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Provisional Peer-Reviewed Toxicity Values for

1,1-Biphenyl
(CASRN 92-52-4)

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 1,1-BIPHENYL (CASRN 92-52-4)

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

1,1-biphenyl, sometimes called diphenyl or phenyl benzene, is found in varying concentrations in coal tar, crude oil, and natural gas, and was historically used in the production of polychlorinated 1,1-biphenyls (PCBs) (Boehncke et al., 1999). The empirical formula for 1,1-biphenyl is $C_{12}H_{10}$ (see Figure 1). A table of physicochemical properties is provided below (see Table 1). In this document, unless otherwise noted, "statistically significant" denotes a *p*-value of <0.05.

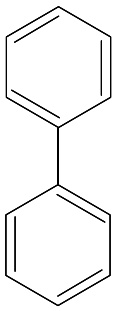

Figure 1. 1,1-Biphenyl Structure

Table 1. Physicochemical Properties Table (1,1-Biphenyl)[a] (CASRN 92-52-4)

Property (unit)	Value
Boiling point (ºC)	256
Melting point (ºC)	70
Density (g/cm^3)	0.992
Vapor pressure (torr or mm Hg at 25ºC)	0.998
pH (unitless)	Not available
Solubility in water (g/100 mL at 25ºC)	Low soluble (4.4)
Relative vapor density (air = 1)	5.3
Molecular weight (g/mol)	154.2
Flash point (°C)	113
Octanol/water partition coefficient (unitless)	3.16/4.09
Conversion factor (ppm to mg/m^3)	1 ppm = 6.31 mg/m^3

[a]IPCS and CEC (1994).

IRIS (U.S. EPA, 2010a) lists a chronic oral reference dose (RfD) of 5×10^{-2} mg/kg-day, but data were inadequate to derive a chronic inhalation reference concentration (RfC). The carcinogenic potential of 1,1-biphenyl is listed as Group D, *Not Classifiable as to Human Carcinogenicity*. No Drinking Water Standards and Health Advisories List values are reported (U.S. EPA, 2006). A subchronic RfD value of 5×10^{-2} mg/kg-day is included in the HEAST document (U.S. EPA, 2010b). CARA (U.S. EPA, 1994a) has provided a Health and Environmental Effects Profile (HEEP) for 1,1-biphenyl (U.S. EPA, 1984) that includes a derived Acceptable Daily Intake (ADI) for oral exposure of 0.05 mg/kg-day. The American Conference of Governmental Industrial Hygienists (ACGIH, 2009) has derived a Threshold Limit Value (TLV) (8-hour time weighted average [TWA]) of 0.2 ppm (1 mg/m^3). The National Institute of Occupational Safety and Health (NIOSH, 2003) has derived a Recommended Exposure Limit (REL) (10-hour TWA) of 1 mg/m^3 (0.2 ppm) as well as an Immediately Dangerous to Life or Health Value of 100 mg/m^3. A Permissible Exposure Limit (PEL) (8-hour TWA) of 0.2 ppm (1 mg/m^3) has been derived by the Occupational Safety and Health Administration (Violintzis et al., 2009). The World Health Organization (Boehncke et al., 1999) reported a provisional Tolerable Daily Intake (TDI) of 38 µg/kg-day and has published a toxicological review of 1,1-biphenyl (Boehncke et al., 1999). The International Agency for Research on Cancer (IARC, 2000) has not reviewed the carcinogenic potential of 1,1-biphenyl, and the compound is not included in the *11th Report on Carcinogens* (NTP, 2005).

Literature searches were conducted on sources published from 1900 through December 7, 2010, for studies relevant to the derivation of provisional toxicity values for 1,1-biphenyl, CAS No. 92-52-4. Searches were conducted using EPA's Health and Environmental Research Online (HERO) evergreen 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 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 toxicity studies. Entries for the principal studies are bolded and identified by the marking "PS".

Table 2. Summary of Potentially Relevant Data for 1,1-Biphenyl (CASRN 92-52-4)

Notes[a]	Category	Number of Male/Female, Species, Study Type, Exposure Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
Human								
				1. Oral (mg/kg-day)				
				None				
				2. Inhalation (mg/m^3)				
	Subchronic			None				
	Chronic			None				
	Developmental			None				
	Reproductive			None				
	Carcinogenic			None				
PR	Occupational	32/1, human, occupational, duration varies between 5 and 16 y	0.6−128 mg/m^3	Liver damage, central and peripheral nervous system effects, increased transaminase levels	None	Not run	None	Hakkinen et al. (1973)
PR		0/1, human, occupational, 25 y	Not reported	Increased transaminase levels, enlarged liver	None	Not run	None	Carella and Bettolo (1994)
Animal								
				1. Oral (mg/kg-day)				
PR	Subchronic	10/0, F344 rat, diet, 7 d/wk, 8 wks	0, 500	Induced microcalculi	None	Not run	5.00×10^2	Shibata et al. (1989)
PR		10/10, Crj:BDF1 mouse, diet, 7 d/wk, 13 wks	Male: 0, 94.6, 378, 1456, 1805, and 2737 Female: 0, 101, 404, 809, 1556, 1929, 2924	Occurrence of peroxisome proliferation, decrease in body weight, increased liver weights in female mice	1.929×10^3	Not run	2.924×10^3	Umeda et al. (2004)

Table 2. Summary of Potentially Relevant Data for 1,1-Biphenyl (CASRN 92-52-4)

Notes[a]	Category	Number of Male/Female, Species, Study Type, Exposure Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
PR		20/0, B6C3F$_1$ mouse, diet, 7 d/wk, 32 wks	0, 1803.8	Increased incidences of interstitial nephritis	1.8038×10^3	Not run	None	Tamano et al. (1993)
IRIS PR	Chronic	15/15, albino rat, diet, 7 d/wk, 700 d	Male: 0, 0.723, 3.62, 7.23, 36.2, 72.3, 362, 723 Female: 0.820, 4.10, 8.20, 41.0, 82.0, 410, 820	Increase in kidney damage, reduced hemoglobin levels, decreased food intake, decreased longevity (animals cohoused, no measurement of individual food intake)	7.23×10	Not run	3.62×10^2	Ambrose et al. (1960); SRI, (1953)
PR		50/50, F344 rat, diet, 7 d/wk, 105 wks	Male: 0, 39.5, 118, 355 Female: 0, 45.9, 138, 413	Calculi in the kidney, dose-dependent lesions found in urinary system	None	Not run	3.95×10	Umeda et al. (2002)
PR		50/50, Wistar rat, diet, 7 d/wk, 75 wks or 104 wks	0, 188, 375 0, 47, 94	75 wks: haematuria, reduction in weight gain, change in serum activities, increased incidence of calculi, increase in relative kidney weights 104 wks: reduction in weight gain, change in serum activities	None	Not run	4.7×10	Takita (1983) (published in Japanese with only an abstract, tables and graphics in English were unavailable for review at this time)
PR		50/50, Crj:BDF mouse, diet, 7 d/wk, 104 wks	Male: 0, 97, 291, 1050 Female: 0, 134, 414, 1420	Mineralization in the inner stripe of the outer medulla of the kidneys in female mice, desquamation in the pelvis in male mice, basophilic cell foci in the liver in female mice	None	Not run	9.7×10	Umeda et al. (2005)

Table 2. Summary of Potentially Relevant Data for 1,1-Biphenyl (CASRN 92-52-4)

Notes[a]	Category	Number of Male/Female, Species, Study Type, Exposure Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
PR PS	**Developmental**	**0/18−20, Wistar rat, 7 d/wk, GDs 6−15**	**Female: 0, 125, 250, 500, 1000**	**Significantly increased number of fetuses with skeletal anomalies, increased fetotoxicity, decreased number of live fetuses, increased mortality, reduced fetal weight, increased dead resorbed fetus (not statistically significant).**	**250**	**9.59**	**500 develop-mental effects)**	**Khera et al. (1979)**
PR	Reproductive	5/10, albino rat, diet, 7 d/wk, 60 d (control and low-dose) 8–9/3–4, rat, diet, 7 d/wk, 60 d (high-dose)	Male: 0, 72.3, 362 Female: 82.0, 410	No difference in reproductive success (litters born), number of rats per litter, or range of litter size	4.10×10^2	Not run	None	Ambrose et al. (1960)
NPR		3/9, long Evans rat, diet, 7 d/wk, 3-gen reprod	Male: 9, 89, 887 Female: 10, 101, 1006	No evidence of a cumulative effect over the three generations. Decreased fertility, smaller litter size, and reduced rate of growth in the 1.0% biphenyl-fed group may have been associated with unpalatability and resultant decreased food intake.	8.87×10^2	Not run	None	Dow Chemical Co. (1953)
PR	Carcinogenic	50/50, F344 rat, diet, 7 d/wk, 105 wks	Male HED: 0, 10.7, 32.1, 96.4 Female HED: 0, 11.0, 32.9, 98.7	An increased incidence of bladder tumors, hematuria, and neoplastic regenerative lesions of the urinary system	3.21×10	Not run	9.64×10	Umeda et al. (2002)

Table 2. Summary of Potentially Relevant Data for 1,1-Biphenyl (CASRN 92-52-4)								
Notes[a]	**Category**	**Number of Male/Female, Species, Study Type, Exposure Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b,c]**	**Reference (Comments)**
PS		**50/50, Crj:BDF mouse, diet, 7 d/wk, 104 wks**	**Male HED: 0, 15.3, 45.8, 154.0 Female HED: 0, 19.7, 59.8, 196.2**	**Increased incidence of hepatocellular adenoma and carcinoma**	**1.97 × 10**	**12.6**	**5.98 × 10**	**Umeda et al. (2005)**
2. Inhalation (mg/m^3)								
PS NPR	**Subchronic**	**50/50, CD1 mouse, inhalation, 7 hr/d, 5 d/wk, 13 wks**	**Respiratory HEC: 0, 72.9, 146.4 for females; 0, 92.6, 189.9 for male. Extra-respiratory HEC: 32.8, 65.5 for both sexes.**	**Congestion and edema in the liver and kidneys and lungs, inflammation in trachea, pneumonia in lungs.**	**None**	**1.65 for respiratory 1.2 for extra-respiratory**	**7.29 × 10 for respiratory effects and 3.28 × 10 for extra-respiratory effects**	**Cannon Laboratories, Inc (1977) (46 mice died after one night of overheating and cannibalism)**
NPR		10 (sex not reported), Sprague-Dawley albino rat, inhalation, 7 hr/d, 5 d/wk, 64 d out of 94 d	HEC: 0, 0.0596	Irritation of the nasal mucosa, death, weight loss	None	Not run	5.96×10^{-2}	Monsanto Chemical Co. (1983)
NPR		6 (sex not reported), Sprague-Dawley albino rat, inhalation, 7 hr/d, 5 d/wk, 46 d out of 68 d	HEC: 0, 0.00789	Irritation of the nasal mucosa	None	Not run	7.89×10^{-3}	Monsanto Chemical Co. (1983)

Table 2. Summary of Potentially Relevant Data for 1,1-Biphenyl (CASRN 92-52-4)

Notes[a]	Category	Number of Male/Female, Species, Study Type, Exposure Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
NPR		4 (sex not reported), Sprague-Dawley albino rat, inhalation, 7 hr/d, 5 d/wk, 62 d out of 92 d	HEC: 0, 0.000934	No reported effects	None	Not run	9.34×10^{-4}	Monsanto Chemical Co. (1983)
NPR		12 (sex and strain not reported), mouse, inhalation, 7 hr/d, 5 d/wk, 62 d out of 92 d	HEC: 0, 0.000934	Irritation of the upper respiratory tract	None	Not run	9.34×10^{-4}	Monsanto Chemical Co. (1983)
PR		50/50 CD1 mouse, aerosol inhalation study, 7 hr/d, 5 d/wk, 13 wks	0, 32.8, 65.5	Hyperemia and focal hemorrhage in the lungs Increase in hyperplasia of the tracheal epithelium	None	Not run	None	Sun Co. Inc. (1977) as cited in Boehncke et al. (1999)
PR		Rabbits Rats Mice exposed to 50% 1,1-biphenyl dust on zeolite, 7 hr/d, 5 d/wk, 13 wks	0, 1.04, 8.33, 62.5	No effects observed in rabbits Irritation of the mucous membranes and increased mortality in rats All mice exhibited irritation of the upper respiratory tract and inflammatory bronchopulmonary changes at 1.04 (the only tested concentration)	None 1.04 for rats None	Not run	None None None	Deichmann et al. (1947) as cited in Boehncke et al. (1999)
	Chronic	None						

[a]Notes: IRIS = Utilized by IRIS, date of last update; PS = Principal study, PR = Peer Reviewed; NPR = Not peer reviewed; HEC = human equivalent concentration.
[b]Dosimetry, NOAEL, BMDL/BMCL, and LOAEL values are converted to human equivalent dose (HED in mg/kg-day), human equivalent concentration (HEC in mg/m^3), or average daily dose (ADD or $Dose_{ADJ}$ in mg/kg-day) units. Noncancer oral data are only adjusted for continuous exposure.
[c]Not reported by the study author but determined from data.

BMDL/BMCL = benchmark dose lower bound 95% confidence interval/benchmark concentration lower bound 95% confidence interval, LOAEL = lowest-observed-adverse-effect level, and NOAEL = no-observed-adverse-effect level.

HUMAN STUDIES

Oral Exposures

No studies investigating the effects of subchronic- or chronic-duration oral exposure to 1,1-biphenyl in humans have been identified.

Inhalation Exposures

Hakkinen et al. (1973) conducted an occupational study of 33 workers (32 men and 1 woman) exposed to 1,1-biphenyl in a citrus packaging plant. The work employment varied between 5 and 16 years. Of the 33 workers, 6 were "oil men," or worked in the mixing room, or "oil room," where 1,1-biphenyl concentrations were found to be higher than in other areas of the plant. Thirteen men worked on the paper machine, seven men worked at the rolling machine, four men handled the residue mass, one man was a maintenance worker, and the remaining man was a stock keeper. The one woman worked as a paper cutter. Air concentrations in the paper machine hall of the plant ranged from 4.4 to 128 mg/m^3 prior to the installation of a "simple exhaust hood," and from 0.6 to 64 mg/m^3 after the installation of the exhaust hood. Concentrations in the oil room were not measured prior to the exhaust hood being installed; they ranged from 3.5 to 123 mg/m^3 after the exhaust hood was installed. No control group was used for this study.

Hakkinen et al. (1973) reported that common complaints of those exposed were headache, gastrointestinal symptoms, polyneuritic symptoms, and fatigue. Ten of the subjects showed elevated transaminase levels. Eight men were admitted to the hospital during the course of the study for further testing based on the results of anamnestic data, clinical findings, or pathological lab tests performed on all subjects. The exposure duration ranged from 5 to 16 years for the eight men admitted for further testing. Hospital patients and 14 additional men were given neurophysiological exams. Out of the 22 men examined, 19 had abnormal pathologies, and 4 had ambiguous pathological findings. Of the remaining 15 men, 3 had abnormal electroencephalograms (EEGs), 5 had abnormal electromyogram (ENMGs), and 7 had both an abnormal EEG and ENMG. The study authors concluded that 1,1-biphenyl exerts a toxic effect on both the brain and peripheral nervous system. A liver biopsy, performed on the eight hospitalized patients, showed liver damage in five patients and three with hepatic cellular changes. Based on these findings, the authors concluded that 1,1-biphenyl exerts a toxic effect on the liver. Confounding factors such as smoking and alcohol use were not accounted for, but all workers had stable employment for many years and were not known to abuse alcohol. Because Hakkinen et al. (1973) did not report quantitative dose-response data, no NOAEL or NOAEL has been established and cannot be used as a principal study.

Other Exposures

An additional study analyzing the occupational risks associated with 1,1-biphenyl is presented as follows. Carella and Bettolo (1994) described the case study of a 46-year-old female patient with chronic-duration exposure, presumed to be from oral and dermal contact with 1,1-biphenyl in a citrus packaging plant. The patient worked for 25 years with 1,1-biphenyl-impregnated paper and claimed to have to "put her finger in her mouth" to facilitate the packaging process. She was admitted to the hospital with twice the normal level of serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase (SGOT/SGPT; 62/90 mU/ml), alkaline phosphatase (ALP; 320 mU/ml), and gamma-glutamyl transferase (GGT; 970 IU/L). Doctors confirmed a moderately enlarged liver by ultrasound. The patient previously reported episodes of asthenia, marked by transaminase levels at two to three times normal. A

gradual reduction in asthenia occurred within 3 years of the patient stopping work in the citrus plant, which was accompanied by the reduction to normal of the transaminase, ALP, and GGT levels. The patient claimed to have never abused alcohol and was not a smoker.

While both the inhalation exposure and case study provide important data that together support the possibility of chronic effects of 1,1-biphenyl, they are limited by the small sample size analyzed, as well as the scope of the outcomes and analysis available. Furthermore, little information is known regarding the measurement and estimation of dose throughout the exposure period. These studies do not support the derivation of a provisional toxicity value.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to 1,1-biphenyl have been evaluated in subchronic-duration (Tamano et al., 1993; Shibata et al., 1989; Umeda et al., 2004), chronic-duration (Ambrose et al., 1960; Takita, 1983; Umeda et al., 2002, 2005), and reproductive (Ambrose et al., 1960) and developmental (Khera et al., 1979) toxicity studies.

Subchronic-duration Studies

Shibata et al. (1989) conducted a peer-reviewed, subchronic-duration study of 12 bladder tumor promoters, including 1,1-biphenyl, on F344 male rats of 5 weeks of age at the commencement of the study. The study authors administered 0.5% 1,1-biphenyl (purity not specified) in a powdered basal diet to 10 males per dose, 7 days a week, for 8 weeks. The corresponding adjusted daily dose ($Dose_{ADJ}$) is 500 mg/kg-day. Simultaneous controls of 10 male mice were fed an untreated powdered basal diet. Animals were observed daily, and body weight and food and water consumption were measured weekly. Four weeks into the study, five rats were sacrificed for histopathologic examination by light microscopy and estimation of deoxyribonucleic acid (DNA) synthesis levels. At the conclusion of the 8-week study, morphological investigation was conducted by light microscopy and scanning electron microscopy in the urinary bladder. No other organs were tested (Shibata et al., 1989).

The study authors reported a significant decrease in body weights compared to the control group at both 4 and 8 weeks. Microcalculi and increased bromodeoxyuridine (BrdU)[1] staining were observed in rats administered 1,1-biphenyl at 4 weeks. At 8 weeks, moderate incidence of simple hyperplasia, pleomorphic microvilli, and short uniform microvilli, and severe incidence of ropy microridges were identified. Table B.1 (see Appendix B) presents the increased incidence of simple hyperplasia and microcalculi formation in exposed animals. Due to the microcalculi incidence and BrdU incorporation observed in the exposed animals, a LOAEL adjusted to continuous exposure duration ($LOAEL_{ADJ}$) of 5.00×10^2 mg/kg-day was established, but a no-observed-adverse-effect level (NOAEL) could not be determined. This study will not be used to support the development of a p-RfD because a NOAEL could not be identified, and while the lowest-observed-adverse-effect level (LOAEL) from this study is lower than the LOAEL from the Umeda et al. (2004) study, the protocol used by Shibata et al. (1989), consisting of fewer animals for a shorter time period and with only one dose-level administered, increases the uncertainty of the results of the study.

[1]Bromodeoxyuridine (BrdU) test is used in the detection of proliferating cells in living tissues.

Umeda et al. (2004) conducted a 13-week subchronic-duration toxicity study using 10 male and 10 female Crj:BDF1 mice of 6 weeks of age per dose group. The study was designed to determine if feeding mice a 1,1-biphenyl-containing diet for 90 days induces peroxisome proliferation in the liver. The mice were treated with 1,1-biphenyl (purity >98%) at 0, 500, 2000, 4000, 8000, 10,000, and 16,000 ppm in the diet, 7 days a week, for 13 weeks. Dose levels were increased stepwise to prevent taste aversion in groups fed more than 4000-ppm 1,1-biphenyl. Mice fed 8000- and 10,000-ppm-1,1-biphenyl diets were first fed 4000 ppm for the first week, and those fed 16,000 ppm were first fed 4000 ppm for the first week and 8000 ppm for the second week. The corresponding $Dose_{ADJ}$ are 0, 94.6, 378, 757, 1456, 1805, and 2737 mg/kg-day and 0, 101, 404, 809, 1556, 1929, and 2924 mg/kg-day for males and females, respectively. The study authors recorded mortality and clinical observations daily, while body weight was measured weekly. At the 13-week point, the study authors recorded weight measurements and microscopic observations of the liver. No other organ or tissue evaluation results were reported (Umeda et al., 2004).

Umeda et al. (2004) reported one mouse death: a female in the 16,000-ppm dose group. After 13 weeks of treatment, body weights of mice in the 8000-, 10,000-, and 16,000-ppm 1,1-biphenyl dose groups were significantly lower than their respective controls (for males: 83.3%, 84.9%, and 75.1%, for females: 93.7%, 91.6%, and 85.8%, respectively). The study authors stated (without giving the quantitative data) that female mice in the 8000- and 16,000-ppm dose groups displayed significantly higher liver weights. Histopathological changes characterized by enlarged centrilobular hepatocytes filled with multiple eosinophilic fine granules in the centrilobular area, and peroxisomes were observed in female mice treated with 16,000-ppm (2924-mg/kg-day) 1,1-biphenyl. The study authors concluded that oral administration of 1,1-biphenyl induced enlargement of hepatocytes filled with eosinophilic fine granules. The study authors also concluded that administration of 2924 mg/kg-day 1,1-biphenyl caused peroxisome proliferation in female mice. Based on this finding, a $LOAEL_{ADJ}$ of 2.924×10^3 mg/kg-day and a NOAEL adjusted to continuous exposure duration ($NOAEL_{ADJ}$) of 1.929×10^3 mg/kg-day are established. The absence of test results of other organs (e.g., bladder, kidneys), statistical data (mean and variance) for body weight and relative liver weight, and histopathological changes limits the utility of the study for drawing a dose-response relationship curve between the 1,1-biphenyl oral exposure and liver effects, as well as its comparability with other available studies in the database.

Tamano et al. (1993) conducted a two-part, peer-reviewed, carcinogenicity study. In the first experiment, the study authors maintained groups of 20 male $B6C3F_1$ mice on drinking water with and without an tumor initiator 0.05% *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine (BBN) supplement for 4 weeks before administering a diet containing 1%-1,1-biphenyl (purity not specified), 7 days a week, for 32 weeks. The corresponding $Dose_{ADJ}$ is 1803.8 mg/kg-day. The study authors recorded clinical observations daily and body weights weekly for the first 5 weeks, every 4 weeks thereafter, and at study termination. At the 37-week point, the study authors recorded weight measurements for the urinary bladder. Additionally, at the 37-week point, the study authors performed histological examinations on the urinary bladder and kidney of every test animal. In the second part of the study, the study authors fed groups of seven male $B6C3F_1$ mice a powdered basal diet containing 1%-1,1-biphenyl, 7 days a week, for 8 weeks. Urinary pH and sodium levels were measured from urine samples collected at Weeks 2, 4, 6, and 8. At the 9-week point, mice were injected with BrdU at a dose of 100 mg/kg body weight, and the

numbers of bladder epithelial cells incorporating BrdU into the DNA per 1000 cells were recorded.

In the first portion of the study, the final average body weight was significantly lower, and relative urinary bladder weights were significantly higher in mice administered a diet containing 1,1-biphenyl following a BBN supplement, but not in those fed 1,1-biphenyl without BBN pretreatment (see Appendix B, Table B.2). One mouse exposed to 1,1-biphenyl alone displayed urolithic residues, which was associated with the induction of papillary nodular (PN) dysplasia of the urinary bladder. No significant differences in the incidences of simple hyperplasia, papillary or nodular dysplasia, or squamous cell carcinoma were observed in mice administered 1,1-biphenyl, but incidences of interstitial nephritis in the kidneys were reported to be 65 and 50% for those with and without BBN pretreatment, respectively, but no further data on that endpoint were provided. In the second experiment, mice administered 1,1-biphenyl did not display elevated urinary pH levels. At Week 4, significantly lower sodium concentrations were observed in mice exposed to 1,1-biphenyl and pretreated with BBN. No significant differences in BrdU labeling of the DNA in the urinary bladder epithelium were observed. Because no effects were observed with 1,1-biphenyl alone, a $NOAEL_{ADJ}$ of 1.8038×10^3 mg/kg-day was established, but no LOAEL could be determined. This study is not used to support a p-RfD because only one dose level was administered, and no effects were observed.

Chronic-duration Studies

Four studies are summarized in this section. The Ambrose et al. (1960) study is used by IRIS (U.S. EPA, 2010a) for deriving a chronic RfD. The Umeda et al. (2005) study is used to support the development of an oral slope factor (OSF), and the other two—Takita (1983) and Umeda et al. (2002)—are supporting studies.

Ambrose et al. (1960) reported the results of a chronic-duration toxicity study funded by the Dow Chemical Company (SRI, 1953 as cited by Ambrose et al., 1960) that examined 1,1-biphenyl toxicity in weanling albino rats (strain not specified). The study authors exposed groups of 15 male and 15 female rats to 0.0, 0.001, 0.005, 0.01, 0.05, 0.10, 0.50, and 1.0% 1,1-biphenyl (purity not specified) in the diet, 7 days a week, for 700 days. The corresponding $Dose_{ADJ}$ are 0, 0.723, 3.62, 7.23, 36.2, 72.3, 362, and 723 mg/kg-day and 0, 0.820, 4.10, 8.20, 41.0, 82.0, 410, and 820 mg/kg-day for males and females, respectively. The study authors recorded body weights weekly during the period of growth, every 50 days thereafter, and at termination. Hemoglobin values for rats in the 0.0- and 1.0%-1,1-biphenyl dose groups were taken every 100 days, while rats in the 0.5%-dose group were hemoglobin tested at the end of 500, 600, and 700 days, and animals in the 0.1%-dose group were hemoglobin tested at the end of 500 and 700 days. Paired feeding experiments were conducted for animals in the 1.0-and 0.5%-dose groups. The study authors recorded all instances of abnormal tissue growth. After 700 days, the study authors recorded weight measurements for the liver, kidneys, heart, and testes. Histopathological examinations were performed on all test animals.

Male and female rats in the 1.0%-dose groups showed lowered hemoglobin values and body weights after 300 and 400 days, respectively, and the 0.5%-dose group had lowered hemoglobin values after 500 and 600 days (Ambrose et al., 1960). However, the study authors concluded that this may be due, in part, to decreased food intake as a result of decreased palatability. Ambrose et al (1960), reported that abnormal tissue growth, mostly in the form of mammary tumors and polyps, was observed after 500 days in 2 male and 26 female rats in 1.0-

and 0.5%-dose groups. Also, Ambrose et al. (1960) reported graphically a positive relationship between growth rate and body weight in rats fed 1.0 and 0.5% biphenyl, pair-fed controls, and controls fed ad libitum (see Figures 1 and 2 in the original article not shown in this PPRTV). After 700 days of treatment, male and female rats in the 1.0- and 0.5%-dose groups displayed significantly decreased body weights and longevity (see Appendix B, Table B.3). The weights of liver and kidneys increased in female rats treated with 0.5% (410 mg/kg-day) (see Appendix B, Table B.3). Growth inhibition of male and female rats in the 0.5- and 1.0%-dose groups was attributed to decrease food intake. Reduced hemoglobin values may also be due, in part, to decreased food intake. Prominent irregular scarring, lymphocytic infiltration, tubular atrophy, and patchy tubular dilation to the point of cyst formation were observed in the kidneys of all male and female mice in the 0.5%- (362 or 410 mg/kg-day) and 1.0%-dose groups (723 or 820 mg/kg-day), respectively, and were attributed to biphenyl treatment. Ambrose et al. (1960) reported mean and standard error of hemoglobin, body weight food intake and organ weights of both male and female rats were, but there is no indication as to what type of statistical test was performed and because only processed data was reported no additional statistical analysis has been performed. Based on these findings, a $LOAEL_{ADJ}$ of 3.62×10^2 mg/kg-day and a $NOAEL_{ADJ}$ of 7.23×10 mg/kg-day are identified.

In a peer-reviewed publication, Umeda et al. (2002) reported the results of a 2-year chronic-duration toxicity and carcinogenicity study. The study authors exposed groups of 50 male and 50 female F344 rats to 0-, 500-, 1500-, or 4500-ppm 1,1-biphenyl (purity >98%) in the diet, 7 days a week, for 105 weeks. The corresponding $Dose_{ADJ}$ are 0, 39.5, 118, or 355 mg/kg-day and 0, 45.9, 138, or 413 mg/kg-day for males and females, respectively. The corresponding human equivalent doses (HEDs) are 0, 10.7, 32.1, or 96.4 mg/kg-day and 0, 11.0, 32.9, or 98.7 mg/kg-day for males and females, respectively. (See Appendix A, "Derivation of Screening Provisional Oral Slope Factor" for a representative step conversion from animal dose to HED). The study authors recorded body weights and clinical observations weekly for the first 14 weeks, every 4 weeks thereafter, and at termination. At the 105-week point, the study authors recorded urinary parameters, including pH and occult blood, of all surviving rats (105-week measurement only). Additionally, at the 105-week point, the study authors recorded weight measurements and macroscopic observations for the bladder, kidney, and ureter. The study authors performed complete histopathological examinations (including neoplastic and nonneoplastic lesions and tissue masses) on all test animals.

After 105 weeks of treatment, male and female rats displayed significantly decreased body weights, and male rats showed decreased survival rates in the 4500-ppm dose group. Thirty-two males in the 4500-ppm dose group displayed clinical hematuria, with nearly half with hematuria showing anemia-colored skin and/or eyes. Urinary pH in male rats and occult blood incidence in male and female rats were significantly increased in the 4500-ppm group. At the 105-week point, male and female rats showed significantly increased relative kidney weights in the 1500- and 4500-ppm dose groups, and increased absolute kidney weights in males in the 4500-ppm dose group only. Forty-three males and eight females in the 4500-ppm group displayed bladder calculi.

Neoplastic and nonneoplastic lesions were observed only in the urinary tract, as shown in Tables B.4 and B.5. Incidences of transitional cell hyperplasia, squamous cell hyperplasia, and squamous cell metaplasia in the urinary bladder and of simple transitional cell hyperplasia and dilatation of the lumen in the ureter were significant only in male rats exposed to 96.4 mg/kg-day

1,1-biphenyl. In the renal pelvis, incidences of simple hyperplasia in the female 1500-ppm were significant, and incidences of nodular hyperplasia were significant in the 4500-ppm group for both male and female rats. Mineralization of the cortico-medullary junction and papilla was significant in males in the 4500-ppm group. Mineralization of papilla, papillary necrosis, infarct, and hemosiderin deposition was significant in females in the 4500-ppm group, with hemosiderin deposition also significant in females exposed in the 1500-ppm dose group. The study authors proposed that the bladder tumors observed were caused by mechanical damage to the tissue by the bladder calculi, which were observed at high incidence (86%) in males in the 4500-ppm dose group. More than 93% of the bladder tumors, hyperplasia of the urinary system, and hematurias of the bladder or kidneys were observed to contain calculi. The study authors further suggested that the difference in response between the male and female exposed rats may be due to differences observed in the sizes and shapes of the calculi, which are proposed to be caused by differences in 1,1-biphenyl metabolism. Based on the histological findings, the study authors concluded that 1,1-biphenyl was carcinogenic to male rats in the conditions used for this assay. An increased incidence of bladder tumors, hematuria, and neoplastic regenerative lesions of the urinary system in males supports a $LOAEL_{HED}$ of 9.64 ×10 mg/kg-day and a $NOAEL_{HED}$ of 3.21 × 10 mg/kg-day. The bladder tumor response was not observed in the first three dose-group levels. It was observed only in male rats at the highest level. Because the effect level was relatively higher, and there was a steep response of about 40% bladder tumors in male rats at the highest dose (96.4 mg/kg-day) after the absence of bladder tumors in the control group and the first two dose-group levels (0, 10.7, 32.1 mg/kg-day) of male rats, this study is less preferred for use as the principal study for deriving a p-OSF.

The original source of Takita (1983), published in Japanese with only an abstract, tables and graphics in English were unavailable for review at this time. The information from this study was reviewed by WHO (Boehncke et al., 1999) and will be used for the purposes of this document. 1,1-Biphenyl (purity not specified) concentrations of 0, 2500, and 5000 mg/kg and 0, 630, and 1250 mg/kg in the diet were administered to Wistar rats (50/sex/dose group), 7 days a week, for 75 or 104 weeks. The corresponding $Dose_{ADJ}$ are 0, 188, and 375 mg/kg-day for the 75-week study and 0, 47, and 94 mg/kg-day for the 104-week study. Method of data collection and analysis are not discussed in the WHO document (Boehncke et al., 1999). The 75-week study reported dose-dependent effects on the reduction of weight gain and activities of serum transaminase, alanine transaminase, and lactate dehydrogenase (LDH). Both males and females showed a dose-dependent increase in stones of the kidney and ureter (see Appendix B, Table B.6), which was seen in conjunction with haematuria from 16 weeks of exposure at a dose of 188 mg/kg-day. At a dose of 375 mg/kg-day, relative kidney weights were found to be significantly increased in the females, and an increase in stones of the urinary bladder was observed in both males and females. Histopathology of urinary bladders showed simple or diffuse hyperplasia and papillomatosis of the epithelium in bladders with stones. Tumor incidence was not increased over controls. Those kidneys with stones also displayed obstructive pyelonephritis, tubular atrophy, and fibrosis. Kidney stones were composed of protein, and urinary stones were composed of magnesium ammonium phosphate. The 104-week study reported no urolithiasis and no increased tumor incidence. Dose-dependent effects were reductions in weight gain and activities of serum transaminase, alanine transaminase, and LDH in both the 47- and 94-mg/kg-day dosed animals (data not reported). The study authors reported a $LOAEL_{ADJ}$ of 4.7 × 10 mg/kg-day based on body-weight loss seen in both sexes. Because this is the lowest dose investigated in the study, a NOAEL could not be identified.

The study by Umeda et al. (2005) is selected as the principal study for deriving the p-OSF. Umeda et al. (2005) published a peer-reviewed, 2-year, chronic-duration toxicity and carcinogenicity study in Crj:BDF1 mice. The study authors exposed groups of 50 male mice to 0, 97, 291, or 1050 mg/kg-day and 50 female mice to 0, 134, 414, or 1420 mg/kg-day 1,1-biphenyl (purity >98%) in the diet, 7 days a week, for 104 weeks. The corresponding HEDs are 0, 15.3, 45.8, or 154.0 mg/kg-day and 0, 19.7, 59.8, or 196.2 mg/kg-day for males and females, respectively. The study authors recorded body weights and clinical observations weekly for the first 14 weeks, every 4 weeks thereafter, and at termination. At the 104-week point, the study authors recorded weight measurements and macroscopic observations of all organs. Additionally, at the 104-week point, the study authors measured hematological and blood biochemical parameters of all surviving mice. Additionally, the study authors performed complete histopathological examinations (including neoplastic and nonneoplastic lesions and tissue masses) on all test animals.

No differences in survival rate, clinical signs, organ weight (with the exception of relative liver weights in female mice), or any hematological parameter were observed in any exposure group, regardless of sex (Umeda et al., 2005). After 104 weeks of treatment, male and female mice displayed significantly decreased body weights in the middle- and high-dose groups. Dose-dependent increases of glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) in the serum were observed in females exposed to 414 and 1420 mg/kg-day. Significant increases of ALP were shown in males and females fed the high-dose diets, and a significant increase of LDH was measured in females fed the high dose. Blood urea nitrogen (BUN) was significantly increased in males in the middle- and high-dose groups and females. Significantly increased levels of sodium and chloride and decreased levels of potassium were observed in males fed 1,1-biphenyl, while sodium and calcium levels increased in females fed 1,1-biphenyl. Relative liver weights of female mice fed 134, 414, and 1420 mg/kg-day in the diet were increased 1.3-, 1.4-, and 1.6-fold, respectively. A dose-related increase of liver nodules was observed in females.

Neoplastic lesions were observed in the liver with a greater increase in the treated females and nonneoplastic lesions in the kidneys of male and female mice (Umeda et al., 2005). A dose-related increase in hepatocellular adenomas and carcinomas was observed in females fed 414- and 1420-mg/kg-day diets, and significantly increased hepatocellular carcinomas were also observed in females fed a 414-mg/kg-day diet (see Appendix B, Table B.7). Significantly increased incidence of basophilic cell foci was observed in females exposed to 414 and 1420 mg/kg-day and males exposed to 97 mg/kg-day (see Appendix B, Table B.8), although the effect in the males was not dose related. Incidence of clear cell foci also was significantly increased in males treated with 97 mg/kg-day (see Appendix B, Table B.8). In the renal pelvis, incidences of desquamation of the urothelium were significantly increased in males and females fed the high-dose diet. In the kidney, incidences of mineralization in the inner stripe of the outer medulla were significantly increased in females fed 414- and 1420-mg/kg-day diets.

Umeda et al. (2005) concluded that chronic-duration oral exposure to 1,1-biphenyl induced preneoplastic and neoplastic lesions in the livers of female mice, and nonneoplastic lesions in the kidneys of male and female mice. The incidence of preneoplastic lesions observed in the males was not dose related and may be an artifact of the staining method used in this study. Microscopic examination of the liver tissue, together with a previous study from this group (Umeda et al., 2004), support the theory suggested by the authors that peroxisome

proliferation in the liver of the female mice causes the incidence of liver tumors observed in the female mice. Based on increased incidence of hepatocellular tumors in females, a $LOAEL_{HED}$ of 5.98×10 mg/kg-day and a $NOAEL_{HED}$ of 1.97×10 mg/kg-day are identified. Umeda et al. (2005) is selected as the principal study to support the development of a p-OSF because the study authors observed a lower LOAEL compared to Umeda et al. (2002), and there was a dose-response trend at all dose levels except the highest, which showed reduced—but statistically significant—incidence of combined hepatocellular adenoma and carcinoma in female mice compared to the control. In addition to liver tumors, Umeda et al. (2005) observed nonneoplastic lesions in the kidneys of both male and female mice. Alternatively, the Umeda et al. (2002) study showed a steep response of about 40% bladder tumors in male rats at the highest dose (96.4 mg/kg-day) following the absence of bladder tumors in the control group and the first two dose levels (10.7, 32.1 mg/kg-day) of male rats. No bladder tumors were observed in female rats, and no other organ response was reported.

Developmental and Reproductive Studies

There are limited data on the reproductive toxicity of 1,1-biphenyl: only one oral developmental study (Khera et al., 1979) and one generation reproductive study (Ambrose et al., 1960). No other developmental or multigeneration studies were located.

The study by Khera et al., 1979 is selected as the principal study for deriving the subchronic p-RfD. In a peer-reviewed teratogenic study, Khera et al. (1979) reported the effects of treating Wistar rats with 1,1-biphenyl (purity not specified) during Gestational Days (GDs) 6 to 15. Female rats, 18 to 20 per dose group, were administered 0, 125, 250, 500, or 1000 mg/kg-day by gavage. The study authors paired females with proven males and considered a positive vaginal smear to be GD 1. Body weights were taken on GD 1, GDs 6−15, and again on GD 22. All females were sacrificed on GD 22 and weighed following removal of uterine contents and counting of the corpora lutea. Necropsies were performed on the dams, and fetuses were weighed and examined for external malformations. Parameters evaluated at autopsy included the number of corpora lutea, fetal weights and viability, and early resorptions. Two-thirds of the live fetuses/litter were examined for skeletal development and the rest were examined for the presence of visceral abnormalities. Five of the 20 high-dose dams died prior to sacrifice. Doses ≤500 mg/kg-day produced no clinical signs of maternal toxicity or evidence of treatment-related effects on maternal weight gain. As shown in Table B.9, a significantly increased number of dams without live fetuses was observed in the high-dose group, compared with controls. Mean numbers of corpora lutea and live fetuses in the high-dose dams were similar to those of controls and dams of all other dose levels. However, the percent of dead fetuses and resorption sites was clearly higher in the high-dose group, and the numbers of anomalous fetuses and litters bearing anomalous fetuses appeared to increase with increasing dose. Khera et al. (1979) noted that the slight increases in the number of fetuses with anomalies, such as missing and unossified sternebrae or delayed calvarial ossification, were not statistically significant, but, as shown in Table B.9, the incidence of litters with any type of fetal anomalies ("anomalous litters/number examined") was elevated ($p < 0.05$ by Fisher's exact test) at 500 mg/kg-day, but not at lower doses, compared with control incidences. This study identified a NOAEL of 500 mg/kg-day and a LOAEL of 1000 mg/kg-day for frank maternal toxicity (increased mortality and decreased dams with live fetuses) and lethal fetal effects. For less severe developmentally toxic effects (increased incidence of anomalous litters), 500 mg/kg-day was a LOAEL and 250 mg/kg-day was a NOAEL.

Ambrose et al. (1960) reported the results of two peer-reviewed, reproductive toxicity studies in rats. Animals were exposed to 0, 0.1, or 0.5% 1,1-biphenyl from mating until weaning of litters (7 days per week during two months for both control and exposed rats). The corresponding $Dose_{ADJ}$ are 0, 72.3, and 362 mg/kg-day and 0, 82.0, and 410 mg/kg-day for males and females, respectively. Ten female and five male albino rats of weanling age were mated: two females to one male. In the subsequent experiment, eight to nine females and three to four male albino rats were exposed and mated in unspecified ratios. Little information is available on the methods used during this study, but the study authors concluded that 1,1-biphenyl exposure had no effect on the reproductive success in either experiment. Table B.10 presents these results (see Appendix B).

Boehncke et al. (1999) summarized results of an unpublished three-generation study. Dietary 1,1-biphenyl concentrations of 100 or 1000 mg/kg (estimated intakes of approximately 7.5 or 75 mg/kg-day) had no effect on reproduction in rats; following intake of 10,000 mg/kg (estimated intake of 750 mg/kg-day), decreased fertility, litter size, and growth per day were noted. The study was performed by SRI (1953); no further information was provided by Boehncke et al. (1999) and the original report was not available for review. Because this study did not provide necessary details of design and performance it is considered unsatisfactory as a multigeneration reproductive study and may not be used in considering the database uncertainty factor (UF_D). Although decreased fertility, litter size, and growth per day were noted at 750 at a dose of 75 mg/kg-day, all necessary parameters were not reported (Boehnche et al., 1999).

Dow Chemical Co. (1953) reported the results of a multigenerational study in which groups of 4-month-old male and female Long Evans rats (three males and nine females/group) were fed diets containing 0, 0.01, 0.1, or 1.0% biphenyl. Based on EPA (1988) subchronic reference values for body weight and food consumption in male and female Long Evans rats, doses of biphenyl for the dietary levels of 0.01, 0.1, and 1.0% are estimated to be 9, 89, and 887 mg/kg-day, respectively, for the males and 10, 101, and 1006 mg/kg-day, respectively, for the females. Average cross-gender doses for males and females were 10, 95, and 947 mg/kg-day. For breeding, three females were placed together with one male. Following the breeding phase, females were separated and number of litters cast, number of days between mating and delivery, and average number of pups/litter at delivery were recorded. F1 pups were weighed and culled to seven/litter at 2 days of age and weaned at 3 weeks of age, and weights were recorded weekly for Postnatal Weeks 3–6. The F1 rats were continued on the same diets as their parents, and, at 10 weeks of age, nine F1 females and three F1 males were mated to produce an F2 generation of pups. F2 pups were selected (by the same procedure) for mating and production of an F3 generation that were sacrificed at 3 weeks of age; twelve F3 pups from each diet group were subjected to gross pathologic examinations. There were no significant differences between controls and 0.01 and 0.1% biphenyl-fed groups regarding litters cast; gestation length; or average number or weight of pups/litter at birth or at 3 or 6 weeks of age. Decreased fertility in the 1% biphenyl-fed group of females was observed (6/9, 7/9, and 8/9 confirmed pregnancies for the three successive generations of 1.0% biphenyl-fed groups vs. 8/9, 9/9, and 8/9 confirmed pregnancies for controls). Averaged for F1, F2, and F3 pups combined, the 1.0% biphenyl-fed group exhibited significantly ($p < 0.05$) decreased number of pups/litter at birth (6.2/litter vs. 8.6/litter for controls) and lower average body weight at 3 weeks of age (36 vs. 48 g for controls) and 6 weeks of age (78 vs. 113 g for controls). Gross pathologic evaluations of F3 weanlings revealed no signs of biphenyl treatment-related effects. There was no evidence of a cumulative effect over the three generations. The study authors indicated that

the decreased fertility, smaller litter size, and reduced rate of growth in the 1.0% biphenyl-fed group may have been associated with unpalatability and resultant decreased food intake.

Inhalation Exposures

The effects of inhalation exposure of animals to 1,1-biphenyl have been evaluated in several subchronic-duration studies (Cannon Laboratories, Inc., 1977; Monsanto Chemical Co., 1983; Boehncke et al., 1999), but no chronic-duration, developmental, or reproductive toxicity studies could be identified. The report by Monsanto Chemical Co. (1983) consists of three separate subchronic-duration inhalation studies.

Subchronic-duration Studies

The study by Cannon Laboratories, Inc. (1977) is selected as the principal study for deriving subchronic and chronic p-RfCs. Cannon Laboratories, Inc. (1977) conducted an unpublished, 90-day, subchronic-duration toxicity study. The study authors exposed groups of 50 male and 50 female CD1 mice to atmospheric concentrations of 0, 25, and 50 ppm 1,1-biphenyl (>99% purity), 7 hours per day, 5 days per week (equivalent to continuous exposure of 0, 32.8, and 65.5 mg/m^3), for 13 weeks. 1,1-Biphenyl was submerged in an oil bath, heated to melt, volatilized, and introduced in a chamber as a 1,1-biphenyl-air mixture. Sampling difficulties resulted in unusable data for the first 3 days of the 32.8-mg/m^3 study and the first 5 days of the 65.5-mg/m^3 study. Overheating and cannibalization by cage mates forced the replacement of 46 mice, causing the 32.8-mg/m^3 study to run 117 days to ensure all replacement mice received exposure according to the protocol. Once the analytical technique was corrected, significant variation in chamber concentration was noted for the next few days and corrected by adjusting the amount of inlet air and the temperature of the oil bath. For the 25-ppm study, the concentration throughout the 117 days was 25 ± 7 ppm (equivalent to a human equivalent concentration [HEC] of 72.9 ± 20 mg/m^3, 92.6 ± 26 mg/m^3 for respiratory effects in females and males, respectively, and 32.8 ± 9 mg/m^3 for extrarespiratory effects in both sexes). During the last 72 days (after the proper chamber parameters were obtained), the concentration was 26.5 ± 1 ppm (HEC of 76 ± 3 mg/m^3, 98.4 ± 4 mg/m^3 for respiratory effects in females and males, respectively, and 34 ± 1 mg/m^3 for extrarespiratory effects in both sexes). For the 50-ppm study, the average concentration throughout the 72 days was 50 ± 16 ppm (HEC of 146.4 ± 36 mg/m^3, 189.9 ± 61 mg/m^3 for respiratory effects in females and males, respectively, and 65.5 ± 21 mg/m^3 for extrarespiratory effects in both sexes). During the last 55 days, the average concentration was 51.4 ± 9.6 ppm (HEC of 150.5 ± 28.1 mg/m^3, 195.2 ± 36.5 mg/m^3 for respiratory effects in females and males, respectively, and 67.8 ± 13 mg/m^3 for extrarespiratory effects in both sexes).

The study authors recorded clinical observations daily and body weights of five mice weekly, from which an average weight per mouse was determined. At the 14-week point, the study authors microscopically observed urine samples and recorded specific gravity, pH, ketones, and glucose levels. Additionally, at the 14-week point, blood for each group of animals was collected and pooled for hematological analysis. Gross and histopathological examinations were performed on all mice. Ten males and 10 females from each group were held for a 30-day recovery period before being analyzed.

Table B.11 (see Appendix B) presents histopathological results for the 13-week study. All (80/80) control mice, 18/98 mice exposed to 32.8 mg/m^3, and 1/71 mice exposed to 65.5 mg/m^3 of 1,1-biphenyl displayed normal tracheas. Hyperplasia with inflammation was

observed in 80/98 mice exposed to 32.8 mg/m^3, and all but one (70/71) mouse exposed to 65.5 mg/m^3 of 1,1-biphenyl. The authors reported that these findings were both significant ($p < 0.05$, Fisher's exact test) and dose dependent. Also, the study authors reported that lungs were within normal limits for all control mice (80/80), while a significant and dose-dependent incidence of congestion, and edema was observed in the majority of mice exposed to 32.8 mg/m^3 (95/98) and all mice exposed to 65.5 mg/m^3 (71/71). This was accompanied by pneumonia in 15/98 and 20/71 mice exposed to the lower and higher doses, respectively. At 32.8 mg/m^3, 1/98 had an abscess, and 2/98 had neoplasia (sarcoma of the lung). All but two (78/80) control mice and 11/98 mice exposed to 32.8 mg/m^3 displayed a liver within normal limits, and abscesses were observed in 2/80 control mice. The majority (87/98) of mice exposed to 32.8-mg/m^3 1,1-biphenyl and all mice (71/71) exposed to 65.5 mg/m^3 1,1-biphenyl had congestion and edema in the liver and kidneys that was significant and dose dependent ($p < 0.05$, Chi-square test). The majority of control mice (76/80) and 11/98 mice exposed to 32.8 mg/m^3 displayed normal kidneys, while 4/80 control mice had abscesses. All control mice (80/80) and all but one (97/98) of the mice exposed to 32.8-mg/m^3 1,1-biphenyl had spleens within normal limits, while a neoplasm (leukemia) was observed in only one (1/98) mouse in this exposure group. A LOAEL adjusted for dosimetric differences across species to a human ($LOAEL_{HEC}$) of 3.28 ×10 mg/m^3 was established for extrarespiratory effects (i.e., congestion and edema in the livers and kidneys of exposed mice). A NOAEL could not be identified.

All mice were allowed a 30-day recovery period, and all control mice (20/20) displayed normal lungs, liver, and kidneys. All mice in the 32.8-mg/m^3 exposure group had normal liver and kidneys; and all mice in the 65.5-mg/m^3 exposure group had normal kidneys (see Appendix B, Table B.12). A normal trachea was observed in 17/20 control mice, 3/15 mice in the 32.8-mg/m^3 exposure group, and 2/19 mice in the 65.5-mg/m^3 exposure group. Chronic inflammation of the trachea was significant at all doses and was determined to be dose dependent by independent statistical analysis conducted for this review (see Appendix B, Table B.12). The incidences were 10/15 and 12/19 in mice exposed to 32.8 mg/m^3 and 65.5 mg/m^3, respectively. A minority of control mice (3/20), mice in the 32.8-mg/m^3 exposure group (2/15), and mice in the 65.5-mg/m^3 exposure group (2/19) displayed hyperplasia with chronic inflammation, and 3/19 mice exposed to the high dose of 1,1-biphenyl had hyperplasia with acute inflammation. Lungs within normal limits were observed in 4/15 and 5/19 mice exposed to low and high doses of 1,1-biphenyl, respectively, while congestion in 6/15 and 2/19 and pneumonia in 5/15 and 12/19 were observed in the lungs of mice exposed to the low and high doses, respectively. A $LOAEL_{HEC}$ of 7.29 × 10 mg/m^3 can be established based on the following respiratory effects: inflammation of the trachea, pneumonia, congestion, and edema in the lungs. No NOAEL could be determined.

Monsanto Chemical Co. (1983) studied the physiological effect of 1,1-biphenyl to Sprague-Dawley albino rats, an unknown sex and strain of mice, and albino rabbits through oral, cutaneous, and inhalation exposures in a unpublished study report. The inhalation exposure was investigated in three separate experiments. The first experiment exposed three rabbits and 10 rats to an average exposure concentration of 0.3 mg/L 1,1-biphenyl (purity not specified), for 7 hours per day, 5 days per week, for a total of 64 out of 94 days. The second experiment exposed three rabbits and six rats to 0.04 mg/L 1,1-biphenyl, for 7 hours per day, 5 days per week, for a total of 46 out of 68 days. The final inhalation experiment exposed four rats and 12 mice to 0.005 mg/L 1,1-biphenyl, for 7 hours per day, 5 days per week, for a total of 62 out of

92 days. The HECs for experiments 1, 2, and 3 are 5.96×10^{-2}, 7.89×10^{-3}, and 9.34×10^{-4} mg/m^3, respectively.

The study authors reported that the rats in the first experiment experienced irritation of the nasal mucosa and serosanguineous and that 5 out of 10 rats died from the first experiments; the surviving rats experienced weight loss averaging 20 grams. The rabbits showed no adverse effects. A $LOAEL_{HEC}$ of 5.96×10^{-2} mg/m^3 was established, but no NOAEL could be determined based on these results. In the second experiment, the rats also experienced irritation of the nasal mucosa. One rat died during the experiment, but the surviving rats gained weight at a normal rate. A $LOAEL_{HEC}$ of 7.89×10^{-3} mg/m^3 was established, but no NOAEL could be determined based on the observed nasal irritation. In the third experiment, rats showed no adverse effects. Mice showed signs of irritation of the upper respiratory tract. A $LOAEL_{HEC}$ of 9.34×10^{-4} mg/m^3 is established, but no NOAEL could be determined based on the documented irritation. Due to poor documentation and a non-Good Laboratory Practice (GLP)-compliant study design, this study is not be used to support derivation of a p-RfC.

The *Concise International Chemical Assessment Document 6: Biphenyl* published by the World Health Organization (WHO) (Boehncke et al., 1999) summarized two subchronic-duration inhalation exposure studies: Sun Co., Inc. (1977) and Deichmann et al. (1947). The study authors of Sun Co. Inc. (1977) exposed groups (n = 50) of male and female CD-1 mice to 25- or 50-ppm (160 or 320 mg/m^3; analytical concentrations) 1,1-biphenyl (99+% purity), for 7 hours/day, 5 days/week, for 13 weeks (correspondent HECs: 0, 32.8, 65.5 mg/m^3), producing hyperemia and focal haemorrhage in the lung and an increase in hyperplasia of the tracheal epithelium. Based on Boehncke et al. (1999), these effects were also observed in some unexposed controls and were attributed to the method of aerosol generation (i.e., inhalation of hot air). The second study, Deichmann et al. (1947), noted marked species differences observed in a study in which rabbits, rats, and mice were exposed by inhalation to 1,1-biphenyl in the form of dust (50% 1,1-biphenyl on zeolite) at 5, 40, or 300 mg/m^3, for 7 hours/day, 5 days/week, for up to 13 weeks. No adverse effects were observed in rabbits (correspondent HECs: 1.04, 8.33, 62.5 mg/m^3). Rats exposed to 40 or 300 mg/m^3 of 1,1-biphenyl exhibited increased mortality and irritation of the mucous membranes; no effects were observed following exposure to 5 mg/m^3 (HEC: 1.04 mg/m^3). Mice were the most sensitive species. Exposure to 5 mg/m^3 (the only concentration tested) resulted in slightly increased mortality, with all mice exhibiting irritation of the upper respiratory tract (no further information was available). Necropsy of dead rats and mice revealed mainly inflammatory bronchopulmonary changes. No information on control animals or particle size was provided. The original articles were not located, and the summary data provided for both studies (Sun Co. Inc., 1977, and Deichmann et al., 1947 as cited in Boehncke et al. [1999]) did not provide sufficient information to support the derivation of a p-RfC.

Chronic-duration Studies

No studies could be located regarding the effects of chronic-duration inhalation exposure of animals to 1,1-biphenyl.

Developmental and Reproductive Studies

No studies could be located regarding the effects of inhalation exposure of animals to 1,1-biphenyl on reproduction and fetal development.

Other Exposures

No pertinent studies could be located regarding the effects of inhalation exposure of animals to 1,1-biphenyl on immunological or neurological toxicity.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

A few studies on the toxicokinetics of 1,1-biphenyl are available (BUA, 1990; Ohnishi et al., 2000; Umeda et al., 2004; Meyer et al., 1976). Results of available studies indicate that 1,1-biphenyl is hydroxylated in the liver upon entering the body in the first phase, irrespective of the route of exposure. The second phase of metabolism is conjugation with sulfate or glucuronide, followed by excretion (Umeda et al., 2005). 1,1-Biphenyl metabolites have been shown to primarily be excreted in the urine of exposed animals, with most of the excretion taking place in the first 24 hours following exposure (Meyer et al., 1976; BUA, 1990). Eight days after administration, only 0.6% of the original dose remained in the tissues of rats (Meyer et al., 1976). No unmetabolized 1,1-biphenyl has been found in excretions (BUA, 1990). The specific metabolism of 1,1-biphenyl seems to be species and sex dependent. 1,1-Biphenyl has been shown to cause calculi in rats, effecting males more than females. An analysis of the composition of these calculi showed that the male stones were composed of potassium 4-hydroxybiphenyl-*o*-sulfate (4-HBPOSK), while the stones in female rats were composed of mostly 4-hydroxybiphenyl (4-HBP) and $KHSO_4$, which were formed by the hydrolysis of 4-HBPOSK (Ohnishi et al., 2000). Mice preferentially metabolize 1,1-biphenyl to 2-hydroxybiphenyl (2-HBP), which is further metabolized to 2,5-dihydroxybiphenyl (2,5-DHBP) and 2-phenyl-1,4-benzoquinone (2-PBQ), a possible peroxisome proliferator and a known genotoxicant, respectively. This pathway difference may be responsible for the hepatotoxicity seen in mice but not rats, as a result of the possible genotoxic mechanism of action of the metabolites (Umeda et al., 2005). Rats, however, particularly males, develop bladder cancers presumed to be a result of calculi formation due to chronic mechanical damage to the bladder epithelium (Umeda et al., 2002). Bentley et al. (1993) studied hepatic peroxisome proliferation in rodents and its significance for humans and reported that marked species differences are apparent in response to peroxisome proliferations. Rats and mice are extremely sensitive, and hamsters show an intermediated response, while guinea pigs, monkeys, and humans appear to be relatively insensitive or nonresponsive at dose levels that produce a marked response in rodents. These findings were consistent with an in vitro study by Clemencet et al. (2005), which evaluated species differences in cell proliferative response to peroxisome proliferators by using rat and human tumor liver cell lines and found that rat 7777 hepatoma cells are more responsive than human hepatocellular liver carcinoma (HepG2) cells.

The genotoxicity of 1,1-biphenyl has been tested in several studies using in vitro test systems (Sasaki et al., 1997; Hirayama et al., 1982; Anderson and Styles, 1978; Wangenheim and Bolcsfoldi, 1988; Williams, 1978; Brouns et al., 1979; Pagano et al., 1983). These test results generally indicate that 1,1-biphenyl does not have mutagenic activity when tested in bacteria, while the majority of mammalian tests indicate some ability to induce gene mutations. Although only one study investigated the genotoxic potential of 1,1-biphenyl in vivo, the results demonstrate that oral exposure can cause DNA damage in the organs of mice, with the kinetics indicating that this activity may be the result of the formation of metabolites (Sasaki et al., 1997). The literature on the mutagenic action of 1,1-biphenyl is equivocal, and further investigations are needed before a conclusive mechanism of action can be established.

Table 3 summarizes the metabolism and genotoxicity studies.

Table 3. Other Studies (CASRN 92-52-4)

Tests	Materials and Methods	Results	Conclusions	References
Metabolism	50 male and 50 female F344/DuCrj rats were treated with 0.45%-1,1-biphenyl in the diet for 104 weeks. Calculi were collected from the urinary bladder upon necropsy. Calculi content was analyzed by high performance liquid chromatography (HPLC). The calculi were analyzed for structure.	86% of treated male rats had calculi in the urinary bladder, and only 16% of female rats had calculi present. Male calculi were primarily composed of potassium salt of 4-hydroxy-biphenyl-*O*-suldfate (4-HBPOSK), while female calculi were composed of 4-hydroxylbiphenyl (4-HBP) and KHSO4. The male calculi were found to have sharp edges composed of multiple layers of $Ca_3(PO_4)_2$, while the female calculi were smoother and more rounded.	Differences in the metabolism of 1,1-biphenyl account for the sex difference seen in calculi incidence in the urinary bladder in rats. Male calculi formation is the result of stable and irreversible metabolism.	Ohnishi et al. (2000)
Metabolism	Single exposure of 1900 mg/kg in an unreported number, strain, and gender of rats and mice.	In rats, rabbits, and pigs, most 1,1-biphenyl metabolites are excreted in the urine. In none of the species examined was unmetabolized 1,1-biphenyl found in the urine.	1,1-biphenyl is conjugated with sulfuric acid or glucuronic acid, followed by excretion in the urine.	The original source of BUA (1990) was unavailable for review at this time. Information presented here is from the WHO report cited as (Boehncke et al., 1999).
Metabolism	Male albino rats were given an oral dose of ^{14}C-biphenyl (100 mg/kg), and excretion was measured every 24 hours for 4 days following dosing.	Urinary excretion was 84.8%, and fecal excretion was 7.3% of the dose. 75.8% and 5.8 % were excreted with urine and feces, respectively, in the first 24 hours. 0.6% of the dose was excreted 96 hours after administration. Nearly 30% of the dose consisted of conjugated phenolic metabolites in the 24-hour samples. Acidic metabolites made up 25% of the administered dose.	1,1-biphenyl was largely excreted by male rats through urine in the first 24 hours.	Meyer et al. (1976)
Genotoxicity	A modified Comet assay was used to test the in vivo genotoxicity of 1,1-biphenyl on stomach, liver, kidneys, bladder, lungs, brain, and bone marrow. Four male CD-1 mice were sacrificed 3, 8, and 24 hours after oral treatment.	2000-mg/kg dose of 1,1-biphenyl induced DNA damage in all the organs studied, with activity peaking 24 hours following exposure, possibly due to the metabolic pathway of 1,1-biphenyl.	Treatment with 1,1-biphenyl caused genotoxicity in all organs examined.	Sasaki et al. (1997)

Table 3. Other Studies (CASRN 92-52-4)

Tests	Materials and Methods	Results	Conclusions	References
Genotoxicity	The mutagenic potential of 1,1-biphenyl and the reactivity of 1,1-biphenyl and NO_x, were assessed using the *Escherichia coli* DNA repair tests in strains WP2, EP2 uvrA, CM571, and WP100 and the Ames test in *Escherichia coli* strains TA98 and TA100, in the absence and presence of metabolic activation (S-9).	1,1-Biphenyl photochemically reacted with NO_x did not have an inhibitory effect on the growth of bacterial cultures. The mixture of 1,1-biphenyl with NOx showed mutagenicity in TA98 and TA100, with more potency observed in the presence of metabolic activation. 1,1-Biphenyl, alone, was not positive for mutagenicity in TA98 or TA100, with or without metabolic activation.	1,1-Biphenyl tested negative in the Ames test for mutagenicity in bacteria. 1,1-biphenyl, reacted with NO_x and was positive for mutagenicity.	Hirayama et al. (1982)
Genotoxicity	Bacterial mutation tests were carried out with four strains of *Salmonella typhimurium* (Ames test), with and without metabolic (S-9) activation.	Results were negative for the induction of revertants for 1,1-biphenyl in all strains of *Salmonella*, with and without metabolic activation at the following concentrations: 4, 20, 100, 500, and 2500 µg/plate.	1,1-Biphenyl tested negative in the Ames test for mutagenicity in bacteria.	Anderson and Styles (1978)
Genotoxicity	The mouse lymphoma TK+/− — TK−/− forward-mutation assay was used to test mutagenicity, with and without metabolic activation (S-9).	Mutation frequency increased between 3- and 4-fold, with metabolic activation at 1,1-biphenyl concentrations greater than 2.96×10^{-4} mol/L.	1,1-Biphenyl tested positive in the mouse lymphoma assay for gene mutations in the presence of metabolic activation.	Wangenheim and Bolcsfoldi (1988)
Genotoxicity	Induced DNA repair in rat hepatocyte primary cultures was assessed following treatment with 1,1-biphenyl and [3H] thymidine for 18 hours after cell attachment. DNA synthesis induced by carcinogens was measured by liquid-scintillation counting.	1,1-Biphenyl (10^{-2} and 10^{-3} M) was not carcinogenic, but some of its derivatives were. Carcinogenicity was determined by the amount of unexpected DNA synthesis observed.	1,1-Biphenyl tested negative in unscheduled DNA synthesis in rat hepatocytes.	Williams (1978); Brouns et al. (1979)
Genotoxicity	The diploid D7 strain of *Saccharomyces cerevisiae* was tested for gene conversion (*trp* locus) and mitotic recombination (*ade* locus), with metabolic activation (S-9) following 4-hour exposure to 1,1-biphenyl. *Salmonella typhimurium* strains TA100, TA98, TA1535, TA1537, TA1538, TA1532, and TA2636 were exposed to 1,1-biphenyl in a microsome assay (Ames test) by standard plate incorporation and by liquid incubation, with and without metabolic activation.	1,1-Biphenyl was positive for mitotic recombination in *S. cerevisiae*, with and without metabolic activation (154 g/mL). Toxicity was only observed when 1,1-Biphenyl was suspended in dimethyl sulfoxide (DMSO), as opposed to in the media directly. 1,1-Biphenyl tested negative under all conditions in the Ames test (0.1 µg/plate to 500 µg/plate).	1,1-Biphenyl was positive for mitotic recombination in yeast but negative for mutagenicity in bacteria.	Pagano et al. (1983)

DERIVATION OF PROVISIONAL VALUES

Table 4 summarizes the noncancer reference values. Table 5 summarizes the cancer values. IRIS data are indicated in the table if available.

Table 4. Summary of Reference Values for 1,1-Biphenyl (CASRN 92-52-4)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-day)	Rat/F	Increased incidence of fetal skeletal anomalies	1×10^{-1}	$BMDL_5$	9.59	100	Khera et al. (1979)
Chronic RfD[a] (mg/kg-day) IRIS, 1989	Rat/M, F	Kidney damage	5×10^{-2}	NOAEL	50	100	Ambrose et al. (1960)
Screening Subchronic p-RfC (mg/m^3)[b]	Mouse/M, F	Congestion and edema of the liver and kidneys	4×10^{-3}	$BMCL_{10HEC}$	1.23	300	Cannon Laboratories, Inc. (1977)
Screening Chronic p-RfC (mg/m^3)[b]	Mouse/M, F	Congestion and edema of the liver and kidneys	4×10^{-4}	$BMCL_{10HEC}$	1.23	3000	Cannon Laboratories, Inc. (1977)

[a]All the reference values obtained from IRIS are indicated with the latest review date. The IRIS RfD was last revised in 1989.
[b]A screening value is provided in Appendix A of this document.

Table 5. Summary of Cancer Values for 1,1-Biphenyl (CASRN 92-52-4)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
Screening p-OSF $(mg/kg\text{-}day)^{-1}$[a]	Mouse/F	Combined hepatocellular adenomas and carcinomas	8×10^{-3}	Umeda et al. (2005)
p-IUR (mg/m^3)	None	None	None	None

[a]A screening value is provided in Appendix A of this document.

DERIVATION OF ORAL REFERENCE DOSES

Table 6 summarizes relevant subchronic- and chronic-duration oral toxicity studies.

Table 6. Summary of Relevant Oral Systemic Toxicity Studies for 1,1-Biphenyl (CASRN 92-52-4)

References	# M/F, Species	Exposure (mg/kg-day)[d]	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/kg-day)	$LOAEL_{ADJ}$[b] (mg/kg-day)	Critical Endpoint
Umeda et al. (2004)	0/10, mouse	0, 101, 404, 809, 1556, 1929, 2924	7 d/wk, for 13 wks, in diet	1.93×10^3	2.92×10^3	Peroxisome proliferation
Shibata et al. (1989)	5/0, rat	500	7 d/wk, for 8 wks, in diet	--[c]	5.00×10^2	Induced microcalculi
Tamano et al. (1993)	20/0, mouse	1803.8	7 d/wk, for 32 wks, in diet	1.80×10^3	None	Increased incidences of interstitial nephritis
Ambrose et al. (1960); SRI (1953)	15/15, rat	Male: 0.723, 3.62, 7.23, 36.2, 72.3, 362, 723 Female: 0.820, 4.10, 8.20, 41.0, 82.0, 410, 820	7 d/wk, for 700 d, in diet	7.23×10	3.62×10^2	Kidney damage
Umeda et al. (2002)	50/50, rat	Male: 0, 39.5, 118, 335 Female: 0, 45.9, 138, 413	7 d/wk for 105 wks in diet	--[c]	3.95×10	Calculi in the kidney and urinary lesions
Khera et al. (1979)	**0/18–20, rat**	**0, 125, 250, 500, 1000**	**7 d/wk, GDs 6–15**	**2.5×10^2**	**5×10^2**	**Increased incidence of fetuses with skeletal anomalies**

[a]$NOAEL_{ADJ}$ = NOAEL × (feeding schedule).
[b]$LOAEL_{ADJ}$ = LOAEL × (feeding schedule).
[c]No NOAEL was identified. NOAEL is considered equal to a LOAEL/10 for screening purposes.
[d]Exposure is given in average daily dose (ADD) in mg/kg-day adjusted for duration ($Dose_{ADJ}$).

Derivation of Subchronic p-RfD

An oral developmental toxicity study by Khera et al. (1979) is selected as the principal study for derivation of subchronic p-RfD. The critical effect is increased numbers of fetuses with skeletal anomalies. This study is a peer reviewed published study with adequate number of dose groups and dose spacing, sufficient group sizes, comprehensive endpoint assessment and quantitation of results to describe dose-response relationships for the critical effects in rats and mice associated with gestational oral exposure to biphenyl. Among the available acceptable studies, Khera et al. (1979) study represents the lowest credible point of departure for developing a subchronic p-RfD.

Of the two subchronic-duration studies available in the database (see Table 2), none presents a dose-response relationship and quantitative data to be utilized as the principal study. Shibata et al. (1989) observed microcalculi in the bladder after administration of 500-mg/kg-day

1,1-biphenyl in a powdered basal diet for 8 weeks. No other organs were examined. Umeda et al. (2004) examined the livers and observed peroxisome proliferation in female mice after administration of 2924 mg/kg-day of 1,1-biphenyl. No other organs were examined. Additional studies are needed to clarify subchronic-duration toxicity associated with 1,1-biphenyl oral exposure. A carcinogenic study by Tamano et al. (1993) observed incidence of interstitial nephritis in the kidneys of mice after administration of 1803.8-mg/kg-day 1,1-biphenyl in the diet for 32 weeks. This study did not investigate other organs such as liver effects. While, there is no consistency on results from subchronic-duration studies, four chronic-duration studies reported in the database consistently observed kidney and urinary bladder effects as the most sensitive endpoint and interim subchronic effects were reported in these chronic studies (Ambrose et al., 1960; Umeda et al., 2002, 2005; Takita, 1983) (see Table 2). The database includes a single developmental toxicity study in pregnant Wistar rats exposed by gavage on GDs 6–15 (Khera et al., 1979), and one- and three-generation reproductive toxicity studies of rats (Ambrose et al., 1960) (see Table 2). No exposure-related effect on the number of dams with litters was found following dietary exposure of male and female albino rats to dietary doses as high as 410 mg/kg-day for 11 or 60 days prior to mating (Ambrose et al., 1960). The oral developmental toxicity study (Khera et al., 1979), reported frank maternal toxicity (increased mortality [5/20 vs. 0/18 in controls] and decreased number of dams with live fetuses [9/20 vs. 16/18 in controls]) at the highest dose (1000 mg/kg-day). Significantly increased incidences of fetuses with skeletal anomalies were noted at doses ≥500 mg/kg-day.

While the selected kidney effects (i.e., transitional cell simple hyperplasia and mineralization in the renal pelvis, hemosiderin deposition in females, and papillary mineralization in males) in chronically-exposed F344 rats (Umeda et al., 2002) are good candidate critical effects for deriving chronic RfD, in the absence of a suitable subchronic study, the fetal skeletal anomalies (on a per litter basis) in litters from biphenyl-treated pregnant Wistar rats by Khera et al. (1979) represent the best option as principal study for deriving a subchronic p-RfD. In the oral developmental toxicity study, pregnant Wistar rats were exposed by gavage to 0, 125, 250, 500, or 1000 mg biphenyl/kg-day on GDs 6–15 (Khera et al., 1979). Significantly increased numbers of fetuses with skeletal anomalies (wavy ribs, extra ribs, small 13th rib, missing or unossified sternebrae, delayed ossification of the calvarium) were noted at doses ≥500 mg/kg-day, and the number of litters exhibiting any of these anomalies was significantly higher at the 500 mg/kg-day dose level relative to controls. Frank maternal toxicity (increased mortality [5/20 vs. 0/18 in controls] and decreased number of dams with live fetuses [9/20 vs. 16/18 in controls]) occurred at the highest dose (1000 mg/kg-day). Khera et al. (1979) is a developmental toxicity resulting from a narrow period of exposure and the developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991). Khera et al. (1979) with a NOAEL and LOAEL of 250 and 500 mg/kg-day for delayed skeletal development is selected as the principal study for deriving subchronic p-RfD.

A BMDL5 of 9.59 mg/kg-day due to fetal skeletal anomalies (on a per litter basis) in litters from biphenyl-treated pregnant Wistar rats was the POD for deriving an oral subchronic p-RfD for 1,1-biphenyl.

Female rats, 18 to 20 per dose group, were administered by gavage a daily dose of 0, 125, 250, 500, or 1000 mg/kg. No additional dose adjustments or units conversion is needed for deriving subchronic p-RfD.

All available core dichotomous models in the EPA BMDS (version 2.1.2) were fit to the incidence data of anomalous litters (see Table 7). The multistage model was run for all polynomial degrees up to n - 1 (where n is the number of dose groups including control). Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the dose-response curve, and a value of <2 for the largest scaled residual for any data point in the dataset (including the control). Among all of the models providing adequate fit to the data, the lowest BMDL was selected as the potential POD when the difference between the BMDLs estimated from these models was more than threefold; otherwise, the BMDL from the model with the lowest AIC was chosen as the candidate POD. In accordance with EPA (2000b) guidance, BMDs and BMDLs associated with an extra risk of 5% were calculated for all models, considering that the critical effect and the principal studies are from a developmental study. When core models failed to provide adequate fit to the data, manipulations of the models (model restriction adjustments, specification of initial parameters, and use of alternative models) were attempted in an effort to achieve adequate fit. If these manipulations failed to achieve better fit, the highest dose was dropped and the entire modeling procedure was repeated. If an adequate fit could not be achieved after dropping the highest dose, then the dataset was determined to be unsuitable for BMD modeling. The log-logistic model with BMD_5 of 27.03 mg/kg-day and $BMDL_5$ of 9.59 mg/kg-day is the best model fit and presents the lowest BMD/BMDL.

Table 7. BMD Modeling Dataset for Incidence of Litters with Fetal Skeletal Anomalies from Wistar Rat Dams Administered Biphenyl by Gavage on GDs 6–15[a]

$(DOSE_{Khera\ et\ al.[1979]})_n$ (mg/kg-day)	$(DOSE_{ADJ})_n$ (mg/kg-day)	Number of Subjects	Litters with Fetal Skeletal Anomalies[b]
0	0	16	8
125	125	20	11
250	250	18	13
500	500	18	15
1000	1000	9	6

[a]Khera et al. (1979).
[b]The study authors reported one runted fetus in the control group and one fetus with kinky tail in the 250-mg/kg-day dose group, which may have influenced the reported incidence data for anomalous litters/litters examined.
[c]Significantly different from controls ($p < 0.05$) according to Fisher's exact test conducted for this review.

Goodness of fit statistics and benchmark results for the gestationally-exposed rats (Khera et al., 1979) dataset are summarized in Table 8. Appendix C presents graphical and textual output of BMDS.

Table 8. Summary of BMD Modeling Results for Incidence of Litters with Fetal Skeletal Anomalies from Wistar Rat Dams Administered Biphenyl by Gavage on GDs 6–15[a]

Model	Goodness-of-Fit			Benchmark Result (mg/kg-d)	
	χ^2 *p*-Value[b]	Largest Residual	AIC	BMD_5	$BMDL_5$
Gamma[b], Weibull[c], Multistage (1-degree)[d]	0.31	-1.25	106.11	54.45	24.15
Logistic	0.28	1.17	106.42	73.97	36.73
Log-Logistic[c,e]	**0.41**	**-1.32**	**105.33**	**27.03**	**9.59**
Log-Probit[c]	0.23	-1.59	106.55	125.14	55.10
Probit	0.28	1.20	106.50	79.59	41.02

[a]Khera et al. (1979).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model; the model with the lowest BMDL was selected because BMDL values for models providing adequate fit differed by more than threefold; this model also had the lowest AIC.

BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_5$ = dose associated with 5% extra risk)

A subchronic p-RfD of 1×10^{-1} mg/kg-day using a $BMDL_5$ of 9.59 mg/kg-day as the POD due to incidence of litters with fetal skeletal anomalies from Wistar rat dams administered biphenyl by gavage on GDs 6–15 (Khera et al., 1979) is derived as follows:

$$\textbf{Subchronic p-RfD} = \textbf{BMDL}_5 \div \textbf{UF}_C$$
$$= 9.59 \text{ mg/kg-day} \div 100$$
$$= \mathbf{1 \times 10^{-1} \text{ mg/kg-day}}$$

Tables 9 and 10, respectively, summarize the UFs and the confidence descriptor for the subchronic p-RfD for 1,1-biphenyl.

Table 9. UFs for Subchronic p-RfD of 1,1-Biphenyl (CASRN 92-52-4)

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 subchronic-duration oral exposure to 1,1-biphenyl.
UF_D	1	A UF_D of 1 is applied because the database includes one acceptable multigeneration reproductive study (Dow Chemical Co, 1953), one acceptable developmental study in rats (Khera et al., 1979).
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 $BMDL_5$.
UF_S	1	A UF_S of 1 is applied because a developmental toxicity study (Khera et al., 1979) is utilized as the principal study.
UF_C	100	

Table 10. Confidence Descriptor for Subchronic p-RfD for 1,1-Biphenyl (CASRN 92-52-4)

Confidence Categories	Designation[a]	Discussion
Confidence in the study	H	Confidence in the principal study (Khera et al., 1979) is high. The design, conduct and reporting of this developmental toxicity study of Wistar rats were adequate.
Confidence in the database	H	Confidence in the database is high due to the availability of chronic-duration oral exposure studies in several rat and mouse strains, an adequate developmental toxicity study in Wistar rats, and the availability of one- and three-generation reproductive toxicity studies in rats.
Confidence in the subchronic p-RfD[b]	H	Overall confidence in the subchronic p-RfD is high.

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than the lowest entry in the table.

Derivation of Chronic p-RfD

IRIS (U.S. EPA, 2010a) has derived a chronic RfD of 5×10^{-2} mg/kg-day based on a chronic-duration toxicity study of albino rats by Ambrose et al. (1960) with kidney damage as the critical effect. The IRIS database (U.S. EPA, 2010a) should be checked to determine if any changes have been made.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Table 11 summarizes relevant inhalation toxicity studies for 1,1-biphenyl.

Table 11. Summary of Relevant Inhalation Toxicity Studies for 1,1-Biphenyl (CASRN 92-52-4)

References	# M/F, Species	Exposure (mg/m^3)	Frequency/ Duration	$NOAEL_{HEC}$[a] (mg/m^3)	$LOAEL_{HEC}$[b] (mg/m^3)	Critical Endpoint
Monsanto Chemical Co. (1983)	4 (sex not reported), rat	0, 9.34×10^{-4}	7 h/d, 5 d/wk, 62 d of 92 d	None	9.34×10^{-4}	No effects
Monsanto Chemical Co. (1983)	10 (sex not reported), rat	0, 5.96×10^{-2}	7 h/d, 5 d/wk, 64 d of 94 d	None	5.96×10^{-2}	Irritation of the nasal mucosa
Monsanto Chemical Co. (1983)	6 (sex not reported), rat	0, 7.89×10^{-3}	7 h/d, 5 d/wk, 46 d of 68 d	None	7.89×10^{-3}	Irritation of the nasal mucosa
Cannon Laboratories, Inc. (1977)	**50/50, mouse**	**Respiratory effects: M: 0, 94.6, 189.9; F: 0, 72.9, 146.4** **Extra-respiratory effects: 0, 32.8, 65.5 for both sexes**	**7 h/d, 5 d/wk, 13 wks**	**--**[c] **--**[c]	**Respiratory effects: 72.9** **Extra-respiratory: 32.8**	**Congestion and edema in the liver the kidneys and the lungs, inflammation in the trachea, and pneumonia in the lungs**
Monsanto Chemical Co. (1983)	12 (sex not reported), mouse	9.34×10^{-4}	7 h/d, 5 d/wk, 62 of 92 d	None	9.34×10^{-4}	Irritation of the upper respiratory tract

[a]$NOAEL_{ADJ}$ = NOAEL × (MW ÷ 24.45) × (hours exposed ÷ 24) × (days exposed ÷ total days).
[b]$LOAEL_{ADJ}$ = LOAEL × (MW ÷ 24.45) × (hours exposed ÷ 24) × (days exposed ÷ total days).
[c]No NOAEL was identified. NOAEL is considered equal to a LOAEL ÷ 10 for screening purposes.

$NOAEL_{HEC} = NOAEL_{ADJ} \times DAF$; DAF = dosimetric adjustment factor for specific site of effects (e.g., respiratory tract region or extrarespiratory).

Derivation of Subchronic p-RfC and Chronic p-RfC

There are no peer-reviewed published studies of subchronic- or chronic-duration human or animal studies suitable for deriving subchronic and chronic p-RfCs. The 13-week inhalation mouse study of Cannon Laboratories, Inc. (1977) is the only available study that employed at least subchronic-duration exposure and included multiple biphenyl exposure levels. This study is considered inadequate for subchronic and chronic p-RfC derivation because: (1) is a nonpeer-reviewed and unpublished report; (2) exposure levels were highly variable during the first half of the 13-week exposure period; (3) one of the exposure groups experienced high losses (46/100) due to an overheating event and cannibalization after 46 exposures, although replacement mice were subsequently added and received a total of 65 exposures; and (4) the steep dose-response at the lowest concentration tested, which resulted in a BMC_{10}/$BMCL_{10}$ well outside the range of experimental data (no tests were performed in the lower exposure ranges). However, the study is suitable to derive screening toxicity values. Cannon Laboratories, Inc. (1977) is a nonpeer-reviewed and unpublished study submitted to the EPA under the Toxic Substances Control Act (TSCA), Section 8d. Exposure concentrations were continuously monitored and reported along with the observed health effects, and the overheating and cannibalization by cage mates which resulted in 46/100 mortality was corrected, animals were replaced with extended exposure time to ensure exposure uniformity under the experimental protocol (Cannon Laboratories, Inc. 1977). Appendix A provides the derivation of screening subchronic and chronic p-RfCs.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 12 identifies the cancer weight-of-evidence (WOE) descriptor for 1,1-biphenyl.

Table 12. Cancer WOE Descriptor for 1,1-Biphenyl			
Possible WOE Descriptor	**Designation[a]**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	No human cancer studies are available.
"Likely to Be Carcinogenic to Humans"	N/A	N/A	There is no adequate evidence of plausible association between human exposure and cancer.
"Suggestive of Evidence of Carcinogenic Potential"	**X**	**Oral administration in the diet only**	**Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the available evidence for oral exposure to 1,1-biphenyl is suggestive of carcinogenicity based on evidence of carcinogenicity in rats in the study by Umeda et al. (2002) and in mice as reported by Umeda et al. (2005), but there are no assessments between exposure to 1,1-biphenyl and increased risk of cancer in humans. Results of both studies show significant increases over the ranges for historical controls and significant positive trends for tumors observed mainly in the rat urinary bladder and mouse liver, which are supported by metabolism studies. Studies evaluating the carcinogenic potential of inhaled 1,1-biphenyl in animals were not located.**
"Inadequate Information to Assess Carcinogenic Potential"	N/A	N/A	Adequate information is available to assess carcinogenic potential.
"Not likely to be Carcinogenic to Humans"	N/A	N/A	No strong evidence of noncarcinogenicity in humans is available.

[a]The designation N/A means not available, and X indicates the assigned cancer WOE descriptor.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of p-OSF

No p-OSF can be derived because the cancer WOE descriptor for 1,1-biphenyl is "*Suggestive of Evidence of Carcinogenic Potential.*" However, Appendix A presents a screening p-OSF.

Derivation of p-IUR

No human or animal studies examining the carcinogenicity of 1,1-biphenyl following inhalation exposure have been located, thereby precluding derivation of a provisional inhalation unit risk (IUR).

APPENDIX A. PROVISIONAL SCREENING VALUES

DERIVATION OF SCREENING PROVISIONAL INHALATION REFERENCE CONCENTRATIONS

For the reasons noted in the main document, it is inappropriate to derive subchronic and chronic p-RfCs for 1,1-biphenyl. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

Derivation of Screening Subchronic p-RfC

The study by Cannon Laboratories, Inc. (1977) is selected as the principal study for the derivation of a screening subchronic p-RfC. Congestion and edema of the lungs were identified as critical respiratory effects, and congestion and edema in the liver and kidneys were identified as critical effects at the remote site of studied CD1 mice. The study authors did not report results separately for male and female mice. Congestion and edema of the lungs, liver, and kidneys can indicate adverse health events in humans and rodents. The study is unpublished but was submitted to EPA under TSCA, Section 8d. The study predates current GLP principles and was not conducted according to the current guidelines. Although the authors reported sampling difficulties during the first 5 days of the experiment, overheating of the chamber, which forced the replacement of 46 mice, and caused the study to run an additional 117 days to ensure all animals were dosed as planned in the protocol. Cannon Laboratories, Inc. (1977) study represents the only available, acceptable study for developing a screening p-RfC. Monsanto Chemical Co. (1983) and WHO (Boehncke et al., 1999) reported similar respiratory effects in mice and rats. No information was reported on extrarespiratory effects in both reports.

The physicochemical characteristics of 1,1-biphenyl; vapor pressure of 0.03 torr (mm Hg), low solubility in water (4.4 mg/L), and a *n*-octanol/water partition coefficient of about 4.0 at 20°C, and the potential to cause both respiratory and remote effects requires that the dosimetric adjustment be based on the regional gas dose ratio ($RGDR_{PU}$) for the affected portion of the respiratory tract (edema of the lungs) and the RGDR for extrarespiratory effects ($RGDR_{ER}$), which are congestion and edema of the liver and kidneys. The most sensitive endpoint is considered as the critical effect (U.S. EPA, 1994b).

Exposure concentration adjustment for continuous exposure

$Conc_{ADJ}$ = $Conc_{Cannon\ Laboratories,\ Inc.,\ 1977} \times (MW \div 24.45) \times$ (hours exposed ÷ 24) × (days exposed ÷ 7 days per week)
= 25 ppm × (154.2 ÷ 24.45) × (7 hours ÷ 24 hours) × (5 days ÷ 7 days)
= 25 × 1.31
= 32.8 mg/m^3

HEC conversion for respiratory effects

$Conc_{HEC}$ = $Conc_{ADJ} \times RGDR_{PU}$

$RGDR_{PU}$ = $\frac{(V_E \div SA_{PU})_{rodent}}{(V_E \div SA_{PU})_{human}}$

V_{Emice} = mice minute volume (mice = 0.0284 L/min and 0.036 L/min, based on a default body weight of 0.0246 kg for $B6C3F_1$ female mice and 0.0316 kg for $B6C3F_1$ male mice, respectively) (see U.S. EPA, 1994b)

V_{Ehuman} = 13.8 L/min

SA_{mice} = Mice default surface area of the pulmonary region (0.05 m^2)

SA_{human} = Human default surface area of the pulmonary region (54 m^2)

Female mice $RGDR_{PU}$ = (0.0284 ÷ 0.05) ÷ (13.8 ÷ 54) = 2.22
Male mice $RGDR_{PU}$ = (0.036 ÷ 0.05) ÷ (13.8 ÷ 54)
= 2.82

$Conc_{HEC,\ RESP}$ = $Conc_{ADJ} \times RGDR_{PU}$
= 32.848 mg/m^3 × 2.22
= 72.9 mg/m^3 for females or 92.6 mg/m^3 for males

Table A.1 below presents HECs for respiratory effects for female mice treated with 1,1-biphenyl for 13 weeks. Use of female data allows for protection of both sexes because no sex-specific data were reported, and the HEC converted from female mice is lower than the HEC obtained from male mice.

Table A.1. Concentration-Response Data for 1,1-Biphenyl-Induced Congestion and Edema of the Lungs (HEC for Respiratory Effects) in Female Mice Exposed by Inhalation for 13 Weeks[a]

Conc (ppm)	$Conc_{ADJ}$ (mg/m^3)[b]	$Conc_{HEC}$ (mg/m^3)[c]	Incidence
0	0	0	0/80
25	32.8	72.9	95/98[d]
50	65.95	146.4	71/71[d]

[a]Cannon Laboratories, Inc. (1977).
[b]$Conc_{ADJ}$ = Conc × 6 ÷ 24 hrs × 5 ÷ 7 d.
[C]$P_{HEC, RESP}$ = (ppm conversion) × (average daily concentration) × RGDR. The critical effect: respiratory effects (congestion and edema of the lungs), Category 2 gas, pulmonary (PU) and the $RGDR_{PU} = (V_E \div SA_{PU})_{mice} \div (V_E \div SA_{PU})_{human}$ = 2.22 for females.
[d]Not listed as statistically significant in the study but significantly different from control ($p < 0.0001$) by Fisher's exact test (two-tailed) performed for this review.

An HEC conversion was performed for remote site effects (congestion and edema in the liver and kidneys).

$$Conc_{HEC, ER} = Conc_{ADJ} \times [(H_{b/g})_{mice} \div (H_{b/g})_{human}]$$

The value of 1.0 is used for the ratio of $(H_{b/g})_A > (H_{b/g})_H$. A value of 1.0 is used as the default when one or both of the partition coefficients are not available.

$$Conc_{HEC, ER} = 32.848 \times 1.0 = 32.8\ mg/m^3$$

Table A.2 below presents HECs for extrarespiratory effects for both female and male mice treated with 1,1-biphenyl for 13 weeks. Use of female data allows for protection of both sexes because no sex-specific data were reported.

Table A.2. Concentration-Response Data for 1,1-Biphenyl-Induced Congestion and Edema of the Liver and Kidneys (HEC for Extrarespiratory Effects) in Male and Female Mice Exposed by Inhalation for 13 Weeks[a]

Conc (ppm)	$Conc_{ADJ}$ (mg/m^3)[b]	$Conc_{HEC}$ (mg/m^3)[c]	Incidence
0	0	0	0/80
25	32.9	32.9	87/98[d]
50	65.5	65.5	71/71[d]

[a]Cannon Laboratories, Inc. (1977).
[b]$Conc_{ADJ}$ = Conc × 6 ÷ 24 hrs × 5 ÷ 7 d.
[c]$Conc_{HEC\ ER} = Conc_{ADJ} \times [(H_{b/g})_{mice} \div (H_{b/g})_{human}]$.
[d]Not listed as statistically significant in the report but significantly different from control ($p < 0.0001$) by Fisher's exact test (two-tailed) performed for this review.

The data for respiratory (see Table A.1) and extrarespiratory (see Table A.2) were modeled and compared in order to determine and identify the most sensitive effects and, ultimately, the critical effect. Tables A.3 and A.4 below are the summary results of the BMDS output for concentration-respiratory effects and concentration-extrarespiratory effects response curve results, respectively.

Table A.3. Model Predictions for Concentration-Respiratory Effects of Congestion and Edema of the Lungs[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC[b] for Fitted Model	BMC_{10HEC} (mg/kg-day)	$BMCL_{10HEC}$ (mg/kg-day)	Conclusions
Log-Logistic	1.00	28.8171	53.2522	0.104152	BMC/BMCL ratio >3
Quantal Linear	**0.9682**	**28.9412**	**2.17812**	**1.65871**	**Selected as the lowest BMCL for the POD with a range of 0.054 to 10.007, among models with a BMC/BMCL ratio <3. Selected as the lowest AIC for the POD with a range of 0.054 to 10.007, among models with a BMC/BMCL ratio <3.**
Multistage	0.4863	23.4848	11.9458	1.44597	BMC/BMCL ratio >3
Gamma	0.9991	30.8171	33.2408	1.66971	BMC/BMCL ratio >3
Weibull	0.9988	30.8171	16.013	1.66971	BMC/BMCL ratio >3
Log-Probit	0.9997	30.817	42.3942	8.55×10^{-9}	BMC/BMCL ratio >3
Probit	0.9997	30.817	43.1953	16.013	
Logistic	0.9997	30.817	55.4769	19.4002	

[a]Cannon Laboratories, Inc. (1977).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

Table A.4. Model Predictions for Concentration-Respiratory Effects of Congestion and Edema of the Liver and Kidneys[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC[b] for Fitted Model	BMC_{10HEC} (mg/kg-day)	$BMCL_{10HEC}$ (mg/kg-day)	Conclusions
Log-Logistic	1.00	28.8171	25.8765	6.00398	BMC/BMCL ratio >3
Quantal Linear	**0.6435**	**28.9412**	**1.49511**	**1.22974**	**Selected as the lowest BMCL for the POD with a range of 0.054 to 10.007, among models with a BMC/BMCL ratio <3. Selected as the lowest AIC for the POD with a range of 0.054 to 10.007, among models with a BMC/BMCL ratio <3**
Multistage	0.9946	23.4848	7.1934	1.31769	BMC/BMCL ratio >3
Gamma	1.000	70.7329	18.0692	1.3176	BMC/BMCL ratio >3
Weibull	0.9995	30.8171	16.7222	1.31769	BMC/BMCL ratio >3
Log-Probit	0.9996	30.817	22.4429	3.59818	BMC/BMCL ratio >3
Probit	0.9996	30.817	21.1293	9.0211	
Logistic	0.9996	72.7326	26.2308	10.8064	

[a]Cannon Laboratories, Inc. (1977).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

Following the above procedure, dichotomous-variable models in the EPA BMDS (version 2.1.1) with a benchmark response (BMR) of 10% extra risk with restricted parameters (U.S. EPA, 2008) were fit to the data shown in Table A.1 for congestion and edema in lungs in female mice, and Table A.2 for congestion and edema in the liver and kidneys in female and male mice (Cannon Laboratories, Inc., 1977). Tables A.3 and A.4 provide summary statistics and outputs for benchmark concentration (BMC) modeling of the 13-week inhalation data for respiratory effects and extrarespiratory effects, respectively. Adequate fit (p-value > 0.1) is achieved for the all the dichotomous-variable models in the EPA BMDS (version 2.1.1) for both respiratory and extrarespiratory effects data. The scaled residuals are all less than 2. The range of BMC lower bound 95% confidence interval (BMCLs) is greater than 3-fold, which requires selecting the lowest BMCL value, independently of the AIC values. The quantal linear model for respiratory and extrarespiratory effects data presented the lowest BMC_{10} and $BMCL_{10}$ values: a BMC_{10HEC} of 2.17 mg/m^3 and a $BMCL_{10HEC}$ of 1.65 mg/m^3, and a BMC_{10HEC} of 1.5 mg/m^3 and a $BMCL_{10HEC}$ of 1.23 mg/m^3, respectively. The lower $BMCL_{10HEC}$ of 1.23 mg/m^3 from extrarespiratory effects in male and female mice is selected as the POD for deriving a screening subchronic p-RfC for 1,1-biphenyl. The POD based on a $BMCL_{10HEC}$ of 1.23 mg/m^3 due to extrarespiratory effects (congestion and edema of the liver and kidneys) in both sexes is also protective respiratory effects with a predicted $BMCL_{10HEC}$ of 1.65 mg/m^3. Appendix C presents details of the BMC analysis and the curve-output statistics.

The screening subchronic p-RfC for 1,1-biphenyl, based on a $BMCL_{10HEC}$ of 1.2 mg/m^3 in mice (Cannon Laboratories, Inc., 1977), is derived as follows:

$$\textbf{Screening Subchronic p-RfC} = \textbf{BMCL}_{\textbf{10HEC}} \div \textbf{UF}_{\textbf{C}} = 1.23 \div 300 = \textbf{4} \times \textbf{10}^{\textbf{-3}}\ \textbf{mg/m}^{\textbf{3}}$$

Table A.5 summarizes the UFs for the screening subchronic p-RfC for 1,1-biphenyl.

Table A.5. UFs for Screening Subchronic p-RfC for 1,1-Biphenyl

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of a UF_A because the toxicokinetic portion ($10^{0.5}$) has been addressed in dosimetric conversions.
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies, and there are no indications of any other studies that may be relevant for the database UF.
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 BMCL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was utilized as the critical study.
UF_C	300	

Derivation of Screening Chronic p-RfC

Chronic-duration toxicity studies for inhalation of 1,1-biphenyl are not available. Therefore, the same POD used for the screening subchronic p-RfC ($BMCL_{10HEC}$ of 1.2 mg/m^3) from 13-weeks inhalation exposure to 1,1-biphenyl in mice (Cannon Laboratories, Inc., 1977) is used for deriving a screening chronic p-RfC.

$$\textbf{Screening Chronic p-RfC} = \textbf{BMCL}_{\textbf{10HEC}} \div \textbf{UF}_{\textbf{C}} = 1.2 \div 3000 = \textbf{4} \times \textbf{10}^{\textbf{-4}}\ \textbf{mg/m}^{\textbf{3}}$$

Table A.6 summarizes the UFs for the screening chronic p-RfC for 1,1-biphenyl.

Table A.6. UFs for Screening Chronic p-RfC for 1,1-Biphenyl		
UF	**Value**	**Justification**
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of a UF_A because the toxicokinetic portion ($10^{0.5}$) has been addressed in dosimetric conversions.
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies, and there are no indications of any other studies that may be relevant for the database UF.
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 to humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a BMCL.
UF_S	10	A UF_S of 10 is applied for using data from a subchronic-duration study to assess potential effects from chronic-duration exposure because data for evaluating response from chronic-duration exposure are unavailable.
UF_C	3000	

Derivation of Screening Provisional Oral Slope Factor (Screening p-OSF)

For the reasons noted in the main document, it is inappropriate to derive a p-OSF for 1,1-biphenyl. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

The study by Umeda et al. (2005) is selected as the principal study. The Umeda et al. (2005) study, a 2-year oral administration of a 1,1-biphenyl-containing diet, produced dose-related increases in benign and malignant hepatocellular tumors and preneoplastic liver lesions in female mice, together with nonneoplastic kidney lesions in both male and female mice at an effect level of 52.5 mg/kg-day. Comparatively, the Umeda et al. (2002) report, a 105-week, carcinogenicity study yielded evidence in male rats of 1,1-biphenyl-induced papillomas and carcinomas in the urinary bladder at 96.4 mg/kg-day. The data set from the female rats did not have statistically significant cancer endpoints; only male rats showed bladder tumor responses (about 40%) at the highest dose. The control group and the first two dose levels showed no bladder response in male rats. No bladder tumors were observed in female rats, and no other organ response was reported. Also, the bladder tumors were observed at a relatively higher dose (96.4 mg/kg-day) compared to the liver tumor observed in mice at 52.5 mg/kg-day (Umeda et al., 2005). Both studies (Umeda et al., 2005, 2002) are peer-reviewed publications, well conducted, and performed according to GLP principles, and otherwise meet the standards of study design and performance in terms of number of animals, examination of endpoints, and presentation of

information. However, the Umeda et al. (2005) study presents a better dose-response trend and is more suitable for a quantitative cancer dose-response assessment.

The dosimetric adjustments shown below were made for dietary treatment in adjusting doses for oral cancer analysis. Umeda et al. (2005) reported mice body weight, average food consumption, and daily 1,1-biphenyl intake (see Table A.7) , which are used for calculations of the adjusted average daily dose and the HED (U.S. EPA, 1988).

$(DOSE_{ADJ, HED})_{Umeda\ et\ al., 2005}$	=	$(Dose)_{Umeda\ et\ al., 2005}$ × (days dosed ÷ 7 days per week) × body-weight adjustment
Body-weight adjustment	=	$(BW_A \div BW_H)^{1/4}$
BW_H	=	70 kg (human reference body [U.S. EPA, 1997])
BW_A and daily food consumption	=	(see Table A.7)
Body-weight adjustment	=	$(0.0431 \div 70)^{1/4} = 0.1575$ for male mice in the 667-ppm (97-mg/kg-day) dose group.
	=	$(0.0325 \div 70)^{1/4}$
	=	0.1468 for female mice in the 667-ppm (134-mg/kg-day) dose group.
$(DOSE_{ADJ, HED})_{Umeda\ et\ al., 2005}$	=	$(Dose)_{Umeda\ et\ al., 2005}$ × (days dosed ÷ total days) × body-weight adjustment
$(DOSE_{ADJ})_{Umeda\ et\ al., 2005}$	=	$(Dose)_n$ × (7 days ÷ 7 days per week)
	=	97 mg/kg-day × 1.0
$(DOSE_{ADJ, HED})_{Umeda\ et\ al., 2005}$	=	97 mg/kg-day × 1.0 × body-weight adjustment
$(DOSE_{ADJ, HED})_{Umeda\ et\ al., 2005}$	=	97 mg/kg-day × 0.1575
$(DOSE_{ADJ, HED})_{Umeda\ et\ al., 2005}$	=	15.2775 mg/kg-day for male mice
$(DOSE_{ADJ, HED})_{Umeda\ et\ al., 2005}$	=	134 mg/kg-day × 1.0 × body-weight adjustment
$(DOSE_{ADJ, HED})_{Umeda\ et\ al., 2005}$	=	134 mg/kg-day × 0.1468 = 19.6712 mg/kg-day for female mice

Table A.7. Body Weight, Food Consumption, and Daily Intake of the Mice Fed Diets Containing 1,1-Biphenyl for 2 Years, and Calculated HED[a]

Concentration in Diet (ppm)	Body Weight[b] (g)	Average Food Consumption (g/day)[c]	Daily 1,1-Biphenyl Intake (mg/kg-day)[c]	$Dose_{ADJ}$[f] (mg/kg-day)	HED[g] (mg/kg-day)
Male					
0	46.9 ± 4.9	5.6	0	0	0
667	43.1 ± 7.9	5.5	97	97	15.3
2000	42.9 ± 6.0[d]	5.5	291	291	45.8
6000	32.4 ± 3.6[e]	5.4	1050	1050	154.0
Female					
0	34.0 ± 4.0	5.9	0	0	0
667	32.5 ± 3.3	5.8	134	134	19.7
2000	30.5 ± 3.1[e]	5.9	414	414	59.8
6000	25.5 ± 3.0[e]	5.9	1420	1420	196.2

[a]Umeda et al. (2005).
[b]Values of body weight were expressed as mean ± standard deviation at the end of the 2-year administration period.
[c]Food consumption and 1,1-biphenyl intake were averaged over the 2-year administration period (reported by Umeda et al., 2005).
[d]Statistically significantly different at $p < 0.05$, by Dunnett's test.
[e]Statistically significantly different at $p < 0.01$, by Dunnett's test.
[f]Adjusted daily average dose ($Dose_{ADJ}$) = Dose × (days dosed/7 days per week).
[g]Human equivalent dose (HED) = $Dose_{ADJ} \times BW_{ADJ}$; Body-weight adjustment (BW_{ADJ}) for HED conversion for OSF derivation = [animal body weight (BW_A) ÷ human body weight (BW_H)]$^{1/4}$.

Table A.8 presents the benchmark dose (BMD) input data for combined hepatocellular adenomas and carcinoma incidence in female mice exposed to 1,1-biphenyl for 2 years.

Table A.8. Dose-Response Data for 1,1-Biphenyl Incidence of Hepatocellular Adenomas and the Combined Incidences of Hepatocellular Adenomas and Carcinomas in Female BDF1 Mice Fed Diet for 2 Years[a]

Dose (ppm)[b]	$Dose_{HED}$ (mg/kg-day)[c]	Incidence of Tumor Response		
		Hepatocellular Adenoma	Hepatocellular Carcinoma	Combined Adenoma + Carcinoma
0	0	2/50	1/50	3/50
667	19.7	3/50	5/50	8/50
2000	59.8	12/50	7/50	16/50
6000	196.2	10/50	5/50	14/50

[a]Umeda et al. (2005).
[b]$Dose_{ADJ}$ = $(Dose)_{Umeda\ et\ al.,\ 2005}$ × food consumption per day × (1 ÷ body weight) × (days dosed ÷ total days).
[c]$Dose_{HED}$ = $(Dose)_{ADJ}$ × body-weight adjustment.

Table A.9 provides BMD multistage model predictions for the cancer OSF (Umeda et al., 2005).

Table A.9. Multistage Cancer Model Predictions for OSF[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC[b] for Fitted Model	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)	Conclusions
Combined hepatocellular adenoma[c] + carcinoma	0.9366	133.357	19.3121	12.5765	Lowest BMDL $\beta 1 = 0$ The BMDL lower than the NOAEL 8.0×10^{-3} $(mg/kg\text{-}day)^{-1}$

[a]Umeda et al. (2005).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]The hepatocellular adenoma data did not fit the BMD model even after dropping the highest dose.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL lower confidence limit (95%) on the benchmark dose.

The $BMDL_{10HED}$, the BMD lower bound 95% confidence interval at 10% extra risk, is 12.58 mg/kg-day, and the cancer p-OSF, the slope of the linear extrapolation from the $BMDL_{10HED}$ to 0, or the screening $p\text{-}OSF_{Umeda\ et\ al.,\ 2005}$, is 8×10^{-3} $(mg/kg\text{-}day)^{-1}$ based on BMD modeling (U.S. EPA, 2008a).

$$\textbf{Screening p-OSF}_{\textbf{Umeda et al., 2005}} = 0.1 \div BMDL_{10HED}$$
$$= 0.1 \div 12.5765\ (mg/kg\text{-}day)^{-1}$$
$$= \mathbf{8 \times 10^{-3}\ (mg/kg\text{-}day)^{-1}}$$

APPENDIX B. DATA TABLES

Table B.1. Organ Weights and Selected Urinary Bladder Lesions Incidence in Male F344 Rats Exposed to 1,1-Biphenyl in the Diet for 8 Weeks[a]

Parameter	Exposure Group (HED, mg/kg-day)	
	Control (0)	0.5% (113)
Sample size	5	5
Average final body weight (g)	327	300[c]
Urinary pH[b]	6.6 ± 0.3	6.6 ± 0.6
Osmolality (mOsm/kgH_20)[b]	2011 ± 181	2023 ± 243
Crystals (urine)	Slight	severe[d,e]
BrdU labeling index (%)[b]	0.13 ± 0.09	0.58 ± 3[c]
Simple hyperplasia[f]	0 (0)	5 (100), moderate[e]
Pleomorphic microvilli[f]	0 (0)	5/5 (100), moderate[e]
Short uniform microvilli[f]	0 (0)	5/5 (100), moderate[e]
Ropy or leafy microridges[f]	0 (0)	5/5 (100), severe[e]

[a]Shibata et al. (1989).
[b]Mean ± standard deviation (SD).
[c]Statistically significantly different from BBN only ($p < 0.05$) by the Student's *t*-test performed by study authors.
[d]Numerous microcalculi seen among crystals.
[e]Grading (mean of group): trace, slight, moderate, severe.
[f]Number of animals with morphologies, () = percent of total, average grading.

Table B.2. Organ Weights and Selected Lesion Incidence in Male B6C3F_1 Mice Exposed to 1,1-Biphenyl in the Diet for 32 Weeks[a]

Parameter	Exposure Group (HED, mg/kg-day)		
	BBN Only (0)	BBN with 1% 1,1-Biphenyl (263)	1% 1,1-Biphenyl Only (263)
Sample size	20	20	10
Final body weight (g)[b]	38.4 ± 2.6	32.2 ± 1.8[c]	30.6 ± 1.9
Urinary bladder (relative weight)[b]	0.11 ± 0.02	0.13 ± 0.02[d]	0.16 ± 0.09
Kidney (relative weight)[b]	1.56 ± 0.11	1.52 ± 0.10	1.62 ± 0.09
Simple hyperplasia[e]	12 (60)	14 (70)	1 (10)
Papillary or nodular dysplasia[e]	2 (10)	1 (5)	1 (10)
Squamous cell carcinoma[e]	0 (0)	0 (0)	0 (0)

[a]Tamano et al. (1993).
[b]Mean ± standard deviation (SD).
[c]Statistically significantly different from BBN only ($p < 0.01$) by the Student's *t*-test performed by study authors.
[d]Statistically significantly different from BBN only ($p < 0.05$) by the Student's *t*-test performed by study authors.
[e]Number of animals with lesions, () = percent of total.

Table B.3. Organ Weights and Survival in Albino Rats Exposed to 1,1-Biphenyl in the Diet for 2 Years[a]

Exposure Group ($Dose_{ADJ}$, mg/kg-day)								
Male rats								
Parameter	**0.0% (0)**	**0.001% (0.723)**	**0.005% (3.62)**	**0.01% (7.23)**	**0.05% (36.2)**	**0.1% (72.3)**	**0.5% (362)[c]**	**1.0%[d] (723)**
Survival at 750 days	9	8	10	11	13	10	2	2
Average final body weight (g)[b]	396 ± 24.6	424 ± 5.1	383 ± 19.8	394 ± 14.2	371 ± 15.8	366 ± 23.7	345	--
Relative liver weight (g/100g bw)[b]	2.89 ± 0.16	2.66 ± 0.06	2.84 ± 0.15	2.47 ± 0.07	3.03 ± 0.12	2.98 ± 0.19	3.12	--
Relative kidney weight (g/100g bw)[b]	0.75 ± 0.02	0.70 ± 0.03	0.73 ± 0.02	0.72 ± 0.01	0.74 ± 0.02	0.83 ± 0.05	1.17	--
Relative heart weight (g/100g bw)[b]	0.32 ± 0.015	0.28 ± 0.008	0.30 ± 0.01	0.31 ± 0.008	0.31 ± 0.007	0.34 ± 0.012	0.36	--
Relative testes weight (g/100g bw)[b]	0.72 ± 0.03	0.62 ± 0.07	0.56 ± 0.06	0.67 ± 0.07	0.65 ± 0.06	0.60 ± 0.08	0.38	--
Female rats								
Parameter	**0.0% (0)**	**0.001% (0.820)**	**0.005% (4.10)**	**0.01% (8.20)**	**0.05% (41.0)**	**0.1% (82.0)**	**0.5% (410)**	**1.0% (820)**
Survival at 750 days	9	6	5	11	5	5	5	2
Average final body weight (g)[b]	333 ± 9.4	414 ± 13.4	335 ± 16.6	341 ± 9.1	306 ± 12.5	327 ± 6.8	226 ± 25.8	-
Relative liver weight (g/100g bw)[b]	3.11 ± 0.15	3.21 ± 0.17	2.81 ± 0.28	3.46 ± 0.74	3.51 ± 0.12	3.18 ± 0.10	4.52 ± 0.20	-
Relative kidney weight (g/100g bw)[b]	0.65 ± 0.01	0.62 ± 0.02	0.64 ± 0.02	0.62 ± 0.02	0.68 ± 0.02	0.65 ± 0.01	1.39 ± 0.14	-
Relative heart weight (g/100g bw)[b]	0.33 ± 0.01	0.28 ± 0.07	0.31 ± 0.03	0.30 ± 0.01	0.31 ± 0.01	0.32 ± 0.01	0.46 ± 0.04	-

[a]Ambrose et al. (1960).
[b]Mean ± standard error (SE).
[c]SE values for 0.5%-exposure group in male rats was not reported**.**
[d]Ambrose et al. (1960) did not report results for 1% dose level.

Table B.4. Selected Incidence of Kidney Lesions in Male F344 Rats Exposed to 1,1-Biphenyl in the Diet for 105 Weeks[a]

Parameter	Exposure Group (HED, mg/kg-day)			
	0 ppm (0)	500 ppm (10.7)	1500 ppm (32.1)	4500 ppm (96.4)
Urinary bladder lesions				
Simple hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	12/50 (24)[c]
Nodular hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	40/50 (80)[c]
Papillary hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	17/50 (34)[c]
Total cell hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	45/50 (90)
Transitional cell papilloma[b]	0/50 (0)	0/50 (0)	0/50 (0)	10/50 (20)[d]
Transitional cell carcinoma[b]	0/50 (0)	0/50 (0)	0/50 (0)	24/50 (48)[d]
Total bladder tumors[b]	0/50 (0)	0/50 (0)	0/50 (0)	31/50 (62)
Squamous metaplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	19/50 (38)[c]
Squamous cell hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	13/50 (26)[c]
Squamous cell papilloma and carcinoma[b]	0/50 (0)	0/50 (0)	0/50 (0)	1/50 (2)
Inflammatory polyp[b]	0/50 (0)	0/50 (0)	0/50 (0)	10/50 (20)[c]
Calculus[b]	0/50 (0)	0/50 (0)	0/50 (0)	43/50 (86)
Ureter lesions				
Simple hyperplasia[b]	1/50 (2)	0/50 (0)	0/50 (0)	8/50 (16)[c]
Nodular hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	1/50 (2)
Dilation[b]	0/50 (0)	0/50 (0)	0/50 (0)	14/50 (28)[c]
Kidney lesions				
Simple hyperplasia[b]	6/50 (12)	8/50 (16)	5/50 (10)	19/50 (38)[e]
Nodular hyperplasia[b]	0/50 (0)	1/50 (2)	1/50 (2)	21/50 (42)[c]
Squamous metaplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	2/50 (4)
Mineralization of pelvis[b]	9/50 (18)	6/50 (12)	10/50 (20)	18/50 (36)
Desquamation: pelvis[b]	1/50 (2)	0/50 (0)	0/50 (0)	11/50 (22)[c]
Calculus[b]	0/50 (0)	0/50 (0)	0/50 (0)	13/50 (26)[c]
Other lesions				
Mineralization of cortico-medullary junction[b]	0/50 (0)	0/50 (0)	0/50 (0)	10/50 (20)[c]
Mineralization of papilla[b]	9/50 (18)	9/50 (18)	14/50 (28)	23/50 (46)[e]
Papillary necrosis[b]	0/50 (0)	0/50 (0)	0/50 (0)	7/50 (14)
Infarct[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Deposit of hemosiderin[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Chronic nephrophathy[b]	45/50 (90)	45/50 (90)	43/50 (86)	34/50 (68)

[a]Umeda et al. (2002).
[b]Number of animals with endpoint/number of animals examined, () = percent of total.
[c]Statistically significantly different from control ($p < 0.01$) by Chi-square test performed by study authors.
[d]Statistically significantly different from control ($p < 0.01$) by Fisher's exact test performed by study authors.
[e]Statistically significantly different from control ($p < 0.05$) by Chi-square test performed by study authors.

Table B.5. Selected Incidence of Kidney Lesions in Female F344 Rats Exposed to 1,1-Biphenyl in the Diet for 105 Weeks[a]

Parameter	Exposure Group (HED, mg/kg-day)			
	0 ppm (0)	500 ppm (11.0)	1500 ppm (32.9)	4500 ppm (98.7)
Urinary bladder lesions				
Simple hyperplasia[b]	0/50 (0)	0/50 (0)	1/50 (20)	1/50 (20)
Nodular hyperplasia[b]	1/50 (20)	0/50 (0)	0/50 (0)	5/50 (10)
Papillary hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	4/50 (8)
Total cell hyperplasia[b]	1/50 (20)	0/50 (0)	1/50 (20)	10/50 (20)
Transitional cell papilloma[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Transitional cell carcinoma[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Total bladder tumors[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Squamous metaplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	4/50 (8)
Squamous cell hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	1/50 (2)
Squamous cell papilloma and carcinoma[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Inflammatory polyp[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Calculus[b]	0/50 (0)	0/50 (0)	0/50 (0)	8/50 (16)
Ureter lesions				
Simple hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	2/50 (4)
Nodular hyperplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Dilation[b]	0/50 (0)	0/50 (0)	0/50 (0)	6/50 (12)
Kidney lesions				
Simple hyperplasia[b]	3/50 (6)	5/50 (10)	12/50 (24)[c]	25/50 (50)[d]
Nodular hyperplasia[b]	0/50 (0)	0/50 (0)	1/50 (2)	12/50 (24)[d]
Squamous metaplasia[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Mineralization of pelvis[b]	12/50 (24)	12/50 (24)	18/50 (36)	27/50 (54)[d]
Desquamation: pelvis[b]	0/50 (0)	0/50 (0)	0/50 (0)	2/50 (4)
Calculus[b]	0/50 (0)	0/50 (0)	0/50 (0)	3/50 (6)
Other lesions				
Mineralization of cortico-medullary junction[b]	21/50 (42)	2/50 (4)	26/50 (52)	18/50 (36)
Mineralization of papilla[b]	2/50 (4)	6/50 (12)	3/50 (6)	12/50 (24)[d]
Papillary necrosis[b]	0/50 (0)	0/50 (0)	0/50 (0)	23/50 (46)[d]
Infarct[b]	1/50 (2)	0/50 (0)	0/50 (0)	8/50 (16)[e]
Deposit of hemosiderin[b]	4/50 (8)	8/50 (16)	22/50 (44)[d]	25/50 (50)[d]
Chronic nephrophathy[b]	33/50 (66)	35/50 (70)	33/50 (60)	26/50 (52)

[a]Umeda et al. (2002).
[b]Number of animals with endpoint/number of animals examined, () = percent of total.
[c]Statistically significantly different from control ($p < 0.01$) by Fisher's exact test performed by study authors.
[d]Statistically significantly different from control ($p < 0.01$) by Chi-square test performed by study authors.
[e]Statistically significantly different from control ($p < 0.05$) by Chi-square test performed by study authors.

Table B.6. Stones of the Urinary System in Wistar Rats Exposed to 1,1-Biphenyl in the Diet for 75 Weeks[a]

Parameter	Exposure Group ($Dose_{ADJ}$, mg/kg-day)		
	0 mg/kg (0)	2500 mg/kg (188)	5000 mg/kg (375)
Male rats			
Kidney stones[b]	0/44 (0)	6/46 (13)	15/47 (32)
Ureter stones[b]	0/44 (0)	0/46 (0)	2/47 (4)
Urinary bladder stones[b]	0/44 (0)	0/46 (0)	13/47 (28)
Female rats			
Kidney stones[b]	0/43 (0)	1/43 (2)	18/39 (46)
Ureter stones[b]	0/43 (0)	1/43 (2)	2/39 (51)
Urinary bladder stones[b]	0/43 (0)	0/43 (0)	6/39 (15)

[a]Boehncke et al. (1999).
[b]Number of animals with litters/number of animals exposed, () = percent of total.

Table B.7. Selected Incidence of Liver Lesions in Female BDF1 Mice Exposed to 1,1-Biphenyl in the Diet for 104 Weeks[a]

Parameter	Exposure Group (HED, mg/kg-day)			
	0 mg/kg-day (0)	123 mg/kg-day (17.5)	414 mg/kg-day (52.5)	1420 mg/kg-day (157.5)
Liver				
Nodule[b]	7/50 (14)	13/50 (16)	24/50 (48)	26/50 (52)
Hepatocellular adenoma[b]	2/50 (4)	3/50 (6)	12/50 (24)[c]	10/50 (20)[c, d]
Hepatocellular carcinoma[b]	1/50 (2)	5/50 (10)	7/50 (14)[c]	5/50 (10)
Hepatocellular adenoma or carcinoma[b]	3/50 (6)	8/50 (16)	16/50 (32)[e]	14/50 (28)[c, d]
Basophilic cell foci[b]	1/50 (2)	1/50 (2)	12/50 (24)[e]	6/50 (12)[c]
Clear cell foci[b]	2/50 (4)	1/50 (2)	3/50 (6)	2/50 (4)
Eosinophilic cell foci[b]	0/50 (0)	1/50 (2)	0/50 (0)	0/50 (0)
Kidney				
Desquamation: pelvis[b]	4/50 (8)	0/50 (0)	0/50 (0)	15/50 (30)[e]
Mineralization in the inner stripe-outer medulla[b]	3/50 (6)	5/50 (10)	12/50 (24)[c]	26/50 (52)[e]

[a]Umeda et al. (2005).
[b]Number of animals with endpoint/number of animals examined, () = percent of total.
[c]Statistically significantly different from control ($p < 0.05$) by Fisher's exact test performed by study authors.
[d]Statistically significantly different from control ($p < 0.05$) by Peto's test performed by researchers.
[e]Statistically significantly different from control ($p < 0.01$) by Fisher's exact test performed by study authors.

Table B.8. Selected Incidence of Liver Lesions in the Male BDF1 Mice Exposed to 1,1-Biphenyl in the Diet for 104 Weeks[a]

Parameter	Exposure Group (HED, mg/kg-day)			
	0 mg/kg-day (0)	97 mg/kg-day (17.5)	360 mg/kg-day (52.5)	1079 mg/kg-day (157.5)
Liver				
Nodule[b]	20/50 (40)	16/50 (32)	14/50 (28)	11/50 (22)
Hepatocellular adenoma[b]	8/50 (16)	6/50 (12)	7/50 (14)	3/50 (6)
Hepatocellular carcinoma[b]	8/50 (16)	8/50 (16)	5/50 (10)	4/50 (8)
Hepatocellular adenoma or carcinoma[b]	16/50 (32)	12/50 (24)	9/50 (18)	7/50 (14)
Basophilic cell foci[b]	0/50 (0)	6/50 (12)[c]	1/50 (2)	2/50 (4)
Clear cell foci[b]	0/50 (0)	6/50 (12)[c]	2/50 (4)	0/50 (0)
Eosinophilic cell foci[b]	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Kidney				
Desquamation: pelvis[b]	0/50 (0)	0/50 (0)	0/50 (0)	10/50 (20)[c]
Mineralization in the inner stripe-outer medulla[b]	9/50 (18)	8/50 (16)	14/50 (28)	14/50 (28)

[a]Umeda et al. (2005).
[b]Number of animals with endpoint/number of animals examined, () = percent of total.
[c]Statistically significantly different from control ($p < 0.01$) by Fisher's exact test performed by study authors.

Table B.9. Prenatal Effects Following Oral Administration of Biphenyl to Pregnant Wistar Rats on GDs 6–15[a]

Effect	Dose (mg/kg-d)				
	0	125	250	500	1000
Rats without live fetuses at term/number mated	2/18	0/20	1/19	2/20	11/20[b]
Corpora lutea/pregnancy (mean ± SE)	12.6 ± 0.4	12.9 ± 0.4	13.7 ± 0.5	13.3 ± 0.4	12.5 ± 0.7
Live fetuses/pregnancy (mean ± SE)	11.3 ± 0.7	11.8 ± 0.6	11.9 ± 0.6	11.2 ± 0.5	10.7 ± 1.3
Dead or resorbed fetuses (%)	4.8	3.3	6.1	7.8	13.7[c]
Fetal weight (g mean ± SE)	5.1 ± 0.1	5.3 ± 0.1	5.2 ± 0.1	5.2 ± 0.1	4.5 ± 0.3
Anomalous fetuses/number examined	17/176	22/236	22/213	35/199[d]	25/107[d]
Anomalous litters/number examined	8/16	11/20	13/18	15/18[d]	6/9
Anomalies (number of fetuses affected)					
Wavy ribs, uni- and bilateral	3	7	9	8	5
Extra ribs, uni- and bilateral	9	12	9	15	6
13th rib, small sized	1	1	2	1	0
Sternebrae, missing or unossified	4	3	4	16	17
Calvarium, delayed ossification	0	2	0	0	8
Miscellaneous	1	1	1	0	0

[a]Khera et al. (1979).
[b]Significantly ($p < 0.05$) different from control incidence according to Fisher's exact test. Five dams died prior to scheduled sacrifice, five other dams were not pregnant at term, and one dam had seven resorption sites and no live fetuses.
[c]Derived from nine pregnant dams with live fetuses and one dam with seven resorptions and no live fetuses. The study author stated that the percentage of dead or resorbed fetuses in the 1000-mg/kg dose group was not statistically significantly different from controls.
[d]Significantly ($p < 0.05$) different from controls according to Fisher's exact test.

Table B.10. Reproductive Summary in Albino Rats Exposed to 1,1-Biphenyl in the Diet[a]

Parameter	Exposure Group (HED, mg/kg-day)[b]		
	Control	0.1% (82.0)	0.5% (410)
Experiment one			
Number casting litters[c]	9/10 (90)	10/10 (100)	8/10 (80)
Total born	59	67	53
Range of litter size	3 to 9	2 to 10	3 to 9
Experiment two			
Number casting litters[c]	8/8 (100)	6/8 (75)	8/9 (89)
Total born	64	63	48
Range of litter size	5 to 13	3 to 10	3 to 9

[a]Ambrose et al. (1960).
[b]Average daily doses are for female mice only because all endpoints are female.
[c]Number of animals with litters/number of animals exposed, () = percent of total.

Table B.11. Histopathology of CD1 Mice Exposed to 1,1-Biphenyl by Inhalation for 13 Weeks[a]

Parameter	Exposure Group (HEC, mg/m^3)		
	0 ppm (control)	25 ppm (32.8)	50 ppm (65.5)
Trachea			
Within normal limits[b]	80/80 (100)	18/98 (18)	1/71 (1)
Hyperplasia with inflammation[b]	0/80 (0)	80/98 (82)[c,d]	70/71 (99)[c,d]
Lungs			
Within normal limits[b]	80/80 (0)	DNR	0/71 (0)
Abscess[b]	0/80 (0)	1/98 (1)	0/71 (0)
Congestion and edema[b]	0/80 (0)	95/98 (97)[c,d]	71/71 (100)[c,d]
Pneumonia [b]	0/80 (0)	15/98 (15)	20/71 (28)
Neoplasia[b]	0/80 (0)	2/98 (2)	0/71 (0)
Liver			
Within normal limits[b]	78/80 (98)	11/98 (11)	0/71 (0)
Abscesses[b]	2/80 (3)	0/98 (0)	0/71 (0)
Congestion and edema[b]	Not reported	87/98 (89)[c,d]	71/71 (100)[c,d]
Kidneys[e]			
Within normal limits[b]	76/80 (95)	11/98 (11)	0/71 (0)
Abscesses [b]	4/80 (5)	0/98 (0)	0/71 (0)
Congestion and edema[b]	0/80 (0)	87/98 (89)[c, d]	71/71 (100)[c, d]
Spleen[e]			
Within normal limits[b]	80/80 (100)	97/98 (99)	DNR
Neoplasia[b]	0/80 (0)	1/98 (1)	DNR

[a]Cannon Laboratories, Inc. (1977).
[b]Number of animals with endpoint/number of animals exposed, () = percent of total.
[c]Significantly different from control ($p < 0.05$) by Fisher's exact test (two-tailed) performed for this review.
[d]Significant association between dose and endpoint ($p < 0.05$) by the Chi-square test for independence performed for this review.
[e]HEC is for extrarespiratory effects (25-ppm dose = 32.8 mg/m^3; 50-ppm dose = 65.5 mg/m^3).

DNR = data not reported.

Table B.12. Histopathology of CD1 Mice Exposed to 1,1-Biphenyl by Inhalation for 13 Weeks Followed by 30-Day Recovery Period[a]

Parameter	Exposure Group (HEC, mg/m^3)		
	0 ppm (control)	25 ppm (32.8 mg/m^3)	65.5 ppm (56.6 mg/m^3)
Trachea			
Within normal limits[b]	17/20 (85)	3/15 (20)	2/19 (11)
Chronic inflammation[b]	DNR	10/15 (67)[c,d]	12/19 (63)[c,d]
Hyperplasia with acute inflammation[b]	0/20 (0)	0/15 (0)	3/19 (16)
Hyperplasia with chronic inflammation[b]	3/20 (15)	2/15 (13)	2/19 (11)
Lungs			
Within normal limits[b]	20/20 (100)	4/15 (27)	5/19 (26)
Congestion and edema[b]	0/20 (0)	6/15 (40)[c,d]	2/19 (11)[c]
Pneumonia[b]	-	5/15 (33)[c,d]	12/19 (63)[c,d]
Neoplasia[b]	0/20 (0)	0/15 (0)	0/19 (0)
Liver[e]			
Within normal limits[b]	20/20 (100)	15/15 (100)	19/19 (100)
Neoplasia[b]	0/20 (0)	0/15 (0)	0/19 (0)
Kidneys[e]			
Within normal limits[b]	20/20 (100)	15/15 (100)	19/19 (100)
Neoplasia[b]	0/20 (0)	0/15 (0)	0/19 (0)
Within normal limits[b]	DNR	DNR	DNR

[a]Cannon Laboratories, Inc. (1977).
[b]Number of animals with endpoint/number of animals exposed, () = percent of total.
[c]Significant association between dose and endpoint ($p < 0.05$) by independent Chi-square test for independence performed for this review.
[d]Significantly different from control ($p < 0.05$) by Fisher's exact test (two-tailed) performed for this review.
[e]HEC is for extrarespiratory effects (25-ppm dose = 24.7 mg/m^3, 50-ppm dose = 49.4 mg/m^3).

DNR = data not reported.

APPENDIX C. BMD MODELING OUTPUTS FOR 1,1-BIPHENYL

DERIVATION OF AN OSF FOR 1,1-BIPHENYL

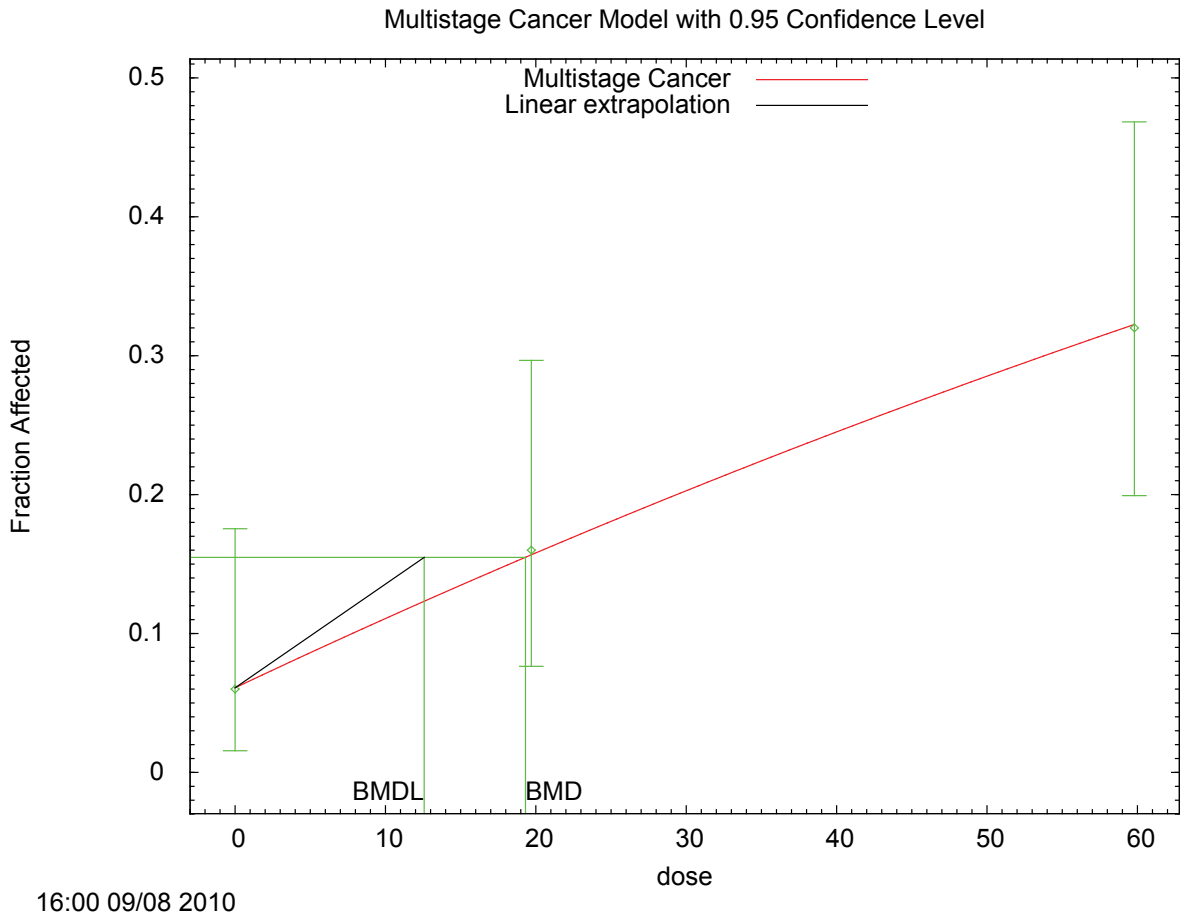

Figure C.1. Multistage Cancer BMDS Model for Combined Hepatocellular Adenoma and Carcinoma in Female BDF1 Mice for 2-Years 1,1-Biphenyl Exposure (Umeda et al. [2005])

Text Output for Multistage Cancer BMDS Model for Combined Hepatocellular Adenoma and Carcinoma in Female BDF1 Mice for 2-Years 1,1-Biphenyl Exposure (Umeda et al. [2005])

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\BMDS21\Data\biphenyl\msc_bip080910_osfbiphenylrecalc.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\Data\biphenyl\msc_bip080910_osfbiphenylrecalc.plt
                                            Wed Sep 08 16:00:12 2010
 =================================================================

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

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Percent
   Independent variable = Conc

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 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
                     Background =    0.0623483
                        Beta(1) =   0.00539322
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)

Background            1         -0.7

   Beta(1)         -0.7            1


                                Parameter Estimates
```

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0608898	*	*	*
Beta(1)	0.00545566	*	*	*
Beta(2)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-64.6753	3			
Fitted model	-64.6785	2	0.00630587	1	0.9367
Reduced model	-70.709	1	12.0674	2	0.002397

AIC: 133.357

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0609	3.044	3.000	50	-0.026
19.7000	0.1566	7.829	8.000	50	0.066
59.8000	0.3223	16.116	16.000	50	-0.035

Chi^2 = 0.01 d.f. = 1 P-value = 0.9366

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 19.3121

BMDL = 12.5765

BMDU = 44.5875

Taken together, (12.5765, 44.5875) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00795133

DERIVATION OF SUBCHRONIC AND CHRONIC P-RFCS FOR 1,1-BIPHENYL

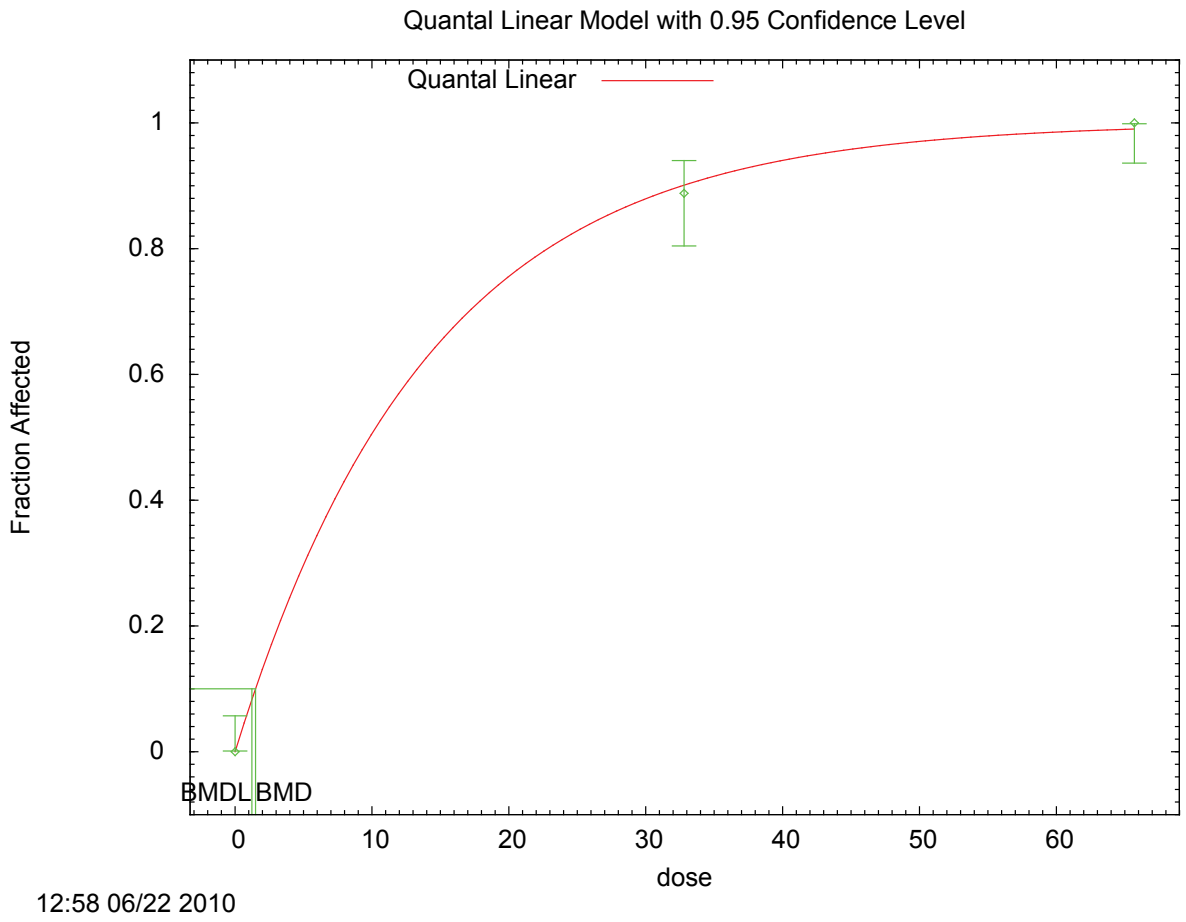

Figure C.2. Quantal Linear BMD Model for CD1 Mouse Liver andKidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

Text Output for Quantal Linear BMD Model of CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

```
        Quantal Linear Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\biphenyl\qln_biphRfC-ER_biphRfC-ER8.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\biphenyl\qln_biphRfC-ER_biphRfC-
ER8.plt
                                                Tue Jun 22 12:58:42 2010
 ========================================================================

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

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose)]


   Dependent variable = Percent
   Independent variable = Conc

   Total number of observations = 3
   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 (and Specified) Parameter Values
                     Background =   0.00617284
                          Slope =    0.0755498
                          Power =           1   Specified


           Asymptotic Correlation Matrix of Parameter Estimates

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

                  Slope

     Slope            1



                                  Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
          Slope        0.0704702       0.00830928           0.0541843
0.0867561

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.3663	3			
Fitted model	-35.1501	1	1.5676	2	0.4567
Reduced model	-163.454	1	258.176	2	<.0001

AIC: 72.3002

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	80	0.000
32.8000	0.9009	88.286	87.024	98	-0.427
65.7000	0.9902	70.307	71.000	71	0.836

Chi^2 = 0.88 d.f. = 2 P-value = 0.6435

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.49511

BMDL = 1.22974

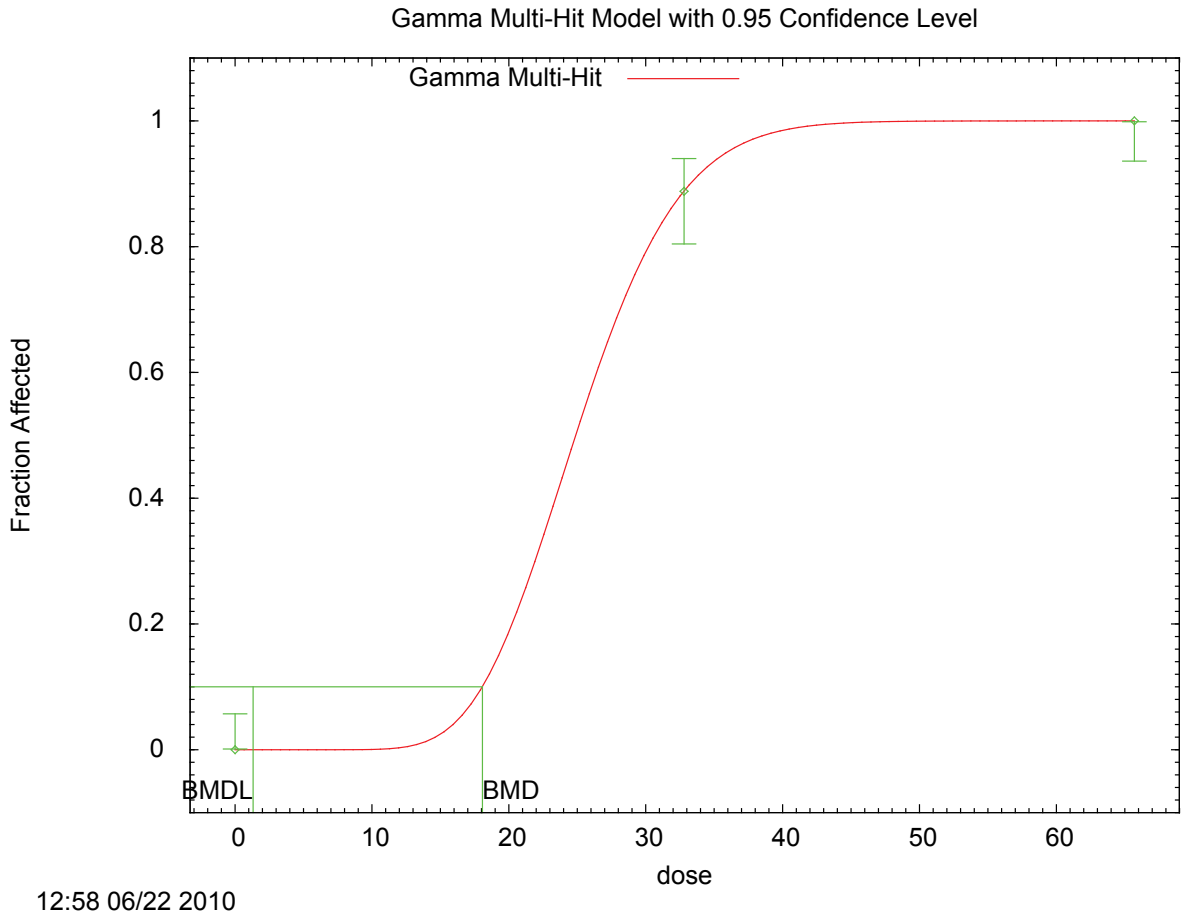

Figure C.3. Gamma BMD Model for CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

Text Output for Gamma BMD Model of CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

```
=============================================================================
        Gamma Model. (Version: 2.13;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\biphenyl\gam_biphRfC-ER_bipRfC-ER1.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\biphenyl\gam_biphRfC-ER_bipRfC-
ER1.plt
                                                Tue Jun 22 12:58:38 2010
 =============================================================================

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

   The form of the probability function is:

   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cumulative Gamma distribution function


   Dependent variable = Percent
   Independent variable = Conc
   Power parameter is restricted as power >=1

   Total number of observations = 3
   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 (and Specified) Parameter Values
                     Background =   0.00617284
                          Slope =    0.0530607
                          Power =          1.3


           Asymptotic Correlation Matrix of Parameter Estimates

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

                  Slope

     Slope            1



                                  Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
          Slope         0.709585       0.0256681            0.659277
0.759894
          Power               18              NA
```

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.3663	3			
Fitted model	-34.3663	1	8.121e-005	2	1
Reduced model	-163.454	1	258.176	2	<.0001

AIC: 70.7327

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	80	0.000
32.8000	0.8880	87.024	87.024	98	-0.000
65.7000	1.0000	71.000	71.000	71	0.006

Chi^2 = 0.00 d.f. = 2 P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 18.0692

BMDL = 1.3176

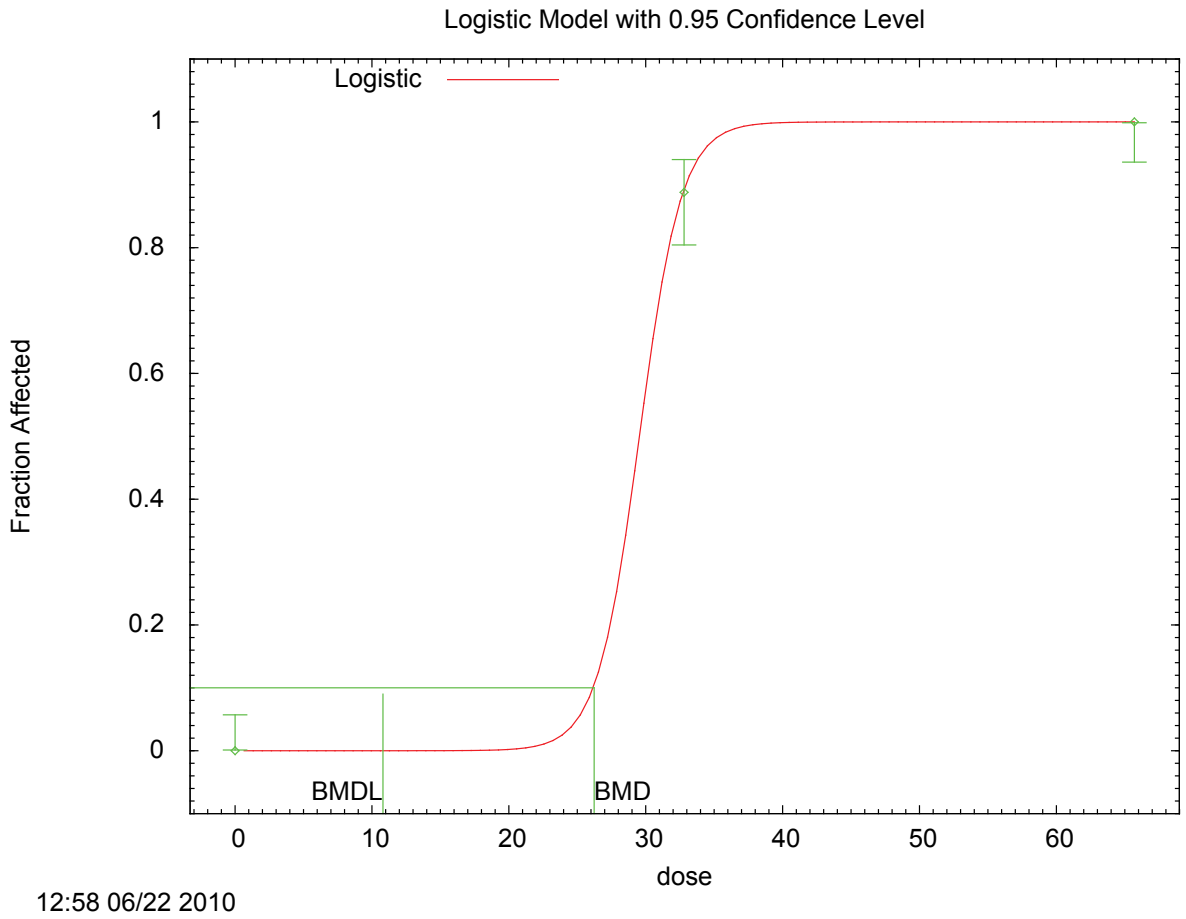

Figure C.4. Logistic BMD Model for CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

Text Output for Logistic BMD Model of CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

```
================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\biphenyl\log_biphRfC-ER_biphRfC-ER2.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\biphenyl\log_biphRfC-ER_biphRfC-
ER2.plt
                                                Tue Jun 22 12:58:39 2010
 ================================================================

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

   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*dose)]


   Dependent variable = Percent
   Independent variable = Conc
   Slope parameter is not restricted

   Total number of observations = 3
   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
                     background =            0   Specified
                      intercept =     -4.38081
                          slope =     0.152848


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept        slope

 intercept            1           -1

     slope           -1            1


                                  Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
      intercept         -19.2382          1469.75            -2899.89
2861.42
          slope         0.649654          44.8094            -87.1751
88.4744
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.3663	3			
Fitted model	-34.3663	2	7.1581e-007	1	0.9993
Reduced model	-163.454	1	258.176	2	<.0001

AIC: 72.7326

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	80	-0.001
32.8000	0.8880	87.024	87.024	98	-0.000
65.7000	1.0000	71.000	71.000	71	0.000

Chi^2 = 0.00 d.f. = 1 P-value = 0.9995

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 26.2308

BMDL = 10.8064

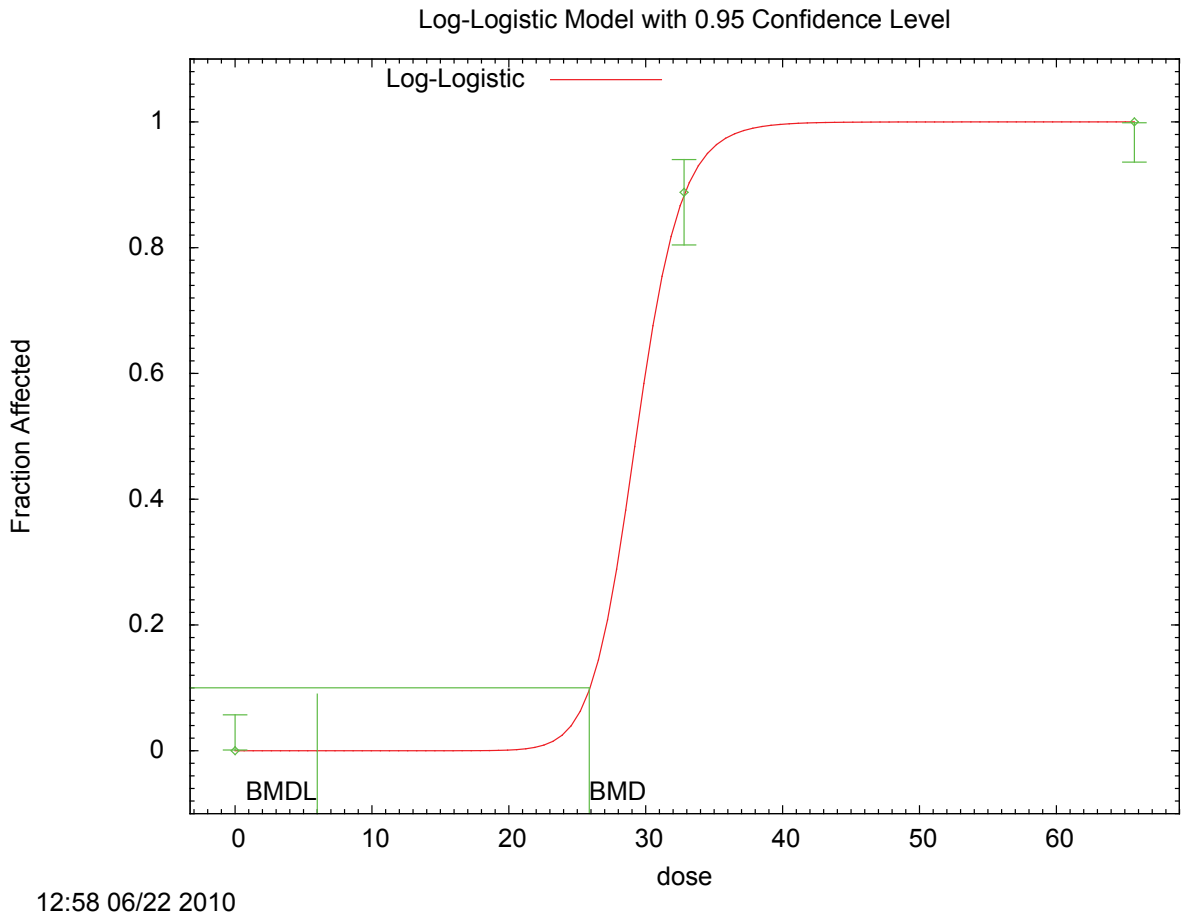

Figure C.5. Log-Logistic BMD Model for CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

Text Output for Logistic BMD Model of CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

```
=============================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\biphenyl\lnl_biphRfC-ER_biphRfC-ER3.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\biphenyl\lnl_biphRfC-ER_biphRfC-
ER3.plt
                                                Tue Jun 22 12:58:40 2010
 =============================================================================

 BMDS Model Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Percent
   Independent variable = Conc
   Slope parameter is restricted as slope >= 1

   Total number of observations = 3
   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



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =           0
                     intercept =     -12.4625
                         slope =      4.16366


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept

 intercept            1



                                  Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background               0            *                *                  *
      intercept         -60.7572            *                *                  *
          slope               18            *                *                  *
```

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.3663	3			
Fitted model	-34.3663	1	6.6473e-005	2	1
Reduced model	-163.454	1	258.176	2	<.0001

AIC: 70.7327

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	80	0.000
32.8000	0.8880	87.024	87.024	98	-0.000
65.7000	1.0000	71.000	71.000	71	0.006

Chi^2 = 0.00 d.f. = 2 P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 25.8765

BMDL = 6.00398

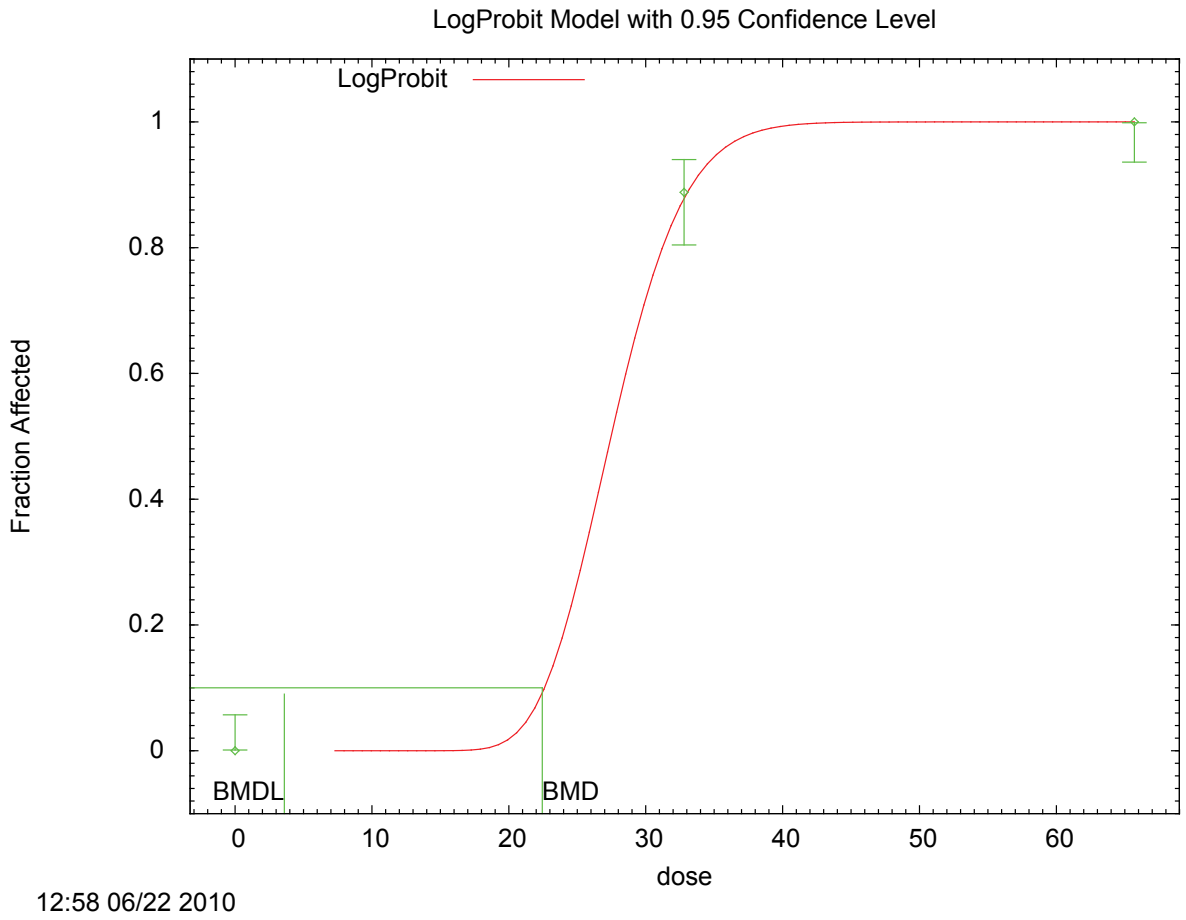

Figure C.6. Log-Probit BMD Model for CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

Text Output for Log-Probit BMD Model of CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

```
=================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\biphenyl\lnp_biphRfC-ER_biphRfC-ER4.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\biphenyl\lnp_biphRfC-ER_biphRfC-
ER4.plt
                                              Tue Jun 22 12:58:40 2010
 =================================================================

 BMDS Model Run
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   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = Percent
   Independent variable = Conc
   Slope parameter is not restricted

   Total number of observations = 3
   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



   User has chosen the log transformed model


                 Default Initial (and Specified) Parameter Values
                    background =            0
                     intercept =     -5.03544
                         slope =      1.79101


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept        slope

 intercept            1           -1

     slope           -1            1


                                Parameter Estimates

                                                      95.0% Wald Confidence
Interval
```

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-21.7575	971.94	-2377.52	2334.01
slope	6.58184	344.354	-668.34	681.503

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.3663	3			
Fitted model	-34.3663	2	5.0521e-007	1	0.9994
Reduced model	-163.454	1	258.176	2	<.0001

AIC: 72.7326

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	80	0.000
32.8000	0.8880	87.024	87.024	98	-0.000
65.7000	1.0000	71.000	71.000	71	0.001

Chi^2 = 0.00 d.f. = 1 P-value = 0.9996

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 22.4429

BMDL = 3.59818

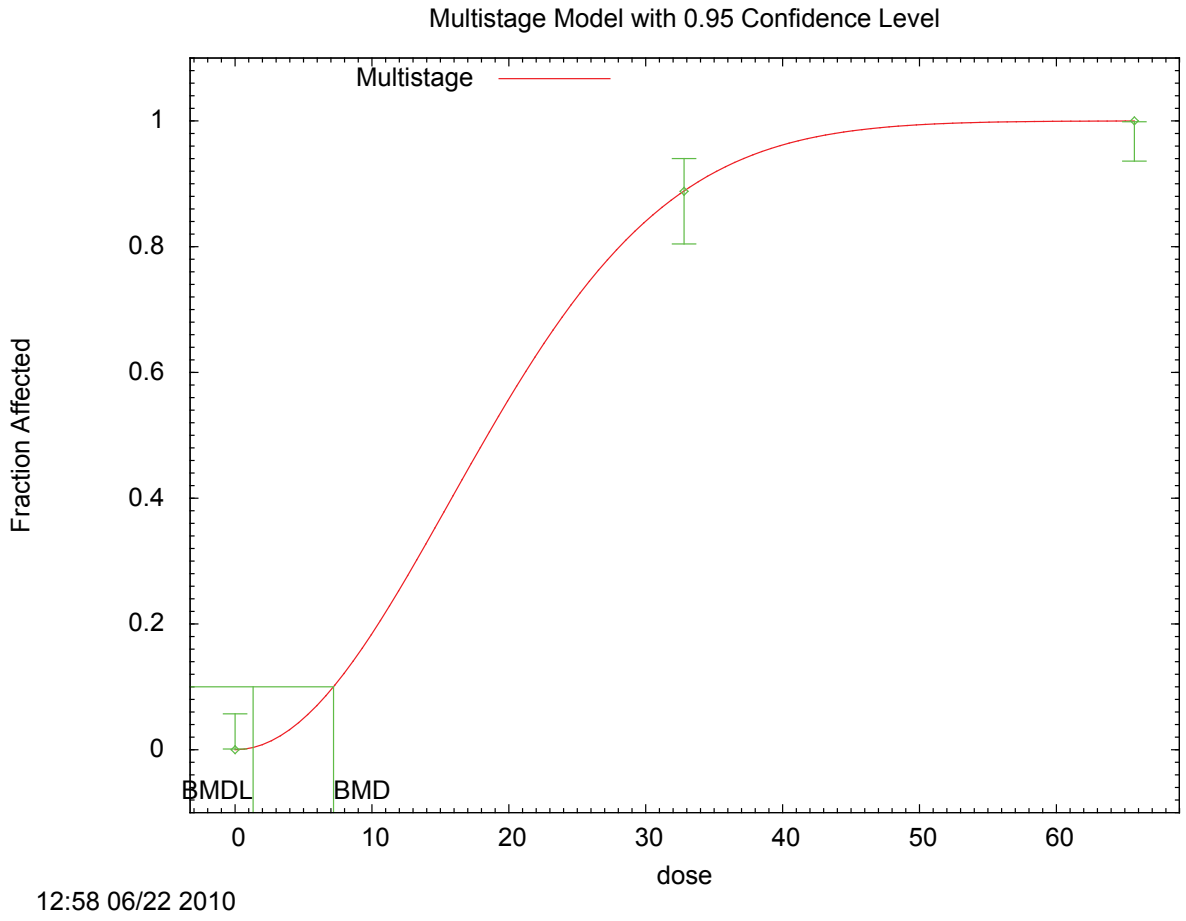

Figure C.7. Multistage BMD Model for CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

Text Output for Multistage BMD Model of CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

```
================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\biphenyl\mst_biphRfC-ER_biphRfC-ER5.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\biphenyl\mst_biphRfC-ER_biphRfC-
ER5.plt
                                              Tue Jun 22 12:58:41 2010
 ================================================================

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

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Percent
   Independent variable = Conc

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 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
                     Background =            0
                        Beta(1) =            0
                        Beta(2) = 2.49482e+016


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(2)

   Beta(2)            1



                                Parameter Estimates

                                                      95.0% Wald Confidence
Interval
```

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.00203615	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.3663	3			
Fitted model	-34.4269	1	0.121117	2	0.9412
Reduced model	-163.454	1	258.176	2	<.0001

AIC: 70.8537

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	80	-0.000
32.8000	0.8881	87.038	87.024	98	-0.005
65.7000	0.9998	70.989	71.000	71	0.104

Chi^2 = 0.01 d.f. = 2 P-value = 0.9946

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.1934

BMDL = 1.31769

BMDU = 8.00427

Taken together, (1.31769, 8.00427) is a 90 % two-sided confidence interval for the BMD

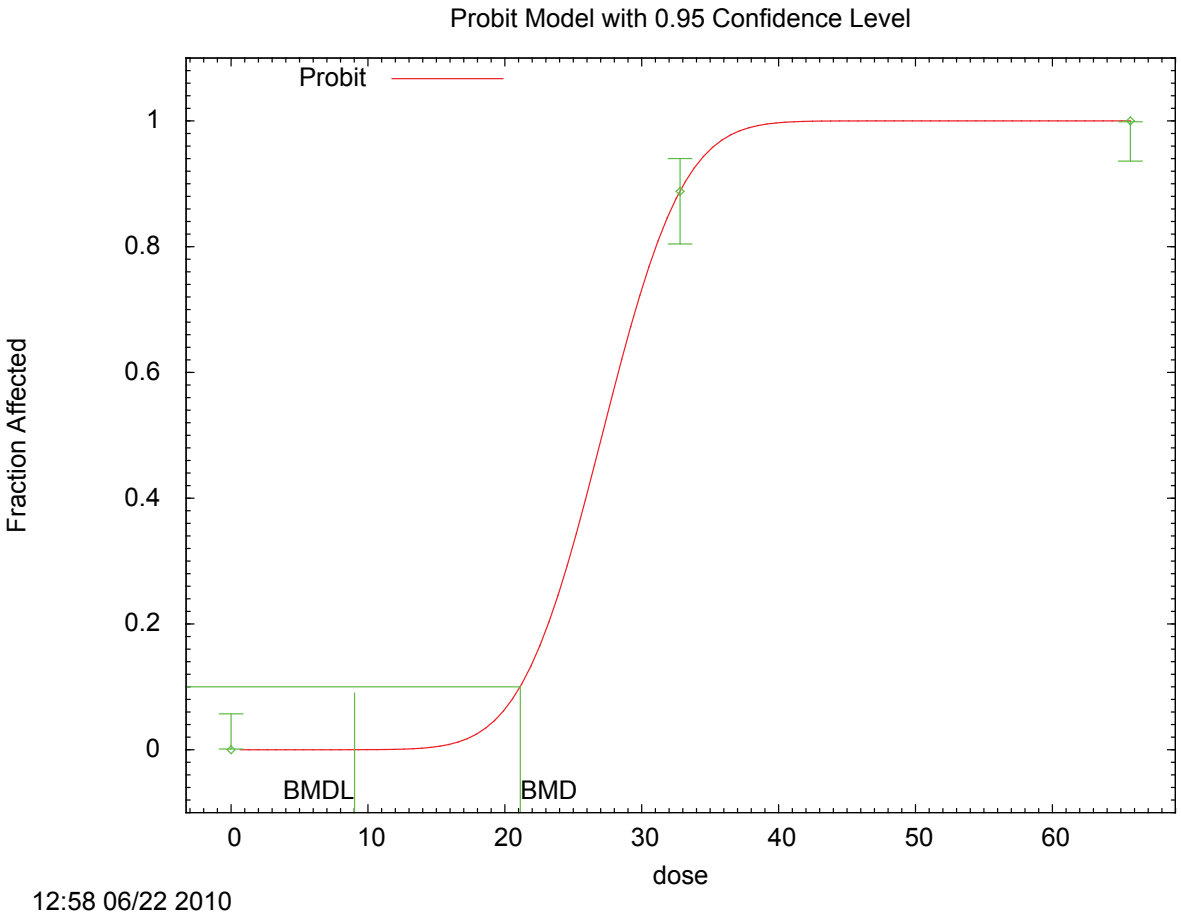

Figure C.8. Probit BMD Model for CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

Text Output for Probit BMD Model of CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

```
=============================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\biphenyl\pro_biphRfC-ER_biphRfC-ER6.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\biphenyl\pro_biphRfC-ER_biphRfC-
ER6.plt
                                                Tue Jun 22 12:58:41 2010
 =============================================================================

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

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = Percent
   Independent variable = Conc
   Slope parameter is not restricted

   Total number of observations = 3
   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 (and Specified) Parameter Values
                     background =            0   Specified
                      intercept =     -2.41713
                          slope =     0.086286


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept        slope

 intercept            1           -1

     slope           -1            1


                                  Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
      intercept          -5.8032          366.377            -723.888
712.282
```

```
          slope         0.213999            11.17           -21.6788
22.1068
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.3663	3			
Fitted model	-34.3663	2	5.20497e-007	1	0.9994
Reduced model	-163.454	1	258.176	2	<.0001

AIC: 72.7326

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	80	-0.001
32.8000	0.8880	87.024	87.024	98	0.000
65.7000	1.0000	71.000	71.000	71	0.000

Chi^2 = 0.00 d.f. = 1 P-value = 0.9996

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 21.1293

BMDL = 9.0211

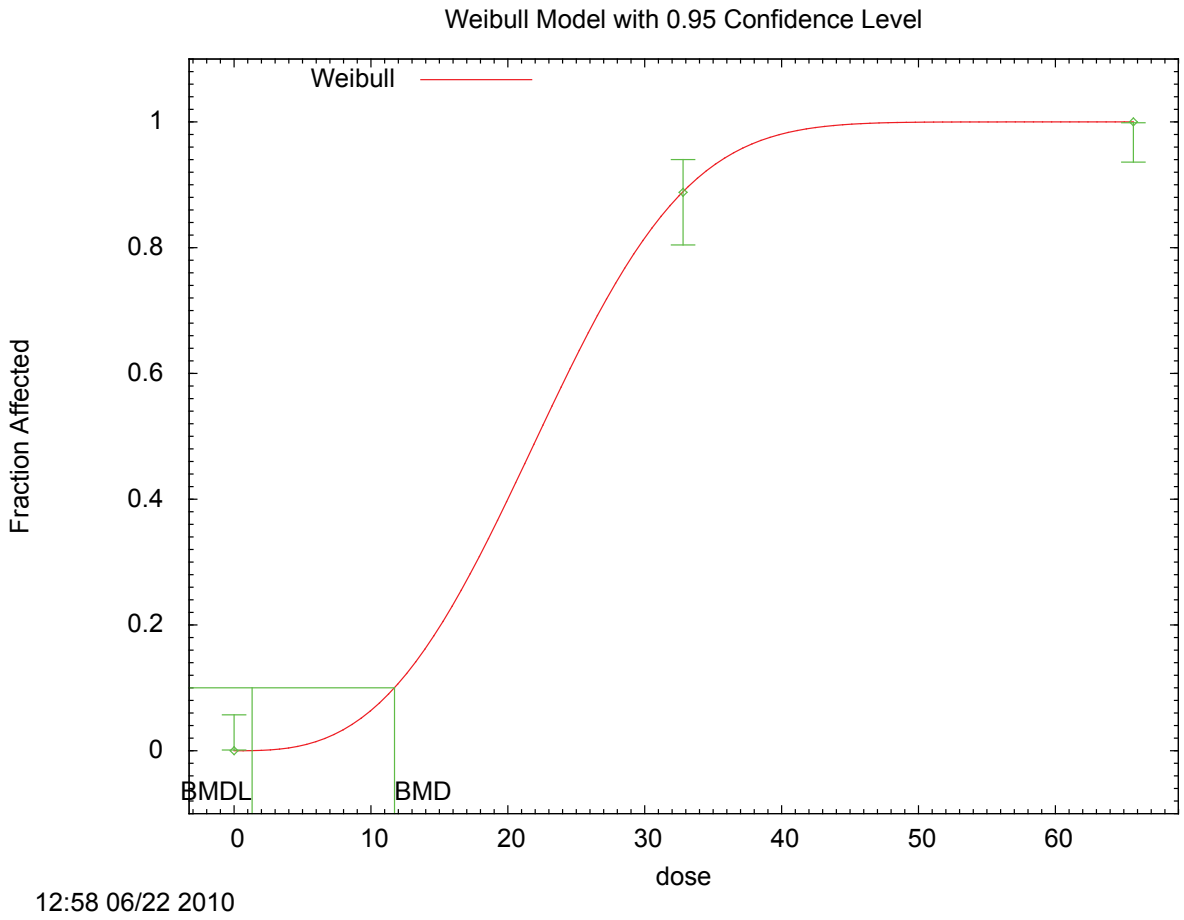

Figure C.9. Weibull BMD Model for CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

Text Output for Weibull BMD Model of CD1 Mouse Liver and Kidney Congestion and Edema (Cannon Laboratories, Inc. [1977])

```
  ================================================================
        Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\biphenyl\wei_biphRfC-ER_biphRfC-ER7.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\biphenyl\wei_biphRfC-ER_biphRfC-
ER7.plt
                                                Tue Jun 22 12:58:41 2010
 ================================================================

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

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = Percent
   Independent variable = Conc
   Power parameter is restricted as power >=1

   Total number of observations = 3
   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 (and Specified) Parameter Values
                     Background =   0.00617284
                          Slope =   0.00728578
                          Power =      1.55886


           Asymptotic Correlation Matrix of Parameter Estimates

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

                  Slope        Power

     Slope            1           -1

     Power           -1            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
          Slope     7.42391e-005       0.00180342          -0.0034604
0.00360888
```

```
          Power          2.94856           6.9597           -10.6922
16.5893

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -34.3663         3
   Fitted model        -34.3663         2  6.06381e-006      1           0.998
  Reduced model        -163.454         1       258.176      2         <.0001

           AIC:         72.7326


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          80        0.000
   32.8000     0.8880        87.023    87.024          98        0.000
   65.7000     1.0000        71.000    71.000          71        0.002

 Chi^2 = 0.00      d.f. = 1        P-value = 0.9986


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        11.7222

     BMDL =     1.3176
```

DERIVATION OF A SUBCHRONIC AND CHRONIC P-RFD FOR 1,1-BIPHENYL

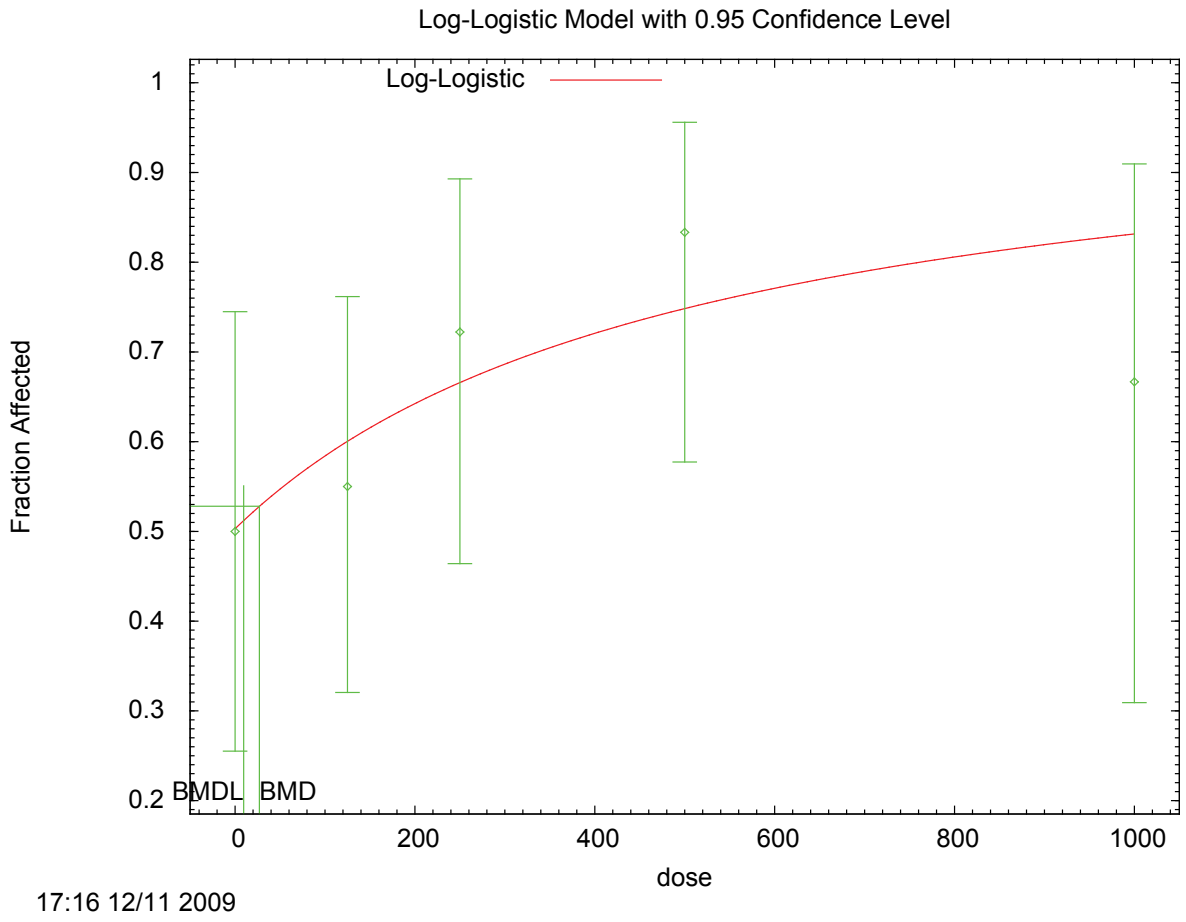

Figure C.10. Log-Logistic BMDS Model for Incidence of Litters with Fetal Skeletal Anomalies from Wistar Rat Dams Administered Biphenyl by Gavage on GDs 6–15 (Khera et al., 1979)

Text Output for Log-Logistic BMDS Model for Incidence of Litters with Fetal Skeletal Anomalies from Wistar Rat Dams Administered Biphenyl by Gavage on GDs 6–15 (Khera et al., 1979)

```
 ================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\biphenyl\rat\develop\anomlitt\lnl_anomlitt_loglogistic.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\biphenyl\rat\develop\anomlitt\lnl_anomlitt_loglogistic.plt
                                          Fri Dec 11 17:16:25 2009
 ================================================================

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

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = incidence
   Independent variable = dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   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



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =          0.5
                     intercept =     -6.54827
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

             background    intercept

background            1        -0.77

 intercept        -0.77            1


                                Parameter Estimates

                                                      95.0% Wald Confidence
Interval
```

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
background	0.503241	*	*	*
intercept	-6.24131	*	*	*
slope	1	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-49.327	5			
Fitted model	-50.6629	2	2.67182	3	0.445
Reduced model	-52.2232	1	5.79233	4	0.2152

AIC: 105.326

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.5032	8.052	8.000	16	-0.026
125.0000	0.6005	12.010	11.000	20	-0.461
250.0000	0.6659	11.986	13.000	18	0.507
500.0000	0.7483	13.469	15.000	18	0.831
1000.0000	0.8315	7.483	6.000	9	-1.321

Chi^2 = 2.90 d.f. = 3 P-value = 0.4065

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 27.028

BMDL = 9.58732

APPENDIX D. REFERENCES

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