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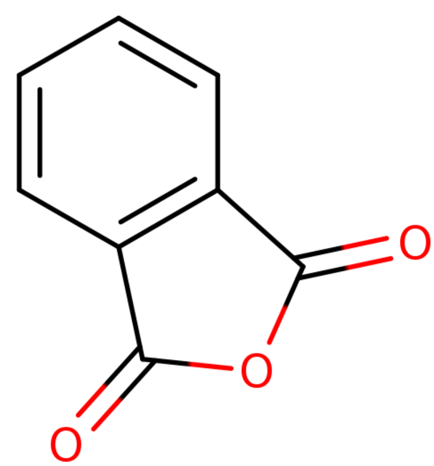
Draft Environmental Hazard Assessment for Phthalic Anhydride

Technical Support Document for the Draft Risk Evaluation

CASRN 85-44-9



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KEY ABBREVIATIONS AND ACRONYMS

AF	Assessment factor
ChV	Chronic value
COC	Concentration(s) of concern
CASRN	Chemical abstracts service registry number
DIDP	Diisodecyl phthalate
DINP	Diisononyl phthalate
DMSO	Dimethyl sulfoxide
ECOSAR	Ecological Structure Activity Relationships (Model)
EC	Effect concentration
EC50	Effect concentration at which 50% of test organisms exhibit an effect

EPA	Environmental Protection Agency (U.S.)
HV	Hazard value
ISO	International Organization for Standardization
LC50	Lethal concentration at which 50% of test organisms die
LD50	Lethal dose at which 50% of test organisms die
LOAEC	Lowest-observed-adverse-effect concentration
LOAEL	Lowest-observed-adverse-effect level
NCI	National Cancer Institute
ND	Not determined
NOAEC	No-observed-adverse-effect concentration
NOAEL	No-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
OPPT	Office of Pollution Prevention and Toxics (EPA)
PECO	Population, exposure, comparator, and outcome
SACC	Science Advisory Committee on Chemicals
SD	Sprague-Dawley
SSD	Species sensitivity distribution
TRV	Toxicity reference value
TSD	Technical support document
TSCA	Toxic Substances Control Act
U.S.	United States
Web-ICE	Web-Based Interspecies Correlation Estimation

SUMMARY

This technical support document (TSD) is part of the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026d) conducted under the Toxic Substances Control Act (TSCA) (see also public docket, EPA-HQ-OPPT-2018-0459).The U.S. Environmental Protection Agency (EPA or the Agency) considered all reasonably available information through its systematic review process under TSCA to characterize environmental hazard for the related chemical *ortho*-phthalic acid (*o*-phthalic acid). For acute exposures to aquatic organisms, the concentration of concern (COC) of 20.6 mg/L was based on a 48-hour effect EC50 (effect concentration at which 50% of test organisms exhibit an effect) in the water flea *Daphnia magna* (Jonsson and Baun, 2003). For chronic exposures to aquatic organisms, the COC was 3.2 mg/L, based on a 60-day embryo/larval stage of development in the rainbow trout *Oncorhynchus mykiss* (Van Leeuwen et al., 1990). The aquatic plants and algae COC was 227 mg/L due to an inhibition of growth in a 72-hour study with the green algae *Pseudokirchneriella subcapitata* (Jonsson and Baun, 2003). For terrestrial organisms, hazard data for *o*-phthalic acid were available for mammals and terrestrial plants. Data for Sprague-Dawley rats from two studies, 14- and 28-day, respectively, were used to determine a hazard value for terrestrial mammals of 250 mg/kg-bw/day using the lowest-observed-adverse-effect level (LOAEL) and based on a decrease in body weight in male rats (Kwack et al., 2010; Kwack et al., 2009). The terrestrial invertebrate hazard threshold was 253.3 mg/kg based on the ECOSAR (Ecological Structure Activity Relationships) Model. The terrestrial plant hazard threshold was derived from the crabapple *Malus prunifolia* where there was a decrease in plant weight (fresh and dry), root length, and shoot length after a 15-day exposure resulting in a LOAEL of 166.1 mg/L (Bai et al., 2009). Hazard thresholds are summarized below in Table S-1.

Table S-1. Environmental Hazard Thresholds for *o*-Phthalic Acid

Receptor Group	Exposure Duration	Hazard Threshold (COC or HV)	Source(s)
Aquatic invertebrates	48-hour	20.6 mg/L	(Jonsson and Baun, 2003)
Aquatic vertebrates	60-day	3.2 mg/L	(Van Leeuwen et al., 1990)
Aquatic plants and algae	72-hour	227 mg/L	(Jonsson and Baun, 2003)
Terrestrial vertebrates	14- and 28-day	250 mg/kg-bw/d	(Kwack et al., 2010; Kwack et al., 2009)
Terrestrial invertebrates	14-day	253.3 mg/kg	ECOSAR
Terrestrial plants	15-day	166.1 mg/L	(Bai et al., 2009)
COC = concentration of concern; HV = hazard value			

1 APPROACH AND METHODOLOGY

Phthalic anhydride is a solid of low volatility and undergoes rapid hydrolysis. It is primarily used in the formation of plasticizers, though it is also used in the production of adhesives, sealants, paints, coatings, rubbers and other applications. In 2020, the chemical data reporting indicated 250 to 500 million pounds (lb) of phthalic anhydride were manufactured or imported into the United States in 2019 (U.S. EPA, 2020a). Data reported during the 2024 chemical data reporting cycle shows similar production volume estimates. During scoping and problem formulation, EPA identified sources of environmental hazard data shown in Figure 2-10 of the *Scope of the Risk Evaluation for Phthalic Anhydride (1,3-Isobenzofurandione* [1]*); CASRN 85-44-9* (also called the "final scope document") (U.S. EPA, 2020b). Phthalic anhydride is expected to be released to the environment via air, water, and biosolids and landfills as detailed within the environmental release assessment presented in the *Draft Environmental Release and Occupational Exposure Assessment for Phthalic Anhydride* (U.S. EPA, 2025a).

As discussed in the final scope document for phthalic anhydride (U.S. EPA, 2020b) and in the *Draft Physical Chemistry and Fate and Transport Assessment for Phthalic Anhydride* (U.S. EPA, 2026c), phthalic anhydride rapidly hydrolyzes to 1,2,-benzenedicarboxylic acid, also known as *o*-phthalic acid (CASRN 88-99-3), when allowed contact with water or moisture in the air. This transformation is immediate and the hydrolysis half-life is estimated to be between 30 to 90 seconds, depending upon pH; complete hydrolysis is achieved in approximately 8 minutes in simulated seawater or physiological fluids (U.S. EPA, 2026c). Given the rapid hydrolysis of phthalic anhydride to *o*-phthalic acid, EPA considered environmental hazard data for both phthalic anhydride and *o*-phthalic acid in this draft TSD. The predominant form is expected to be *o*-phthalic acid in the environment. Since the final scope was submitted, EPA received 11 public comments. All relevant comments have been incorporated into this TSD, as appropriate.

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, Version 1.0: A Generic TSCA Systematic Review Protocol with Chemical-Specific Methodologies* (U.S. EPA, 2021) (also called "Draft Systematic Review Protocol") and *Draft Systematic Review Protocol for Phthalic Anhydride* (U.S. EPA, 2026e). An updated literature search was conducted in 2025 and additional study (HEROID 61572) that met population, exposure, comparator, and outcome (PECO) criteria was moved onto full-text screening and data extraction. Studies were assigned an overall quality determination of high, medium, low, or uninformative.

No data were reasonably available for the assessment of terrestrial vertebrates; therefore, mammalian studies were considered from human health model organisms (mice and rats) to assess dietary exposure to *o*-phthalic acid. These studies were used to calculate a hazard value for mammals, which is expressed as doses in units of mg/kg-bw/day. Although the hazard value for *o*-phthalic acid is derived from laboratory rat and mouse studies, the independent Science Advisory Committee on Chemicals (SACC) indicated, in the context of comment responses to risk evaluations for diisodecyl phthalate (DIDP) and diisononyl phthalate (DINP), that using hazard data from studies in laboratory rodents is protective—even if the rodents sometimes have higher variability and are not as sensitive as some wildlife species (U.S. EPA, 2025b). Because terrestrial invertebrate data were not available, the ECOSAR Model was used to determine the hazard threshold for terrestrial invertebrates.

[1] 1,3-Isobenzofurandione is a primary synonym for phthalic anhydride.

2 AQUATIC SPECIES HAZARD

2.1 Toxicity to Aquatic Organisms

EPA considered four aquatic toxicity studies to *o*-phthalic acid that were rated high/medium quality to determine hazard to aquatic organisms (Table 2-1). Some studies included multiple endpoints, species, and test durations. Studies that received an overall quality determination of low, uninformative, or did not meet systematic review criteria were not considered quantitatively to develop hazard thresholds (see Appendix A).

Aquatic Invertebrates and Aquatic Plants and Algae

The only acute invertebrate study to receive a high-quality ranking assessed the lethality of *o*-phthalic acid to the water flea *Daphnia magna* for 48-hour exposure duration (Jonsson and Baun, 2003). The standardized toxicity tests in the study were conducted as concentration-response experiments. Each test consisted of five to eight concentrations (not identified in the study) of test solution and a control group of eight replicates. The 48-hour immobilization tests with *D. magna* were performed in accordance with the International Organization for Standardization (ISO) standard *Determination of the Inhibition of the Mobility of Daphnia Magna Straus (Cladocera, Crustacea)*. Tests were repeated if the mortality in the control group exceeded 5%. The number of immobilized animals was counted after 24 and 48 hours, and results of replicates were pooled for the statistical treatment. The study authors indicated that the test strategy included range-finding tests covering several decades of concentrations and definitive tests to establish EC values and corresponding 95% confidence intervals. In all tests, EC10 and EC50 values were estimated. The 10% effect was assumed to represent beginning toxicity at a statistically significant level whereas EC50 values were used as lowest-observed-adverse-effect concentration (LOAEC) estimates. Statistical treatment of data was done by probit analysis with maximum likelihood estimation using a standard software program. Test concentrations where physical entrapment of organisms was observed were excluded from the dataset. The 48-hour EC50 was estimated at 103 mg/L (Jonsson and Baun, 2003).

The same authors conducted a study that evaluated the growth of the green algae *Pseudokirchneriella subcapitata* after exposure to *o*-phthalic acid over a 72-hour period (Jonsson and Baun, 2003). The study received a high-quality ranking. Each test consisted of 11 to 16 test concentrations (not identified in the study) with 6 controls per test. The methodology followed ISO standard *Fresh water algal growth inhibition test with Scenedesmus subspicatus and Selenastrum capricornutum.* Growth rate was based on biomass following exposure to 11 to 16 concentrations (not identified in the study) diluted with freshwater algal test medium. Concentration-response curves were fitted to data using nonlinear regression, and the EC50 values and 95% confidence intervals were estimated. The 72-hour EC50 was 2,270 mg/L based on an inhibition of growth (Jonsson and Baun, 2003).

Another study that received a high-quality ranking evaluated growth of the freshwater algae *Desmodesmus subspicatus* over a 72-hour exposure duration to *o*-phthalic acid (Bayer Industry Services, 2004). Growth rate based on cell density and cell density over time was assessed after a limit test of 100 mg/L *o*-phthalic acid solution. At the end of the treatment period, no effects were observed and the EC50 was determined to exceed 100 mg/L.

No studies with a high or medium overall quality ranking were available to assess the hazard of *o*-phthalic acid to pelagic invertebrates on a chronic exposure or sediment-dwelling invertebrates with acute or chronic exposure.

Aquatic Vertebrates – Acute

One study with a high-quality ranking assessed the effects of *o*-phthalic acid on adult rainbow trout (*Oncorhynchus mykiss*) under static conditions at nominal concentrations of 6.25, 12.5, 25, 50, and 100 mg/L (Author Withheld, 1996). This study was based on OECD Guidelines for Testing of Chemicals number 203: Fish Acute Toxicity Test (1992) and the EC Methods for the Determination of Ecotoxicity Guideline No. L 383A, Method No. C.1 (1992). At the start of the treatment, recovery ranged from 83.5 to 106.7% and at the end of the study it ranged from 41.7 to 86.0%. Ten fish were exposed per test concentration. Fish were exposed for 96 hours to determine effects on mortality and other physical characteristics. The study authors reported the LC50 (lethal concentration at which 50% of test organisms die) to be greater than 100 mg/L due to an absence of effects. The no-observed-adverse-effect concentration (NOAEC) and LOAEC were, respectively, 100 mg/Land greater than 100 mg/L (Author Withheld, 1996).

Aquatic Vertebrates – Subchronic and Chronic

Chronic fish hazard data for *o*-phthalic acid were identified in one study evaluating two fish species at two durations and outcomes (zebrafish [*Danio rerio*]; rainbow trout [*O. mykiss*]). No studies were available to assess the hazard of *o*-phthalic acid to amphibians.

One study was conducted on zebrafish at the embryo/larval stage (early life stage). This experiment received a medium quality ranking. In the 7-day subchronic early life stage exposure of *o*-phthalic acid to zebrafish*,* five to seven concentrations of *o*-phthalic acid and a control were evaluated (Van Leeuwen et al., 1990). Although the test concentrations were not identified in the study, the range between the concentrations was 3.2. The test solution was renewed three times per week. A solvent, dimethyl sulfoxide (DMSO) was used in control experiments. It was not reported if test concentrations were analytically verified. The LC50 (with 99% confidence interval) and LOAEC were reported at 560 (320–1,000 mg/L) and 1,000 mg/L, respectively, with no effects on hatching delays or teratogenic effects reported. The LC50 was calculated based on the American Society for Testing and Materials Method (ASTM) for assessing additive toxicity of chemical mixtures which describes methodologies for deriving LC50 values (Van Leeuwen et al., 1990). Because there is uncertainty regarding test concentrations used, and the LC50 reported is lower than the LOAEC in addition to the LC50 extrapolation, this endpoint was not considered for quantitative assessment.

In the same study, a second experiment was conducted on the embryo/larval stage of rainbow trout in a 60-day chronic test with exposure to *o*-phthalic acid (Van Leeuwen et al., 1990). That experiment received a medium quality ranking. Test concentrations were not reported but the study authors indicated they ranged by a ratio of 3.2. A reference was provided by the study authors further detailing the test methodology. At the end of the study, the LC50 (and 95% confidence interval) was reported as 44.2 (40.4–48.3) mg/L. The LOAEC was reported as 32.0 mg/L based on mortality, total embryotoxicity, length, and weight (a NOAEC was not reported). The LC50 and 95% confidence intervals were calculated based on parametric analysis of mortality rates in bioassays. Mortality generally occurred in the egg stage during late gastrulation. Significant differences were also reported in length and weight of the fish compared to controls, but not whether the differences were an increase or decrease (Van Leeuwen et al., 1990).

Aquatic Organism Hazard Conclusions

Although uncertainties in the studies exist and there is slight confidence in the quality of the database and strength and precision of endpoints, and moderate confidence in consistency, taken together, effects on aquatic species were observed at concentrations that are relatively high in organisms across taxonomic groups, habitats, exposure types, and exposure durations (Table 2-1). Only one study was available to assess hazard to aquatic organisms on a chronic exposure basis, and no studies were available to assess hazard to sediment-dwelling organisms or amphibians. Studies of *o*-phthalic acid exposure via water to fish on an acute exposure basis and aquatic plants and algae reported no effects up to the highest concentration tested. Given the available hazard data show low toxicity of phthalic anydride to aquatic taxa with most hazard values greater than 100 mg/L on an acute or chronic basis, EPA has robust confidence in the evidence that *o*-phthalic acid has low hazard potential to aquatic species.

Table 2-1. Summary of Aquatic Organism Environmental Hazard Studies Used for *o*-Phthalic Acid

Study Type	Test Organism (Species)	Test Substance[a b]	Hazard Value (mg/L)	Duration	Effect	Citation (Study Quality)
Aquatic invertebrates						
Acute	Water flea *(Daphnia magna)*	*o*-Phthalic acid	EC50 = 103	48 hours	Mortality	(Jonsson and Baun, 2003) (High)
Aquatic vertebrates						
Acute	Rainbow trout (*Oncorhynchus mykiss*)	*o*-Phthalic acid	NOAEC/LOAEC = 100/>100	96 hours	Mortality	(Author Withheld, 1996) (High)
Chronic	Zebrafish (*Danio rerio*)	Phthalic Anhydride	LC50 = 560	7 days	Mortality	(Van Leeuwen et al., 1990) (Medium)
	Rainbow trout (*Oncorhynchus mykiss*)	Phthalic Anhydride	LC50 = 44.2 LOAEC = 32	60 days	Mortality, growth, and development	(Van Leeuwen et al., 1990) (Medium)
Aquatic plants and algae						
Green algae (*Pseudokirchneriella Subcapitata*)		*o*-Phthalic acid	EC50 = 2270	72 hours	Growth	(Jonsson and Baun, 2003) (High)
Freshwater Algae (*Desmodesmus subspicatus*)		*o*-Phthalic acid	EC50 > 100	72 hours	Growth	(Bayer Industry Services, 2004) (High)

EC50 = Effect concentration at which 50% of test organisms exhibit an effect; LC50 = Lethal concentration at which 50% of test organisms die
[a] Test substance as reported by the authors of each study
[b] 1:1 conversion from phthalic anhydride to *o*-phthalic acid is expected to be instantaneous

3 TERRESTRIAL SPECIES HAZARD

EPA assigned an overall quality level of high or medium to six terrestrial mammal studies and two terrestrial plant studies. Terrestrial toxicity studies considered for hazard threshold determination are presented in Table 3-1. These studies contained relevant *o*-phthalic acid terrestrial toxicity data for terrestrial mammals including Sprague-Dawley (SD) rats and the terrestrial plants crabapple (*Malus prunifolia*) and Lanzhou lily (*Lilium davidii var. unicolor*). Because no empirical data were reasonably available for terrestrial invertebrates, the Ecological Structure Activity Relationships (ECOSAR) Model was used to estimate toxicity. Remaining terrestrial hazard studies can be found in Appendix A. No studies were reasonably available to assess hazard to birds.

3.1 Toxicity to Terrestrial Organisms

Terrestrial Vertebrates

Two high-quality rat studies were used to evaluate hazard to terrestrial mammals. The two studies had the same LOAEL, which was the most sensitive value from all terrestrial vertebrate studies. Terrestrial vertebrate studies not considered for hazard threshold determination can be found in Appendix A (Kwack et al., 2010; Kwack et al., 2009).

In a 14-day oral gavage investigation with a 250 mg/kg-bw/day *o*-phthalic acid exposure in male SD rats (Kwack et al., 2010), a 14% reduction in body weight was reported. Food consumption was unaffected and no significant effects were observed in mortality, relative weight of any organs, or hematological parameters. No clinical chemistry or urinalysis parameters were significantly altered following treatment with *o*-phthalic acid. Overall, a LOAEL of 250 mg/kg-bw/day for *o*-phthalic acid was reported based on the 14% reduction in body weight. The reduction in body weight was not accompanied by any other signs of toxicity (Kwack et al., 2010).

In a 28-day oral gavage investigation with 250 mg/kg-bw/day *o*-phthalic acid exposure in 4-week-old male SD rats (Kwack et al., 2009), male terminal body weight was reduced by approximately 22% starting on day 6 and remained reduced for the study duration. The *o*-phthalic acid treatment did not significantly affect the mean sperm count, mean percent motile sperm, or most other sperm motility parameters—with the exception of one velocity parameter. Curvilinear velocity was reduced (33%) from 261.3 µm/s in control sperm to 174.05 µm/s from animals treated with *o*-phthalic acid. No mortality or significant differences in food consumption were observed in the treatment group. Compared to controls, treatment with *o*-phthalic acid did not significantly affect any organ weight, hematological, or clinical chemistry parameters. Overall, this study supports a LOAEL of 250 mg/kg-bw/day *o*-phthalic acid for reduced (22%) body weight (Kwack et al., 2009).

Terrestrial Invertebrates

No studies were reasonably available to assess the hazard thresholds of *o*-phthalic acid to terrestrial invertebrates on apical endpoints (growth, mortality, reproduction). Using ECOSAR (U.S. EPA, 2022) resulted in an estimated LC50 of 253.3 mg/kg for earthworms exposed to *o*-phthalic acid over 14 days (Appendix C).

Terrestrial Plants

For terrestrial plant species, one medium- and one high-quality study were identified by EPA as relevant for quantitative assessment. A 75-day study (medium-quality) measured the effects of *o*-phthalic acid in solution by pouring an unknown volume of 0 (control), 0.01, 0.05, 0.25, 0.5, and 1.0 µmol/g soil on the Lanzhou lily (*Lilium davidii var. unicolor*) onto the plants as opposed to mixing the soil (Hua et al., 2019). Root length significantly decreased at 0.5 µmol/g soil exposure, while plant weight and bulb weight significantly decreased at 0.25 µmol/g soil. Chlorophyll A and B significantly decreased starting at 0.25 and 0.05 µmol/g soil, respectively. Compared to controls, enzymatic activity of superoxide dismutase was significantly decreased at 1.0 µmol/g soil, catalase at 0.5 and 1.0 µmol/g soil, while peroxidase was significantly increased at 0.25 and 0.5 µmol/g soil, but not a 1 µmol/g. The NOAEL and LOAEL were determined to be 0.05 and 0.25 µmol/g soil, respectively, based on both the fresh weight of the plant and fresh weight of the bulb (Hua et al., 2019).

A high-quality ranking study evaluated a 15-day hydroponically in a Hoagland nutrient solution exposure of *o*-phthalic acid in a nutrient solution to the crabapple (*Malus prunifolia*) (Bai et al., 2009). Seeds were watered once a week with a Hoagland nutrient solution. Plant weight (fresh and dry) and root and shoot length were measured following exposure to a single 1 mM (166.1 mg/L) concentration and a control, both containing solvent (0.1% ethanol). Although this is not a soil concentration, given the high solubility, low K_{OC}, and other physical chemical properties of *o*-phthalic acid, this is roughly equivalent to 166.1 mg/kg soil. After the 15-day treatment period, each endpoint was significantly decreased compared to controls. Fresh and dry weights were 3.09 and 1.61 g in control plants compared to 2.63 and 0.79 g in plants treated with 1 mM (166.1 mg/L) *o*-phthalic acid. Additionally, malondialdehyde, superoxide dismutase, catalase, and peroxidase activity significantly increased after 5-days, while hydrogen peroxide, superoxide radical, and ascorbate peroxidase increased after 10-days. Although apical and subapical endpoints were reported, the plants did not dye at the concentrations tested. Based on fresh and dry plant weight, root, and shoot length, the LOAEC is 166.1 mg/L (Bai et al., 2009).

Avian

No studies were reasonably available to assess the hazard of *o*-phthalic acid to birds.

Terrestrial Organism Hazard Conclusions: No studies on *o*-phthalic acid exposure to birds were available suggesting that no hazard has been observed in these groups under realistic exposure conditions. EPA reviewed eight studies of laboratory rats to derive a hazard threshold of 250 mg/kg-bw/day via oral gavage exposure. This represents the potential chronic exposure dose at which the effects of *o*-phthalic acid may affect a general mammal. There are uncertainties in both Kwack and colleague studies, however. Only a single dose level was evaluated, study authors evaluated only male rats (no females), and the sample size was small (5–6 rats per dose group). Rats were exposed via oral gavage, which is expected to lead to high serum concentrations and observed body weight effects may be related to the maximum (or peak) serum concentration of *o*-phthalic acid. Although no studies were available to assess hazard to terrestrial invertebrates, EPA used ECOSAR to model a hazard threshold. Two studies were available to assess hazard to terrestrial plants. However, both studies contained uncertainties with the exposure methodology, consistency, biological gradient, or precision of endpoints. Given the strength of the database, strength and precision of endpoints, and consistency of results, EPA has moderate confidence in the evidence that *o*-phthalic acid may pose hazard to terrestrial mammals. Due to the lack of data and reliance on ECOSAR, EPA has slight-to-moderate confidence phathalic anhdride may pose risk to terrestrial invertebrates. EPA has moderate confidence *o*-phthalic acid may pose risk to terrestrial plants based on two studies which showed effects after exposure (Table 3-1).

Table 3-1. Summary of Terrestrial Organism Environmental Hazard Studies Used for *o*-Phthalic Acid

Test Organism	Test Substance[a b]	Hazard Value (NOAEL / LOAEL)	Duration (days)	Effect	Citation (Study Quality)
Terrestrial vertebrates					
Sprague-Dawley rats	*o*-Phthalic acid[a]	LOAEL = 250 mg/kg-bw/day	28	Growth	(Kwack et al., 2009) (High)
Sprague-Dawley rats	*o*-Phthalic acid[a]	LOAEL = 250 mg/kg-bw/day	14	Growth	(Kwack et al., 2010) (High)
Terrestrial invertebrates					
Earthworm	Phthalic Anhydride[a b]	LC50 = 253.3 mg/kg	14	Mortality	ECOSAR
Terrestrial plants					
Crabapple (*Malus prunifolia*)	*o*-Phthalic acid[a]	LOAEL = 1mM (166.1 mg/L)	15	Growth	(Bai et al., 2009) (High)
Lanzhou lily (*Lilium davidii* var. *unicolor*)	*o*-Phthalic acid[a]	NOAEL/LOAEL = 0.05/0.25 µmol/g soil	75	Growth	(Hua et al., 2019) (Medium)

LC50 = Lethal concentration at which 50% of test organisms die; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

[a] Test substance as reported by the authors of each study

[b] 1:1 conversion from phthalic anhydride to *o*-phthalic acid is expected to be instantaneous

4 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 4-1 summarizes the concentrations of concern identified for *o*-phthalic acid. See Section 5 and Appendix B for more details about how EPA weighed the scientific evidence.

4.1 Aquatic Species COCs

In aquatic species, EPA uses probabilistic approaches (*e.g.,* species sensitivity distribution [SSD]) when sufficient data are available and deterministic approaches (*e.g.,* deriving a geometric mean of several comparable values, using the most sensitive value) when limited data are available. 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) as shown in Equation 4-1. Due to the lack of reasonably available studies review to consider a probabilistic approach, the most sensitive value from the available data was selected to assess hazard in aquatic taxa. EPA then applied an AF where appropriate and when data are limited to account for species-to-species differences and extrapolating from laboratory studies to the field (Zeeman, 1995; Zeeman and Gilford, 1993). With limited data, EPA uses AFs of 5 for acute exposures and 10 for chronic exposures as protective for an ecosystem on a national level (U.S. EPA, 2020c; ECB, 2003). Data were not reasonably available to determine a hazard threshold for sediment-dwelling organisms.

Equation 4-1.

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

EPA received and reviewed four studies categorized as high or medium quality rated studies for toxicity to aquatic organisms. Studies that received an overall quality determination of low, unacceptable, or did not meet systematic review criteria were likewise not considered quantitatively for determination of hazard values. The two acute and two chronic studies found in Table 2-1 were considered by EPA for COC calculations. Two studies were considered for aquatic plants and algae COC calculations. Given the rapid hydrolysis of phthalic anhydride to phthalic acid as well as the high water solubility and low K_{OC}, it is difficult to measure these chemicals in the aquatic environment. Although EPA has data for key taxa, it is limited by the few studies for each type. Each study included uncertainty, making reliability of endpoints questionable.

Acute Aquatic Threshold

Two acute aquatic toxicity studies with high quality determinations were submitted to EPA. The first study was with the rainbow trout under static conditions for 96-hour at nominal concentrations up to 100 mg/L (Author Withheld, 1996). Because the LC50 was determined to be greater than 100 mg/L, an unbounded value, EPA selected the second study hazard value as the hazard threshold. The second study endpoint was based on a 48-hour EC50 (immobility) of 103 mg/L with the water flea (Jonsson and Baun, 2003). When incorporating an AF of five to account for interspecies variability and lab-to-field uncertainty, the acute aquatic COC was determined to be 20.6 mg/L.

Chronic Aquatic Threshold

Two chronic hazard studies were received for exposure to *o*-phthalic acid in the zebrafish and rainbow trout. The LC50 (with 99% confidence interval) and LOAEC were reported at 560 (320–1,000) and 1,000 mg/L, respectively, with no effects on hatching delays or teratogenic effects reported. (Van Leeuwen et al., 1990). The second study was with the embryo/larval stage with the rainbow trout in a 60-day exposure to *o*-phthalic acid (Van Leeuwen et al., 1990). The endpoint reported mortality (embryotoxicity) and a change in the weight and length of the fish, resulting in a LOAEC of 32 mg/L (NOAEC was not reported). The chronic value (ChV) was determined to be 32 mg/L based on the LOAEC of the rainbow trout study. Thus, the COC (ChV ÷ by AF of 10 to account for interspecies variability and lab-to-field uncertainty) was 3.2 mg/L (Van Leeuwen et al., 1990).

Amphibian Threshold

No studies were reasonably available to assess the hazard of *o*-phthalic acid to amphibians. Therefore, a hazard threshold could not be established.

Aquatic Plants and Algae Threshold

Two aquatic plants and algae studies were reviewed. One conducted a limit test concentration and found no effects resulting in an EC50 greater than 100 mg/L (Bayer Industry Services, 2004). The aquatic plant and algae threshold was based on a second study with green algae using the *o*-phthalic acid 72-hour EC50 of 2,270 mg/L (Jonsson and Baun, 2003). This value was divided by an AF of 10 to account for interspecies variability and lab-to-field uncertainty to get a COC of 227 mg/L.

Acute and Chronic Benthic Threshold

No studies were reasonably available to assess the hazard of *o*-phthalic acid to benthic taxa on an acute or chronic exposure basis. Therefore, a hazard threshold could not be established.

Calculations

The *o*-phthalic acid hazard threshold for (1) aquatic organisms on an acute exposure basis is 20.6 mg/L; (2) for aquatic vertebrates on a chronic exposure basis it is 3.2 mg/L; and (3) for aquatic plants and algae it is 227 mg/L.

4.1 Terrestrial Species Hazard Values

For terrestrial species, EPA estimates hazard by calculating a toxicity reference value (TRV) or by assigning the hazard value as the hazard threshold in the case of mammals, birds, and terrestrial plants when data are available. Because limited data for terrestrial organisms were identified, the most sensitive hazard value was selected for terrestrial mammals and plants. AFs are generally not applied by EPA when deriving hazard thresholds for terrestrial organisms because they are typically not continuously exposed to chemicals like aquatic organisms. There is a less consistent relationship between laboratory and field-based hazard effects on mammals and plants and, given that variability, applying AFs to terrestrial organisms could lead to risk assessments that are overly cautious when data are limited (Chapman, 1998). *o*-Phthalic acid in soils is attributable to deposition from air where it is expected to rapidly migrate to groundwater. In soils it is not expected to show strong affinity and sorption potential for organic carbon, will undergo significant indirect photolysis, and has an expected biodegradation half-life on the order of days to weeks (estimated half-life of 6 days). It is not expected to be present in the terrestrial environment for an extended duration. Because of these factors, EPA did not apply terrestrial AFs as the hazard values without the AF are expected to be protective for *o*-phthalic acid. ECOSAR was used to estimate a hazard threshold to terrestrial invertebrates. Data were not available to assess hazard to birds. Phthalic anhydride is expected to rapidly hydrolyze to *o*-phthalic acid, and *o*-phthalic acid is expected to have negligible sorption to soil, sediment, and rapidly migrate to ground and surface water. *o*-Phthalic acid is expected to have a biodegradation half-life of days to weeks in soil, and weeks in sediment. It is uncertain whether terrestrial organisms will be exposed to phthalic anhydride and *o*-phthalic acid for a long enough duration to cause hazard.

Terrestrial Mammal Threshold

For terrestrial vertebrate species exposed to *o*-phthalic acid, EPA used the most sensitive values from two studies with male SD rats with the same hazard value (Kwack et al., 2010; Kwack et al., 2009). Both studies support a LOAEL of 250 mg/kg-bw/day *o*-phthalic acid for reduced (22%) body weight (Kwack et al., 2009).

The LOAEL value of 250 mg/kg-bw/day was used as the hazard threshold for terrestrial mammals.

Avian Threshold

No studies were available to assess the hazard of *o*-phthalic acid to birds. Therefore, a hazard threshold could not be established.

Terrestrial Invertebrate Threshold

No studies were reasonably available to assess the hazard of *o*-phthalic acid to terrestrial invertebrates. The potential extension of information from ECOSAR to create hazard thresholds for terrestrial invertebrates was used as an alternative approach in the absence of empirical data. The LC50 hazard value estimated by ECOSAR as 253.3 mg/kg for earthworms Appendix C). There is uncertainty using the ECOSAR to generate a hazard value for terrestrial invertebrates because the data set used by the model uses log Kow for predicting hazard and may not be appropriate for chemicals with certain physical-chemical properties. This dataset only had eight chemicals from three references when generating a regression curve.

The ECOSAR value of 253.3 mg/kg is used as the hazard threshold for terrestrial invertebrates.

Terrestrial Plant Threshold

Two studies were identified to assess hazard to terrestrial plants. The first observed the effects of *o*-phthalic acid on the Lanzhou lily over 75 days at 0 (control), 0.01, 0.05, 0.25, 0.5, and 1.0 µmol/g soil test concentrations (Hua et al., 2019). Although the study received a medium overall quality ranking and the established NOAEL/LOAEL was 0.05/0.25 µmol/g soil, there is uncertainty regarding the methodology and actual exposure of *o*-phthalic acid to the Lanzhou lily. According to the study report, the authors poured an unknown volume of different concentrations of *o*-phthalic acid solution onto the plants as opposed to mixing the soil with the test chemical. This introduces uncertainty regarding the actual exposure of *o*-phthalic acid onto the plants since it may have been unevenly poured and distributed, and whether any of the test chemical partitioned to the soil or material in the container reducing bioavailability. Additionally, the units are in µmol/g soil with an unknown amount of total soil used to normalize the hazard value (Hua et al., 2019).

The terrestrial plant hazard threshold was derived from the 15-day exposure of *o*-phthalic acid to the crabapple (Bai et al., 2009). Based on fresh and dry plant weight, root, and shoot length, the LOAEL is less than 166.1 mg/L (Bai et al., 2009). The LOAEL value of 166.1 mg/L was used as the *o*-phthalic acid hazard threshold. Although this is a hydroponic study, *o*-phthalic acid is not expected to bind to soil or undergo degradation, which will result in an overestimation of exposure. However, this study can be used for a quantitative assessment by converting the *o*-phthalic acid exposure value in soil from mg/kg to mg/L and assuming a one-to-one approximation of soil concentration to interstitial (pore) water concentrations for a screening-level assessment.

Summary of Terrestrial Values

The *o*-phthalic acid hazard threshold for (1) mammals is 250 mg/kg-bw/d; (2) for terrestrial plants is 166.1 mg/L; and (3) for terrestrial invertebrates is 253.3 mg/kg (Table 4-1).

Table 4-1. Environmental Hazard Thresholds for Environmental Toxicity

Environmental Assessment	Assessment Medium	Hazard Threshold
Acute Aquatic Assessment	Surface water	20.6 mg/L
Chronic Aquatic Vertebrate Assessment	Surface water	3.2 mg/L
Chronic Sediment Invertebrate Assessment	Sediment porewater	ND
Algal Assessment	Surface water	227 mg/L
Mammal: Hazard Value	Dietary	250 mg/kg-bw/d
Terrestrial Invertebrate	Soil	253.3 mg/kg
Avian: Hazard Value	Dietary	ND
Terrestrial Plants: Hazard Value	Soil	166.1 mg/L
ND = not determined		

5 WEIGHT OF SCIENTIFIC EVIDENCE FOR ENVIRONMENTAL HAZARD

EPA uses several considerations when weighing the scientific evidence to determine confidence in environmental hazard data. These considerations include the quality of the database, consistency, strength and precision, biological gradient/dose response, and relevance. This approach agrees with the Draft Systematic Review Protocol (U.S. EPA, 2021) regarding the evaluation of these considerations for the determination of each environmental hazard threshold. Criteria for assessing confidence is described in Appendix B.1, Evidence Integration.

Quality of the Database; Consistency; Strength (Effect Magnitude), and Precision

All studies that factored into the confidence rating received an overall quality determination of high or medium. Based on systematic review data quality evaluation of studies, three studies with an overall quality determination of high and one study with an overall quality determination of medium were considered for the aquatic environmental hazard assessment. The two studies considered for the terrestrial mammal hazard threshold determination received an overall study quality determination of high, and one study with a high overall quality determination and one with a medium overall quality determination, and were considered for the terrestrial plants hazard threshold determination.

For aquatic organisms on an acute exposure basis, only one invertebrate study was available (Jonsson and Baun, 2003). No aquatic vertebrate, amphibians, or acceptable sediment-dwelling organism studies were available. On a chronic exposure basis for aquatic invertebrates, two studies were available. There is uncertainty of the effects of *o*-phthalic acid on aquatic vertebrates, amphibians, and sediment-dwelling organisms on an acute exposure basis due to the lack of data.

Although two acute toxicity studies were reviewed for aquatic taxa, they both received an overall study quality ranking of high (Jonsson and Baun, 2003). The LC50 was determined to be greater than 100 mg/L due to the absence of any measured effects on rainbow trout (Author Withheld, 1996). The other study evaluated water flea exposure to *o*-phthalic acid and the resulting EC50 was found to be 103 mg/L. The estimated ECOSAR value for the freshwater fish and water flea are 105.5 and 60.3 mg/L, respectively, which are within an order of magnitude of the empirical value and support the endpoint value reached in the study (Appendix C). The 96-hour acute mortality study with the rainbow trout did not find any effects from *o*-phthalic acid exposure resulting in a LOAEC/NOAEC of exceeding 100 mg/L, leading to uncertainty regarding the actual hazard value.

A chronic study evaluated *o*-phthalic acid exposure in both the zebrafish (medium-quality ranking) and rainbow trout (medium-quality ranking) for 7 and 60 days, respectively (Van Leeuwen et al., 1990). In the 7-day zebrafish study, the LC50 was determined to be 560 mg/L (99% confidence intervals from 320 to 1,000) and 1,000 mg/L LOAEC and in the 60-day rainbow trout study, the LC50 was 44.2 mg/L and the LOAEC was reported to be 32 mg/L. Test concentrations were not reported and it was not determined if test concentrations were analytically verified in either study. Because there is uncertainty regarding the LC50 being lower than the LOAEC in addition to the LC50 extrapolation, the subacute zebrafish endpoint will not be considered for quantitative assessment. Although there are few studies on aquatic taxa, the acute and chronic hazard values range about an order of magnitude apart. The estimated ECOSAR LC50 and chronic values (chronic value is a geometric mean of the modeled LOAEC and NOAEC) for the fish on an acute and chronic exposure basis were 105.5 and 10.4 mg/L, respectively (see Appendix C). Although the zebrafish endpoints have uncertainty regarding the extrapolated LC50 value and LOCEC, empirical acute and chronic values are within an order of magnitude of the ECOSAR estimated values for aquatic vertebrates. Due to the uncertainty, zebrafish endpoints will not be considered for quantitative assessment.

Two freshwater green algae studies were received, both receiving an overall study quality ranking of high (Bayer Industry Services, 2004; Jonsson and Baun, 2003). One study showed no effects to green algae, while the other showed effects from exposure to *o*-phthalic acid over 72-hour in which an EC50 value was estimated. The estimated ECOSAR chronic value (geometric mean of the modeled LOAEC and NOAEC) for green algae is 46.1 for 96-hourr and 12.6 mg/L for an unspecified chronic duration, which is more than an order of magnitude from the empirical value, but the modeled duration was 96-hour and greater than the 72-hour empirical study duration. Algal growth (*i.e.* biomass, frond yield, and weight) can undergo multiple generations in a shorter period of time compared to other aquatic taxa. A difference of 3 compared to 4 days introduces uncertainty in growth time.

Although EPA has data for key taxa (*i.e.,* fish, aquatic invertebrates, algae), it is limited by the few studies for each group. Each study had uncertainty associated with it making reliability of endpoints questionable. Confidence in the quality of the database and strength and precision of the database for aquatic organisms on an acute exposure basis is considered slight, while confidence in consistency is moderate, confidence in the quality of the database, consistency, and strength and precision of the database for aquatic organisms on a chronic exposure basis is considered slight-to-moderate. Confidence in the quality of the database as well as in the strength and precision of the database for aquatic plants and algae is considered slight; confidence in consistency is moderate. Confidence could not be assigned to sediment-dwelling organisms (Table Apx B-2).

For terrestrial organisms, two mammalian and two terrestrial plant studies were considered for quantitative assessment, as well as terrestrial invertebrates using the ECOSAR Model. No avian studies were received which makes the effects of *o*-phthalic acid on this taxa unknown.

Two terrestrial plant studies were identified, and both exhibited effects from *o*-phthalic acid exposure. The first study received an overall quality determination of medium for a 15-day exposure to *o*-phthalic acid (Bai et al., 2009). In a hydroponic study in a Hoagland nutrient solution, significant effects on the crabapple occurred for the only concentration tested, 166.1 mg/L, for multiple endpoints including plant length and weight, chlorophyll content, and enzymatic activity. There is uncertainty in this study; however, since only one concentration was used and a NOAEL was not established. A hydroponic study is not reflective of a soil environment which is the typical exposure pathway for terrestrial plant exposure to phthalic anhydride or *o*-phthalic acid. There are assumptions in the conversion from a hydroponic study to a soil study (*i.e.,* no partitioning of the chemical to soil, more complete root uptake, different degradation). A second terrestrial plant study that received an overall high-quality study ranking for a 75-day *o*-phthalic acid exposure (Hua et al., 2019). In that study, root and shoot length of the Lanzhou lily were significantly decreased compared to controls as well as multiple antioxidant enzyme systems. However, the study authors did not mix the *o*-phthalic acid solution into the soil but poured it onto the plants. This introduces uncertainty regarding the actual exposure of *o*-phthalic acid to the lily because it may have been unevenly distributed, and whether the test chemical partition or sorbed to the soil, other material in the container, or the container itself reducing bioavailability. Additionally, the units are in μmol/g soil with an unknown amount of soil used to normalize the *o*-phthalic acid solution.

Two studies were considered to evaluate hazard to terrestrial mammals from human health. For terrestrial mammals, two studies with high-quality rankings with the most sensitive LOAEL values were used to represent hazard to terrestrial mammals (Kwack et al., 2010; Kwack et al., 2009). Both studies examined *o*-phthalic acid exposure in male SD rats with a single 250 mg/kg-bw/d exposure. Although the study durations were different, 14 and 28 days, significant decreases in body weight were observed. No mortality or significant differences in food consumption were observed in the treatment group, and the treatment did not significantly affect the relative weight of any organs. Compared to controls, treatment with *o*-phthalic acid did not significantly affect any hematological or clinical chemistry parameters. In both Kwack and colleague studies, only a single dose level was evaluated, study authors evaluated male (but not female) rats, and the sample size was small (5–6 rats per dose group). Rats were exposed via oral gavage, which is expected to lead to high serum concentrations and observed body weight effects may be related to the maximum (or peak) serum concentration of *o*-phthalic acid. Further information can be found in the *Draft Human Health Assessment for Phthalic Anhydride* (U.S. EPA, 2026b). Additionally, although these studies showed effects, four other studies with overall quality determinations of medium with male Wistar rats showed no effects at concentrations ranging 850 to 5,558 mg/kg-bw/d (Murakami et al., 1986; Oishi and Hiraga, 1980; NCI, 1979; Lake et al., 1975). The studies did not show effects decrease confidence regarding the hazard potential of *o*-phthalic acid. Two studies of high- and medium-quality, respectively, reported NOAELs of 1,021 and 1,763 mg/kg-bw/day (Rahmani et al., 2015; Ema et al., 1997). One study with three endpoints measured adverse effects resulting in NOAEL/LOAELs from 278/556 to 226/1,853 mg/kg-bw/d (NCI, 1979). Because two studies (Kwack et al., 2010; Kwack et al., 2009) demonstrated lower thresholds of toxicity, they were selected for this screening-level assessment. These are further discussed in the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026d).

No studies were reasonably available to assess the hazard of *o*-phthalic acid to terrestrial invertebrates. ECOSAR was used as an alternative approach to model hazard thresholds to this taxonomic group. However, there is uncertainty in the hazard value generated (253.3 mg/kg) because it is not based on empirical data and there is no other information that it can be compared to. There is also uncertainty using ECOSAR to generate a hazard value for terrestrial invertebrates because the training set used by the model uses log K_{OW} for predicting hazard and may not be appropriate for chemicals with certain physical chemical properties. This dataset only had eight chemicals from three references when generating a regression curve. However, *o*-phthalic acid is not expected to show strong affinity and sorption potential for organic carbon in soil, undergo significant indirect photolysis, and biodegradation half-life in aerobic environments on the order of days to weeks, and mainly partition to surface and groundwater when released to the environment.

Confidence in the quality, consistency, strength and precision of the database for terrestrial mammals were all considered moderate. Confidence in the quality of the database, consistency, and strength and precision for terrestrial plants were considered moderate, moderate, and slight, respectively. Confidence in the quality of the database, consistency, and strength and precision for terrestrial invertebrates were all considered slight-to-moderate. Confidence could not be assigned for birds (Table Apx B-2).

Biological Gradient/Dose-Response

In the acute toxicity test with the aquatic invertebrate, the study authors reported that range finding tests were preliminarily used prior to the definitive study to establish EC50 values (Jonsson and Baun, 2003). Each test consisted of five to eight concentrations (not identified in the study) of test solution and a control group of eight replicates. The 48-hour immobilization tests with *D. magna* tests were performed in accordance with ISO standard *Determination of the inhibition of the mobility of Daphnia magna Straus (Cladocera, Crustacea)*. However, it was also reported that all EC50 values were estimated. In the chronic studies with the zebrafish and rainbow trout, though the study authors reported using five to seven toxicant concentrations plus a control (Van Leeuwen et al., 1990), these concentrations nor any analytical verification were reported. Although the test concentrations were not identified, the range between the concentrations was 3.2. Confidence in the biological gradient/dose-response is considered moderate for acute and chronic fish and aquatic invertebrate studies.

In the green algae study, 11 to 16 test concentrations were used, not including controls (Jonsson and Baun, 2003). The concentrations were made using freshwater algal medium. Each test consisted of 11 to 16 test concentrations (not identified in the study) with 6 controls per test. The methodology followed ISO standard *Fresh water algal growth inhibition test with Scenedesmus subspicatus and Selenastrum capricornutum.* Growth rate was based on biomass following exposure to 11 to 16 concentrations (not identified in the study) diluted with freshwater algal test medium. No additional aquatic plants and algae studies received. Because of this, confidence in the biological gradient/dose-response is considered moderate for aquatic plants and algae.

The terrestrial plant study with the crabapple used a single 166.1 mg/L concentration of *o*-phthalic acid (Bai et al., 2009). While effects were observed at this concentration, a dose-response relationship was not established leading to uncertainty regarding the actual hazard threshold. The terrestrial plant study with the Lanzhou lily used five micromolar test concentrations and a control, and a dose-response relationship was established (Hua et al., 2019). The dose-response pattern was observed in each of the apical and mechanistic parameters, and a NOAEL/LOAEL was established. Confidence in the biological gradient/dose-response is considered slight for terrestrial plants.

Two SD rat studies were considered to evaluate hazard to terrestrial mammals from the human health animal model data set (Kwack et al., 2010; Kwack et al., 2009). Although effects were observed at 250 mg/kg-bw/d in both studies (*i.e.,* a decrease in body weight), it was administered via oral gavage and was the only concentration used. This introduces uncertainty regarding the threshold of toxicity of *o*-phthalic acid on SD rats. Additionally, only male rates were used which is fewer than recommended by OECD guidelines. Although EPA considered this appropriate as a first tier for a terrestrial vertebrate screen, overall confidence in the biological gradient/dose-response is considered slight for terrestrial mammals. Additionally, four studies were unable to demonstrate effects from *o*-phthalic acid (Murakami et al., 1986; Oishi and Hiraga, 1980; NCI, 1979; Lake et al., 1975).

Biological, Physical-Chemical, Environmental Relevance

The available data sources provided robust supporting evidence that the phthalic anhydride to *o*-phthalic acid hydrolysis half-life is estimated to be between 30 to 90 seconds. *o*-Phthalic acid is a water soluble solid that may be present in the atmosphere as suspended particles/dust, likely to partition to surface and groundwater, not likely to volatilize from water and dry surfaces, not likely to bioaccumulate, and likely to rapidly biodegrade under normal environmental conditions as described in the *Draft Physical Chemistry and Fate and Transport Assessment for Phthalic Anhydride* (U.S. EPA, 2026c).

In the aquatic environment, the main exposure pathway would be uptake through the water. The 48-hour mortality endpoint evaluated in an acute aquatic invertebrate hazard study is a relevant endpoint for ecological hazard (Jonsson and Baun, 2003). The subchronic and chronic endpoints measured at the embryo/larval stage of development evaluated mortality in the zebrafish and rainbow trout reported LC50s of 506 and 44.2 mg/L, respectively, and LOAECs of 1,000 and 32.0 mg/L, respectively—based on reported embryotoxicity (Van Leeuwen et al., 1990). Although the 95% confidence intervals encompass the LC50 (320–1,000), the zebrafish LC50 being less than the LOAEC introduces uncertainty. These values are relevant endpoints for biological and ecological hazard. The aquatic green algae 72-hour inhibition of growth on the basis of biomass endpoint is also biologically relevant (Jonsson and Baun, 2003). There is uncertainty regarding the test concentrations and analytical verification for the sub-acute zebrafish and chronic rainbow trout study. However, the endpoint values were well below the *o*-phathalic acid solubility limit of 6,994 mg/L reported in the *Draft Physical*

Chemistry and Fate and Transport Assessment for Phthalic Anhydride (U.S. EPA, 2026c), suggesting that the chemical is in solution. Notably, the paucity of studies received increases uncertainty. Confidence in biological, physical/chemical, and environmental relevance is considered robust.

In the terrestrial environment, the main exposure pathway would be soil exposure or ingestion for mammals. There was a decrease in body weight at exposure to 250 mg/kg-bw/d for rats exposed to *o*-phthalic acid. For terrestrial plants, exposure via atmospheric deposition is also included. One terrestrial plant study demonstrated effects in multiple endpoints at multiple test concentrations (Hua et al., 2019) while the other study showed effects at the only concentration tested (Bai et al., 2009). The chemical effects observed included decreases in plant and bulb weight, root and shoot length, and chlorophyll content which are biologically and environmentally relevant. However, while apical and subapical endpoints were reported by the authors, the plants were not dying, suggesting that the LC50 is greater than the single concentration used in the study. Confidence in biological, physical/chemical, and environmental relevance is considered robust for all terrestrial plants.

Overall Confidence

EPA has slight-to-moderate overall confidence due to the paucity of aquatic studies received for individual taxa but, taken together, higher confidence that *o*-phthalic acid is not hazardous to aquatic organisms. Although studies were scientifically sound and of medium- or high-quality, there were relatively few studies identified for each taxa to make comparisons. The quality of the database and strength and precision were all slight for aquatic taxa. EPA has even less certainty with sediment-dwelling organisms because no studies were received.

Within the terrestrial environment, EPA has moderate overall confidence in the evidence for terrestrial plants. EPA received two studies, both of which showed effects (Hua et al., 2019; Bai et al., 2009), and four studies that did not (Murakami et al., 1986; Oishi and Hiraga, 1980; NCI, 1979; Lake et al., 1975). Three studies reported effects greater than 250 mg/kg-bw/day (Rahmani et al., 2015; Ema et al., 1997; NCI, 1979). Although there is uncertainty regarding actual exposure concentrations in the Lanzhou lily study, a clear dose-response relationship was observed for multiple endpoints (Hua et al., 2019). However, only two studies were received by EPA decreasing the confidence in the quality of the database and strength and precision for this taxonomic group. EPA has moderate confidence in the evidence for terrestrial mammals (Kwack et al., 2010; Kwack et al., 2009). The quality of the database, strength and precision, consistency, and relevance were all rated as moderate, and due to only one dose establishing a LOAEL, the dose-response gradient was rated as slight. Because the terrestrial invertebrate hazard threshold was modeled due to the lack of data, and because the rapid movement of *o*-phthalic acid out of the terrestrial environment, the overall confidence for this taxonomic group is slight-to-moderate. There is no reasonably available data to determine confidence to birds.

Due to the limited amount of data, the weight of scientific evidence leads EPA to have slight-to-moderate overall confidence for aquatic taxa on an acute and chronic exposure basis, including fish and invertebrates, and slight-to-moderate overall confidence for aquatic plants and algae. EPA anticipates *o*-phthalic acid to predominantly be found in water and groundwater with a half-life of days (aerobic biodegradation half-life of less than three), and to have limited partitioning to suspended organic matter and aquatic sediments. Considering the short-term exposure, aquatic organisms may not be largely exposed. Therefore, EPA, considering all the available information on *o*-phthalic acid, EPA has high confidence that *o*-phthalic acid is not hazardous to aquatic organisms. The Agency has moderate overall hazard confidence in the evidence for terrestrial plants, and robust overall hazard confidence in the evidence for terrestrial mammals. *o*-Phthalic acid in soils is attributable to deposition from air and potential land application of biosolids where it is expected to rapidly migrate to groundwater. In soils, it is expected to have a half-life on the order of days to weeks (based on the estimated half-life of 6 days). For aquatic and terrestrial taxa, the overall relevance was robust and moderate, as *o*-phthalic acid is expected to be present in aquatic systems over the terrestrial environment. A more detailed explanation of the weight of scientific evidence, uncertainties, and overall confidence is presented in Appendix B.

6 CONCLUSIONS FOR ENVIRONMENTAL HAZARD: STRENGTHS, LIMITATIONS, ASSUMPTIONS, AND KEY SOURCES OF UNCERTAINTY

EPA determined that *o*-phthalic acid may pose hazard to aquatic and terrestrial organisms on an acute or chronic exposure basis. The Agency acknowledges the aquatic hazard conclusions are limited by the low number of studies received to assess *o*-phthalic acid. However, the range of acute and chronic aquatic hazard values demonstrate that *o*-phthalic acid poses low hazard, and the physical and chemical properties of the chemical suggest it will not remain in the environment for long periods of time. Other than terrestrial mammals, EPA did not have considerable data on aquatic and terrestrial taxa, which leads to uncertainty regarding the effects of the chemical on aquatic and terrestrial wildlife. Although no chronic aquatic invertebrate, sediment-dwelling organisms, amphibian, or avian studies were reasonably available, the limited partitioning and rapid aquatic half-life, and along with a rapid half-life in soil and migration to water, suggests organisms and unlikely to be exposed to *o*-phthalic acid long enough to cause harm. A further listing of studies can be found in Appendix A.

The hazard to acute aquatic organisms is based on high-quality water flea (aquatic invertebrate) and rainbow trout studies, where the LC50 values were determined to be 103 and greater than 100 mg/L, respectively (Jonsson and Baun, 2003; Author Withheld, 1996). In the acute toxicity study with the water flea, at the start of the experiment, recovery ranged from 83.5 to 106.7% and at the end of the study it ranged from 41.7 to 86.0% . The study authors stated that since analytical measurements indicated nominal concentrations were achieved, as well as the high solubility and low volatility of the chemical, they were reported as nominal concentrations. The COC was based on the water flea study because a definitive value was preferred over an unbound value. Given the few studies received there are uncertainties in the consistency of the database and strength and precision of the data. The Web-Based Interspecies Correlation Estimation (Web-ICE) tool was considered to reduce uncertainty for aquatic organisms on an acute exposure basis (*i.e.* fish, invertebrates, and amphibians). However, Web-ICE was not used because the model does not allow unbounded LC50 values or different exposure durations among included studies as model input parameters. The overall hazard confidence was slight-to-moderate for aquatic organisms on an acute exposure basis.

On a chronic exposure basis, one study, which included both zebrafish (7 days) and rainbow trout (60 days), was used to establish a hazard threshold (Van Leeuwen et al., 1990). TheLC50 values were roughly an order of magnitude different, 560 and 44.2 mg/L, for the zebrafish and rainbow trout, respectively. The zebrafish LC50 being less than the LOAEC does introduce uncertainty but falls within the confidence intervals. In both studies, the authors stated a concentration gradient was used, but those concentrations were not included in the study report, nor was it reported if the concentrations were analytically verified. Because there is uncertainty regarding the LC50 being lower than the LOAEC in addition to the LC50 extrapolation, the zebrafish endpoint will not be considered for quantitative assessment. Because these were the only two studies received, the quality of the database, strength and precision of the results, and biological gradient/dose response of those studies were all ranked as slight. The overall hazard confidence was ranked as slight-to-moderate for aquatic organisms on a chronic exposure basis.

Two aquatic plants and algae studies were received with the hazard value based on a decrease in biomass (Bayer Industry Services, 2004; Jonsson and Baun, 2003). Although both studies received a high-quality ranking, there is uncertainty regarding the strength and precision of results as it pertains to effects to this taxonomic group overall.

Although there is slight-to-moderate confidence based on the weight of scientific evidence evaluation criteria for aquatic organisms, EPA has higher confidence that *o*-phthalic acid is not highly toxic to aquatic taxa overall. The acute aquatic hazard values exceeded 100 mg/L and the 60-day LOAEC for rainbow trout was 32 mg/L. The aquatic plants and algae hazard value was 2,270 mg/L after 72 hours.

EPA reviewed eight studies and has moderate confidence *o*-phthalic acid poses hazard to terrestrial mammals. The conclusion that *o*-phthalic acid poses hazard to terrestrial mammals is based on rat and mice studies including two oral gavage SD rat studies that resulted in a significant decrease in body weight (Kwack et al., 2010; Kwack et al., 2009). Three other studies showed effects within an order of magnitude or slightly more than the selected hazard threshold, supporting the quality of the database and consistency of effects at similar concentrations. One study reported a NOAEL/LOAEL of 278/556 mg/kg-bw-d (based on a decrease in male body weight), which is similar to the 250 mg/kg-bw-d LOAEL selected as the most sensitive hazard threshold. Two studies reported in NCI (1979) found no effects, though those studies were deemed medium-quality. Two other studies also reported no effects (Oishi and Hiraga, 1980; Lake et al., 1975). Additionally, utilizing human health rodent models as a surrogate for terrestrial models introduces uncertainty into the terrestrial hazard characterization because these species may not be fully representative of effects in a more diverse array of wild animal populations. The terrestrial hazard data are limited by uncertainties surrounding the lack of available studies for wild mammal populations. For purposes of a screening-level assessment, 250 mg/kg-bw/d was selected as the most sensitive value. This is further discussed in the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026d).

The conclusion that *o*-phthalic acid poses hazard to terrestrial plants is supported by two terrestrial plant studies that identified effects (Hua et al., 2019; Bai et al., 2009). The study with the Lanzhou lily demonstrated a clear dose-response relationship for root length establishing a NOAEL/LOAEL of 0.25/0.5 μmol/g soil and plant and bulb weight NOAEL/LOAEL of 0.05/0.25 μmol/g soil (Hua et al., 2019). However, the study authors poured an unknown volume of the different *o*-phthalic acid concentrations onto the plants as opposed to mixing the soil with the test chemical. This introduces uncertainty regarding the actual exposure of *o*-phthalic acid onto the plants since it may have been unevenly poured and distributed, and whether any of the test chemical absorbed to the soil or material in the container reducing bioavailability. Additionally, the units are in μmol/g soil with an unknown amount of soil used to normalize the endpoint. However, though the study design standardized *o*-phthalic acid concentrations to grams of soil, it was clear effects were occurring after exposure to the *o*-phthalic acid solution (Hua et al., 2019). It may have been possible to still use these endpoints quantitatively with assumptions (*i.e.* as porewater) if a second study with a more certain measurement was available.

Overall, EPA has robust confidence in the evidence that *o*-phthalic acid has low hazard potential to aquatic species. Although uncertainties in the studies exist and there is slight confidence in the quality of the database and strength and precision of endpoints, and moderate confidence in consistency, taken together, effects on aquatic species were observed at concentrations that are relatively high in organisms across taxonomic groups, habitats, exposure types, and exposure durations. Only one study is available in the database to assess hazard to aquatic organisms on a chronic exposure basis, and no studies are available to assess hazard to sediment-dwelling organisms or amphibians. Studies of *o*-phthalic acid exposure via water to fish on an acute exposure basis and aquatic plants and algae reported no effects up to the highest concentration tested. Aquatic hazard data can be used for a screening-level assessment; this is further discussed in the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026d).

The second study with the crabapple showed effects on dry weight and root and shoot length at 166.1 mg/L and was used to determine the COC, but it was the only test concentration used. However, because it was the only test concentration used resulting in an unbound LOAEL, there is uncertainty regarding the threshold of toxicity and actual hazard value to terrestrial plants. There is also uncertainty converting from a mg/L hazard value to mg/kg. In the terrestrial environment, *o*-phthalic acid is expected to be released via fugitive emissions resulting in atmospheric depiction. *o*-Phthalic acid will be taken up by the roots during rainfall events; thus, exposure would be similar to a porewater exposure. In a conservative scenario assuming no minimal degradation or partitioning to soil, there is a one-to-one approximation of interstitial water. *o*-Phthalic acid via fugitive release can then be converted from mg/kg to mg/L with a soil density conversion leading a quantitative endpoint (Bai et al., 2009).

No studies were available to assess the hazard of *o*-phthalic acid to terrestrial invertebrates. ECOSAR was used as an alternative approach to model hazard thresholds to these taxa. This introduces uncertainty because there are no other data to compare these data to and model parameters may be different than occur in the natural environment.

Overall, EPA has (1) moderate confidence in the evidence that *o*-phthalic acid may pose hazard to terrestrial mammals, (2) slight-to-moderate confident confidence that it poses hazard to soil invertebrates, and (3) moderate confidence that it poses hazard to terrestrial plants. No studies on *o*-phthalic acid exposure to birds were available suggesting that no hazard has been observed in these groups under realistic exposure conditions. EPA reviewed eight studies of laboratory rats to derive a hazard threshold of 250 mg/kg-bw/day via oral gavage exposure. This represents the potential chronic exposure dose at which the effects of *o*-phthalic acid may affect a general mammal. Although no studies were available to assess hazard to terrestrial invertebrates, EPA used ECOSAR to model a hazard threshold. Two studies were available to assess hazard to terrestrial plants. However, both studies contained uncertainties with the exposure methodology, consistency, biological gradient, or precision of endpoints. Nevertheless, the terrestrial hazard data can be used for a screening-level assessment.

The aquatic COCs and terrestrial hazard values identified in this draft TSD are used in the *Draft Environmental Hazard Assessment for Phthalic Anhydride* (U.S. EPA, 2026a) to characterize environmental risk.

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APPENDICES

Appendix A ENVIRONMENTAL HAZARD TABLE OF STUDIES

Table_Apx A-1. List of Aquatic Studies Not Considered for Quantitative Assessment

Study Type	Test Organism (Species)	Test Substance	Hazard Value (NOAEC/ LOAEC or LC50)	Duration	Endpoint(s)	Citation (Study Quality)
Benthic invertebrates						
Chronic	Midge (*Chironomus plumosus*)	*o*-Phthalic acid	LC50/EC50 > 27 mg/L	48 hours	Mortality	(Streufort, 1978) (Uninformative)
Aquatic plants and algae						
Karenia brevis		*o*-Phthalic acid	NR (1–1,000 ppm)	96 hours	Growth	(Wilson et al., 1978) (Low)
NOAEC = no-observed-adverse-effect-concentration; LOAEC = lowest-observed-adverse-effectconcentration; LC50 = lethal concentration at which 50% of test organisms die; NR = not reported						

Table_Apx A-2. List of Terrestrial Studies Not Considered for Quantitative Assessment

Test Organism	Hazard Value (NOAEL/LOAEL or EC50)	Duration	Endpoint	Citation (Study Quality)
Terrestrial vertebrates				
Male wistar rats	NOAEL = 850 mg/kg-bw/d	7 days	None (no effect study) [a]	(Lake et al., 1975) (Medium)
Male wistar rats	NOAEL = 2,000 mg/kg-bw/d	7 days	None (no effect study)	(Oishi and Hiraga, 1980) (ND)
Male wistar rats	NOAEL = 5,000 mg/kg-bw/d	34–36 days	None (no effect study)	(Murakami et al., 1986) (Medium)
Pregnant wistar rats (females)	NOAEL = 1,021 mg/kg-bw/d	7–16 days	Decrease in maternal weight gain and food consumption	(Ema et al., 1997) (High)
F1 Wistar rats (male and female)	LOAEL = 1,763 mg/kg-bw/d	7–16 days	Decrease in F1 offspring body weight on PND 90, cardiovascular effects	(Rahmani et al., 2015) (Medium)
F344 rats (male and female)	NOAEL/LOAEL = 926/1,853 mg/kg-bw/d	7 weeks	Decrease (24–26%) in body weight (both sexes)	(Murakami et al., 1986) (Medium)
B6C3F1 mice (male and female)	NOAEL = 5,558 mg/kg-bw/d	7 weeks	None (no effect study)	(Murakami et al., 1986) (Medium)
F344 Rats (male and female)	NOAEL/LOAEL = 278/556 mg/kg-bw/d	2 years	Decreased male body weight	(Murakami et al., 1986) (Medium)
B6C3F1 mice (male and female)	LOAEL = 1,803 mg/kg-bw/d (males); 1,336 mg/kg-bw-d (females)	2 years	Decrease terminal body weight (12–27%), increased incidence of histopathology in lung	(NCI, 1979) (Medium)

Test Organism	Hazard Value (NOAEL/LOAEL or EC50)	Duration	Endpoint	Citation (Study Quality)
			and kidney (both sexes) and adrenal cortex and thalamus (males only)	
Terrestrial avian				
Chicken (*Gallus gallus*)	EC50 = 0.38 µmol	2, 5, and 14 days	Mortality/ development	(Korhonen et al., 1983) (Uninformative)
Terrestrial plants				
Tobacco (NC80 variety)	0.1 g/L (NR)	7 days	Growth	(Huiyong et al., 2014) (Uninformative)
Fungus (*Sclerotinia sclerotiorum*)	NOAEL/LOAEL <100/100	13 days	Population	(Loffredo and Traversa, 2014) (Medium)

NOAEL = no-observed-adverse-effect-level; LOAEL = lowest-observed-adverse-effect-level; EC50 = effect concentration at which 50% of test organisms exhibit an effect; ND = not determined; NR = not reported

[a] No-effect studies are discussed above in Section 5 (Murakami et al., 1986; Oishi and Hiraga, 1980; NCI, 1979; Lake et al., 1975).

Appendix B ENVIRONMENTAL HAZARD DETAILS

B.1 Evidence Integration

Data integration includes analysis, synthesis, and integration of information for the draft risk evaluation. During data integration, EPA considers quality, consistency, relevancy, coherence, and biological plausibility to make final conclusions regarding the weight of scientific evidence. As stated in the Draft Systematic Review Protocol (U.S. EPA, 2021), data integration involves transparently discussing the significant issues, strengths, and limitations as well as the uncertainties of the reasonably available information and the major points of interpretation.

The general analytical approaches for integrating evidence for environmental hazard is discussed in Section 7.4 of the 2021 Draft Systematic Review Protocol.

The organization and approach to integrating hazard evidence is determined by the reasonably available evidence regarding routes of exposure, exposure media, duration of exposure, taxa, metabolism and distribution, effects evaluated, the number of studies pertaining to each effect, as well as the results of the data quality evaluation.

The environmental hazard integration is organized around effects to aquatic and terrestrial organisms as well as the respective environmental compartments (*e.g.,* pelagic, benthic, soil). Environmental hazard assessment may be complex based on the considerations of the quantity, relevance, and quality of the available evidence.

For *o*-phthalic acid, environmental hazard data from toxicology studies identified during systematic review used evidence that characterizes apical endpoints; that is, endpoints that could have population-level effects such as reproduction, growth, and/or mortality. Additionally, mechanistic data that can be linked to apical endpoints will add to the weight of scientific evidence supporting hazard thresholds.

B.1.1 Weight of Scientific Evidence

After calculating the hazard thresholds that were carried forward to characterize risk, a narrative describing the weight of scientific evidence and uncertainties was completed to support EPA's decisions. The weight of 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 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 using evidence Table Apx B-2 for environmental hazard. 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 dataset. 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 determination 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 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.

Confidence Levels

- 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 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 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.

B.1.2 Data Integration Considerations Applied to Aquatic and Terrestrial Hazard Representing the *o*-Phthalic Acid Environmental Hazard Database

Types of Uncertainties

The following uncertainties may be relevant to one or more of the weight of scientific evidence considerations listed above and will be integrated into that property's rank in the evidence (Table Apx B-2):

- *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_Apx B-1 summarizes the weight of 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, though 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 B-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. • 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	• 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. • 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

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)
	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).	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 dataset 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.

Table Apx B-2. *o*-Phthalic Acid 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 [a]	Hazard Confidence
Aquatic						
Acute aquatic assessment	+	++	+	++	+++	Slight-to-moderate
Chronic aquatic assessment	+	++	+	+	+++	Slight-to-moderate
Chronic benthic assessment	ND	ND	ND	ND	ND	ND
Algal assessment	+	++	+	++	+++	Slight-to-moderate
Terrestrial						
Chronic mammalian assessment	++	++	++	+	++	Moderate
Chronic avian assessment	ND	ND	ND	ND	ND	ND
Terrestrial invertebrate assessment [b]	+	+	+	+	++	Slight-to-moderate
Terrestrial plant assessment	++	++	+	+	++	Moderate

ND = not determined
[a] Relevance includes biological, physical/chemical, and environmental relevance
[b] Terrestrial invertebrate hazard threshold was estimated using ECOSAR
+++ 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.

Appendix C ECOSAR REPORT ON PHTHALIC ANHYDRIDE PREDICTIVE MODEL

Created on May 21, 2025 11:19:01 AM

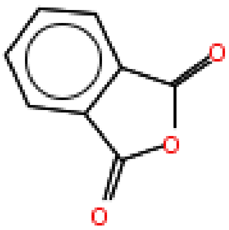
ECOSAR v 2.0

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
85449	1,3-Isobenzofurandione	O=C(OC(=O)c1cccc2)c12

Structure



Details	
Mol Wt	148.12
Selected LogKow	2.07
Selected Water Solubility (mg/L)	6200
Selected Melting Point (°C)	130.8
Estimated LogKow	2.07
Estimated Water Solubility (mg/L)	774.74
Measured LogKow	1.6
Measured Water Solubility (mg/L)	6200
Measured Melting Point (°C)	130.8

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	105.54	5	
Daphnid	48h	LC50	60.31	5	
Green Algae	96h	EC50	46.12	6.4	
Fish		ChV	10.39	8	
Daphnid		ChV	5.99	8	
Green Algae		ChV	12.25	8	
Fish (SW)	96h	LC50	132.92	5	

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Mysid	96h	LC50	94.29	5	
Fish (SW)		ChV	15.05	8	
Mysid (SW)		ChV	7.99	8	
Earthworm	14d	LC50	253.32[a]	6	

[a] Dataset for the earthworm is in mg/kg