Biphenyl; CASRN 92-52-4

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at www.epa.gov/iris/backgrd.html.

STATUS OF DATA FOR Biphenyl

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/27/2013
Inhalation RfC (I.B.)	qualitative discussion	08/27/2013
Carcinogenicity Assessment (II.)	yes	08/27/2013

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Biphenyl
CASRN — 92-52-4
Last Revised — 08/27/2013

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please

refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

The RfD of 0.5 mg/kg-day replaces the previous RfD of 0.05 mg/kg-day entered on the IRIS database on 08/01/1989. The previous RfD was based on a no-observed-adverse-effect level (NOAEL) of 50 mg/kg-day for kidney damage in the rat (Ambrose et al., 1960), and a composite uncertainty factor (UF) of 1,000 (10 for extrapolation from rats to humans, 10 for human variation, and an additional modifying factor of 10 to account for intraspecies variability demonstrated by uncertainty in the threshold suggested by the data in the principal study).

I.A.1. Chronic Oral RfD Summary

Critical Effect	Experimental Doses*	UF	Chronic RfD
Renal papillary mineralization in male F344 rats **2-year dietary study** **Umeda et al. (2002)**	$BMDL_{10/HED}$ = 13.9 mg/kg-day	30	0.5 mg/kg-day

*Conversion Factors and Assumptions — Rats in the principal study were exposed continuously via diet; therefore, no adjustment for intermittent dosing was required. $BMDL_{10/HED}$ = 95% lower confidence limit on the maximum likelihood estimate of the dose corresponding to a 10% extra risk, and expressed as a human equivalent dose (HED) using $BW^{3/4}$ scaling (U.S. EPA, 2011).

I.A.2. Principal and Supporting Studies (Oral RfD)

Umeda et al. (2002) exposed F344 rats (50/sex/group) to biphenyl in the diet for 2 years at concentrations of 0, 500, 1,500, or 4,500 ppm (corresponding to doses of 36.4, 110, and 378

mg/kg-day, respectively, for males, and 42.7, 128, and 438 mg/kg-day, respectively, for females).

Mean body weights of 4,500 ppm male and female rats were lower than those of controls throughout most of the study period and were approximately 20% lower than respective controls at terminal sacrifice. There was no statistically significant effect on mean body weights of 500 or 1,500 ppm males or females. Survival of low- and mid-dose male and female rats was reported not to differ statistically significantly from controls.

The study authors reported that 3/50 of the 4,500 ppm female rats died after 13–26 weeks of biphenyl exposure and attributed the deaths to marked mineralization of the kidneys and heart. However, they also indicated that survival of this group was not adversely affected thereafter. Significantly decreased survival was noted only for the group of 4,500 ppm male rats, 19/50 of which died prior to terminal sacrifice. The first death occurred around treatment week 36; this rat exhibited urinary bladder calculi. Survival data for the other groups were not provided. Evidence of hematuria (blood in the urine) was first noted in 4,500 ppm male rats around week 40 and was observed in a total of 32/50 of the 4,500 ppm males during the remainder of the treatment period; 14 of these rats appeared anemic. Hematuria and bladder tumors were considered as primary causes of death among the 4,500 ppm males (n = 19) that died prior to terminal sacrifice.

Urinalysis performed during the final treatment week revealed statistically significantly increased urinary pH in the 31 remaining 4,500 ppm male rats (pH of 7.97 versus 7.66 for controls; $p < 0.05$), with occult blood noted in the urine of 23 of these males. Urine samples in 10/37 surviving 4,500 ppm females tested positive for occult blood. Relative kidney weights of 1,500 and 4,500 ppm males and females and absolute kidney weights of 4,500 ppm males were statistically significantly increased (actual data were not reported).

Gross pathologic examinations at premature death or terminal sacrifice revealed the presence of calculi in the bladder of 43/50 of the 4,500 ppm males and 8/50 of the 4,500 ppm females, but not in the other dose groups. It was noted that 30/32 of the 4,500 ppm male rats with hematuria also exhibited kidney or urinary bladder calculi.

Histopathological lesions of the ureter, kidney, and urinary bladder associated with biphenyl exposure were reported in male and female rats. The incidences of transitional cell hyperplasia and dilatation in the ureter were increased in the 4,500-ppm rats compared to controls. In the renal pelvis, incidences of hyperplasia and mineralization showed dose-related increases in males and females; the incidence of desquamation and calculi were increased primarily in male rats. Other treatment-related lesions in the kidney of male and female rats included mineralization of the corticomedullary junction and mineralization of the papilla; treatment-related increases in the incidence of papillary necrosis, infarct, and hemosiderin deposition in the kidney occurred predominantly in exposed females. In the urinary bladder, nonneoplastic lesions were found

predominantly in male rats, and included transitional cell hyperplasia, squamous cell metaplasia and hyperplasia, inflammatory polyps, and calculi. An increased incidence of tumors associated with biphenyl administration was limited to tumors of the urinary bladder in male rats (see Section II.A).

In summary, this study identified a NOAEL of 500 ppm (42.7 mg/kg-day) and a lowest-observed-adverse-effect level (LOAEL) of 1,500 ppm (128 mg/kg-day) for nonneoplastic kidney lesions (simple transitional cell hyperplasia in the renal pelvis and hemosiderin deposits) in female F344 rats exposed to biphenyl in the diet for 2 years.

Methods of Analysis. No biologically-based dose-response models are available for biphenyl. In this situation, EPA evaluates a range of empirical dose-response models thought to be consistent with underlying biological processes to model the dose-response relationship in the range of the observed data. Consistent with this approach, all standard models available as part of EPA's Benchmark Dose Software (BMDS, version 2.1.2) were evaluated.

The kidney was identified as the most sensitive target of biphenyl toxicity based on data from the 2-year bioassay in F344 rats by Umeda et al. (2002). Dose-response modeling using BMDS was performed for the following nonneoplastic renal lesions: transitional cell hyperplasia (nodular and simple) and mineralization of the renal pelvis, hemosiderin deposits, and papillary mineralization. Consistent with EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012) for dichotomous data, the benchmark dose (BMD) and the 95% lower confidence limit on the BMD (BMDL) were estimated using a benchmark response (BMR) of 10% extra risk in the absence of information regarding what level of change is considered biologically significant, and also to facilitate a consistent basis of comparison across endpoints, studies, and assessments. In general, adequate model fit was judged by the chi-square goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the fit of the dose-response curve to the data points, scaled residuals, and fit in the low-dose region and in the vicinity of the BMR. Among all of the models providing adequate fit to a dataset, the model with the lowest Akaike's Information Criterion (AIC) was chosen as the best-fitting model when the difference between the BMDLs estimated from a set of models was less than threefold. Otherwise, the model with the lowest BMDL was selected as the best-fitting model for a dataset (U.S. EPA, 2012).

Based on the results of dose-response modeling as shown below, the BMD_{10} values for five kidney endpoints ranged from 45 to 92 mg/kg-day. In the kidney medulla, papillary mineralization falls on a continuum of effects progressing (at higher doses) to papillary necrosis, and is consistent with a functional change in the kidney. Papillary mineralization was a more sensitive endpoint among male rats than female rats, with BMD_{10} values of 92 and 292 mg/kg-day, respectively. At the same time, the female rats showed more sensitive results than the males for renal pelvis simple transitional cell hyperplasia and mineralization, with BMD_{10} values of 71–88 mg/kg-day, compared with 208–314 mg/kg-day in the males. Although the BMD_{10} for

hemosiderin deposits in the female rat was lower (by about twofold) than the value associated with papillary mineralization, the biological relevance of hemosiderin deposits as reported in Umeda et al. (2002) is unclear. Papillary mineralization in male rats was selected as the critical effect and the basis for derivation of the RfD because it was judged to be the more serious outcome in this range of BMD_{10} values, given its likely progression to necrosis at higher exposures. Similar results for the other kidney histopathology outcomes support this selection.

Summary of candidate PODs for selected nonneoplastic effects of biphenyl

	Male F344 rats				Female F344 rats			
	Best fitting model	BMR	Benchmark result (mg/kg-d)		Best fitting model	BMR	Benchmark result (mg/kg-d)	
			BMD	BMDL			BMD	BMDL
Renal pelvis								
Transitional cell nodular hyperplasia	Logistic	10%	234	192	Multistage 2 degree	10%	274	212
Transitional cell simple hyperplasia	Gamma	10%	314	113	Gamma	10%	71	52
Mineralization	Log-probit	10%	208	138	Multistage 1 degree	10%	88	56
Kidney – other								
Hemosiderin deposit	Not observed				Dichotomous-Hill	10%	45	23
Papillary mineralization	Multistage 1 degree	10%	92	58	Logistic	10%	292	219

Source: Umeda et al. (2002)

As described in EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011), an HED was derived from the point of departure

(POD) (i.e., $BMDL_{10}$) using a body weight scaling to the 3/4 power (i.e., $BW^{3/4}$) approach to extrapolate toxicologically equivalent doses of orally administered biphenyl from adult laboratory rats to adult humans. Specifically, the POD was converted to an HED employing a standard dosimetric adjustment factor (DAF) derived as follows:

$DAF = (BW_a^{1/4} / BW_h^{1/4})$,
Where BW_a = animal body weight and BW_h = human body weight

Using a BW_a of 0.25 kg for rats and a BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF for rats was 0.24. Applying this DAF to the POD identified for the critical effect (i.e., the $BMDL_{10}$ for papillary mineralization in male rats) yields a POD_{HED} as follows:

POD_{HED} = laboratory animal dose (mg/kg-day) x DAF
= $BMDL_{10}$ (mg/kg-day) x DAF
= 58 mg/kg-day x 0.24
= 13.9 mg/kg-day

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 30

An interspecies uncertainty factor of 3 ($UF = 10^{1/2} = 3.16$, rounded to 3) is applied because $BW^{3/4}$ scaling is being used to extrapolate oral doses from laboratory animals to humans. Although $BW^{3/4}$ scaling addresses some aspects of cross-species extrapolation of toxicokinetic and toxicodynamic processes, some residual uncertainty remains. In the absence of chemical-specific data to quantify this uncertainty, EPA's $BW^{3/4}$ guidance (U.S. EPA, 2011) recommends use of an uncertainty factor of 3.

An UF of 10 was applied to account for intraspecies variability in susceptibility to biphenyl, as quantitative information for evaluating toxicokinetic and toxicodynamic differences among humans are not available.

An UF of 1 for subchronic to chronic extrapolation was applied in this assessment because the candidate principal study was chronic in duration.

An UF of 1 was applied for LOAEL to NOAEL extrapolation because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of 10% increased incidence of papillary mineralization in the rat kidney was selected under the assumption that it represents a minimal biologically significant change.

An UF of 1 to account for database deficiencies was applied. The biphenyl database includes chronic toxicity studies in rats (Umeda et al., 2002; Shiraiwa et al., 1989; Ambrose et al., 1960; Pecchiai and Saffiotti, 1957; Dow Chemical Co, 1953) and mice (Umeda et al., 2005; Imai et al., 1983); subchronic toxicity studies in rats (Shibata et al., 1989b; Shibata et al., 1989a; Kluwe, 1982; Søndergaard and Blom, 1979; Booth et al., 1961) and mice (Umeda et al., 2004); a developmental toxicity study in rats (Khera et al., 1979); and one- and three-generation reproductive toxicity studies in rats (Ambrose et al., 1960; Dow Chemical Co, 1953). Epidemiological studies provide some evidence that biphenyl may induce functional changes in the nervous system at concentrations in excess of occupational exposure limits. Seppalainen and Hakkinen (1975) reported abnormal electroencephalography (EEG) and electroneuromyography (ENMG) findings and increases in clinical signs in workers exposed to biphenyl during the production of biphenyl-impregnated paper at concentrations that exceeded the occupational limit by up to 100-fold, and Wastensson et al. (2006) reported an increased prevalence of Parkinson's disease in a Swedish factory manufacturing biphenyl-impregnated paper where exposures were likely to have exceeded the threshold limit value (TLV) of 1.3 mg/m^3. The evidence of an association between biphenyl exposure and increased prevalence of Parkinson's disease was not confirmed by the earlier study by Seppalainen and Hakkinen (1975), despite workplace concentrations that appeared to be considerably higher than those in the plant investigated by Wastensson et al. (2006). Wastensson et al. (2006) acknowledged that chance is an alternative explanation for the cases identified in the Swedish factory workers. Animal studies did not include examination of sensitive measures of neurotoxicity. The 2-year oral bioassays in rats and mice (Umeda et al., 2005; Umeda et al., 2002) did, however, include daily observations for clinical signs and histopathological examination of nervous system tissues. No nervous system effects were reported, suggesting that the nervous system is not a sensitive target of oral biphenyl toxicity. Overall, the findings from studies of occupational (predominantly inhalation) exposure to biphenyl introduce some uncertainties in the characterization of biphenyl hazard by ingestion, but were not considered a data gap sufficient to warrant a database UF.

I.A.4. Additional Studies/Comments (Oral RfD)

The primary targets of toxicity of ingested biphenyl in experimental animals are the kidney, urinary bladder, liver, and developing fetus. Decreased body weight has also been associated with oral biphenyl exposure. No information was located regarding possible associations between oral exposure to biphenyl and health outcomes in humans.

Chronic oral studies identified the kidney as one of the noncancer targets of biphenyl in both rats and mice. Exposure to biphenyl in the diet for 2 years produced a range of histopathological changes in the kidney in F344 rats (Umeda et al., 2002). Mineralization of the papilla (part of the renal medulla) showed a dose-related increase in both male and female rats; papillary necrosis was observed in both sexes of rats at the high dose only. Papillary mineralization can be found in

association with papillary necrosis (Bach and Nguyen, 1998), and the histopathological changes in the medulla overall suggest a continuum of increasing severity of damage with increasing biphenyl dose. Effects in the papillary region of the medulla were supported by dose-related histopathological changes in the renal pelvis of male and female rats in the Umeda et al. (2002) bioassay, including mineralization, transitional cell hyperplasia (simple and nodular), desquamation, and calculus formation. A dose-related increase in the incidence of hemosiderin deposits was observed in female rats, but not in male rats at any dose level. Hemosiderin, an iron-protein complex that may be present as a product of hemoglobin degradation, can arise from various conditions (Jennette et al., 2007). Without information in Umeda et al. (2002) on severity and location of hemosiderin within the kidney, the biological significance of this endpoint is unclear. Kidney findings were consistently observed in other studies in rats, including tubular dilation or mild tubuli degeneration in albino and Sprague-Dawley rats (Ambrose et al., 1960; Pecchiai and Saffiotti, 1957; Dow Chemical Co, 1953) and calculi formation in the renal pelvis in Wistar and albino rats (Shiraiwa et al., 1989; Ambrose et al., 1960). Dose-related pathological changes in the kidney in BDF_1 mice following 2-year dietary exposure to biphenyl included desquamation of the renal pelvis and mineralization of the medulla (Umeda et al., 2005). A dose-related increase in blood urea nitrogen (BUN) levels in mice in this study (Umeda et al., 2005) provides evidence of biphenyl-induced functional disruption of the kidney. Imai et al. (1983) did not find histopathological changes in the kidney of ddY mice exposed to biphenyl in diet for 2 years; however, only ~60% of the animals were subjected to pathological examination in this study. There is a hazard potential for kidney toxicity based on consistent evidence of biphenyl-induced kidney toxicity in studies in rats and some support from studies in mice.

Urinary bladder toxicity associated with oral exposure to biphenyl was observed in rats only. Increased incidences of urinary bladder hyperplasia and calculi or stones were observed in male and female F344 rats exposed to biphenyl in the diet (approximately 400 mg/kg-day) for 2 years (Umeda et al., 2002) and in male and female Wistar rats exposed to biphenyl in the diet (approximately 360 mg/kg-day) for up to 75 weeks (Shiraiwa et al., 1989). In a subchronic study by Shibata et al. (1989b), increases in 5-bromo-2-deoxyuridine (BrdU) labeling index and simple hyperplasia in urinary bladder epithelium were observed in male F344 rats given biphenyl in the diet (500 mg/kg-day) for 4 weeks. Ambrose et al. (1960) and Dow Chemical Co (1953) did not find lesions in urinary bladder in albino and Sprague-Dawley rats exposed to biphenyl in the diet for 2 years; however, both studies used relatively small group sizes and provided limited necropsy data. Biphenyl did not induce changes in the urinary bladder in mice (Umeda et al., 2005; Imai et al., 1983). There is a hazard potential for urinary bladder toxicity from biphenyl exposure based on evidence of calculi formation and epithelial lesions in the urinary bladder of rats. Because urinary bladder toxicity was not found in a second species, the evidence for hazard potential is weaker than for the kidneys.

Liver toxicity, including histopathological changes and increased liver weight and serum liver enzymes, was observed in studies of mice and rats. Relative liver weight was increased by more than 10% in female albino and Sprague-Dawley rats exposed to 420 and 732 mg/kg-day biphenyl for 2 years, respectively (Ambrose et al., 1960; Dow Chemical Co, 1953), and in rhesus monkeys exposed to 1% biphenyl in the diet for 1 year (Dow Chemical Co, 1953). The only histopathological change observed in rats was moderate degeneration of parenchymal hepatocytes within 2 months followed by regenerative hyperplasia and nuclear hypertrophy that persisted to 13 months in male albino rats exposed to ≥250 mg/kg-day biphenyl (Pecchiai and Saffiotti, 1957). Liver toxicity was not reported in F344 rats exposed to biphenyl in diet up to 438 mg/kg-day for 2 years (Umeda et al., 2002). Differences in response in the two studies may be due to differences in strain susceptibility. In BDF_1 mice, relative liver weight of female mice exposed to 134–1,420 mg/kg-day biphenyl in the diet for 2 years was increased by 1.3–1.6-fold (Umeda et al., 2005); biphenyl exposure did not affect liver weight in male mice. Histopathological changes included enlarged centrilobular hepatocytes filled with eosinophilic granules identified as peroxisomes in BDF_1 mice exposed to 2,989 mg/kg-day biphenyl in diet for 13 weeks (Umeda et al., 2004) and basophilic foci in female BDF_1 mice exposed to biphenyl in the diet (≥414 mg/kg-day) for 2 years (Umeda et al., 2005). Significantly increased plasma enzyme levels (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and lactate dehydrogenase) were observed primarily in female BDF_1 mice exposed to biphenyl in the diet for 2 years (Umeda et al., 2005). No liver toxicity was found in female ddY mice exposed to 855 mg/kg-day biphenyl for 2 years (Imai et al., 1983) based on histopathological examination of ~60% of the animals (34 of 60). In summary, biphenyl exposure resulted in increased liver weight and histopathological changes of the liver in mice and rats and increased liver weight in monkeys; however, liver toxicity was not observed consistently across different strains of rats and mice or across sexes. Based on these findings, liver toxicity may be a hazard potential from biphenyl exposure.

In the only available oral developmental toxicity study of biphenyl (Khera et al., 1979), the incidence of anomalous fetuses and litters bearing anomalous fetuses (including wavy ribs, extra ribs, missing and unossified sternebrae, or delayed calvarium ossification) generally increased with dose. When the anomalies were considered individually, only the incidence of missing or unossified sternebrae exhibited an increasing trend with dose. As noted in EPA's *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), a significant, dose-related increase in a variation (e.g., delayed ossification) should be evaluated as a possible indication of developmental toxicity, although an assessment of the biological significance of such variations should take into consideration knowledge of the developmental stage, background incidence of certain variations, other strain- or species-specific factors, and maternal toxicity. Carney and Kimmel (2007) observed that the biological significance of skeletal variations that seem to be readily repairable via postnatal skeletal remodeling should be interpreted in the context of other maternal and fetal findings, information on normal skeletogenesis patterns, mode of action of the

agent, and historical control incidence. The Khera et al. (1979) study showed a 10% decrease in body weight gain and increased mortality in dams at the high dose of 1,000 mg/kg-day, but not at doses of 125, 250, or 500 mg/kg-day. Therefore, the increasing trend of fetuses with missing or unossified sternebrae at ≤500 mg/kg-day cannot be attributed to maternal toxicity. In summary, findings from a single developmental toxicity study (Khera et al., 1979) provide evidence that biphenyl may directly target skeletal development in Wistar rats independent of maternal toxicity; however, no other developmental toxicity studies are available to confirm these findings. Based on these findings, there may be a hazard potential for developmental toxicity from biphenyl exposure.

Reproductive effects of biphenyl were evaluated in one- and three-generation reproductive toxicity studies (Ambrose et al., 1960; Dow Chemical Co, 1953). There was some indication in Dow Chemical Co (1953) of reduced fertility and decreased pup growth at an estimated oral dose of 887 mg/kg-day, similar to the dose used in a developmental toxicity study (Khera et al., 1979) that caused maternal toxicity (reduced survival and body weight gain). Ambrose et al. (1960) reported limited findings and concluded that biphenyl had no significant effect on reproduction in albino rats exposed to biphenyl in the diet at doses up to 525 mg/kg-day. Overall, the available reproductive toxicity studies in rats (Ambrose et al., 1960; Dow Chemical Co, 1953) did not fully evaluate effects of biphenyl exposure on reproductive function as would studies conducted using current study protocols, but suggested that possible reproductive toxicity would occur at doses similar to the dose associated with frank maternal toxicity in another developmental toxicity study.

Decreased body weight gain associated with biphenyl exposure was observed in both rats and mice. Following a 2-year dietary exposure to biphenyl, more than a 10% decrease in body weight relative to controls was reported in F344 rats of both sexes (approximately 400 mg/kg-day) (Umeda et al., 2002) and in BDF_1 mice in both sexes (males—291 mg/kg-day; females—≥414 mg/kg-day) (Umeda et al., 2005). A 75-week study in male and female Wistar rats also found more than a 10% body weight decrease at doses greater than approximately 170 mg/kg-day (Shiraiwa et al., 1989). Shorter-duration oral exposure (13 weeks) of mice to biphenyl at higher dietary concentrations (estimated doses ≥1,500 mg/kg-day) was also associated with >17% decreased body weight (Umeda et al., 2004). Ambrose et al. (1960) and Dow Chemical Co (1953) reported >10% reduced body weight gain, but the authors attributed low body weight to low palatability of the feed. In summary, decreased body weight gain appears to be associated with oral exposure to biphenyl.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — High
Database — Medium to high
RfD — Medium to high

The overall confidence in the RfD assessment is medium to high. Confidence in the principal study (Umeda et al., 2002) is high. Umeda et al. (2002) is a well-conducted study performed in accordance with Organisation of Economic Co-operation and Development (OECD) test guidelines and Good Laboratory Practices (GLPs). Confidence in the database is medium to high. The database is robust in that it includes well-conducted chronic oral exposure studies in the rat and mouse, other supporting repeated dose studies in multiple species, a developmental toxicity study in Wistar rats, and one- and three-generation reproductive toxicity studies in rats. Confidence in the database is reduced because the reproductive toxicity studies come from the older toxicological literature (1953 and 1960) and do not fully evaluate effects of biphenyl exposure on reproductive function as would studies conducted using current study protocols.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — *Toxicological Review of Biphenyl* (U.S. EPA, 2013).

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and the Executive Office of the President, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Biphenyl* (U.S. EPA, 2013).

Agency Completion Date — 08/27/2013

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Biphenyl
CASRN — 92-52-4
Section I.B. Last Revised — 08/27/2013

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An inhalation RfC for biphenyl was not previously available on the IRIS database.

I.B.1. Chronic Inhalation RfC Summary

No inhalation RfC was derived due to the lack of inhalation studies of biphenyl toxicity following chronic exposure and studies involving subchronic exposure that were inadequate for RfC derivation. Repeated exposure of mice to biphenyl vapors for 13 weeks resulted in high incidences of pneumonia and tracheal hyperplasia, and high incidences of congestion and edema in the lungs, liver, and kidney (Sun, 1977); however, study limitations and lack of supporting data preclude the use of this study for deriving an RfC for biphenyl. Study limitations include highly variable biphenyl exposure concentrations during the first half of the study, high mortality after 46 exposures in one group of biphenyl-exposed mice due to an overheating event and cannibalization that necessitated the use of replacement animals, and limitations in the reporting of histopathological findings.

I.B.2. Principal and Supporting Studies

Not applicable.

I.B.3. Uncertainty Factors

Not applicable.

I.B.4. Additional Studies/Comments

Human studies are preferred over animal studies when quantitative measures of exposure are reported and the reported effects are determined to be associated with exposure (U.S. EPA,

2002). The available human data for biphenyl are limited to two occupational epidemiology studies and a case report of workers engaged in the production of biphenyl-impregnated fruit wrapping paper (Carella and Bettolo, 1994; Seppalainen and Hakkinen, 1975; Häkkinen et al., 1973; Häkkinen et al., 1971). These studies provide some evidence of liver damage (including elevated levels of serum enzymes) and effects on the central and peripheral nervous systems. In a study of a different facility manufacturing biphenyl-impregnated paper prompted by the finding of three cases of Parkinson's disease at that facility, an elevated RR of Parkinson's disease among biphenyl workers was reported (Wastensson et al., 2006). None of these studies provided air monitoring data adequate to characterize workplace exposures to biphenyl. Therefore, data from the available human studies could not be used for dose-response analysis and derivation of an RfC.

Limited information is available regarding the effects of inhaled biphenyl in laboratory animals. In three separate studies that included repeated inhalation exposure of rabbits, rats, and mice to air containing 300, 40, or 5 mg/m^3 biphenyl, respectively, for periods of 68–94 days (Deichmann et al., 1947; Monsanto, 1946), rabbits exhibited no signs of exposure-related adverse effects at concentrations as high as 300 mg/m^3. Irritation of mucous membranes was observed in rats at concentrations of 40 and 300 mg/m^3. Mice were the most sensitive to inhaled biphenyl; irritation of the upper respiratory tract was noted at a concentration of 5 mg/m^3 (Deichmann et al., 1947; Monsanto, 1946). Limitations in study design, including lack of control animals and use of a single exposure level, as well as poorly reported study details, preclude the use of these studies for RfC derivation.

Repeated exposure of mice to biphenyl at vapor concentrations of 25 or 50 ppm (157.75 or 315.5 mg/m^3) for 13 weeks resulted in high incidences of pneumonia and tracheal hyperplasia, and high incidences of congestion and edema in the lungs, liver, and kidney (Sun, 1977a). Study limitations and lack of supporting data preclude the use of this study for deriving an RfC for biphenyl. Measured biphenyl exposure concentrations varied greatly during the first half of the 13-week exposure period; for example, in the high concentration group (target concentration of 50 ppm), the measured concentrations ranged from 5 to 102 ppm during the first 45 exposure sessions. High mortality after 46 exposures (as a result of accidental overheating of the chambers) necessitated the use of 46 replacement animals. Histopathological findings were reported only for males and females combined. Reports of lung congestion and hemorrhagic lungs in some control mice were not confirmed histopathologically, and congestion in the lung, liver, and kidney were considered by the study pathologist a likely effect of the anesthetic used for killing the mice. The severity of reported histopathological lesions was not specified.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Chronic Inhalation RfC

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)

I.B.6. EPA Documentation and Review of the Chronic Inhalation

Source Document — *Toxicological Review of Biphenyl* (U.S. EPA, 2013).

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and the Executive Office of the President, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Biphenyl* (U.S. EPA, 2013).

Agency Completion Date — 08/27/2013

I.B.7. EPA Contacts

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Biphenyl
CASRN — 92-52-4
Section I.B. Last Revised — 08/27/2013

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see

Section II.B.1.) or per µg/m^3 air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

In the previous IRIS assessment (posted in 1987), biphenyl had a classification of D (not classifiable as to human carcinogenicity). The previous IRIS assessment did not provide quantitative estimates of carcinogenic risk from oral or inhalation exposure.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for biphenyl provides "suggestive evidence of carcinogenic potential" based on increased incidence of urinary bladder tumors (transitional cell papillomas and carcinomas) in male F344 rats (Umeda et al., 2002) and liver tumors (hepatocellular adenomas and carcinomas) in female BDF_1 mice (Umeda et al., 2005) exposed to biphenyl in the diet for 104 weeks, as well as information on mode of carcinogenic action. The carcinogenic potential of biphenyl in humans has not been investigated.

As emphasized in the Cancer Guidelines (U.S. EPA, 2005a), selection of the cancer descriptor followed a full evaluation of the available evidence. The biphenyl case could be considered a borderline case between two cancer descriptors—"suggestive evidence of carcinogenic potential" and "likely to be carcinogenic to humans." The descriptor of "suggestive evidence of carcinogenic potential" is appropriate when a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion, given "an extensive database that includes negative studies in other species," and that "additional studies may or may not provide further insights." The database for biphenyl includes studies in rats and mice that did not show clear evidence of carcinogenicity (Shiraiwa et al., 1989; Imai et al., 1983; NCI, 1968; Ambrose et al., 1960; Dow Chemical Co, 1953), but that were conducted in different strains, and also limited in large part in design, conduct, or reporting of results. These studies were therefore considered less informative for evaluating the carcinogenicity of biphenyl than the studies by Umeda et al. (2005) and Umeda et al. (2002). The range of evidence regarding each tumor type is described further in Section II.A.3.

Exposure to biphenyl produced a positive tumor response at more than one site (urinary bladder and liver) and in more than one species (rat and mouse), corresponding most closely to one of the examples in the Cancer Guidelines (U.S. EPA, 2005a) for the descriptor "likely to be carcinogenic to humans," i.e., "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans." However, as discussed further below, mechanistic data for urinary bladder tumors

and limitations in liver tumor data better support the descriptor of "suggestive evidence of carcinogenic potential" for biphenyl.

Mode-of-action information indicates that the induction of urinary bladder tumors in F344 male rats by dietary biphenyl exposure is a high-dose phenomenon closely related to the formation of urinary bladder calculi. As discussed in more detail in Section 4.7.3.1 of the *Toxicological Review of Biphenyl* (U.S. EPA, 2013), the mode-of-action information is sufficient to conclude that urinary bladder tumors in male F344 rats will not occur without the development of calculi, and that the induction of these tumors by biphenyl is specific to male rats. Gender-specific differences in urinary conditions such as pH and potassium concentrations appear to play a role in the differences in calculi formation and composition. While the proposed mode of action for urinary bladder tumors in male rats is assumed to be relevant to humans, the available evidence suggests that humans would be less susceptible to these tumors than rats [see discussion in Section 4.7.3.1.4 of the *Toxicological Review of Biphenyl* (U.S. EPA, 2013)]. Overall, the mode-of-action analysis supports the conclusion that biphenyl should not pose a risk of urinary bladder tumors in humans at exposure levels that do not cause calculi formation.

Liver tumors induced by dietary exposure to biphenyl for 104 weeks occurred in female BDF_1 mice only. In contrast, the incidence of liver tumors in male mice decreased with increasing exposure (Umeda et al., 2005). The decreased incidences were still within the range of historical controls, and similar decreased trends in liver tumors that were associated with decreased body weight gain in $B6C3F_1$ mice, as also occurred in the BDF_1 mice exposed to biphenyl, have been judged not to demonstrate anticarcinogenicity (e.g., Leakey et al., 2003; Haseman and Johnson, 1996). Mechanistic data to support a mode of action for biphenyl-induced liver tumors in the mouse are not available [see Section 4.7.3.2 of the *Toxicological Review of Biphenyl* (U.S. EPA, 2013)]. In the absence of information to indicate otherwise, the development of liver tumors in female BDF_1 mice with chronic exposure to biphenyl (Umeda et al., 2005) is assumed to be relevant to humans. EPA acknowledges that the relative susceptibility of some mouse strains to liver tumors and the somewhat high and variable background incidence of this tumor contribute to controversy in the use of mouse liver tumor data in risk assessment (e.g., King-Herbert and Thayer, 2006)). According to historical control data from Japan Bioassay Research Center (JBRC), the institute that conducted the mouse bioassay published by Umeda et al. (2005), the mean incidences of liver tumors (hepatocellular adenoma or carcinoma) in male and female control BDF_1 mice are 32.2 and 7.1%, respectively. These incidences are consistent with the concurrent controls in the mouse bioassay of biphenyl. The relatively low background incidence of liver tumors in female control mice from Umeda et al. (2005) minimizes the possible confounding of compound-related liver tumors in this sex.

In summary, while the cancer descriptor "likely to be carcinogenic to humans" is plausible and the positive evidence of tumors at two sites in two species raises a concern for carcinogenic

effects in humans, this assessment acknowledges: (1) the lack of evidence for either tumor type in a second study, strain, or species and (2) the existence of a mode of action for urinary bladder tumors, specific to the male rat, establishing these tumors as a high-dose phenomenon closely related to the formation of urinary bladder calculi. Recognizing that each cancer descriptor covers a continuum of evidence, this assessment concludes that biphenyl shows "suggestive evidence of carcinogenic potential."

EPA's Cancer Guidelines (U.S. EPA, 2005a) indicate that for tumors occurring at a site other than the initial point of contact, the cancer descriptor may apply to all routes of exposure that have not been adequately tested at sufficient doses. An exception occurs when there is convincing toxicokinetic data that absorption does not occur by other routes. Information available on the carcinogenic effects of biphenyl demonstrates that tumors occur in tissues remote from the site of absorption following chronic oral exposure (urinary bladder in male rats and liver in female mice). No information on the carcinogenic effects of biphenyl via the inhalation or dermal routes in humans and animals is available. Studies in rats, rabbits, and guinea pigs demonstrate that biphenyl is rapidly and extensively absorbed by the oral route of exposure, and an in vitro model using human skin provides evidence of dermal absorption of biphenyl (DuPont, 2005). Qualitative evidence for absorption of inhaled biphenyl comes from inhalation toxicity studies in rats and mice that reported systemic (liver and kidney) effects following inhalation exposure to biphenyl for 46–90 days (Sun, 1977; Deichmann et al., 1947; Monsanto, 1946). A case report of hepatic toxicity produced by a probable combination of inhalation and dermal exposures in a worker in a biphenyl-impregnated fruit wrapping paper production facility (Häkkinen et al., 1973) provides qualitative evidence of human absorption by these routes. Therefore, based on the observation of systemic tumors following oral exposure and limited qualitative evidence for inhalation and dermal absorption, it is assumed that an internal dose will be achieved regardless of the route of exposure. In the absence of information to indicate otherwise, the database for biphenyl provides "suggestive evidence of carcinogenic potential" by all routes of exposure.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

None. There are no epidemiological studies of biphenyl carcinogenicity in humans.

II.A.3. Animal Carcinogenicity Data

Urinary bladder tumors were found in F344 male rats in a well-designed 2-year cancer bioassay by Umeda et al. (2002). This is a rare tumor type, not having been observed in historical control male F344 rats of the JBRC or the National Toxicology Program (NTP)—1,148 and 1,858 rats, respectively (Umeda et al., 2002). Although the other available bioassays evaluated exposure ranges comparable to those used by Umeda et al. (2002), they did not report increased urinary bladder tumors. However, these other studies could not confirm or contradict these findings due either to smaller group sizes and shorter effective exposure durations; they were also conducted in different rat strains than the Umeda et al. (2002) study. In the 75-week dietary study in Wistar rats (Shiraiwa et al., 1989), some of the male rats exhibited urinary bladder calculi and simple or diffuse hyperplasia and papillomatosis of the urinary bladder mucosa in the absence of neoplastic lesions. The duration, being much shorter than the standard 104-week bioassay, may not have been sufficiently long to observe late-occurring tumors. Ambrose et al. (1960) exposed albino rats to biphenyl in the diet at concentrations ranging from 10 to 10,000 ppm for 2 years; urinary bladder tumors occurred in most groups. Because of decreased survival in rats exposed to 5,000 or 10,000 ppm and the evaluation of histopathology only for rats surviving to study termination (as few as two per group at the higher doses), however, this study was not adequate for evaluation of the tumorigenic potential of biphenyl. In the 2-year dietary study of biphenyl conducted by Dow Chemical Co (1953) in Sprague-Dawley rats (12/sex/group), a pneumonia outbreak (resulting in deaths of all control male rats by the end of 1 year), relatively small group sizes, and decreased survival may have impaired the ability to detect late-developing tumors. Overall, the evidence for urinary bladder tumors shows differing, as opposed to conflicting, results.

Evidence concerning liver tumors includes positive findings in one sex of one species (i.e., female BDF_1 mice) from a well-conducted 2-year dietary study by Umeda et al. (2005). Male mice in this study showed a statistically significant decreasing trend in liver tumor incidence with increasing dose, but the incidences at all dose levels were within the range of historical controls for the laboratory. There was no liver tumor response in either sex of $B6C3F_1$ mice or $B6AKF_1$ mice (NCI, 1968), but these evaluations were carried out at a lower exposure than those used by Umeda et al. (2005), for a shorter duration (18 months rather than 24 months), and with treated groups of no more than 18 animals. There was no observed liver tumor response in female ddY mice (Imai et al., 1983)—males were not tested—with exposure at a level intermediate to the higher exposures tested by Umeda et al. (2005). Umeda et al. (2005) suggested that the difference in response between the two studies might be due to differences in susceptibility between the two mouse strains, but specific support for this hypothesis is not available. Overall, the evidence for liver tumors shows differing, as opposed to conflicting, results.

The 18-month (NCI, 1968) bioassay showed a statistically significant elevation in the incidence of reticular cell sarcoma in treated $B6AKF_1$ female mice, but not in $B6C3F_1$ female mice or

$B6C3F_1$ or $B6AKF_1$ male mice. Although this bioassay was unique among those available in starting exposure during early life at 1 week of age (i.e., versus 6 weeks for Umeda et al., 2005), specific support for early life susceptibility to sarcomas in response to biphenyl exposure is not available. In light of the inconsistency in this finding across mouse strains and sexes in the NCI (1968) study and the lack of confirmation in other studies in mice at higher exposures, the biological significance of the elevated incidence of reticular cell sarcoma in female mice is unclear.

II.A.4. Supporting Data for Carcinogenicity

The in vitro evidence does not indicate that biphenyl is mutagenic; however, in vivo data suggest that biphenyl metabolites that are capable of redox cycling may induce genetic damage resulting from oxidative damage and cytotoxicity.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1.1. Oral Slope Factor – 8.2 x 10^{-3} (mg/kg-day)$^{-1}$ rounded to 8 x 10^{-3} (mg/kg-day)$^{-1}$

The oral slope factor is derived from the LED_{10}, the 95% lower bound on the exposure associated with an 10% extra cancer risk, by dividing the risk (as a fraction) by the LED_{10}, and represents an upper bound, continuous lifetime exposure risk estimate:

LED_{10}, lower 95% bound on exposure at 10% extra risk – 12.2 mg/kg-day
ED_{10}, central estimate of exposure at 10% extra risk – 18.7 mg/kg-day
The slope of the linear extrapolation from the central estimate ED_{10} is 0.1/(18.7 mg/kg-day) = 5.3 x 10^{-3} per mg/kg-day.

The slope factor for biphenyl should not be used with exposures exceeding the POD (12.2 mg/kg-day), because above this level, the fitted dose-response model better characterizes what is known about the carcinogenicity of biphenyl.

II.B.1.2. Drinking Water Unit Risk* — 2.3 x 10^{-7} per µg/L

Drinking water concentrations at specified risk levels

Risk level	Lower bound on concentration estimate*
E-4 (1 in 10,000)	430 µg/L
E-5 (1 in 100,000)	43 µg/L
E-6 (1 in 1,000,000)	4 µg/L

*The unit risk and concentration estimates assume a water consumption of 2 L/day by a 70-kg human.

II.B.1.3. Extrapolation Method

Multistage model with linear extrapolation from the POD (LED_{10}).

II.B.2. Dose-Response Data

Tumor type – Liver adenomas or carcinomas
Test species – female BDF_1 mice
Route – Oral (diet)
Reference – Umeda et al. (2005)

Incidence of liver adenomas or carcinomas in female BDF_1 mice fed diets containing biphenyl for 2 years

Biphenyl dietary concentration (ppm)	0	667	2,000	6,000
HED (mg/kg-d)	0	19	59	195
Incidence of adenoma or carcinoma (combined)	3/48[a]	8/50	16/49[a,]*	14/48[a,]*

[a]Two control, one mid-dose, and two high-dose female mice were excluded from the denominators because they died prior to week 52. It is assumed that they did not have tumors and were not exposed for a sufficient time to be at risk for developing a tumor. Umeda et al. (2005) did not specify the time of appearance of the first tumor.
*Statistically significant (Fisher's exact test, $p < 0.05$) as reported by study authors.

Source: Umeda et al. (2005).

II.B.3. ADDITIONAL COMMENTS

Biphenyl induced urinary bladder tumors in F344 male rats in a 2-year cancer bioassay (Umeda et al., 2002). There is strong evidence that the occurrence of urinary bladder tumors in male rats chronically exposed to biphenyl in the diet is a high-dose phenomenon involving occurrence of calculi in the urinary bladder leading to transitional cell damage, sustained regenerative cell proliferation, and eventual promotion of spontaneously initiated tumor cells in the urinary bladder epithelium. Based on the proposed mode of action, exposure to biphenyl at doses that would not result in calculi formation and subsequent key events would not be associated with bladder tumors. As noted in the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA,

2005a), a nonlinear approach to dose-response analysis is used when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses. Therefore, consistent with the Cancer Guidelines, a nonlinear extrapolation approach for biphenyl-induced urinary bladder tumors was selected.

Bladder calculi, the formation of which is a key event in the mode of action for urinary bladder tumors, were observed in male rats in the Umeda et al. (2002) bioassay at a dose of 378 mg/kg-day; the NOAEL for this effect was 110 mg/kg-day. The human equivalent dose (HED) for this NOAEL is 26 mg/kg-day, derived by application of a dose adjustment factor (DAF) of 0.24. A candidate RfD for bladder calculi of 0.9 mg/kg-day is derived by applying a composite UF of 30 to this HED. The RfD of 0.5 mg/kg-day based on papillary mineralization in kidney is approximately twofold below the candidate RfD for bladder calculi induction of 0.9 mg/kg-day. Based on the proposed mode of action, it is anticipated that exposure to biphenyl at doses that would not result in

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

An inhalation unit risk for biphenyl was not derived in this assessment. The potential carcinogenicity of inhaled biphenyl has not been evaluated in human or animal studies, and route-to-route extrapolation was not possible in the absence of a physiologically based pharmacokinetic (PBPK) model.

II.C.1. Summary of Risk Estimates

Not applicable.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — *Toxicological Review of Biphenyl* (U.S. EPA, 2013).

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and the Executive Office of the President, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Biphenyl* (U.S. EPA, 2013).

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Completion Date — 08/27/2013

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Biphenyl
CASRN — 92-52-4

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VII. Revision History

Substance Name — Biphenyl
CASRN — 92-52-4
File First On-Line 01/31/1987

Date	Section	Description
08/01/1989	I.A.	RfD added
03/01/1991	II.	Carcinogenicity assessment added
08/27/2013	I., II., VI.	RfD and cancer assessment updated; RfC discussion added.

VIII. Synonyms

Substance Name — Biphenyl
CASRN — 92-52-4
Section VIII. Last Revised — 08/27/2013

- 92-52-4

- Bibenzene
- Biphenyl
- Biphenyl, 1,1-
- Diphenyl
- Lemonene
- Phenador-X
- Phenylbenzene
- PHPH
- Xenene