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Draft Environmental Hazard Assessment for Butyl Benzyl Phthalate (BBP)

Technical Support Document for the Draft Risk Evaluation

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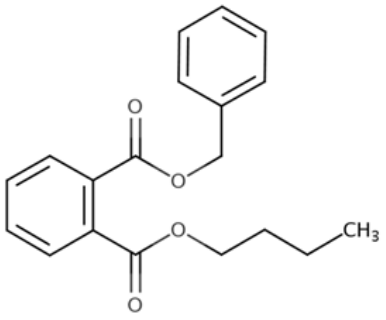

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ABBREVIATIONS AND ACRONYMS

AF	Assessment factor
BMD	Benchmark dose
BMDL	Benchmark dose limit
COC	Concentration(s) of concern
EC50	Effect concentration at which 50% of test organisms exhibit an effect
HC05	Hazard concentration that is protective of 95 percent of the species in the sensitivity distribution
LC50	Concentration which is lethal to 50 percent of test organisms
LD50	Dose which is lethal to 50 percent of test organisms
LOAEL	Lowest-observable-adverse-effect-level
LOEC	Lowest-observable-effect concentration
NAM	New approach method
NITE	National Institute of Technology and Evaluation
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
OCSPP	Office of Chemical Safety and Pollution Prevention
OPPT	Office of Pollution Prevention and Toxics
PND	Postnatal day
POD	Point of departure
QSAR	Quantitative structure-activity relationship (model)
SSD	Species sensitivity distribution
TRV	Toxicity reference value
TSCA	Toxic Substances Control Act
U.S.	United States
Web-ICE	Web-based Interspecies Correlation Estimation

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SUMMARY

This technical document is in support of the TSCA Draft Risk Evaluation for butyl benzyl phthalate (BBP) (U.S. EPA, 2025). BBP is a common chemical name for the chemical substance 1,2-benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester (CASRN 85-68-7).

EPA considered all reasonably available information identified through the systematic review process under the Toxic Substances Control Act (TSCA) to characterize environmental hazard endpoints for BBP. After evaluating the reasonably available information, environmental hazard thresholds were derived for aquatic vertebrates, aquatic invertebrates, aquatic plants and algae, and terrestrial vertebrates (Table S-1).

Table S-1 Environmental Hazard Thresholds for BBP

Receptor Group	Exposure Duration	Hazard Threshold (COC or HV)	Citation
Aquatic Vertebrates	Acute	197 µg/L	From SSD; See Section 5
	Chronic	1.9 µg/L	(Battelle, 2018c)
Aquatic Invertebrates	Acute	197µg/L	From SSD; See Section 5
	Chronic	62.6 µg/L	(Rhodes et al., 1995)
Aquatic Plants and Algae	Chronic	21 µg/L	(Adams et al., 1995)
Terrestrial Vertebrates	Chronic	311 mg/kg/day	(TNO, 1993)

1 INTRODUCTION

Butyl benzyl phthalate is a clear, oily liquid with a total production volume in the United States between 10 and 50 million pounds (U.S. EPA, 2020). Butyl benzyl phthalate is manufactured (including imported) in the United States. The chemical is processed as a reactant, incorporated into a formulation, mixture, or reaction product, and incorporated into articles.

2 APPROACH AND METHODOLOGY

TSCA requires that EPA use data and/or information in a manner consistent with the best available science and that EPA base decisions on the weight of scientific evidence. To meet the TSCA science standards, EPA applies a systematic review process to identify data and information across taxonomic groups for both aquatic and terrestrial organisms with a focus on apical endpoints (*e.g.*, those affecting survival, growth, or reproduction). The data collection, data evaluation, and data integration stages of the systematic review process are used to develop the hazard assessment to support the integrative risk characterization. EPA uses several considerations when weighing and weighting the scientific evidence to determine confidence in the environmental hazard data. These considerations include the quality of the database, consistency, strength and precision, biological gradient/dose response, and relevance. EPA completed the review of environmental hazard data/information sources during risk evaluation using the data quality review evaluation metrics and the rating criteria described in the *2021 Draft Systematic Review Protocol supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021) and *Draft Risk Evaluation for Butyl Benzyl Phthalate* (BBP) – Systematic Review Protocol (U.S. EPA, 2024c). Studies identified and evaluated by OPPT through 2020 were assigned an overall quality level of high, medium, low, or uninformative. Data on toxicity of BBP are numerous and, in some instances, vary substantially, thus EPA systematically evaluated all data for this hazard characterization, but relied upon only high-quality and medium-quality studies for purposes of quantitative risk characterization. References receiving an overall quality determination of low or uninformative either exceeded the BBP limit of solubility in all treatments, showed no effects at the highest concentration tested, evaluated a biotransformation (mechanistic) endpoint, and/or were part of a mixture.

EPA reviewed potential environmental hazards associated with BBP. EPA considered all available studies to characterize the environmental hazards of BBP to surrogate species representing various receptor groups, including aquatic vertebrates, aquatic invertebrates, amphibians, aquatic plants, algae, and birds. Mechanistic (transcriptomic and metabolomic) and behavioral points of departure from one study of an acute exposure of BBP to fathead minnows were used to inform of the potential mechanisms that lead to the acute and chronic aquatic vertebrate hazard thresholds (Bencic et al., 2024). Hazard studies with mammalian wildlife exposed to BBP were not available, therefore EPA used ecologically relevant endpoints from human health laboratory rat and mouse model organisms to establish a hazard threshold for terrestrial mammals.

A Species Sensitivity Distribution (SSD) analysis was used to derive an acute aquatic hazard threshold. An SSD is a model of the variation in sensitivity of species to a particular chemical stressor and is generated by fitting a statistical distribution function to the proportion of species affected as a function of concentration or dose. Empirical data that were included in the SSD analysis were limited to LC50 values (concentration which is lethal to 50% of test organisms) that were at or below the limit of water solubility of 2690 µg/L for BBP (U.S. EPA, 2024a). Specifically, predicted hazard data were generated using EPA's Web-Based Interspecies Correlation Estimation Web-ICE (v4.0) toxicity predictions tool (Raimondo, 2010). The species and corresponding empirical data are outlined in Section 5 and Appendix A. EPA derived concentrations of concern (COC) for all other organism and exposure durations using studies that report hazard effects at or below the limit of water solubility of 2690 µg/L g/L for BBP.

Environmental Hazard from Previous Assessments

Environment Canada previously assessed environmental hazard effects of BBP (EC, 2000). Through a survey of acute exposure (48-hour and 96-hour durations) studies of organism mortality that estimated concentrations which are lethal to 50% of test organisms (LC50s), aquatic acute hazard was determined

to be 510 µg/L for the shiner perch (*Cymatogaster aggregata*). Aquatic chronic exposure hazards and algal exposure hazards were not identified (EC, 2000). The European Union (EU) Risk Assessment Report (ECJRC, 2007) reports the lowest acute aquatic hazard value as 510 µg/L BBP for *C. aggregata* (ECJRC, 2007). The EU assessment also reports the lowest chronic NOEC (No-observed-effect concentration) values as 140 µg/L BBP to fish (30-day exposure to *Pimephales promelas*), 75 µg/L BBP to an invertebrate (28-day exposure to *Americamysis bahia*), and 200 µg/L BBP to a diatom (72-hour exposure to *Navicula pelliculosa*) (ECJRC, 2007). Neither assessment reports hazard threshold data on the effects of BBP to terrestrial organisms.

3 AQUATIC SPECIES HAZARD

EPA reviewed 51 studies for BBP toxicity to aquatic organisms. Some studies may have included multiple endpoints, species, and test durations. Four of these studies received an overall quality determination of low, uninformative, or did not meet systematic review criteria. The data from these low or uninformative studies were not used to derive hazard thresholds because they either exceeded the BBP limit of solubility in all treatments, showed no effects at the highest concentration tested, evaluated a biotransformation (mechanistic) endpoint, and/or were part of a mixture. Forty-seven studies received an overall quality determination high or medium quality, were used to derive hazard thresholds, and are detailed in the subsections below. Studies that demonstrated no acute or chronic adverse effects at the highest concentration tested (unbounded NOECs), or where hazard values exceeded the limit of solubility for DBP in water as determined by EPA at 2690 µg/L, (U.S. EPA, 2024, 11799672) are included in Table 3-1, Table 3-2, Table 3-3, Table 3-4, and Table 3-5, but were excluded from consideration for the development of hazard thresholds (Section 5). Additionally, predicted hazard data for 18 species were generated using EPA's Web-ICE (v4.0) tool (Raimondo, 2010), including predictions for 14 fish, and four invertebrate species. No toxicity studies using spiked sediment for benthic exposures were identified for BBP. Thus, all hazard data to benthic invertebrates were represented by water exposures.

Acute Aquatic Vertebrates

EPA reviewed seven high/medium quality studies for acute toxicity in aquatic vertebrates (Table 3-1). Of these studies, six contained acceptable endpoints that identified definitive hazard values below the BBP limit of water solubility (2690 µg/L). For the fathead minnow (*Pimephales promelas*), bluegill (*Lepomis macrochirus*), rainbow trout (*Oncorynchus mykiss*), and shiner perch (*Cymatogaster aggregata)* the 96-hour mortality LC50s ranged from 510 to 2100 µg/L BBP (Adams et al., 1995; Ozretich et al., 1983; EG&G Bionomics, 1979a, c, d). These values were combined with acute hazard effects values of BBP to aquatic invertebrates to derive an SSD and subsequent acute exposure threshold (Appendix A).

Table 3-1. Acute Aquatic Vertebrate Toxicity of BBP

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
Fathead minnow (*Pimephales promelas*)	1500 µg/L [a]	96-hour LC50	Mortality	(Adams et al., 1995) (High)
	2100 µg/L [a]	96-hour LC50	Mortality	(EG&G Bionomics, 1979d) (High)
Bluegill (*Lepomis macrochirus*)	1700 µg/L [a]	96-hour LC50	Mortality	(EG&G Bionomics, 1979c) (Medium)
Sheepshead minnow (*Cyprinodon variegatus*)	3000 µg/L [b]	96-hour NOEC	Mortality	(EG&G Bionomics, 1979a) (Medium)

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
Rainbow trout (*Oncorynchus mykiss*)	820 µg/L [a]	96-hour LC50	Mortality	(Ozretich et al., 1983) (High)
	3300 µg/L [b]	96-hour LC50	Mortality	(EG&G Bionomics, 1979d) (High)
Shiner perch (*Cymatogaster aggregata*)	510 µg/L [a]	96-hour LC50	Mortality	(Ozretich et al., 1983) (Medium)

[a] Value used as input for SSD derivation of acute aquatic hazard threshold.
[b] Hazard value is greater than the BBP limit of solubility (2690 µg/L).

TSCA section 4(h)(1)(B) requires EPA to encourage and facilitate the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions. In line with EPA's New Approach Methods Work Plan, EPA OPPT and ORD have been collaborating on developing new methods for use in TSCA risk evaluations. Specifically, a project was conducted to generate omics-based PODs and compared them to traditional endpoints using fathead minnow as the model organism for three of the phthalates undergoing a TSCA risk evaluation, including BBP (Bencic et al., 2024). In this study, points of departure (PODs) were derived for transcriptomic change (tPOD; 60 µg/L), metabolomic change (mPOD; 120 µg/L), and behavioral change (bPOD 90 µg/L) resulting from 24-hour duration of aquatic BBP exposure to fathead minnows. Additionally, a 24-hour mortality NOEC/LOEC of 1000 /2000 µg/L was identified. In 2000 µg/L BBP exposures, 38 percent mortality was observed. These results suggest that fathead minnow larvae exhibited changes in gene expression, metabolite levels, and swimming behavior at sublethal concentrations of BBP. While hazard thresholds are usually calculated with *in vivo* data measuring an apical endpoint (*e.g.*, mortality, reproduction, growth), these mechanistic (transcriptomic and metabolomic) and behavior points of departure represent potential information that may be used for reducing the time needed for toxicity testing *in vivo* and provide an alternate method to characterize hazard as well as provide important evidence for mechanisms of action. At this time, EPA has not used the omics-based PODs in the BBP draft risk evaluation. There are uncertainties with respect to the extent to which these sub-organismal and individual-level effects (*e.g.*, behavior) at short exposure durations are comparable to ecologically relevant outcomes, such as survival and reproduction, in wild fish populations.

Chronic Aquatic Vertebrates

EPA reviewed eight high or medium quality studies for chronic toxicity in aquatic vertebrates (Table 3-2). Of these studies, four contained acceptable chronic endpoints that identified definitive hazard values below the BBP limit of water solubility (2690 µg/L), for four fish species. One study found effects of BBP on amphibian growth (Battelle, 2018a). Another study of dietary BBP exposure to the fish, *Sander lucioperca*, found slightly reduced growth and female skewed sex ratios after five weeks of high doses (360 g/kg bw/day) of BBP amended diets (Jarmołowicz et al., 2014). However, feeding treatments were not replicated and diet concentrations were not verified analytically.

Chronic water exposure studies include a 21-day reproduction test of BBP exposure to zebrafish (*Danio rerio*), which found 3% lower fecundity, 2% lower fertilization success, 100% increase in plasma vitellogenin, and reduced gonad weight in males in treatments with 33 µg/L BBP (Lowest-observable-

effect concentration, LOEC) (Battelle, 2018c). No effects were observed at 11 µg/L BBP (NOEC).

In a separate study, fewer (10% less) eggs per Japanese medaka (*Oryzias latipes*) female were found after five weeks of exposure to 95 µg/L BBP, but no effects on fertilization rates, growth, gonad weight, or plasma vitellogenin were found in the same study (Battelle, 2018b). Other chronic exposure studies resulted in no growth or reproductive effects of BBP to rainbow trout (*Oncorhynchus mykiss*) (Rhodes et al., 1995) or fathead minnow (*Pimephales promelas*) (ABC Laboratories, 2008) (Table 3-2). Fish behaviors may also be altered due to chronic BBP exposure, as Mummichog (*Fundulus heteroclitus*) shoaled with smaller fish when exposed for 28-days to 100 µg/L BBP compared to control fish that shoaled with larger fish (Kaplan et al., 2013).

Table 3-2. Chronic Aquatic Vertebrate Toxicity of BBP

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
African clawed frog (*Xenopus laevis*)	No hazard effects; Greater growth in all BBP exposures	21-day LOEC	Growth	(Battelle, 2018a) (High)
Zebrafish (*Danio rerio*)	**11/33 µg/L** [a]	21-day NOEC/LOEC	Reproduction	(Battelle, 2018c) (High)
Rainbow trout *(Oncorhynchus mykiss)*	>200 µg/L No effects observed	21-day	Mortality and Growth	(Rhodes et al., 1995) (High)
Japanese medaka (*Oryzias latipes*)	35/95 µg/L [b]	5-week NOEC/LOEC	Growth (10% reduction in egg production)	(Battelle, 2018b) (Medium)
Fathead minnow (*Pimephales promelas)*	>65 µg/L	164-day NOEC	Growth and Reproduction	(ABC Laboratories, 2008) (High)
	> 82 µg/L	6-week	Reproduction	(ABC Laboratories, 2008) (High)
Mummichog (*Fundulus heteroclitus*)	100 µg/L	28-day LOEC	Behavior	(Kaplan et al., 2013) (High)
European pikeperch (*Sander lucioperca*)	180.0/360.0 g/kg bw/day NOEC/LOEC	5-week diet exposure	Reproduction and Growth	(Jarmołowicz et al., 2014) (Medium)

[a] 3% lower fecundity; 2% lower fertilization success; 100% increase in plasma vitellogenin; reduced gonad weight in males.
[b] 10% fewer eggs per female; no effects on fertilization rates, growth, gonad weight, or plasma vitellogenin.
Bolded number indicates the values used to derive the chronic exposure Concentration of Concern (COC).

Acute Aquatic Invertebrates

EPA reviewed 17 high or medium quality studies for acute toxicity in aquatic invertebrates (Table 3-3). Fifty percent mortality effects (LC50s) or short-term effects (EC50s) of acute exposures of BBP to aquatic invertebrates ranged from 0.46 mg/L to concentrations of BBP above the limit of water solubility (*i.e.*, >2690 µg/L). Of these studies, seven contained acceptable endpoints that identified definitive hazard values below the BBP limit of water solubility (2690 µg/L). These values were combined with acute hazard effects values of BBP to aquatic invertebrates to derive an SSD and subsequent acute exposure threshold (Appendix A). For midge (*Chironomus tentans*), amphipod (*Hyalella azteca*), mayfly, (*Hexagenia sp.*) opossum shrimp (*Americamysis bahia*), Taiwan abalone (*Haliotis diversicolor*), and Virginia oyster (*Crassostrea virginica*), acute BBP water exposure resulted in LC50 values ranging from 460 µg/L to 2650 µg/L BBP.

Table 3-3. Acute Aquatic Invertebrate Toxicity of BBP

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
Midge *(Chironomus tentans)*	1640 µg/L [a]	48-hour LC50 (no sediment)	Mortality	(Monsanto, 1982) (Medium)
	3600 µg/L [b]	48-hour LC50	Mortality	(SRI International, 1984) (Medium)
Amphipod (*Hyalella azteca*)	460 µg/L [a]	10-day LC50 (no sediment)	Mortality	(Call et al., 2001a) (High)
Mayfly (*Hexagenia sp.*)	1100 µg/L [a]	96-hour LC50	Mortality	(ABC Laboratories, 1986c) (High)
Opossum shrimp (*Americamysis bahia*)	1100 µg/L [a]	96-hour LC50	Mortality	(Springborn Bionomics, 1988) (High)
	900 µg/L [a]	96-hour LC50	Mortality	(EG&G Bionomics, 1979b) (High)
Moina macrocopa (Water Flea)	3690 µg/L [b]	48-hour LC50	Immobilization	(Wang et al., 2011) (High)
Crayfish (*Procambarus sp.*)	>2400 µg/L	96-hour LC50	Mortality	(ABC Laboratories, 1986b) (high)
(Polychaete worm) (*Nereis virens*)	> 3000 µg/L [b]	96-hour LC50	Mortality	(Springborn Bionomics, 1986b) (High)
Taiwan abalone (*Haliotis diversicolor*)	2650 µg/L [a]	96-hour EC50	Growth	(Liu et al., 2009) (High)
Virginia oyster (*Crassostrea virginica*)	1300 µg/L [a]	96-hour EC50	Growth	(ABC Laboratories, 1986a) (High)
Hydra (*Hydra littoralis*)	>1920 µg/L	96-hour LC50	Mortality	(ABC Laboratories, 1986a) (High)
Pink shrimp (*Penaeus duorarum*)	>3400 µg/L	96-hour LC50	Mortality	(Springborn Bionomics, 1986a) (High)
Midge (*Paratanytarsus*	>3600 µg/L	48-hour LC50	Mortality	(SRI International, 1984) (Medium)

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
dissimilis)				
Midge (*Paratanytarsus parthenogenetica*)	7200 µg/L [b]	48-hour LC50	Mortality	(Monsanto, 1983a) (High)
Waterflea (*Daphnia magna*)	>1400 µg/L	48-hour LC50	Immobilization	(Springborn Bionomics, 1984) (Medium)
	>960 µg/L	48-hour LC50	Immobilization	(Adams et al., 1995) (High)

[a] Value used as input for SSD derivation of acute aquatic hazard threshold.
[b] Hazard value is greater than the BBP limit of solubility (2690 µg/L).

Chronic Aquatic Invertebrates

EPA reviewed six high or medium quality studies for chronic toxicity in aquatic invertebrates (Table 3-4). All six studies contained acceptable chronic endpoints that identified definitive hazard values below the BBP limit of water solubility (2690 µg/L). Chronic effects of BBP on aquatic invertebrates ranged from reduced opossum shrimp (*Americamysis bahia*) reproduction after 28-days at 170 µg/L BBP (Springborn Bionomics, 1986c) to growth reduction in midges (*Chironomus tentans*) after 10-days at 1420 µg/L BBP (Call et al., 2001b).

In a 21-day study of *Daphnia magna*, 80% mortality and 70% fewer offspring per female occurred when exposed to 1400 µg/L BBP compared to no-BBP control treatments (Rhodes et al., 1995). *Daphnia magna* exposed to BBP in a 21-day static renewal bioassay produced 50% fewer offspring at 220 µg/L BBP (LOEC) but were not affected at 350 µg/L BBP (NOEC) (Monsanto, 1983b). In a study that lasted 42-days, 35% fewer *D. magna* survived in 760 µg/L BBP compared to control treatments (EG&G Bionomics, 1979e).

Rotifer (*Brachionus calyciflorus*) population growth rates were also reduced in chronic BBP exposures (Cruciani et al., 2015; Zhao et al., 2009). In a 96-hour exposure experiment, *B. calyciflorus* population growth rates were reduced by 25% at 2000 µg/L (Cruciani et al., 2015). In another study with a 144-hour chronic exposure duration, *B. calyciflorus* population growth rates were reduced by 15% at 500 µg/L BBP (Zhao et al., 2009). In a 28-day exposure experiment, *Americamysis bahia* reproductive success (offspring/female/day) was reduced by 50% when exposed to 170 µg/L BBP (Springborn Bionomics, 1986c). In a 10-day water exposure experiment, the oligochaete worm (*Lumbriculus variegatus*) survival was reduced by 50% when exposed to 1230 µg/L BBP (Call et al., 2001b). In a 10-day water exposure experiment, the midge (*Chironomus tentans*) dry weight was reduced by 50% when exposed to 1420 µg/L BBP (Call et al., 2001b).

Table 3-4. Chronic Aquatic Invertebrate Toxicity of BBP

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
Rotifer (*Brachionus calyciflorus*)	1000/2000 µg/L NOEC/LOEC	96-hour	Population growth rate	(Cruciani et al., 2015) (Medium)
	50/500 µg/L NOEC/LOEC	144-hour	Population growth rate	(Zhao et al., 2009) (Medium)
Waterflea	**280/1400 µg/L**	21-day	Mortality	(Rhodes et al., 1995)

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
(*Daphnia magna*)	NOEC/LOEC			(High)
	4800 µg/L	160-hour EC50	Immobilization	(Monsanto, 1983c) (Medium)
	220/350 µg/L NOEC/LOEC	21-day	Reproduction	(Monsanto, 1983b) (Medium)
	260/760 µg/L NOEC/LOEC	Two generation (42-day)	Mortality	(EG&G Bionomics, 1979e) (High)
Opossum shrimp (*Americamysis bahia*)	75/170 µg/L (NOEC/LOEC)	28-day	Reproduction	(Springborn Bionomics, 1986c) (High)
Oligochaete worm (*Lumbriculus variegatus*)	1230 µg/L	10-day (no sediment)	Mortality	(Call et al., 2001b) (High)
Midge (*Chironomus tentans*)	1420 µg/L	10-day EC50 (no sediment)	Growth	(Call et al., 2001b) (High)
Bolded number indicates the values used to derive the chronic exposure Concentration of Concern (COC).				

Aquatic Plants and Algae

EPA reviewed nine high or medium quality studies for toxicity in aquatic plants and algae (Table 3-5). Eight of these studies found population level hazard effects (96-h EC50) that ranged from 210 µg/L (green algae *Raphidocelis subcapitata*) to 600 µg/L (diatoms *Navicula pelliculosa* and *Skeletonema costatum*) and were less than the BBP limit of water solubility (2690 µg/L) (Adams et al., 1995; EG&G Bionomics, 1978). A study of the cyanobacterium, *Microcystis aeruginosa*, did not find effects of BBP on population growth rate (EG&G Bionomics, 1978). Cyanobacterium are bacteria and not algae or plants, but EPA includes this study to illustrate the differential types of effects of BBP on different taxa (U.S. EPA, 2021).

Table 3-5. Aquatic Plant and Algae Toxicity of BBP

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
Raphidocelis subcapitata (Green Algae)	**210 µg/L**	96-hour EC50	Population	(Adams et al., 1995) (High)
	400 µg/L	96-hour EC50	Population	(EG&G Bionomics, 1978) (Medium)
Navicula pelliculosa (Diatom)	600 µg/L	96-hour EC50	Population	(EG&G Bionomics, 1978) (Medium)
	410 µg/L	72-hour E50	Population	(Carolina Ecotox, 1995a) (High)
Skeletonema costatum (Diatom)	600 µg/L	96-hour EC50	Population	(EG&G Bionomics, 1978) (Medium)
Dunaliella tertiolecta (Green Algae)	1000 µg/L	96-hour EC50	Population	(EG&G Bionomics, 1978) (Medium)
Microcystis aeruginosa (Blue-Green Algae) [a]	>1000000 µg/L	96-hour EC50	Population	(EG&G Bionomics, 1978) (Medium)
Scenedesmus	330 µg/L	72-hour EC50	Population	(Carolina Ecotox,

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
subspicatus (Green algae)				1995b) (High)
Chlorella vulgaris (Green Algae)	>2880 µg/L	72-hour EC50	Population	(Carolina Ecotox, 1997) (High)
[a] Cyanobacterial species, not algae. Bolded number indicates the values used to derive the algal Concentration of Concern (COC).				

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4 TERRESTRIAL SPECIES HAZARD

EPA assigned an overall quality level of high or medium to five acceptable studies containing hazard data for seven different taxa. These studies contained relevant toxicity data for the Norway rat (*Rattus norvegicus*), the chicken (*Gallus gallus*), the nematode (*Caenorhabditis elegans*), and four plant species (*Ipomoea aquatica*, *Trifolium repens*, *Sinapis alba*, *Brassica rapa*).

Terrestrial Vertebrates

No reasonably available information was identified for exposures of BBP to wild mammalian populations. In lieu of wild mammal studies, EPA reviewed nine studies on BBP hazard to laboratory rodents that were designed to determine human health hazards of BBP that also contained ecologically relevant reproductive endpoints (Table_Apx B-1). Thus, EPA used data from laboratory rodent studies as surrogates for the potential BBP hazards to wild mammal populations. EPA's decision to focus on ecologically relevant (population level) reproductive endpoints in the rat and mouse data set for BBP for consideration of a hazard threshold in terrestrial mammals is due to the sensitivity of these taxa to BBP in eliciting phthalate syndrome (U.S. EPA, 2024b). Of the nine rat and mouse studies containing ecologically relevant reproductive endpoints, EPA selected the study with the most sensitive LOAEL (lowest observed adverse effect level) for evaluating data quality and for deriving the hazard threshold for terrestrial mammals. The most sensitive reproductive endpoint was from a study that involved the Sprague-Dawley strain of Norway rat (*Rattus norvegicus*) (TNO, 1993), with a 136-day LOAEL of 446 mg/kg-bw/day BBP and NOAEL (no observed adverse effect level) of 217 mg/kg-bw/day for reduced pup weight. This study was assigned an overall quality determination of high. This study found significantly decreased pup weights (males, females, and combined) on postnatal day (PND) 21 in the second litter only (no effect in first litter) at 446 mg/kg-bw/day. Males were exposed for 10 weeks pre-mating, during mating and until sacrifice on day 161. Exposure to F0 females was for 2 weeks pre-mating, during mating (up to 3 weeks), gestation (~3 weeks) and lactation (~3 weeks) of litter F0a, for 7-13 days after weaning (1-2 weeks), and during mating (up to 3 weeks), gestation (~3 weeks) and lactation (~3 weeks) of litter F0b. The female premating mean dose was used for the NOAEL and LOAEL because it is the lowest mean dose value for females across premating, gestation, and lactation.

One study of BBP effects on chicken (*Gallus gallus*) hens administered 5 g/kg bw/day BBP to birds on days 1 to 3 and again on days 21 to 23 of a 42-day experiment (University of Arizona, 1978). Hens fed this regime of BBP laid >90% fewer eggs over the course of 42 days compared to control hens. This study exposed hens to BBP at only one dose; therefore, EC50s were not derived. Also, oral doses were administered directly but by unknown methods and BBP doses were not analytically verified.

Table 4-1. Terrestrial Vertebrate Toxicity of BBP

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
Norway rat (*Rattus norvegicus*)	217 mg/kg bw/d NOAEL and 446 mg/kg bw/d LOAEL 311 mg/kg bw/d geometric mean of NOAEL and LOAEL	136 days	Reduced pup weight during lactation; increased pup mortality at PND 2-4	(TNO, 1993) (High)
Chicken (*Gallus gallus*)	5g/kg bw/d	BBP added to diet on days 1 to 3 and days 21 to 23 of 42 day	Reproduction; >90% fewer eggs produced in one treatment dose	(University of Arizona, 1978) (Medium)

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
		experiment		

Terrestrial Invertebrates

EPA reviewed one medium quality study for BBP toxicity in a terrestrial invertebrate (Table 4-2). The study exposed the soil nematode *Caenorhabditis elegans* to water solutions of BBP. No nematode mortality after 24-hours occurred up to and including 100,000 µg/L BBP (Kwon et al., 2011). Also, the exposure concentration of 100,000 µg/L is well above the limit of water solubility for BBP (2690 µg/L (U.S. EPA, 2024b)), indicating that these experimental conditions are unlikely to occur in ecosystems.

Table 4-2. Terrestrial Invertebrate Toxicity of BBP

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
Nematode (*Caenorhabditis elegans*)	>100,000 µg/L NOEC	24-hour	Mortality	(Kwon et al., 2011) (Medium)

Terrestrial Plants

EPA reviewed four high or medium quality studies for BBP toxicity in terrestrial plants (Table 4-3). A study of *Ipomoea aquatica* (Swamp Morning glory) found a 50% reduction in plant biomass after 21-days of hydroponic water exposure to 100,000 µg/L BBP (LOEC), but plant biomass was not affected when exposed to 50,000 µg/L BBP (Chen et al., 2011). The exposure concentration of 100,000 µg/L is well above the limit of water solubility for BBP (2690 µg/L (U.S. EPA, 2024b)), indicating that these experimental conditions are unlikely to occur in ecosystems. One study exposed three plant species to BBP vapor over 21-days. No BBP vapor-phase concentration affected plant growth to *Trifolium repens* (Dutch Clover), *Sinapis alba* (White Mustard), *Brassica rapa* (Bird Rape) (Gorsuch et al., 2008).

Table 4-3. Terrestrial Plant Toxicity of BBP

Test Organism	Hazard Values	Duration	Endpoint	Citation (Study Quality)
Ipomoea aquatica (Swamp morning glory)	50,000 µg/L NOEC and 100,000 µg/L LOEC	28-day	Growth	(Chen et al., 2011) (High)
Trifolium repens (Dutch clover)	>5.7 µg/m^3 NOEL	21-day	Vapor-phase toxicity	(Gorsuch et al., 2008) (High)
Sinapis alba (White mustard)	>5.7 µg/m^3 NOEL	21-day	Vapor-phase toxicity	(Gorsuch et al., 2008) (High)
Brassica rapa (Bird rape)	>5.7 µg/m^3 NOEL	21-day	Vapor-phase toxicity	(Gorsuch et al., 2008) (High)

5 ENVIRONMENTAL HAZARD THRESHOLDS

EPA calculates hazard thresholds to identify potential concerns to aquatic and terrestrial species. After weighing the scientific evidence, EPA selects the appropriate toxicity value from the integrated data to use for hazard thresholds. Table 5-1 summarizes the concentrations of concern (COCs) identified for BBP. See Section 6 for more details about how EPA weighed the scientific evidence.

In aquatic species, EPA uses probabilistic approaches (*e.g.*, SSD) when data from at least eight species (Raimondo, 2010) are available and deterministic approaches (*e.g.*, deriving a geometric mean of several comparable values) when limited data are available. For BBP, an SSD was derived for acute aquatic exposure hazards and a deterministic approach was used to assess chronic hazard in aquatic and terrestrial taxa. For the deterministic approaches, COCs are calculated by dividing a hazard value by an assessment factor (AF) according to EPA methods (U.S. EPA, 2016, 2013, 2012).

Equation 5-1

$$COC = toxicity\ value \div AF$$

For terrestrial species, EPA estimates hazard by calculating a toxicity reference value (TRV) or by assigning the hazard threshold as the most sensitive and ecologically relevant reproductive endpoint in the case of mammals, birds, and terrestrial plants.

5.1 Aquatic Species COCs

Acute Aquatic Concentration of Concern

For aquatic species, EPA uses probabilistic approaches (*e.g.*, SSD) when data from at least eight species (Raimondo, 2010) data are available. An SSD is a model of the variation in sensitivity of species to a particular chemical stressor and is generated by fitting a statistical distribution function to the proportion of species affected as a function of concentration or dose. It can be used to visualize which species are most sensitive to a toxic chemical exposure, and to predict the concentration of a toxic chemical that is hazardous to a percentage of test species. This hazardous concentration (HC) is represented as an HCp, where p is the percent of species below the threshold. EPA used an HC05 (a hazardous concentration threshold for 5% of species) to estimate a concentration that is protective of 95% of species. This HC05 can then be used to derive a COC, and the lower bound of the 95th percent confidence interval (CI) of the HC05 can be used to account for uncertainty instead of dividing by an AF. EPA has more confidence in the probabilistic approach compared to the deterministic approach when enough data are available because an HC05 is representative of a larger proportion of species in the environment.

The aquatic acute COC for BBP was derived from an SSD that contained LC50s for five fish species and six invertebrate species identified in systematic review, bolstered by an additional 18 predicted LC50 values from the Web-ICE v4.0 toxicity value estimation tool. Web-ICE is a tool developed by U.S. EPA's Office of Research and Development that estimates the acute toxicity of a chemical to a species, genus, or family from the known toxicity of the chemical to a surrogate species. It was used to obtain estimated acute toxicity values for BBP in species that were not represented in the empirical data set. (Figure 5-1). SSDs were derived using EPA's SSD Toolbox (v1.1) (Etterson, 2020) and plotted using R Statistical Software (v4.4.1) (R Core Team, 2019) using the ssdtools R package (v1.0.6) and the ggplot2 R package (v3.5.1; Appendix A). All studies included in the SSD were rated high or medium quality. The Maximum Likelihood method and a Weibull distribution model were used. The Weibull distribution was based on an examination of Akaike's Information Criterion corrected for sample size

(aicc) for goodness of fit (Burnham and Anderson, 2002), visual examination of Q-Q plots, and evaluation of the line of best fit near the low-end of the SSD. The HC05 for this distribution was 327 µg/L BBP with a 95% confidence interval of 197 µg/L to 552 µg/L. After taking the lower 95th percent confidence interval of this HC05 as an alternative to the use of assessment factors, the acute aquatic COC for vertebrates and invertebrates was **197 µg/L BBP (**Figure 5-1**)**.

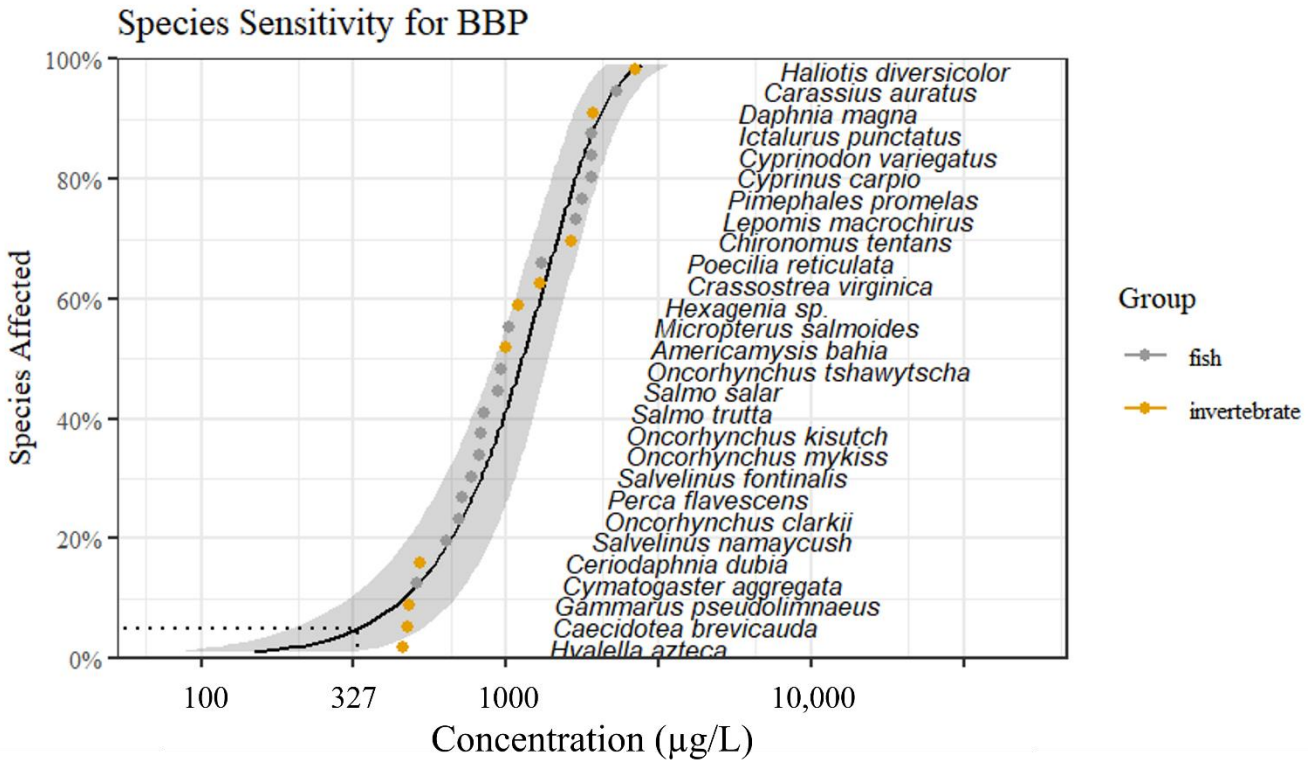

Figure 5-1. Species Sensitivity Distribution (SSD) of Acute Hazard Effects of BBP on Aquatic Organisms. The shaded band indicates the 95 percent confidence interval. The dotted line indicates the 5 percent Hazard Concentration (HC05 = 327 µg/L).

Chronic Aquatic Vertebrate Concentration of Concern

EPA reviewed eight high or medium quality studies for chronic toxicity in aquatic vertebrates (Table 3-2). The most sensitive organism for which a clear population-level fitness endpoint could be obtained was the zebrafish (*Danio rerio*) (Battelle, 2018c). This 21-day reproduction test of BBP exposure to *D. rerio* found 3% lower fecundity, 2% lower fertilization success, 100% increase in plasma vitellogenin, and reduced gonad weight in males in treatments with 33 µg/L BBP (LOEC) (Battelle, 2018c). No effects were observed at 11 µg/L BBP (NOEC). Based on the presence of a clear dose-response relationship and a population-level fitness endpoint, the 21-day reduction in reproduction was selected to derive the chronic COC for aquatic vertebrates. EPA calculated the COC as the geometric mean of the LOEC (33 µg/L) and NOEC (11 µg/L), equal to 19 µg/L, and applied an AF of 10 resulting in a **COC = 1.9 µg/L BBP**.

Chronic Aquatic Invertebrate Concentration of Concern

In a 21-day study of *Daphnia magna*, 80% mortality and 70% fewer offspring per female occurred when exposed to 1400 µg/L BBP compared to those exposed to 280 µg/L and no-BBP control treatments (Rhodes et al., 1995). EPA calculated a COC using the geometric mean of this NOEC and LOEC equal

to 626 µg/L (626 µg/L) and applied an AF of 10, resulting in a **COC = 62.6 µg/L BBP**.

Aquatic Algae Concentration of Concern

Of the eight studies that investigated the effects of BBP on algae, EPA derived a COC based on the lowest and most protective EC50 value which was 210 µg/L for BBP hazard effects on the green algae *Raphidocelis subcapitata*. EPA calculated a COC by applying an AF of 10, resulting in a **COC = 21 µg/L BBP**.

5.2 Terrestrial Species Hazard Values

Terrestrial Mammal Hazard Threshold

Nine laboratory rat and mouse studies were assessed with the most sensitive and ecologically relevant reproductive endpoint value chosen to represent the terrestrial mammalian hazard threshold. Phthalates were filtered to identify those with reproductive effects as the most sensitive endpoints. The terrestrial mammalian hazard threshold was derived from the most sensitive among acceptable-quality studies involving the Sprague-Dawley strain of Norway rat (*Rattus norvegicus*) (TNO, 1993), with a 136-day LOAEL of 446 mg/kg-bw/day BBP and NOAEL of 217 mg/kg-bw/day for reduced pup weight. EPA calculated a geometric mean of the NOAEL and LOAEL from this study to equal the hazard threshold of **311 mg/kg-bw/day BBP**.

Avian Hazard Threshold

One study of BBP effects on chicken (Gallus gallus) hens administered 5 g/kg bw/day BBP to birds on days 1 to 3 and again on days 21 to 23 of a 42-day experiment (University of Arizona, 1978). Hens fed this regime of BBP laid >90% fewer eggs over the course of 42 days compared to control hens. This study exposed BBP to hens at only one dose; therefore, EC50s via a dose-response experimental design could not be derived. Also, oral doses were administered directly but by unknown methods. The methods do not describe if or how BBP was added to food rations or any methods for analytically verifying BBP doses. No other evidence of BBP toxicity to birds was reasonably available to consider for a hazard threshold. EPA did not derive an avian hazard threshold due to these uncertainties in experimental design and analysis from the one available study.

Terrestrial Invertebrate Hazard Threshold

EPA reviewed one medium quality study for BBP toxicity in a terrestrial invertebrate (Table 4-2). The study exposed the soil nematode *Caenorhabditis elegans* to water solutions of BBP. No nematode mortality after 24 hours occurred up to and including 100,000 µg/L BBP (Kwon et al., 2011). No other evidence of BBP toxicity to terrestrial invertebrates was reasonably available to consider for a hazard threshold. Thus, EPA did not derive a terrestrial invertebrate hazard threshold.

Terrestrial Plants Hazard Threshold

EPA reviewed four high or medium quality studies for BBP toxicity in terrestrial plants (Table 4-3). A study of *Ipomoea aquatica* (Swamp Morning glory) found a 50% reduction in plant biomass after 21 days of hydroponic exposure to 100,000 µg/L BBP (LOEC), but plant biomass was not affected when exposed to 50000 µg/L BBP (Chen et al., 2011). This study exposed plants to water well above the BBP limit of water solubility (2690 µg/L) in a hydroponic scenario. Other available studies exposed plants to BBP fumigant and found no hazard effects up to and including the highest concentrations of exposure. No other evidence of BBP toxicity to terrestrial plants in soil was reasonably available to consider for a hazard threshold. Thus, EPA did not derive a terrestrial plant hazard threshold.

Table 5-1. Environmental Hazard Thresholds for BBP

Receptor Group	Exposure Duration	Hazard Threshold (COC or HV)	Citation
Aquatic Vertebrates	Acute	197 µg/L	From SSD
	Chronic	1.9 µg/L	(Battelle, 2018c)
Aquatic Invertebrates	Acute	197 µg/L	From SSD
	Chronic	62.6 µg/L	(Rhodes et al., 1995)
Aquatic Plants and Algae	Chronic	21 µg/L	(Adams et al., 1995)
Terrestrial Vertebrates	Chronic	311 mg/kg/day	(TNO, 1993)

6 WEIGHT OF THE SCIENTIFIC EVIDENCE CONCLUSIONS FOR ENVIRONMENTAL HAZARD

EPA uses several considerations when weighing and weighting the scientific evidence to determine confidence in the environmental hazard data. These considerations include the quality of the database, consistency, strength and precision, biological gradient/dose response, and relevance. This approach is described in the Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances (U.S. EPA, 2021). Table 6-1 summarizes how these considerations were determined for each environmental hazard threshold. Criteria for assessing confidence is described in Appendix C Evidence Integration.

EPA determined that BBP poses hazards from acute and chronic exposures to aquatic vertebrates, acute and chronic exposures to aquatic invertebrates, chronic exposure to algae, and chronic dietary exposure to terrestrial mammals. EPA has robust confidence in the weight of evidence in these findings.

6.1 Strengths, Limitations, Assumptions, and Key Sources of Uncertainty for Environmental Hazard

The weight of evidence suggests that BBP poses acute hazard effects to vertebrate and invertebrate animals at **197 µg/L BBP**. EPA has robust confidence in this hazard threshold because the quality of the database of studies included 11 high or medium quality studies that consistently resulted in LC50s between 460 µg/L (Lake Superior Research Institute, 1997) up to 2650 µg/L BBP (Liu et al., 2009). These studies all were conducted with reasonable dose-response designs and results, which enabled precise LC50 calculations (Table 3-1 and Table 3-3). These hazard effects were documented across a range of species that live in freshwater and marine environments in the water column as well as in or near the benthos/sediment. Additional consideration of acute (24-hour) larval fish transcriptomics, metabolomics, and behavior data revealed within-organism effects occurring in the same order of magnitude (ranging from 60 µg/L to 120 µg/L BBP), consistent with the hypothesis that hazard occurs at similar exposures. EPA used a probabilistic technique (SSD) to derive a COC that is protective of 95% of the aquatic animals in a community by incorporating hazard values across species and habitats. Limitations of SSDs include its reliance on model species that may not exist or interact in the same ecological community and are weighted equally. Another assumption that may limit the scope of SSD inference is whether the number of species used is adequate. The shape of the data distribution that is fitted to the effects data can be subjective and dependent on the three or four lowest values (Newman et al., 2000). Notwithstanding the limitations of SSD analyses, this method is widely used and accepted in risk assessments. Thus, EPA has robust confidence in the quality, consistency, strength and precision, and relevance of the studies used in determining the acute aquatic COC (**197 µg/L BBP**).

The weight of evidence suggests that BBP poses chronic hazard effects to vertebrate animals at **1.9 µg/L BBP**. EPA has robust confidence in the hazard threshold for four reasons. First, the reasonably available database of studies used for this determination includes eight high or medium quality studies to determine growth or reproduction effects using standard methods. Second, these studies were conducted on a range of different species including zebrafish (*Danio rerio*), fathead minnow (*Pimephales promelas*), and Japanese medaka (*Oryzias latipes*) (Table 3-2). Third, these studies found consistent effects within the same order of magnitude of BBP concentrations. Finally, all of these studies were conducted with reasonable dose-response designs and results, which enabled precise estimations of effect concentrations. Thus, EPA has robust confidence in the quality, consistency, strength and precision, and relevance of the studies used in determining the chronic aquatic COC for vertebrates (**1.9 µg/L BBP**).

The weight of evidence suggests that BBP poses chronic hazard effects to invertebrate animals at **62.6 µg/L BBP**. EPA has robust confidence in the hazard threshold for four reasons. First, the reasonably available database of studies used for this determination includes six high or medium quality studies to determine growth or reproduction effects using standard methods. Second, these studies were conducted on a range of different species including rotifers (*Brachionus calyciflorus*), water fleas (*Daphnia magna*), opossum shrimps (*Americamysis bahia*), oligochaete worms (*Lumbriculus variegatus*), and midges (*Chironomus tentans*), representing three different phyla (Table 3-4). Third, these studies found consistent effects within the same order of magnitude of BBP concentrations. Finally, all of these studies were conducted with reasonable dose-response designs and results, which enabled precise estimations of effect concentrations. Thus, EPA has robust confidence in the quality, consistency, strength and precision, and relevance of the studies used in determining the chronic aquatic COC for invertebrates (**62.6 µg/L BBP**).

The weight of evidence suggests that BBP poses chronic hazard effects to algae at **21 µg/L BBP**. EPA has robust confidence in the hazard threshold for four reasons. First, the reasonably available database of studies used for this determination includes eight high or medium quality studies to determine population growth effects of BBP using standard methods. Second, these studies were conducted on a range of different species including green algae (*Raphidocelis subcapitata*, *Dunaliella tertiolecta*, *Scenedesmus subspicatus*, and *Chlorella vulgaris*) and diatoms (*Navicula pelliculosa* and *Skeletonema costatum*) representing two different phyla (Table 3-5). Third, these studies found consistent effects within the same order of magnitude of BBP concentrations. Finally, all of these studies were conducted with reasonable dose-response designs and results, which enabled precise estimations of effect concentrations. Thus, EPA has robust confidence in the quality, consistency, strength and precision, and relevance of the studies used in determining the chronic aquatic COC for algae (**21 µg/L BBP**).

No studies on terrestrial wildlife involving mammals were identified. In lieu of terrestrial wildlife studies, nine references for rat studies as human health model organisms were used to determine a lowest and most conservative BBP concentration that affected apical endpoints (survival, reproduction, growth) in rodents and that could serve as an indication of hazard effects in wild mammal populations. The weight of evidence suggests that BBP poses chronic dietary exposure hazard effects to terrestrial mammals at **311 mg/kg bw/day BBP**. EPA has robust confidence in this hazard threshold for three reasons (Table 6-1). First, the reasonably available database of studies used for this determination include nine high or medium quality studies to determine reproductive effects of BBP using standard methods. The terrestrial mammalian hazard threshold was derived from the most sensitive among acceptable-quality studies involving the Sprague-Dawley rat (*Rattus norvegicus*) (TNO, 1993), with a 136-day LOAEL of 446 mg/kg-bw/day BBP and NOAEL of 217 mg/kg-bw/day for reduced pup weight. Second, these nine studies found consistent effects within the same order of magnitude of BBP doses. Finally, all of the studies were conducted with reasonable dose-response designs and results, which enabled precise estimation of effect concentrations. However, ecologically relevant population level effects were not observed in ecologically relevant species. Considerable uncertainties surround whether or how these effects on individual growth and reproductive development translate into effects on wild mammal fitness and population parameters. Because of these uncertainties of extrapolations to wildlife mammal species, EPA has moderate confidence that the hazards are representative of the range of wild mammal species. Therefore, EPA has robust confidence in the quality, consistency, and strength and precision, of the studies used in determining the hazard threshold for terrestrial mammals (**311 mg/kg bw/day BBP**), but moderate confidence in their relevance to wild mammal populations.

EPA has less confidence in the use of one avian study (University of Arizona, 1978), one terrestrial

invertebrate study (Kwon et al., 2011), and one terrestrial plant study (Chen et al., 2011) to derive hazard thresholds for these groups for many reasons. First, as only one study is available for each taxa, consistency across studies is unknown. Second, each study has at least one limitation in study design or analysis that limits the precision, biological gradient/dose response, and/or relevance of their results. For example, the study of *C. elegans* worms and the study of plant *Ipomoea aquatica* (Swamp Morning glory) exposed organisms to concentrations (100000 µg/L in both cases) well above the limit of solubility of BBP (2690 µg/L). The study of BBP effects on chicken egg production had limited descriptions of the methods and of dose administration and analytical verification (University of Arizona, 1978). Therefore, EPA has slight confidence in the quality, consistency, strength and precision, and relevance of these studies and did not derive hazard thresholds for these organisms.

Table 6-1. BBP Evidence Table Summarizing the Overall Confidence Derived from Hazard Thresholds

Types of Evidence	Quality of the Database	Consistency	Strength and Precision	Biological Gradient/Dose-Response	Relevance	Hazard Confidence
Aquatic						
Acute aquatic assessment	+++	+++	+++	+++	+++	Robust
Chronic aquatic assessment	+++	+++	+++	+++	+++	Robust
Algal assessment	+++	+++	+++	+++	+++	Robust
Terrestrial						
Chronic mammalian assessment	+++	+++	+++	+++	++	Robust
Chronic avian assessment	+	+	+	+	++	Slight
Terrestrial invertebrate assessment	+	+	+	+	++	Slight
Terrestrial plant assessment	+	+	+	+	++	Slight

[a] Relevance includes biological, physical/chemical, and environmental relevance.
+++ Robust confidence suggests thorough understanding of the scientific evidence and uncertainties. The supporting weight of scientific evidence outweighs the uncertainties to the point where it is unlikely that the uncertainties could have a significant effect on the hazard estimate.
++ Moderate confidence suggests some understanding of the scientific evidence and uncertainties. The supporting scientific evidence weighed against the uncertainties is reasonably adequate to characterize hazard estimates.
+ Slight confidence is assigned when the weight of scientific evidence may not be adequate to characterize the scenario, and when the assessor is making the best scientific assessment possible in the absence of complete information. There are additional uncertainties that may need to be considered.

7 ENVIRONMENTAL HAZARD ASSESSMENT CONCLUSIONS

EPA considered the quality, consistency, strength and precision, biological gradient/dose response, and relevance of the reasonably available data to weigh the scientific evidence in determining the environmental hazards of BBP. EPA determined that BBP poses acute and chronic exposure hazards to aquatic vertebrates, acute and chronic exposure hazards to aquatic invertebrates, chronic exposure hazards to algae, and chronic dietary exposure hazards to terrestrial mammals. BBP hazards include:

Aquatic species

- LC50 values from 11 acute duration exposures of BBP to aquatic fish and invertebrates were used to develop an SSD. The lower 95% confidence value of the HC05 was used as the COC at 197 µg/L BBP.
- The most sensitive aquatic vertebrate for which a clear population-level fitness endpoint could be obtained was for the zebrafish (*Danio rerio*). This 21-day reproduction test of BBP exposure to *D. rerio* found 3% lower fecundity, 2% lower fertilization success, 100% increase in plasma vitellogenin, and reduced gonad weight in males in treatments with 33 µg/L BBP (LOEC). No effects were observed at 11 µg/L BBP (NOEC). Based on the presence of a clear dose-response relationship and a population-level fitness endpoint, the 21-day ChV for reduction in reproduction was selected to derive the chronic COC for aquatic vertebrates as 1.9 µg/L BBP.
- A 21-day study of *Daphnia magna* found 80% mortality and 70% fewer offspring per female due to BBP chronic exposure, leading to a COC of 62.6 µg/L BBP for chronic invertebrate hazard.
- EPA derived a COC for chronic algal BBP exposure from the EC50 value of 210 µg/L to the green algae *Raphidocelis subcapitata* resulting in a COC of 21 µg/L BBP.

Terrestrial Species

- The terrestrial mammalian hazard threshold was derived from the most sensitive among acceptable-quality studies involving the Sprague-Dawley rat (*Rattus norvegicus*) with a 136-day dietary exposure hazard threshold of 311 mg/kg-bw/day BBP.
- No evidence of BBP toxicity to terrestrial invertebrates was reasonably available to consider for a hazard threshold. Thus, EPA did not derive a terrestrial invertebrate hazard threshold.
- No evidence of BBP toxicity to terrestrial plants in soil was reasonably available to consider for a hazard threshold. Thus, EPA did not derive a terrestrial plant hazard threshold.

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Appendix A SPECIES SENSITIVITY DISTRIBUTION

An SSD was derived using only acute duration exposure studies that calculated LC50s. The SSD Toolbox is a resource that can fit SSDs to environmental hazard data (Etterson, 2020). It runs on Matlab 2018b (9.5) for Windows 64 bit. For this draft BBP risk evaluation, EPA created one SSD with the SSD Toolbox Version 1.1 to evaluate acute aquatic vertebrate and invertebrate toxicity. The use of this probabilistic approach increases confidence in the hazard threshold identification as it is a more data-driven way of accounting for uncertainty. For the acute SSD, acute exposure hazard data for aquatic vertebrates and invertebrates were curated to prioritize study quality and to assure comparability between toxicity values. For example, the empirical data set included only LC50s for high and medium quality acute duration assays that measured mortality for aquatic vertebrates and invertebrates. Table_Apx A-1 shows the empirical data and Table_Apx A-2 shows the modelled data from Web-ice that were used in the SSD.

With this data set, the SSD Toolbox was used to apply a variety of algorithms to fit and visualize SSDs with different distributions. An HC05 was calculated for each. The SSD Toolbox's output contained several methods for choosing an appropriate distribution and fitting method, including goodness-of-fit, standard error, and sample-size corrected Akaike Information Criterion (AICc, (Burnham and Anderson, 2002)). Most p-values for goodness-of-fit were less than 0.05, showing no evidence of lack of fit. The distribution and model with the lowest AICc value, and therefore the best fit for the data was the Weibull Distribution (**Table_Apx A-3**). Because numerical methods may lack statistical power for small sample sizes, a visual inspection of the data were also used to assess goodness-of-fit. For the Q-Q plot, the horizontal axis gives the empirical quantiles while the vertical axis gives the predicted quantiles (from the fitted distribution). The Q-Q plot demonstrates a good model fit with the data points in close proximity to the line across the data distribution. Q-Q plots were visually used to assess the goodness-of-fit for the distributions with the Weibull distribution demonstrating the best fit near the low end of the distribution, which is the region from which the HC05 is derived. The results for this model (**Figure 5-1**) predicted 5 percent of the species (HC05) to have their LC50s exceeded at 377 µg/L (154 to 531 µg/L 95% CI).

Table_Apx A-1. SSD Model Input for BBP Acute Exposure Toxicity in Aquatic Vertebrates and Invertebrates – Empirical Data

Species	Description	Acute Toxicity Value LC50 (µg/L)	Citation(s)
Hyalella azteca	Aquatic invertebrate	460	(Lake Superior Research Institute, 1997; Adams et al., 1995; EG&G Bionomics, 1984)
Cymatogaster aggregata	Aquatic vertebrate	510	(Chen et al., 2014; Ozretich et al., 1983)
Oncorhynchus mykiss	Aquatic vertebrate	820	(Ozretich et al., 1983)
Americamysis bahia	Aquatic invertebrate	1100	(EG&G Bionomics, 1979b)
		900	(Springborn Bionomics, 1988)
Hexagenia sp.	Aquatic invertebrate	1100	(Adams et al., 1995; EnviroSystem, 1991; ABC Laboratories, 1986c; EG&G Bionomics, 1983)

Species	Description	Acute Toxicity Value LC50 (µg/L)	Citation(s)
Crassostrea virginica	Aquatic invertebrate	1300	(ABC Laboratories, 1986a; Linden et al., 1979)
Chironomus tentans	Aquatic invertebrate	1640	(Monsanto, 1982)
Lepomis macrochirus	Aquatic vertebrate	1700	(EG&G Bionomics, 1979c; Streufort, 1978)
Pimephales promelas	Aquatic vertebrate	1500	(Adams et al., 1995)
		2100	(EG&G Bionomics, 1979d)
Haliotis diversicolor	Aquatic invertebrate	2650	(Liu et al., 2009)

986
987 **Table_Apx A-2. SSD Model Input for BBP Acute Exposure Toxicity in Aquatic Vertebrates and**
988 **Invertebrates – WebICE Data**

Species	Description	Acute Toxicity Value LC50 (µg/L)
Caecidotea brevicauda	Invertebrate	447
Gammarus pseudolimnaeus	Invertebrate	480
Ceriodaphnia dubia	Invertebrate	523
Salvelinus namaycush	Fish	637
Oncorhynchus clarkii	Fish	702
Perca flavescens	Fish	715
Oncorhynchus kisutch	Fish	766
Salmo trutta	Fish	851
Salmo salar	Fish	937
Oncorhynchus tshawytscha	Fish	965
Micropterus salmoides	Fish	1022
Poecilia reticulata	Fish	1306
Cyprinus carpio	Fish	1902
Cyprinodon variegatus	Fish	1915
Ictalurus punctatus	Fish	1916
Daphnia magna	Invertebrate	1919
Carassius auratus	Fish	2315

Table_Apx A-3. SSD[a] Model Predictions for Acute BBP Exposure Toxicity to Aquatic Vertebrates

Distribution[b]	HC05 (µg/L)	p- value
Weibull	**327**	**0.93**
Normal	475	0.70
Logistic	467	0.66
Gumbel	487	0.38
Burr	464	0.63

[a] The SSD was generated using SSD Toolbox v1.1.
[b] The model with the lowest AICc value, and therefore the best model fit, is bolded in this table.

Appendix B TERRESTRIAL VERTEBRATE TOXICITY OF BBP

In lieu of wild mammal studies, EPA considered nine studies on BBP to laboratory rodents that were designed to determine human health hazards of BBP that also contained ecologically relevant reproductive endpoints (Table_Apx B-1). Of the studies containing ecologically relevant reproductive endpoints to rat and mouse, EPA selected the study with the most sensitive LOAEL (lowest observed adverse effect level) for evaluating data quality and for deriving the hazard threshold for terrestrial mammals (Table_Apx B-1).

Table_Apx B-1. Terrestrial Vertebrate Toxicity of BBP

Test Organism (Species)	Hazard Values	Duration	Endpoint	Citation
Rat (*Rattus norvegicus*)	250/500 mg/kg-bw/day	GD 15 - 17	Reproduction	(Ema and Miyawaki, 2002)
	500/750 mg/kg-bw/day	GD 5 - 17		(Ema et al., 1992)
	247/821 mg/kg-bw/day	Two generation		(Springborn Bionomics, 1986d; Nikonorow et al., 1973)
	500/1000 mg/kg-bw/day	29 days		(Wolf et al., 1999; Piersma et al., 1995)
	419/1641 mg/kg-bw/day	GD 6 - 15		(RTI International, 1989)
	254/2270 mg/kg-bw/day	10 weeks		(Hazelton Labs, 1985)
	0.115/0.321 mg/kg-bw/day	9 weeks drinking water		(TNO, 1998)
Mice	247/821 mg/kg-bw/day	Two generation		(NTP, 1990)
	910/2330 mg/kg-bw/day	GD 6 - 15		

Appendix C RUBRIC FOR WEIGHT OF THE SCIENTIFIC EVIDENCE

The weight of the scientific evidence fundamentally means that the evidence is weighed (*i.e.*, ranked) and weighted (*i.e.*, a piece or set of evidence or uncertainty may have more importance or influence in the result than another). Based on the weight of the scientific evidence and uncertainties, a confidence statement was developed that qualitatively ranks (*i.e.*, robust, moderate, slight, or indeterminate) the confidence in the hazard threshold. The qualitative confidence levels are described below.

The evidence considerations and criteria detailed within U.S. EPA (2021) guides the application of strength-of-evidence judgments for environmental hazard effect within a given evidence stream and were adapted from Table 7-10 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021).

EPA used the strength-of-evidence and uncertainties from U.S. EPA (2021) for the hazard assessment to qualitatively rank the overall confidence rating for environmental hazard (Table_Apx C-1). Confidence levels of robust (+ + +), moderate (+ +), slight (+), or indeterminant are assigned for each evidence property that corresponds to the evidence considerations (U.S. EPA, 2021). The rank of the *Quality of the Database* consideration is based on the systematic review overall quality determination (High, Medium, or Low) for studies used to calculate the hazard threshold, and whether there are data gaps in the toxicity data set. Another consideration in the *Quality of the Database* is the risk of bias (*i.e.*, how representative is the study to ecologically relevant endpoints). Additionally, because of the importance of the studies used for deriving hazard thresholds, the *Quality of the Database* consideration may have greater weight than the other individual considerations. The high, medium, and low systematic review overall quality determinations ranks correspond to the evidence table ranks of robust (+ + +), moderate (+ +), or slight (+), respectively. The evidence considerations are weighted based on professional judgment to obtain the overall confidence for each hazard threshold. In other words, the weights of each evidence property relative to the other properties are dependent on the specifics of the weight of the scientific evidence and uncertainties that are described in the narrative and may or may not be equal. Therefore, the overall score is not necessarily a mean or defaulted to the lowest score. The confidence levels and uncertainty type examples are described below.

C.1 Confidence Levels

- Robust (+ + +) confidence suggests thorough understanding of the scientific evidence and uncertainties. The supporting weight of the scientific evidence outweighs the uncertainties to the point where it is unlikely that the uncertainties could have a significant effect on the exposure or hazard estimate.
- Moderate **(**+ +) confidence suggests some understanding of the scientific evidence and uncertainties. The supporting scientific evidence weighed against the uncertainties is reasonably adequate to characterize exposure or hazard estimates.
- Slight (+) confidence is assigned when the weight of the scientific evidence may not be adequate to characterize the scenario, and when the assessor is making the best scientific assessment possible in the absence of complete information. There are additional uncertainties that may need to be considered.

C.2 Types of Uncertainties

The following uncertainties may be relevant to one or more of the weight of the scientific evidence considerations listed above and will be integrated into that property's rank in the evidence table:

- *Scenario Uncertainty:* Uncertainty regarding missing or incomplete information needed to fully

define the exposure and dose.
    - The sources of scenario uncertainty include descriptive errors, aggregation errors, errors in professional judgment, and incomplete analysis.
- *Parameter Uncertainty:* Uncertainty regarding some parameter.
    - Sources of parameter uncertainty include measurement errors, sampling errors, variability, and use of generic or surrogate data.
- *Model Uncertainty:* Uncertainty regarding gaps in scientific theory required to make predictions on the basis of causal inferences.
    - Modeling assumptions may be simplified representations of reality.

Table 6-1 summarizes the weight of the scientific evidence and uncertainties, while increasing transparency on how EPA arrived at the overall confidence level for each exposure hazard threshold. Symbols are used to provide a visual overview of the confidence in the body of evidence, while de-emphasizing an individual ranking that may give the impression that ranks are cumulative (*e.g.,* ranks of different categories may have different weights).

Table_Apx C-1. Considerations that Inform Evaluations of the Strength of the Evidence within an Evidence Stream (*i.e.*, Apical Endpoints, Mechanistic, or Field Studies)

Consideration	Increased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)	Decreased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)
The evidence considerations and criteria laid out here guide the application of strength-of-evidence judgments for an outcome or environmental hazard effect within a given evidence stream. Evidence integration or synthesis results that do not warrant an increase or decrease in evidence strength for a given consideration are considered "neutral" and are not described in this table (and, in general, are captured in the assessment-specific evidence profile tables).		
Quality of the database[a] (risk of bias)	• A large evidence base of *high*- or *medium*-quality studies increases strength. • Strength increases if relevant species are represented in a database.	• An evidence base of mostly *low*-quality studies decreases strength. • Strength also decreases if the database has data gaps for relevant species, *i.e.*, a trophic level that is not represented. • Decisions to increase strength for other considerations in this table should generally not be made if there are serious concerns for risk of bias; in other words, all the other considerations in this table are dependent upon the quality of the database.
Consistency	Similarity of findings for a given outcome (*e.g.*, of a similar magnitude, direction) across independent studies or experiments increases strength, particularly when consistency is observed across species, life stage, sex, wildlife populations, and across or within aquatic and terrestrial exposure pathways.	• Unexplained inconsistency (*i.e.*, conflicting evidence; see U.S. EPA (2005) decreases strength.) • Strength should not be decreased if discrepant findings can be reasonably explained by study confidence conclusions; variation in population or species, sex, or life stage; frequency of exposure (*e.g.*, intermittent or continuous); exposure levels (low or high); or exposure duration.
Strength (effect magnitude) and precision	• Evidence of a large magnitude effect (considered either within or across studies) can increase strength. • Effects of a concerning rarity or severity can also increase strength, even if they are of a small magnitude. • Precise results from individual studies or across the set of studies increases strength, noting that biological significance is prioritized over statistical significance. • Use of probabilistic model (*e.g.*, Web-ICE, SSD) may increase strength.	Strength may be decreased if effect sizes that are small in magnitude are concluded not to be biologically significant, or if there are only a few studies with imprecise results.
Biological gradient/dose-response	• Evidence of dose-response increases strength. • Dose-response may be demonstrated across studies or within studies and it can be dose- or duration-dependent.	• A lack of dose-response when expected based on biological understanding and having a wide range of doses/exposures evaluated in the evidence base can decrease strength.

Consideration	Increased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)	Decreased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)
	• Dose response may not be a monotonic dose-response (monotonicity should not necessarily be expected, *e.g.*, different outcomes may be expected at low vs. high doses due to activation of different mechanistic pathways or induction of systemic toxicity at very high doses). • Decreases in a response after cessation of exposure (*e.g.*, return to baseline fecundity) also may increase strength by increasing certainty in a relationship between exposure and outcome (this particularly applicable to field studies).	• In experimental studies, strength may be decreased when effects resolve under certain experimental conditions (*e.g.*, rapid reversibility after removal of exposure). • However, many reversible effects are of high concern. Deciding between these situations is informed by factors such as the toxicokinetics of the chemical and the conditions of exposure, see (U.S. EPA, 1998), endpoint severity, judgments regarding the potential for delayed or secondary effects, as well as the exposure context focus of the assessment (*e.g.*, addressing intermittent or short-term exposures). • In rare cases, and typically only in toxicology studies, the magnitude of effects at a given exposure level might decrease with longer exposures (*e.g.*, due to tolerance or acclimation). • Like the discussion of reversibility above, a decision about whether this decreases evidence strength depends on the exposure context focus of the assessment and other factors. • If the data are not adequate to evaluate a dose-response pattern, then strength is neither increased nor decreased.
Biological relevance	Effects observed in different populations or representative species suggesting that the effect is likely relevant to the population or representative species of interest (*e.g.*, correspondence among the taxa, life stages, and processes measured or observed and the assessment endpoint).	An effect observed only in a specific population or species without a clear analogy to the population or representative species of interest decreases strength.
Physical/chemical relevance	Correspondence between the substance tested and the substance constituting the stressor of concern.	The substance tested is an analog of the chemical of interest or a mixture of chemicals which include other chemicals besides the chemical of interest.
Environmental relevance	Correspondence between test conditions and conditions in the region of concern.	The test is conducted using conditions that would not occur in the environment.

[a] Database refers to the entire data set of studies integrated in the environmental hazard assessment and used to inform the strength of the evidence. In this context, database does *not* refer to a computer database that stores aggregations of data records such as the ECOTOX Knowledgebase.