.7 ± 2.8	27.6 ± 1.6	28.3 ± 1.8	27.9 ± 1.7
Absolute Organ weight (g)				
Liver/gallbladder	1.20 ± 0.13	1.28 ± 0.11	1.37 ± 0.12* (↑14)	1.53 ± 0.11* (↑28)
Spleen	0.7 ± 0.01	0.6 ± 0.01* (↓14)	0.6 ± 0.01* (↓14)	0.6 ± 0.01* (↓14)
Relative Organ/body weight ratio (%)				
Liver/gallbladder	4.172 ± 0.290	4.646 ± 0.291* (↑11)	4.860 ± 0.275* (↑16)	5.470 ± 0.280* (↑31)
Spleen	0.244 ± 0.036	0.231 ± 0.061	0.205 ± 0.034* (↓16)	0.211 ± 0.036
Female				
Terminal mean body weight (g)	23.0 ± 2.1	23.9 ± 1.8	22.5 ± 1.8	22.6 ± 1.9
Organ weight (g)				
Liver/gallbladder	0.98 ± 0.13	1.11 ± 0.10* (↑13)	1.15 ± 0.14* (↑17)	1.32 ± 0.10* (↑35)
Adrenal	0.014 ± 0.004	0.012 ± 0.003	0.011 ± 0.003* (↓21)	0.010 ± 0.002* (↓29)
Ovary	0.033 ± 0.007	0.028 ± 0.006 (↓15)	0.026 ± 0.005* (↓21)	0.026 ± 0.007* (↓21)
Organ/body weight ratio (%)				
Liver/gallbladder	4.273 ± 0.388	4.644 ± 0.339* (↑9)	5.092 ± 0.476* (↑19)	5.856 ± 0.409* (↑37)
Adrenal	0.0596 ± 0.0157	0.0495 ± 0.0114* (↓17)	0.0476 ± 0.0112* (↓20)	0.0457 ± 0.0102* (↓23)
Ovary	0.1429 ± 0.0326	0.1170 ± 0.0225* (↓18)	0.1171 ± 0.0213* (↓18)	0.1166 ± 0.0270* (↓18)

[a]Data were obtained from Tables 8A and 8B on pages 69−74 (U.S. EPA, 1989). Directionality of percentage difference from control is included in parentheses.
[b]n = 20/group, except for 700 mg/kg-day male (n = 19) and female (n = 17).
*$p < 0.05$ by Dunnett's Test.

Table B.3. Incidence of Centrilobular Hepatocellular Hypertrophy in CD-1 Mice After Gavage Administration of Acenaphthene in a 90-Day Subchronic-Duration Toxicity Study[a]

Parameter	Dose (mg/kg-d)			
	0	175	350	700
Male				
(# examined)	20	20	20	19
Minimal	2	2	18	0
Slight	0	0	0	19
Total	2	2	18*	19*
% Incidence	10	10	90	100
Female				
(# examined)	20	20	20	17
Minimal	0	0	5	10
Slight	0	0	0	7
Total	0	0	5*	17*
% Incidence	0	0	25	100

[a]Data were obtained from Table I on page 34 (U.S. EPA, 1989).
*$p < 0.05$ by Fisher's Exact Test.

APPENDIX C. BENCHMARK DOSE CALCULATIONS FOR THE RFD

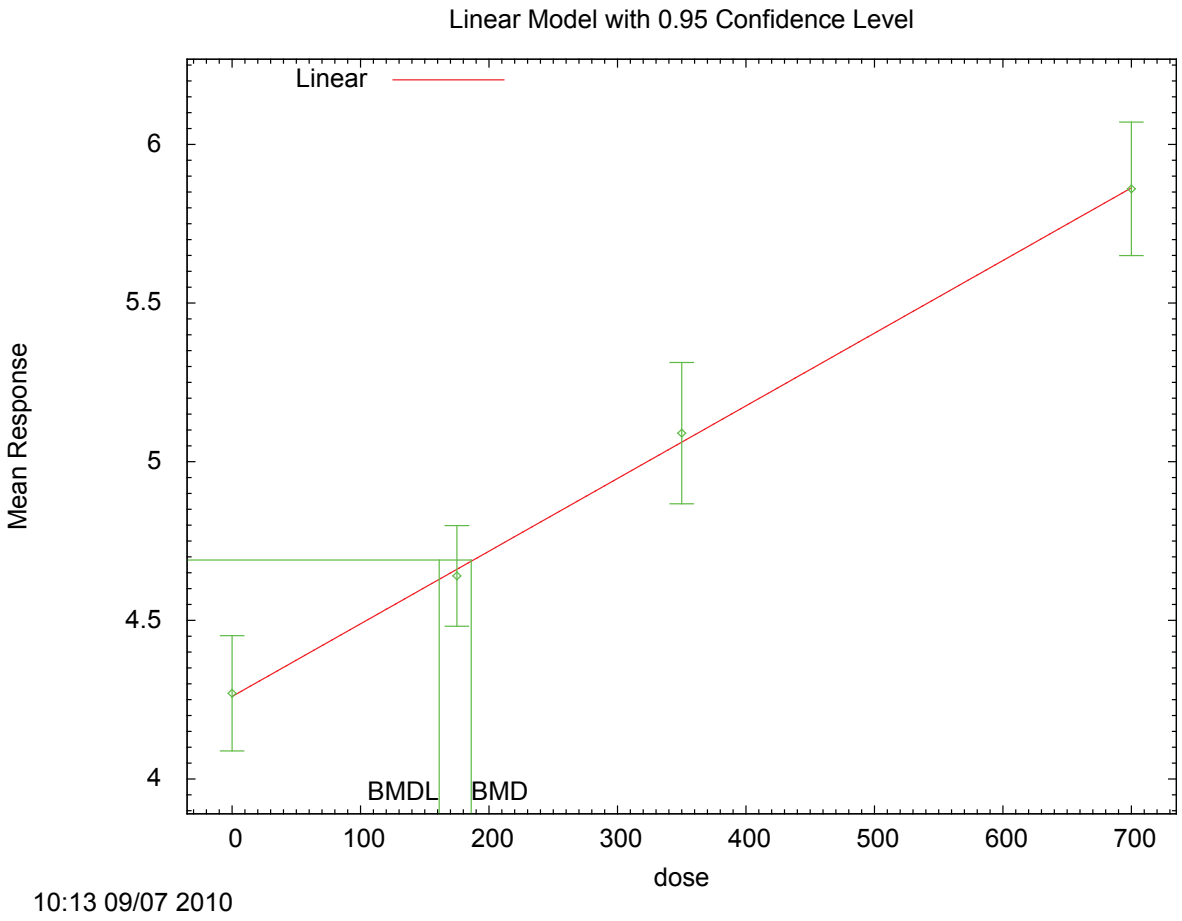

Figure C.1. Dose Response Modeling for Increased Relative Liver Weight in Female CD-1 Mice Gavaged with Acenaphthene for 90-Days

```
================================================================
        Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS21/Data/lin_relliv_acenapthene_f_Lin-
ConstantVariance-BMR10.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS21/Data/lin_relliv_acenapthene_f_Lin-
ConstantVariance-BMR10.plt
                                          Tue Sep 07 10:13:51 2010
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = mean
   Independent variable = dose
```

rho is set to 0
The polynomial coefficients are restricted to be positive
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
alpha = 0.16473
rho = 0 Specified
beta_0 = 4.264
beta_1 = 0.00228898

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	-1.3e-009	7.2e-009
beta_0	-1.3e-009	1	-0.76
beta_1	7.2e-009	-0.76	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.156508	0.0252235	0.10707	0.205945
beta_0	4.26378	0.0689118	4.12872	4.39885
beta_1	0.00229056	0.000179155	0.00193942	0.0026417

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	20	4.27	4.26	0.388	0.396	0.0703
175	20	4.64	4.66	0.339	0.396	-0.278
350	20	5.09	5.07	0.476	0.396	0.277
700	17	5.86	5.87	0.409	0.396	-0.0748

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                     Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1           32.986597            5     -55.973195
            A2           34.169641            8     -52.339282
            A3           32.986597            5     -55.973195
        fitted           32.904061            3     -59.808122
             R          -10.938532            2      25.877064


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              90.2163          6          <.0001
   Test 2              2.36609          3             0.5
   Test 3              2.36609          3             0.5
   Test 4             0.165073          2          0.9208

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =           0.1
```

```
Risk Type        =     Relative risk

Confidence level =          0.95

             BMD =       186.146


            BMDL =       161.229
```

Table C.1. Benchmark Dose Continuous Modeling Results for Toxicological Effects in CD-1 Mice (U.S. EPA, 1989)

Endpoint[f]	Species	Sex	Model	Homogeneity Variance *p*-Value[a]	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)	Conclusions
Increased absolute liver weight	Mouse	M	Continuous-Hill	0.8528	N/D	-252.91	252.17	156.34	Invalid *p*-score 4
			Continuous-Linear	0.8528	0.9787	-256.86	253.39	210.65	Lowest AIC
			Continuous-Polynomial	0.8528	0.9787	-256.86	253.39	210.65	Lowest AIC
			Continuous-Power	0.8528	0.9787	-256.86	253.39	210.65	Lowest AIC
Increased absolute liver weight	Mouse	F	Continuous-Hill	0.3132	0.1978	-244.54	178.13	100.11	
			Continuous-Linear	0.3132	0.3641	-246.17	214.92	175.56	Lowest AIC
			Continuous-Polynomial	0.3132	0.3641	-246.17	214.92	175.56	Lowest AIC
			Continuous-Power	0.3132	0.3641	-246.17	214.92	175.56	Lowest AIC
Increased incidence of hepatocellular hypertrophy	Mouse	M	Dichotomous-Gamma[c]	N/A	0.8969	43.23	194.35	150.7	Data not amendable to BMD modeling
			Dichotomous-Multistage[d]	N/A	0.0227	46.87	137.22	95.09	χ^2 *p*-value <0.1 Data not amendable to BMD modeling
			Dichotomous-Logistic	N/A	0.0149	49.76	115.96	77.52	χ^2 *p*-value <0.1 Data not amendable to BMD modeling

Table C.1. Benchmark Dose Continuous Modeling Results for Toxicological Effects in CD-1 Mice (U.S. EPA, 1989)									
			Dichotomous-Log-logistic[e]	N/A	1	43.01	275.98	154.7	Lowest AIC Data not amendable to BMD modeling
			Dichotomous-Probit	N/A	0.0133	51.32	95.49	65.6	χ^2 *p*-value <0.1 Data not amendable to BMD modeling
			Dichotomous-Log-probit[e]	N/A	0.9995	45.01	248.03	155.62	Data not amendable to BMD modeling
			Dichotomous-Weibull[c]	N/A	0.9951	45.01	270.21	146.07	Data not amendable to BMD modeling
			Dichotomous-Quantal-Linear	N/A	0.0002	64.57	29.91	21.85	χ^2 *p*-value <0.1 Data not amendable to BMD modeling
Increased incidence of hepatocellular hypertrophy	Mouse	F	Dichotomous-Gamma[c]	N/A	0.9865	24.76	297.01	246.44	
			Dichotomous-Multistage[d]	N/A	0.5247	28.48	227.9	183.52	
			Dichotomous-Logistic	N/A	1	26.49	339.22	249.06	
			Dichotomous-Log-logistic[e]	N/A	1	24.49	329.28	263.07	Lowest AIC of passing models
			Dichotomous-Probit	N/A	1	26.49	329.08	238.77	
			Dichotomous-Log-probit[e]	N/A	1	26.49	327.59	258.14	

Table C.1. Benchmark Dose Continuous Modeling Results for Toxicological Effects in CD-1 Mice (U.S. EPA, 1989)									
			Dichotomous-Weibull[c]	N/A	1	26.49	328.58	234.14	
			Dichotomous-Quantal-Linear	N/A	0.0006	26.49	69.26	48.95	χ^2 *p*-value <0.1
Decreased relative adrenal weight	Mouse	F	Continuous-Hill	0.2147	0.9174	-595.33	330.914	1.60E-05	
			Continuous-Linear	0.2147	0.1097	-592.92	692.19	451.66	Best fitting model
			Continuous-Polynomial	0.2147	0.1097	-592.92	692.19	451.66	Best fitting model
			Continuous-Power	0.2147	0.1097	-592.92	692.19	451.66	Best fitting model
Decreased absolute adrenal weight	Mouse	F	Continuous-Hill	0.0411	0.6429	-812.97	711.734	244.06	
			Continuous-Linear	0.0411	0.4254	-813.47	793.63	520.69	Best fitting model
			Continuous-Polynomial	0.0411	0.4254	-813.47	793.63	520.69	Best fitting model
			Continuous-Power	0.0411	<.0001	727368.26	N/D	N/D	BMD and BMDL not provided χ^2 *p*-value <0.1
Decreased relative ovary weight	Mouse	F	Continuous-Hill	0.2048	0.6892	-481.47	N/D	N/D	BMD and BMDL not provided
			Continuous-Linear	0.2048	0.0057	-473.3	1034.14	555.61	χ^2 *p*-value <0.1
			Continuous-Polynomial	0.2048	0.0057	-473.3	1034.14	555.61	χ^2 *p*-value <0.1
			Continuous-Power	0.2048	<.0001	-465.52	745.39	710.14	χ^2 *p*-value <0.1

Table C.1. Benchmark Dose Continuous Modeling Results for Toxicological Effects in CD-1 Mice (U.S. EPA, 1989)									
Decreased absolute ovary weight	Mouse	F	Continuous-Hill	0.4274		-696.77	205.15	0.059	χ^2 *p*-value not provided
			Continuous-Linear	0.4274	0.04067	-694.47	683.83	407.76	χ^2 *p*-value <0.1
			Continuous-Polynomial	0.4274	0.04067	-694.47	683.83	407.76	χ^2 *p*-value <0.1
			Continuous-Power	0.4274	<.0001		N/D	N/D	χ^2 *p*-value <0.1 AIC, BMD, and BMDL not provided

[a]N/A = Not applicable.
[b]N/D = Not determined.
[c]Restrict power ≥1.
[d]Restrict betas ≥0.
[e]Slope restricted to >1.
[f]Data for decreased absolute adrenal and ovary weights and decreased relative ovary weight were modeled by BMDS using model variance.

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