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Environmental Hazard Assessment for Diisodecyl Phthalate (DIDP)

Technical Support Document for the Risk Evaluation

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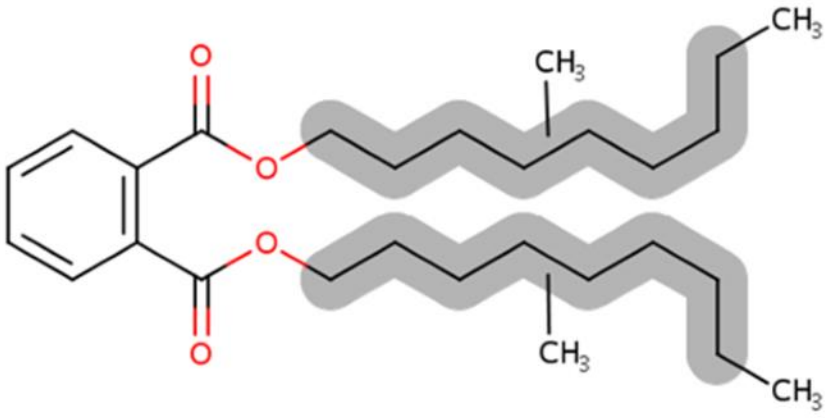

(Representative Structure)

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KEY ABBREVIATIONS AND ACRONYMS

AF	Assessment factor
AIM	Analog Identification Methodology
ChV	Chronic value
COC	Concentration(s) of concern
DIDP	Diisodecyl phthalate
DINP	Diisononyl phthalate
DW	Dry weight
EC50	Effect concentration at which 50 percent of test organisms exhibit an effect
EPA	(U.S.) Environmental Protection Agency (or the Agency)
HC05	Hazard concentration that is protective of 95 percent of the species in the SSD
LC50	Lethal concentration at which 50 percent of test organisms die
LOAEC	Lowest-observed-adverse-effect concentration
LOAEL	Lowest-observed-adverse-effect level
LOEC	Lowest-observed-effect concentration
NOAEC	No-observed-adverse-effect concentration
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
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

SUMMARY

Diisodecyl Phthalate (DIDP) – Environmental Hazards: Key Points

EPA considered all reasonably available information identified by the Agency through its systematic review process under the Toxic Substances Control Act (TSCA) to characterize environmental hazard endpoints for DIDP. The following bullets summarize key points of this assessment.

- Aquatic species:
  - Hazard data for fish and aquatic invertebrates indicated no acute or chronic toxicity up to and exceeding the limit of water solubility.
  - No toxicity was observed from hazard studies with bulk sediment or pore water exposure to sediment-dwelling organisms on an acute or chronic exposure basis.
  - No toxicity was observed in two species of algae up to the highest tested concentration.
- Terrestrial species:
  - Because terrestrial hazard data for DIDP were not available for birds or mammalian wildlife species, studies in laboratory rodents were used to derive hazard values for mammalian species.
  - Diisononyl phthalate (DINP) was used as an analog for read-across to DIDP for earthworm (*Eisenia fetida*) hazard based on structural similarity; similar physical, chemical, and environmental fate and transport behavior in soil; and similar toxicological behavior in other sediment-dwelling and aquatic invertebrates.
  - Empirical toxicity data for rats were used to estimate a chronic toxicity reference value (TRV) for terrestrial mammals at 128 of mg/kg-bw/day.

1 INTRODUCTION

DIDP is an organic substance primarily used as a plasticizer in a wide variety of consumer, commercial, and industrial products. DIDP may be released during industrial activities and through consumer use, with most releases occurring into air and water. Like most phthalates, EPA expects DIDP to cause adverse effects on aquatic organisms through a non-specific, narcosis mode of action (Parkerton and Konkel, 2000); however, previous assessments have found few to no effects of DIDP on organism survival and fitness (EC/HC, 2015a; ECJRC, 2003). The Agency reviewed studies of the toxicity of DIDP to aquatic and terrestrial organisms and its potential environmental hazards. Also, due to a lack of DIDP hazard data for terrestrial invertebrates, EPA reviewed one diisononyl phthalate (DINP) earthworm hazard study to be used as read-across to DIDP.

2 APPROACH AND METHODOLOGY

During scoping and problem formulation, EPA reviewed potential environmental health hazards associated with DIDP. The Agency identified sources of environmental hazard data shown in Figure 2-10 of the *Final Scope of the Risk Evaluation for Di-isodecyl phthalate (DIDP) (1,2-benzenedicarboxylic acid, 1,2-diisodecyl ester and 1,2-benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich); CASRN 26761-40-0 and 68515-49-1* (also called the "Final Scope for the Risk Evaluation of DIDP") (U.S. EPA, 2021b).

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* (also called the "Draft Systematic Review Protocol") (U.S. EPA, 2021a) and *Systematic Review Protocol for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024g). Studies were assigned overall quality determination of high, medium, low, or uninformative.

In lieu of terrestrial mammalian studies with wildlife species, controlled laboratory studies that used mice and rats as human health model organisms were used to calculate a TRV, which is expressed as a dose in units of mg/kg-bw/day. The TRV is based on *Guidance for Developing Ecological Soil Screening Levels (Eco-SSLs): Review of Background Concentration for Metals* (U.S. EPA, 2007, 2005a). The TRV can be used as the hazard value for ecologically relevant mammalian wildlife species (body weight normalized) to evaluate risk from chronic dietary exposure to DIDP. Exposure to representative terrestrial wildlife species is evaluated in the trophic transfer section (U.S. EPA, 2024a), and these exposure levels from trophic transfer are compared to the TRV to determine risk.

In lieu of terrestrial invertebrate hazard data for DIDP, EPA reviewed one diisononyl phthalate (DINP) earthworm hazard study to be used as read-across to DIDP. DINP was selected as an analog with high confidence for read-across of soil invertebrate hazard data based on excellent structural similarity, similar physical, chemical, environmental fate and transport behavior in soil, and similar toxicological behavior in other invertebrates (sediment-dwelling and aquatic). The DINP soil invertebrate hazard data to be used as analog data for DIDP received an overall quality determination of high (ExxonMobil, 2010). No avian studies were available to assess potential hazards from DIDP exposure. Avian hazard data is also not reasonably available for the read across analog DINP; however, hazard data from an egg injection study of DEHP in chicken is presented as a comparison, with DEHP represented as a low-confidence analog. The similarities between DIDP and analog DINP are described in detail in Appendix A.

3 AQUATIC SPECIES HAZARD

Toxicity to Aquatic Organisms

EPA assigned an overall quality determination of high and medium to 13 references summarized in Table 3-1 as the most relevant for quantitative assessment. Several references evaluated multiple endpoints, species, and test durations. Three references receiving an overall quality determination of low or uninformative for a chronic duration either exceeded the DIDP limit of solubility, showed no effects at the highest concentration tested, evaluated a biotransformation (mechanistic) endpoint, and/or were part of a mixture.

Aquatic Vertebrates

Acute fish hazard data for DIDP were identified in five studies representing five species of fish, including fresh and saltwater species (fathead minnows [*Pimephales promelas*], rainbow trout [*Oncorhynchus mykiss* (formerly *Salmo mykiss*)], bluegill [*Lepomis macrochirus*], zebra fish [*Danio rerio*], and sheepshead minnow [*Cyprinodon variegatus*]). Two studies (Poopal et al., 2020; Chen et al., 2014) reported acute hazard values in fish from nominal concentrations that were over six orders of magnitude greater than the limit of water solubility for DIDP identified by EPA (1.7×10^{-4} mg/L (U.S. EPA, 2024b)). To achieve target doses, these studies were conducted with a solvent to enhance solubility. However, the reported values exceed typical environmental conditions; therefore, this study was not used quantitatively for hazard characterization.

In one acute study (Adams et al., 1995), a replicate for one of the treatment groups displayed signs of distress (*i.e.*, discoloration, rapid respiration); however, these signs were considered unrelated to treatment, because they were not observed at higher test concentrations. Therefore, the no-observed-effect concentration (NOEC) for the tests on rainbow trout was the highest concentration tested (0.62 mg/L) and the lethal concentration at which 50 percent of test organisms die (LC50) exceeded the highest concentration tested. Additionally, because 100 percent mortality occurred in one of the control replicates, this study was not used quantitatively for hazard characterization. In all remaining acute hazard studies conducted on fathead minnow, bluegill, and sheepshead minnows, mortality in 50 percent of the test organisms was not achieved up to the highest concentrations tested, the resulting insufficient mortality observed at the highest test concentrations (represented as >0.37 to >1.0 mg/L within Table 3-1) to calculate acute toxicity values.

Chronic fish hazard data for DIDP were identified in one study representing one fish species (Japanese medaka [*Oryzias latipes*]). In this multigenerational study, medaka were exposed to DIDP via the diet at a single dose level of 1 mg/kg-bw/day for up to 140 days. No effects of treatment were observed on any reproductive or developmental endpoints, resulting in a NOEC of greater than 1 µg DIDP/g (1 mg/kg-bw/day) (Patyna et al., 2006). The study authors reported elevated testosterone metabolism in treated females; however it was not associated with an apical response, in that there were no effects of treatment on reproduction, egg production, sex ratio, or embryo development in either generation (Patyna et al., 2006).

Aquatic Invertebrates

Acute invertebrate hazard data for DIDP were identified in four studies representing two different species, including fresh and saltwater species (water flea [*Daphnia magna*] and mysid shrimp [*Americamysis bahia*, formerly *Mysidopsis bahia*]). In all four studies, LC50s were not able to be determined as they exceeded the highest concentrations tested and ranged from greater than 0.02 to greater than 0.32 mg/L (Adams et al., 1995; EG & G Bionomics, 1984a; Springborn Bionomics, 1984a; Brown and Thompson, 1982). In one of these studies, entrapment of *D. magna* was reported due to undissolved test material on the surface of the testing solution in the two highest treatment levels, and

the observations of immobility and/or decreased survival in these treatment groups was considered to be due to physical entrapment and not a specific toxic response from exposure to the phthalate (Springborn Bionomics, 1984a).

Chronic invertebrate hazard data for DIDP were identified in two acceptable studies evaluating mortality and reproduction within *Daphia magna* over the course of 21-day exposures (Brown et al., 1998; Rhodes et al., 1995). *D. magna* exposed to nominal concentrations of DIDP for 21 days resulted in a reduced survival lowest-observed-effect concentration (LOEC) of 0.060 mg/L and a NOEC of 0.030 mg/L, for a chronic value (ChV) of 0.04 mg/L (Rhodes et al., 1995). The resulting ChV is two orders of magnitude greater than the reported solubility for DIDP of 1.7×10^{-4} mg/L (U.S. EPA, 2024b). In addition, authors reported that although no visible film was observed, physical entrapment of *D. magna* with the water surface boundary was observed within test vessels at the LOEC. The authors concluded that this physical entrapment contributed to their observed animal mortality and reproduction effects (Rhodes et al., 1995). Rhodes et al., (1995) prepared test solutions daily with no cosolvent and injected a measured amount of the test chemical directly into a chemical mixing chamber of the diluter prior to each dilution cycle. Due to previous observations and impacts of entrapment on test organisms, a similar 21-day exposure study conducted by (Brown et al., 1998) with increased the solubility of DIDP in solution via the addition of a dispersant, castor oil 40 ethoxylate and found no differences in reproduction, growth, or mortality from a 1 mg/L exposure to DIDP when compared to the control or dispersant control.

Benthic Invertebrates

Hazard data for sediment dwelling organisms for DIDP were identified in three studies represented by four species (amphipod [*Hyalella azteca*], midge [*Paratanytarsus parthenogeneticus*], midge [*Chironomus tentans*]), and midge [*Chironomus riparius*]). Studies ranged from acute, 96-hour to chronic, 28-day with measured benthic pore water and sediment concentrations (Call et al., 2001; Brown et al., 1996; Adams et al., 1995). Effects on mortality and/or development were not observed up to the highest tested concentrations which ranged from 0.64 to 1.18 mg/L for benthic pore water and 2,090 to 2,680 mg/kg dw (Call et al., 2001; Adams et al., 1995). One study with the midge (*C. riparius*) observed no effects up to the highest spiked bulk sediment concentration tested, with a NOEC/LOEC of 4,300/ greater than 4,300 mg/kg wet weight (Brown et al., 1996). Because no effects were seen for benthic invertebrates, a quantitative hazard value could not be derived for acute or chronic effects on benthic invertebrates.

Amphibians

One amphibian study was considered to assess hazard from DIDP exposure (IVL, 1997). In this study, moorfrog (*Rana arvalis*) eggs were exposed to DIDP in sediment up to 600 mg DIDP/kg-dw to assess hatching and survival. Although no effects were seen after the 14- or 29-day exposures, the study authors observed and noted small differences in growth (that were not statistically significant) were possibly due to temperature variations in different parts of the experimental chambers and exposure system. It was also indicated that fungal or bacterial contamination occurred in some of the beakers and was associated with mortality. Because no effects were seen for amphibians, a quantitative hazard value could not be derived for subchronic or chronic effects on amphibians.

Aquatic Algae

Aquatic plants and algae data for DIDP were identified in two studies representing one species (freshwater green algae, *Selenastrum capricornutum*). No effects were seen at any concentration tested spanning 0.80 to 1.3 mg/L DIDP (Adams et al., 1995; Springborn Bionomics, 1984b). Because no effects were seen for aquatic plants and algae, a quantitative hazard value could not be derived for these

species.

3.1 Aquatic Organism Hazard Conclusions

Overall, EPA has robust confidence in the evidence that DIDP has low hazard potential in aquatic species (see Table 5-1). No consistent effects of DIDP on aquatic organism survival or reproduction were observed in studies of aquatic organisms across taxonomic groups, habitats, exposure type, and exposure duration. Studies of DIDP exposure via water to fish, amphibians, invertebrates, and algae reported no effects up to and well above the solubility limit in the water column and in the sediment pore water. Studies of dietary exposure of DIDP to fish indicate no consistent population-level DIDP effects. Uncertainties do exist within the data set. Given the number aquatic studies that passed through systematic review screening, the data set may not have been large enough to capture all potential effects in aquatic organisms. Reported no-observed-adverse-effect concentrations and lowest-observed-adverse-effect concentrations (NOAEC/LOAEC) values are unbound, and tested concentrations are orders of magnitude apart. Additionally, no studies were conducted using concentrations of DIDP less than the EPA reported limit of solubility (0.00017 mg/L); however, the use of a surfactant with chronic exposure assays with *Daphnia* demonstrated no impacts to survival and reproduction up to 1 mg/L DIDP.

Table 3-1. Aquatic Organisms Environmental Hazard Studies Used for DIDP

Duration	Test Organism	Endpoint	Hazard Value[a]	Effect	Citation (Study Quality)
Aquatic vertebrates					
Acute	Fathead minnow (*Pimephales promelas*)	96-hour LC50	ND (>0.66 mg/L)	Mortality	(EG & G Bionomics, 1983a) (high)
	Fathead minnow (*Pimephales promelas*)	96-hour LC50	ND (>0.47 mg/L)	Mortality	(Adams et al., 1995) (high)
	Fathead minnow (*Pimephales promelas*)	96-hour LC50	ND (>1.0 mg/L)	Mortality	(Adams et al., 1995) (high)
	Bluegill (*lepomis macrochirus*)	96-hour LC50	ND (>0.55 mg/L)	Mortality	(EG & G Bionomics, 1983b) (high)
	Bluegill (*lepomis macrochirus*)	96-hour LC50	ND (>0.37 mg/L)	Mortality	(Adams et al., 1995) (high)
	Sheepshead minnow (*Cyprinodon variegatus*)	96-hour LC50	ND (>0.47 mg/L)	Mortality	(Adams et al., 1995) (high)
	Rainbow trout (*Oncorhynchus mykiss*)	96-hour LC50	ND (>0.62 mg/L)	Mortality	(Adams et al., 1995) (high)
	Zebrafish (*Danio rerio*)	96-hour LC50	300 mg/L	Mortality	(Poopal et al., 2020) (high)
	Zebrafish (*Danio rerio*)	72-hour LOEC	ND (>500 mg/L)	Mortality	(Chen et al., 2014) (medium)

Duration	Test Organism	Endpoint	Hazard Value[a]	Effect	Citation (Study Quality)
Subchronic/ Chronic	Japanese medaka (*Oryzias latipes*)	42,81-day LOEC	ND (>1 mg/kg bw/day)	Post-hatch survival	(Patyna et al., 2006) (high)
	Japanese medaka (*Oryzias latipes*)	140-day LOEC	ND (>1 mg/kg bw/day)	Survival/ growth	(Patyna et al., 2006) (high)
Aquatic invertebrates					
Acute	Water flea (*Daphnia magna*)	48-hour LC50	ND (>0.18 mg/L)	Mortality	(Springborn Bionomics, 1984a) (high)
	Water flea (*Daphnia magna*)	48-hour LC50	ND (>0.02 mg/L)	Mortality	(Adams et al., 1995) (high)
	Water flea (*Daphnia magna*)	48-hour LC50	ND (>0.32 mg/L)	Mortality	(Brown and Thompson, 1982) (medium)
	Mysid shrimp (*Americamysis bahia*)	96-hour LC50	ND (>0.08 mg/L)	Mortality	(Adams et al., 1995) (high)
	Mysid shrimp (*Americamysis bahia*)	96-hour LC50	ND (>0.15 mg/L)	Mortality	(EG & G Bionomics, 1984a) (high)
Subchronic/ Chronic	Water flea (*Daphnia magna*)	21-day LOEC	0.06 mg/L[b]	Mortality	(Rhodes et al., 1995) (high)
	Water flea (*Daphnia magna*)	21-day LOEC	0.14 mg/L[b]	Reproduction/ Growth	(Rhodes et al., 1995) (high)
	Water flea (*Daphnia magna*)	21-day NOEC	ND (>1.0 mg/L)	Mortality, Reproduction, Growth	(Brown et al., 1998) (High)
Benthic invertebrates					
Acute	Midge (*Paratanytarsus parthenogenica*)	96-hour LC50	ND (>0.64 mg/L)	Mortality	(Adams et al., 1995) (high)
Subchronic/ Chronic	Amphipod Crustacean (*Hyalella azteca*)	10-day LC50	ND (>0.931 mg/L PW; >2,090 mg/kg BS)	Mortality	(Call et al., 2001) (high)
	Midge (*Chironomus tentans*)	10-day LC50	ND (>1.18 mg/L PW; >2,680 mg/kg BS)	Mortality	(Call et al., 2001) (high)
	Midge (*Chironomus riparius*)	28-day NOEC/LOEC	4,300/>4,300 mg/kg	Development	(Brown et al., 1996) (high)

Duration	Test Organism	Endpoint	Hazard Value[a]	Effect	Citation (Study Quality)
Aquatic plants and algae					
Acute	Freshwater green algae (*Selenastrum capricornutum*)	96-hour LC50	ND (>0.80 mg/L)	Chlorophyll [c] increase	(Adams et al., 1995) (high)
Subchronic/ Chronic	Freshwater green algae (*Selenastrum capricornutum*)	8-day EC50	ND (>1.3 mg/L)	Chlorophyll [c] increase	(Springborn Bionomics, 1984b) (high)

DS = dry sediment; PW = pore water; BS = bulk sediment; ND = not determined
[a] Values in parentheses represent the highest exposure concentration in the reported experiment.
[b] Study authors indicate that the observed toxicity may be due to entrapment within the surface layer of the test chamber.
[c] Feed study.

4 TERRESTRIAL SPECIES HAZARD

Toxicity to Terrestrial Organisms

EPA assigned an overall quality determination of high or medium to six acceptable terrestrial toxicity studies (ExxonMobil, 2010; Cho et al., 2008; Hushka et al., 2001; Waterman et al., 1999; Hellwig et al., 1997; BIBRA, 1986). All studies contained relevant terrestrial toxicity data for different laboratory strains of Norway rat (*Rattus norvegicus*). In addition, due to lack of reasonably available DIDP soil invertebrate hazard data, a DINP hazard study on earthworm (*Eisenia fetida)* was used in a quantitative read-across to DIDP.

Terrestrial Vertebrates

No terrestrial vertebrate studies were reasonably available to assess the potential effects or hazards from DIDP exposure in bird or mammalian wildlife species. Therefore, EPA considered ecologically relevant definitive hazard data from studies conducted on laboratory mammals (*e.g.*, rats) that are routinely used to inform human health hazard. These data were then used in accordance with the Agency's Guidance for Developing Ecological Soil Screening Levels (Eco-SSLs) (U.S. EPA, 2007) to formulate a TRV to represent terrestrial mammals (Table 4-1).

Mammals

Terrestrial mammalian studies with ecologically relevant ecologically relevant effects were considered for deriving the TRV. Observed NOAELs ranged from 38 to 1,042 mg/kg-bw/day in rats (Table 4-1).

Reproduction: EPA identified reproductive data for terrestrial mammals from two studies on reproduction and development in rats (Hushka et al., 2001; Waterman et al., 1999).

Waterman et al. (1999), which received a high overall quality determination, conducted a developmental toxicity study on the effects of DIDP in Sprague-Dawley rats. Female rats were administered DIDP via oral gavage once daily during gestation days 6 to 15. Maternal body weight gain was significantly reduced in the 1,000 mg/kg-bw/day treatment group. DIDP was also evaluated for reproductive effects in SD rats in a pair of two-generation feeding studies of reproduction (termed Studies A and B), which received a medium overall quality determination (Hushka et al., 2001; Exxon Biomedical, 2000, 1998). This data is represented by an unpublished report (Exxon Biomedical, 2000) and a peer-reviewed journal article resulting from the original unpublished work (Hushka et al., 2001). In the first two-generation study (Study A), a significant decrease in the percentage of live offspring at birth was observed in the highest dose group (0.8% DIDP in feed) when parents were fed DIDP for 18 weeks, resulting in a reproductive NOAEL and lowest-observed-adverse-effect level (LOAEL) of 253 mg/kg-day and 508 mg/kg-day, respectively. Similar effects were observed in the F2 offspring in Study A, with significant decrease in F2 survival at post-natal day (PND) seven as well as at weaning (PND 4–21) with a reproductive NOAEL and LOAEL of 262 mg/kg-day and 566 mg/kg-day, respectively. When the two-generation study was repeated in SD rats with lower doses of DIDP (termed Study B), significant decrease in F2 pup survival was again demonstrated with a reproductive NOAEL and LOAEL of 38 mg/kg-day and 134 mg/kg-day, respectively. F2 female body weight in Study B was also significantly decreased at sexual maturation resulting in a NOAEL/LOAEL of 134/256 mg/kg-day. Studies are described further detail in the *Human Health Hazard Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024d).

Growth: EPA identified data for terrestrial mammalian vertebrates from three studies for the growth endpoint (Cho et al., 2008; Hushka et al., 2001; BIBRA, 1986).

F344 rats were fed diets containing DIDP for 21 days (BIBRA, 1986). Female body weight was significantly reduced in the 2.5 percent DIDP group from day 10 onward, resulting in a NOAEL of 1,042 and a LOAEL of 1,972 mg/kg-bw/day. While body weight in the DIDP-treated male rats was also reduced, these data were deemed uninformative due to excessive decrease in food consumption and were therefore not used quantitatively (BIBRA, 1986).

F344 rats fed DIDP in the diet for 2 years had significantly reduced body weights in both sexes in the highest dose group, resulting in NOAEL/LOAEL of 110/479 mg/kg-day in males and 128/620 mg/kg-bw/day in females (Cho et al., 2008). In the two-generation study termed Study A described above where F0 rats were administered DIDP in feed for 10 weeks prior to mating as well as during mating, gestation, and lactation, male F0 rats in the highest dose group (0.8% DIDP in feed) had significantly reduced body weights during the pre-mating period, resulting in a NOAEL and LOAEL of 211 mg/kg-bw/day and 427 mg/kg-bw/day (Hushka et al., 2001). Similarly, female F0 rats in the highest dose group (0.8% DIDP in feed) had significantly reduced body weights during premating and lactation, resulting in a NOAEL and LOAEL of 253 mg/kg-bw/day and 508 mg/kg-bw/day. Significant decrease in bodyweight in F1 adult males was also observed in Study A in the highest dose group (NOAEL and LOAEL 117 mg/kg-bw/day and 229 mg/kg-bw/day) (Hushka et al., 2001). A preliminary one-generation study by the same authors observed similar findings in SD rats fed DIDP for 10 weeks prior to mating and two weeks during mating with significant decrease in male F0 body weights in the two highest dose groups (NOAEL and LOAEL 262 mg/kg-bw/day and 414 mg/kg-bw/day).

Survival: EPA identified data for terrestrial mammalian vertebrates from two studies for the survival endpoint (Cho et al., 2008).

In the 2-year feeding study described above Cho et al. (2008) (medium overall quality determination) observed significantly decreased survival in F344 rats exposed to the highest dose of DIDP, resulting in a NOAEL/LOAEL of 110/479 and 128/620 mg/kg-bw/day for male and female rats, respectively (Cho et al., 2008).

Avian

No avian studies were reasonably available to assess potential hazards from DIDP exposure. Avian hazard data were also not reasonably available for the preferred read across analog DINP. There are avian hazard data available for DEHP; however, EPA has less confidence in DEHP to use in a quantitative read-across for DIDP. DEHP can serve as a comparator compound in the absence of avian hazard data from DIDP. These avian study results containing DEHP will be compared qualitatively within the environmental risk characterization for DIDP and will not represent a hazard threshold for DIDP.

Chicken (*Gallus gallus domesticus*) were examined for effects of pre-hatch egg injections with single concentrations of 0, 5, 20, 50, and 100 mg/kg DEHP administered on incubation day 0 (Abdul-Ghani et al., 2012). There was no significant decrease in hatching or late hatchings between controls and DEHP treated groups at any test concentration. Developmental effects, including gastroschisis and omphalocele, were reported but it was not clear if the effects were from DEHP-treated groups only as the study authors pooled DEHP and DBP results together for that metric. Alkaline phosphatase and 8-hydroxydeoxyguanosine were significantly greater in chicks within the 100 mg/kg exposure group. Significant effects were observed in juvenile imprinting when eggs were injected with a single concentration of 100 mg/kg DEHP, resulting in a behavior (imprinting) LOAEL of 100 mg/kg (Abdul-Ghani et al., 2012).

A 45-day gavage study on DEHP in 8-day-old male quail (*Coturnix coturnix*) was conducted at concentrations of 250, 500, and 750 mg/kg with control (water) and vehicle control (corn oil) treatments (Wang et al., 2019). Quail within the 500 mg/kg and 750 mg/kg-bw/day treatment groups exhibited cardiac muscle fiber expansion and cell necrosis which was accompanied by myocardial disorganization and some cells with lysed or absent nuclei. Observations of abnormal myocardial cells within the 500 mg/kg-bw/d were 4.95 percent or approximately double observations within the control and vehicle control treatments of 2.81 and 2.55 percent, respectively. Wang et al. (2019) concluded that DEHP exposures of 500 and 750 mg/kg-bw/day induced myocardial injury in quail from this 45-day study.

Wang et al. (2020) exposed 8-day-old female quail to gavage treatments of 250, 500, and 1,000 mg/kg-bw/day with control (water) and vehicle control (corn oil) groups. Total cytochrome P450 and cytochrome *b5* content (nmol/mg protein) within renal tissue from the 500 and 1,000 mg/kg-bw/day treatments were significantly elevated compared to control treatments.

Kidney histology after the 45-day exposure period was performed with scoring for renal tubule and glomerulus features, and renal interstitial congestion. This semiquantitative assessment indicated disorganized renal structures, swelling within renal tubules (50–75%) and glomeruli (10–25 %), and renal congestion (>75%) for DEHP exposure treatments at and above 250 mg/kg-bw/day.

Table 4-1. Terrestrial Mammal Hazard Studies of DIDP Used for TRV Derivation

Test Organism	NOAEL/ LOAEL (mg/kg-day)	Effect	Study Description	Citation, Reference# [a], (Study Quality)
Sprague-Dawley Rats (*Rattus norvegicus*)	500/1,000	Reproduction: reduced maternal body weight gain at 1,000 mg/kg-day	Pregnant rats (22–25/dose) gavaged with 0 (corn oil vehicle), 100, 500, 1,000 mg/kg/day DIDP on GDs 6–15. Dams terminated on GD 21	(Waterman et al., 1999), 3, (High)
Sprague-Dawley Crl:CD BR-VAF/Plus Rat (*Rattus norvegicus*)	253/508	Reproduction: decreased F1/F2 percent live births	P1 female rats during premating and gestation fed diets containing 0, 0.2, 0.4, and 0.8% (0, 127, 253, and 508 mg/kg/day) DIDP continuously for two-generations (Study A). Received doses in units of mg/kg/day shown in See Table 3-7 of the Human Health Hazard Assessment (U.S. EPA, 2024d)	(Hushka et al., 2001), 4, (Medium)
	262/566	Reproduction: decreased survival of F2 offspring at PND 7.	F1 female rats during premating, gestation, and lactation fed diets containing 0, 0.2, 0.4, 0.8% (0, 135, 262, and 588 mg/kg-day) DIDP continuously for two-generations (Study A). Received doses in units of mg/kg/day shown in Table 3-7 of the Human Health Hazard Assessment (U.S. EPA, 2024d).	
Sprague-Dawley Crl:CD BR Rat (*Rattus norvegicus*)	38/134	Reproduction: decreased survival of F2 pups on PND 1 and 4	F1 female rats during premating, gestation, and lactation fed diets containing 0, 0.02, 0.06, 0.2, 0.4% (0, 13, 38, 134, and 256 mg/kg/day) DIDP continuously for two generations (Study B). Received doses in units of mg/kg/day shown in Table 3-10 of Human Health Hazard Assessment (U.S. EPA, 2024d). Dosing for F2 females began on PND 21, but dose estimations and food ingestion rates were not provided.	(Hushka et al., 2001), 4, (Medium), (Hushka et al., 2001), 5, (Medium)
	134/256	Reproduction: decreased body weight at vaginal patency for F2 females		

Test Organism	NOAEL/ LOAEL (mg/kg-day)	Effect	Study Description	Citation, Reference# [a], (Study Quality)
Fischer 344 Rat (*Rattus norvegicus*)	1,042/1,972	Growth: reduced female body weight	Female rats fed diets containing 0, 0.3, 1.2, or 2.5% (0, 264, 1042, 1972 mg/kg/day) DIDP for 21 days.	(BIBRA, 1986), 1, (High)
Fischer 344 Rat (*Rattus norvegicus*)	110/128	Growth: reduced male body weight	Rats fed diets containing 0, 400, 2,000, or 8,000 ppm (0/0, 22/23, 110/128, 479/620 mg/kg/day for males/females) for 2 years	(Cho et al., 2008), 2, (Medium)
	128/620	Growth: reduced female body weight		
Sprague-Dawley Crl:CD BR-VAF/Plus Rat (*Rattus norvegicus*)	262/414	Growth: reduced male parental body weight	Preliminary one-generation study in which rats fed diets of 0.25, 0.50, 0.75 and 1.0% (0, 132, 262, 414, and 542 mg/kg/day) DIDP during pre-mating period	(Hushka et al., 2001), 4, (Medium)
	211/427	Growth: reduced male P1 body weight during premating period	P1 male premating rats fed diets containing 0, 0.2, 0.4, 0.8% (0, 103, 211, 427 mg/kg/day) DIDP continuously for two-generations. Received doses in units of mg/kg/day shown in Table 3-7 of the Human Health Hazard Assessment (U.S. EPA, 2024d)	
	253/508	Growth: reduced female P1 body weight during premating period	P1 female premating and lactation rats fed diets containing 0, 0.2, 0.4, 0.8% (0, 127, 253, 508 mg/kg/day) DIDP continuously for two-generations. Received doses in units of mg/kg/day shown in Table 3-7 of the Human Health Hazard Assessment (U.S. EPA, 2024d)	
	117/229	Growth: decrease in male F1 body weight	F1 male premating rats fed diets containing 0, 0.2, 0.4, 0.8% (0, 117, 229, 494 mg/kg/day) DIDP continuously for two generations. Received doses in units of mg/kg/day shown in Table 3-7 of the Human Health Hazard Assessment (U.S. EPA, 2024d)	
Fischer 344 Rat (*Rattus norvegicus*)	110/479	Survival: reduced survival in males	Rats fed diets containing 0, 400, 2,000, or 8,000 ppm (0/0, 22/23, 110/128, 479/620 mg/kg-day for males/females) for 2 years	(Cho et al., 2008), 2, (Medium)
	128/620	Survival: reduced survival in females		

The LOAEL value of 135 mg/kg-day for decreased F2 offspring survival in Study A is the achieved intake during the gestation period for the second generation, corresponding to the lowest dietary concentration of DIDP tested (0.2% DIDP). NOAEL/LOAEL values of 38/134 mg/kg-day for decreased F2 offspring survival in Study B are the achieved intakes during the gestation period for the second generation, corresponding to the 0.06 and 0.2% DIDP treatment groups (Hushka et al., 2001). Mean measured doses of DIDP for Study A and B are provided in the human health hazard assessment (U.S. EPA, 2024d).

[a] Reference number corresponding to the mammalian TRV derivation for DIDP (Figure 4-1).

Terrestrial Invertebrates

No terrestrial invertebrate studies were reasonably available to assess potential hazards from DIDP exposure. However, a quantitative read-across was conducted using DINP soil invertebrate hazard data

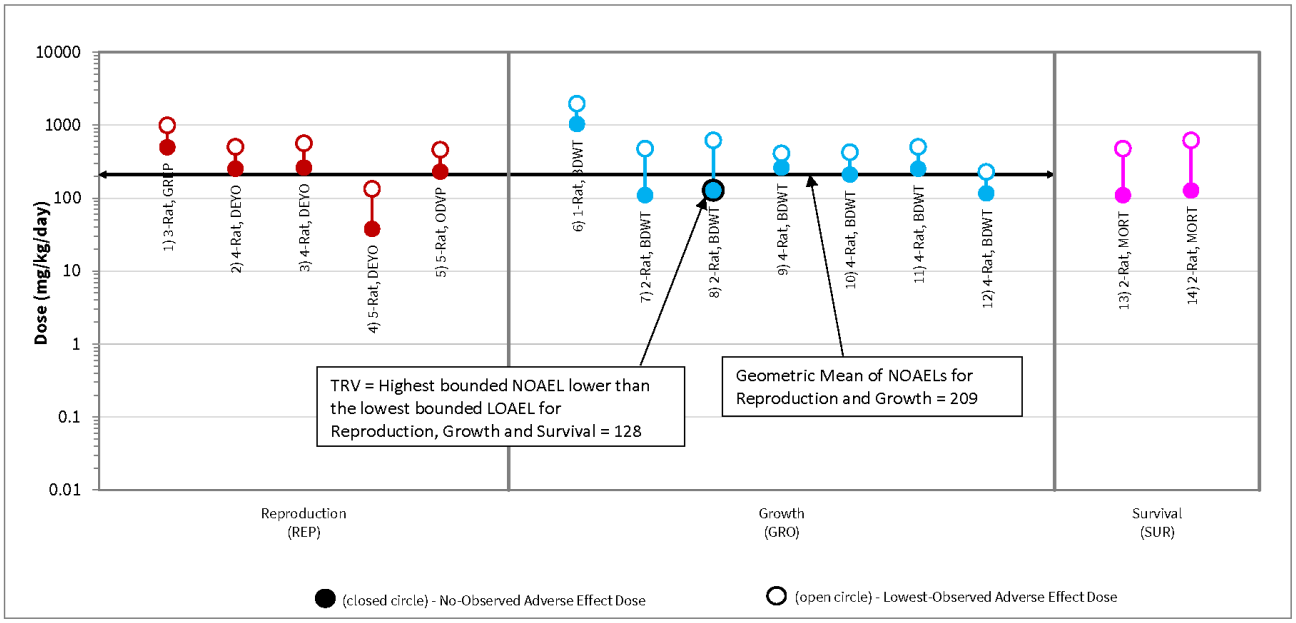
as described in Appendix A. DINP was considered appropriate for use as an analog for read-across to DIDP soil invertebrate hazard based on excellent structural similarity, similar physical, chemical, environmental fate and transport behavior in soil, and similar toxicological behavior in other invertebrates (Appendix A). EPA identified one study of DINP chronic exposure to the earthworm *Eisenia fetida* in artificial soil (ExxonMobil, 2010). This study, determined to have a data quality rank of high, found no difference in mortality of adults after the 28-day exposure period between earthworms in control soil and soil containing nominal concentrations of 1,000 mg/kg dw DINP. The soil concentrations were analyzed by gas chromatography with flame ionization detection and ranged from 925.2 to 1052 mg/kg on Day 0 and from 651.4 to 795.8 mg/kg on Day 28 and from 389.6 to 477.1 mg/kg on Day 56 (ExxonMobil, 2010). Although no adverse reproductive effects were observed at the conclusion of the study, there were significantly more juvenile worms in the DINP treatment group than control at the conclusion of the 56-day exposure period.

Terrestrial Plants

No terrestrial plants studies were reasonably available to assess potential hazards from DIDP exposure, however, Environment Canada's State of the Science report on DIDP (EC/HC, 2015b) summarized previous terrestrial hazard studies and found no adverse effects were observed for acute 5-day seed germination toxicity testing conducted with lettuce (*Luctuca sativa*) and rye grass (*Lolium sp.*) with treatment concentrations at or greater than 8,630 mg DIDP/kg dw soil. EPA did not have access to the terrestrial plant hazard studies summarized within Environment Canada's State of the Science Report on DIDP (EC/HC, 2015b).

4.1 Terrestrial Organism Hazard Conclusions

Overall, EPA has robust confidence in the evidence that DIDP has hazard to terrestrial mammals, and moderate confidence that DIDP poses no hazard to soil invertebrates (Table 5-1). No studies on DIDP exposure to wild mammals, birds, or terrestrial plants were available to assess DIDP hazard, indicating that no hazard has been observed in these groups under realistic exposure conditions. This absence of data introduces uncertainty. EPA reviewed studies of laboratory rodents to derive a TRV of 128 mg/kg-bw/day dietary DIDP exposure (Figure 4-1). This TRV represents the potential chronic exposure dose at which the dietary effects of DIDP might affect a general mammal. Uncertainties do exist within the data set—namely the absence of wildlife, bird, and terrestrial plant studies. Using human health data from studies conducted on laboratory mammals (mice/rats) introduces uncertainty regarding the relevance to wild mammal populations. Thus, EPA has moderate confidence that the TRV represents realistic hazards to wild populations. Chronic DINP exposure to an earthworm species in soil did not affect earthworm survival, indicating little to no hazard of DIDP to soil dwelling invertebrates as well. Avian hazard data is not reasonably available for the read across analog DINP; however, hazard data from an egg injection of DEHP in chicken and two gavage studies within quail are presented as a comparison, with DEHP represented as a low-confidence analog. The use of an analog does introduce significant uncertainty regarding effects of DIDP on birds which is why a quantitative analysis is not conducted.



Result number → 1) 10 - Rat, MORT

Reference number — Test Species — Effect Measure

Effect Measure Key:

BDWT - body weight changes
DEYO - death of young
GREP - general reproduction
MORT - mortality
ODVP - offspring development

Lowest-Observed Adverse Effect Dose
Paired values from same study when joined by line
No-Observed Adverse Effect Dose

Wildlife TRV Derivation Process

1) There are at least three results available for two test species and/or strains within the growth, reproduction, and survival effect groups. There are enough data to derive a TRV.
2) There are at least three NOAEL results available in the growth and reproduction effect groups for calculation of a geometric mean.
3) The geometric mean of the NOAEL values for growth and reproductive effects equals 209 mg Di-isodecyl phthalate/kg BW/day, which is greater than the lowest bounded LOAEL of 134 mg Di-isodecyl phthalate/kg BW/day for reproduction, growth or survival.
4) The Mammalian wildlife TRV for Di-isodecyl phthalate is equal to 128 mg Di-isodecyl phthalate/kg BW/day, which is the highest bounded NOAEL below the lowest bounded LOAEL for reproduction, growth or survival.

Figure 4-1. Mammalian TRV Derivation for DIDP

5 WEIGHT OF 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 in agreement with the Draft Systematic Review Protocol (U.S. EPA, 2021a). Table 5-1 summarizes how these considerations were determined for each environmental hazard threshold. Overall, EPA has determined that DIDP has low hazard potential in aquatic species and has robust confidence in the evidence for acute aquatic hazard, chronic aquatic hazard, algal hazard and moderate confidence in the evidence for chronic benthic hazard (Aquatic Organism Hazard Conclusions). Within the terrestrial environment, EPA has robust confidence in the evidence for terrestrial mammalian hazard and moderate confidence in the evidence for soil invertebrate hazard (see Section 4.1). Therefore, the weight of scientific evidence leads the Agency to having robust confidence in the overall conclusion that DIDP has little to no hazards to wild organism populations. However, EPA has more uncertainty and less confidence in the size and quality of the studies in the database, the strength and precision of more subtle and mechanistic effects found within a few studies, and whether study design allowed for dose-response effects to be detected for mechanistic endpoints. Due to lack of reasonably available hazard data, the confidence for avian and terrestrial plant hazard is indeterminate. A more detailed explanation of the weight of scientific evidence, uncertainties, and overall confidence is presented in Appendix B.

Table 5-1. DIDP 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[b]
Aquatic						
Acute aquatic assessment	+++	+++	+++	+	+++	Robust
Chronic aquatic assessment	+	+	+	+	+++	Robust
Chronic benthic assessment	++	+++	++	+	+++	Moderate
Algal assessment	+	+	+	+	+++	Robust
Terrestrial						
Chronic avian assessment	ND	ND	ND	ND	ND	Indeterminate
Chronic mammalian assessment	+++	++	++	+++	++	Robust
Terrestrial invertebrate assessment	+	Not applicable	+	+	++	Moderate
Terrestrial plant assessment	ND	ND	ND	ND	ND	Indeterminate

[a] Relevance includes biological, physical and chemical, and environmental relevance.

[b] Hazard Confidence reflects the overall confidence in the conclusions about the presence or absence of hazard thresholds and the weight of support and uncertainties around all the available data and does not necessarily represent a summation of the individual evidence properties.

+++ 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.

6 ENVIRONMENTAL HAZARD THRESHOLDS

EPA calculates hazard thresholds to identify potential concerns to aquatic and terrestrial species. After weighing the scientific evidence, the Agency selects the appropriate toxicity value from the integrated data to use for hazard thresholds. Table 6-1 summarizes the concentrations of concern identified for DIDP. See Appendix B for more details about how EPA weighed the scientific evidence. Hazard predictions generated by the Ecological Structure Activity Relationships (ECOSAR) Model were not considered as supplementing empirical hazard data for DIDP due to DIDP's log K_{OW} exceeding the model's domain of applicability for acute and chronic hazard predictions (U.S. EPA, 2022).

For aquatic species, EPA uses probabilistic approaches (*e.g.,* Species Sensitivity Distribution [SSD]) when enough data are available and deterministic approaches (*e.g.,* deriving a geometric mean of several comparable values) when more limited data are available. An SSD is a type of probability distribution of toxicity values from multiple species. It can be used to visualize which species are most sensitive to a toxic chemical exposure, and to predict a concentration of a toxic chemical that is hazardous to a percentage of test species. This hazardous concentration is represented as an HCp, where p is the percent of species. EPA uses an HC05 (a hazardous concentration threshold for 5% of species) to estimate a concentration that would protect 95 percent of species. This HC05 can then be used to derive a concentration of concern (COC); the lower bound of the 95 percent confidence interval of the HC05 can be used to account for uncertainty instead of dividing by an assessment factor (AF). EPA has more confidence in the probabilistic approach when enough data are available because an HC05 is representative of a larger portion of species in the environment. For the deterministic approaches, COCs are calculated by dividing a hazard value by an AF according to EPA methods (U.S. EPA, 2016, 2013, 2012).

Equation 6-1.

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

For terrestrial species, EPA estimates hazard by calculating a TRV, in the case of terrestrial mammals and birds, or by assigning the hazard value as the hazard threshold in the case of terrestrial plants and soil invertebrates. The TRVs generated for the EPA's Eco-SSLs are defined as doses, "above which ecologically relevant effects might occur to wildlife species following chronic dietary exposure and below which it is reasonably expected that such effects will not occur" (U.S. EPA, 2007, 2005a). The Agency prefers to derive the TRV by calculating the geometric mean of the NOAELs across sensitive endpoints (growth and reproduction) rather than using a single endpoint. The TRV method is preferred because the geometric mean of NOAELs across studies, species, and endpoints provides greater representation of environmental hazard to terrestrial mammals and/or birds. However, when the criteria for using the geometric mean of the NOAELs as the TRV are not met, the TRVs for terrestrial mammals and birds are derived using a single endpoint.

COC for Aquatic Toxicity

EPA did not identify any reasonably available data with definitive hazard values to be used in deriving a hazard threshold for acute/chronic aquatic species, including sediment-dwelling organisms and aquatic plants and algae. Thus, the Agency found no acute or chronic hazard of DIDP to aquatic organisms.

Hazard Value or TRV for Terrestrial Toxicity

Terrestrial Vertebrate Threshold: For terrestrial species exposed to DIDP, EPA estimates hazard using a deterministic approach for plants and soil invertebrates or by calculating a TRV (for mammals) (Figure 6-1). For terrestrial mammals, the TRV is expressed as doses in units of mg/kg-day. Although the TRV

for DIDP is derived from laboratory rat studies, body weight is normalized; therefore, the TRV can be used as the hazard value for ecologically relevant wildlife species to evaluate chronic risk from dietary exposure to DIDP. The TRV is based on *Guidance for Developing Ecological Soil Screening Levels (Eco-SSLs): Review of Background Concentration for Metals* (U.S. EPA, 2007, 2005a). The following criteria were used to select the data to calculate the TRV with NOAEL and/or LOAEL data.

Step 1: The minimum data set required to derive either a mammalian or avian TRV consists of three results (NOAEL or LOAEL values) for reproduction, growth, or mortality for at least two mammalian or avian species.

- Because this condition was met, proceed to Step 2.

Step 2: Calculation of a geometric mean requires at least three NOAEL results from the reproduction and growth effect groups.

- Because this condition was met, then proceed to Step 4.

Step 4: When the geometric mean of the NOAEL for reproduction and growth is higher than the lowest bounded LOAEL for reproduction, growth, or mortality,

- Then the TRV is equal to the highest bounded NOAEL below the lowest bounded LOAEL.

For DIDP, the geometric mean of the NOAELs for reproduction and growth was 209 mg/kg-bw/day, which was higher than the lowest bounded LOAEL for reproduction, growth, or mortality of 134 mg/kg-bw/day. Therefore, according to the Eco-SSL decision flowchart in Figure 6-1 (U.S. EPA, 2007, 2005a), the TRV was set as the highest bounded NOAEL below the lowest bounded LOAEL for reproduction and growth resulting in a TRV of 128 mg/kg-bw/day (Figure 4-1).

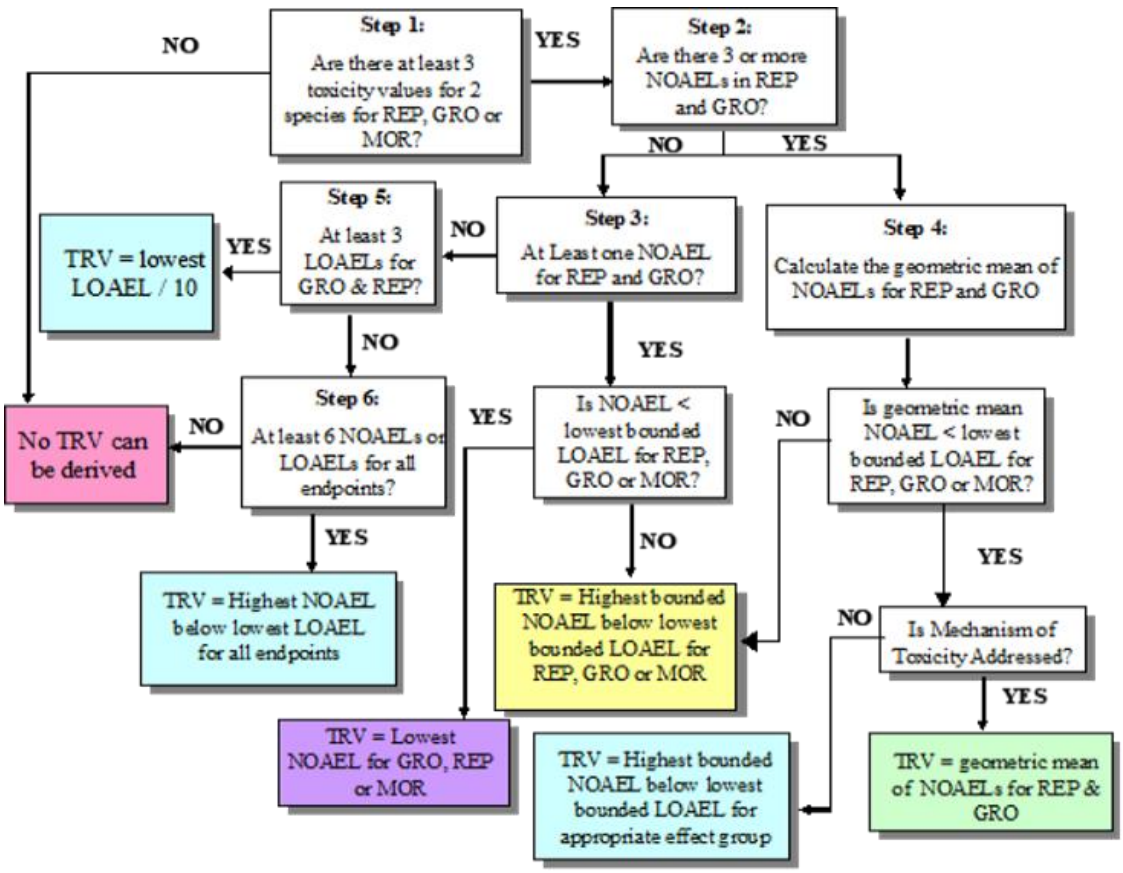


Figure 6-1. Terrestrial Mammal TRV Flow Chart

Soil Invertebrate Threshold: No terrestrial invertebrate studies were available to assess potential hazards from DIDP exposure. However, a read-across was conducted using DINP as described in Appendix A. EPA identified one study examining chronic exposure of DINP on the earthworm *E. fetida* in artificial soil (ExxonMobil, 2010). DINP was considered appropriate for use as an analog for read-across to DIDP based on similarities in structure, physical and chemical/environmental fate and transport properties, and toxicity. This study found no difference in mortality between earthworms exposed to 1,000 mg DINP/kg dw soil compared to control worms after 28 days. At 56-days of exposure the study found a statistically significant increase between the number of juveniles found in 1,000 mg DINP/kg dw soil compared to controls. This study found no adverse effects in earthworms from chronic DINP exposure and was not considered as an endpoint usable for hazard threshold determination.

Terrestrial Plant Threshold: Due to the lack of reasonably available toxicity data for terrestrial plants exposed to DIDP, a screening level hazard threshold for terrestrial plants could not be obtained.

Calculations: The TRV for mammals based on DIDP hazard was 128 mg/kg-bw/day (Table 6-1).

Summary of Environmental Hazard Thresholds

Aquatic Species: Hazard data for fish and aquatic invertebrates indicated no acute or chronic toxicity up to and exceeding the limit of water solubility. No toxicity was observed from hazard studies with bulk sediment or pore water exposure to sediment-dwelling organisms on an acute or chronic exposure basis. Two species of aquatic plant and algae hazard data indicated no toxicity up to the highest tested concentration. The reasonably available environmental hazard data indicate that DIDP does not present hazard to aquatic species as described in Table 6-1.

Terrestrial Species: Because terrestrial hazard data for DIDP were not available for birds, terrestrial plants, or terrestrial mammalian wildlife species, studies in laboratory rodents were used to derive hazard values for mammalian species. Empirical toxicity data for rats were used to estimate a chronic TRV for terrestrial mammals at 128 mg/kg-bw/day. Due to lack of reasonably available data for terrestrial plants, no environmental hazard thresholds for those taxa could be established. The reasonably available environmental hazard data indicate that DIDP presents hazard to terrestrial species as described in Table 6-1.

Table 6-1. Environmental Hazard Thresholds for Environmental Toxicity

Environmental Assessment	Assessment Medium	Hazard Threshold
Acute Aquatic Assessment	Surface Water	No Hazard
Chronic Aquatic Assessment	Surface Water	No Hazard
Chronic Benthic Assessment	Sediment	No Hazard
Algal Assessment	Surface Water	No Hazard
Mammal: TRV	Dietary (Trophic Transfer)	128 mg/kg-bw/day
Soil Invertebrate	Soil	No Hazard
Avian	ND	ND
Terrestrial Plants	ND	ND
ND = not determined		

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APPENDICES

Appendix A ANALOG SELECTION FOR ENVIRONMENTAL HAZARD

No hazard data were identified for DIDP for soil invertebrates; therefore, analog selection was performed to identify an appropriate analog to read-across to DIDP. DINP was selected as an analog for quantitative read-across of soil invertebrate hazard data based on excellent structural similarity; similar physical, chemical, environmental fate and transport behavior in soil; and similar toxicological behavior in benthic and aquatic invertebrates. Because DIDP and its analog DINP lacked avian hazard data that could be used in a quantitative assessment, avian hazard data from an analog less similar to DIDP (specifically diethylhexyl phthalate, DEHP) was used qualitatively to assess avian hazard. The DINP soil invertebrate hazard data to be used quantitatively as analog data for DIDP received an overall quality determination of high (ExxonMobil, 2010) and the DEHP avian hazard data to be used qualitatively as analog data for DIDP received an overall quality determination of high (Abdul-Ghani et al., 2012). The similarities between DIDP and analogs DINP and DEHP are described in detail below.

A.1 Structural Similarity

Structural similarity between DIDP and candidate analogs was assessed using two NAMs identified in the TSCA section 4(h)(2)(C) List of NAMs (the Analog Identification Methodology (AIM) program and the Organisation of Economic Cooperative Development Quantitative Structure Activity Relationship (OECD QSAR) Toolbox) and two additional EPA Office of Research products (Search Module within the Cheminformatics Modules and Generalized Read-Across [GenRA]) as shown in Table_Apx A-1.

AIM analysis was performed on CBI-side and analogs were described as 1st or 2nd pass. Tanimoto-based PubChem fingerprints were obtained in the OECD QSAR Toolbox (v4.4.1, 2020) using the Structure Similarity option with SMILES C1=CC=C(C(=C1)C(OCCC(CC(CCC)C)C)=O)C(OCCC(CC(CCC)C)C)=O (DIDP) and C(C(CCCCOC(=O)C1=CC=CC=C1C(=O)OCC(CCCCCC)C)C)(C)C (DINP) based on representative structures for DIDP and DINP (U.S. EPA, 2024e, f). Tanimoto scores were obtained in the Cheminformatics Search Module using Similar analysis with CASRNs 26761-40-0 (DIDP) and 28553-12-0 (DINP). The same DIDP SMILES used in OECD QSAR Toolbox was also user-defined in GenRA (v3.3) to generate chemical Morgan fingerprints for DIDP (limit of 100 analogs, no ToxRef filter).

AIM 1st and 2nd pass analogs were compiled with the top 100 analogs with indices greater than 0.5 generated from the OECD QSAR Toolbox and the Cheminformatics Search Module and indices greater than 0.1 generated from GenRA. Analogs generated from GenRA with molecular weight 418.62 g/mol underwent a visual assessment of structure based on their SMILES as to whether those analogs would fall under the chemical category of substances known as DINP. Analogs that appeared in three out of four programs were identified as potential analog candidates. Using these parameters, 25 analogs were identified as potentially suitable analog candidates for DIDP based on structural similarity. Only the results for structural comparison of DIDP to DINP, DEHP (CASRN 117-81-7), diisobutyl phthalate (DIBP, CASRN 84-69-5), and dibutyl phthalate (DBP, CASRN 84-74-2) are shown below due to the environmental hazard data of these analog candidates having completed data evaluation and extraction according to the procedures described in the Draft Systematic Review Protocol Supporting (U.S. EPA, 2021a). DINP was ultimately selected for quantitative read-across of soil invertebrate hazard to DIDP based on the additional lines of evidence (physical, chemical, and environmental fate and transport similarity and ecotoxicological similarity). The qualitative use of DEHP avian data in read-across to

DIDP was based on structural similarity between DEHP and DIDP but less agreement in the physical, chemical, and environmental fate and transport properties as well as uncertainty in establishing ecotoxicological similarity for avian hazard.

DINP, DEHP, DIBP, and DBP were indicated as structurally similar to DIDP in AIM (analogs were 1st or 2nd pass), OECD QSAR Toolbox (PubChem features = 0.97–1.00), and in the Cheminformatics Search Module (Tanimoto coefficients = 0.84–1.00). Additionally, DINP and DBP were indicated as structurally similar to DIDP in GenRA (Morgan fingerprints = 0.45–0.58, Table_Apx A-1). The structural similarity of DIDP to its analogs indicated in these tools supported the ultimate selection of DINP in the quantitative read-across to DIDP soil invertebrate hazard and DEHP in a qualitative read-across to DIDP avian hazard.

Table_Apx A-1. Structural Similarity between DIDP and Analog DINP

Phthalate	AIM	OECD QSAR Toolbox	Cheminformatics	GenRA
DIDP (target)	Exact Match	1.00	1.00	1.00
DINP	1st pass	1.00	1.00	0.45–0.58
DEHP	1st pass	0.98	0.89	–
DIBP	1st pass	0.97	0.84	–
DBP	2nd pass	0.97	0.93	0.5

A.2 Physical, Chemical, and Environmental Fate and Transport Similarity

DIDP analog candidates from the structural similarity analysis were preliminarily screened based on similarity in log octanol-water partition coefficient (log K_{OW}) and log organic carbon-water partition coefficient (log K_{OC}) obtained using EPI Suite™. For this screening step, DIDP, DINP, DEHP, DIBP, and DBP values were obtained from their respective scope documents (U.S. EPA, 2021b, c, 2020a, b, c). Analog candidates with log K_{OW} and log K_{OC} within one log unit relative to DIDP were considered potentially suitable analog candidates for DIDP. This preliminary screening analysis narrowed the analog candidate list from 25 candidate analogs to 4 candidate analogs. One of the four candidate analogs was DINP (CASRN 28553-12-0). DEHP was not one of the four candidate analogs due to a lower log K_{OW} value (7.6), which decreased confidence in the use of DEHP's avian hazard data to be used in a quantitative read-across to DIDP. This combined with uncertainty in the ecotoxicological line of evidence (Appendix A.3) lead to a qualitative, rather than quantitative, read-across of DEHP avian hazard to DIDP. Because DINP was ultimately selected for quantitative read-across of soil invertebrate hazard to DIDP based on the additional line of evidence (toxicological similarity) and the availability of DIDP soil invertebrate hazard data which had been systematically reviewed and assigned an overall quality determination of high according to the procedures outlined in the Draft Systematic Review Protocol Supporting (U.S. EPA, 2024h, 2021a), a more expansive analysis of physical, chemical, environmental fate and transport similarities between DIDP and DINP was conducted but not for the other candidate analogs.

Physical, chemical, and environmental fate and transport similarities between DIDP and DINP were assessed based on properties relevant to the soil compartment are shown in Table_Apx A-2. Physical, chemical, and environmental fate and transport values for DIDP and DINP are specified in the *Physical Chemistry Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024e), *Fate Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024b), *Physical Chemistry Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2024f), and *Fate Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2024c). DIDP and DINP water solubilities are within 10-fold (170 ng/L and 610 ng/L, respectively) as

are their vapor pressures (5.28×10^{-7} and 5.40×10^{-7} mmHg, respectively), indicating both target and analog are highly insoluble in water and not volatile.

The similarity in the properties described in Table_Apx A-2 support the quantitative read-across to DIDP from DINP soil invertebrate hazard data. For all physical and chemical properties of DIDP, see *Physical Chemistry Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024e). Bioaccumulation potential of DIDP and DINP in soil invertebrates is identical (bioaccumulation factor = 0.01–0.02 in earthworm *E. fetida*), indicating low bioaccumulation potential for both target and analog. Behavior of DIDP and DINP in soil is also similar, with identical estimated aerobic biodegradation (28–52 days), similar anaerobic degradation (minimal), and similar ranges in their log organic carbon-water partition coefficients (log K_{OC} range of 5.04–5.78 and 5.5–5.7, respectively), indicating both target and analog will be tightly bound to soil with faster biodegradation in aerobic vs. anaerobic conditions. Similar biodegradation rates between target and analog can increase confidence when considering read-across of chronic hazard as is the case for DINP soil invertebrate hazard data (ExxonMobil, 2010). The selected octanol/water partition coefficients (log K_{OW}), although exceeding ± 1 log unit, are generally similar (10.21 and 8.8 for DIDP and DINP, respectively)—indicating low affinity for water and higher sorption potential to soils and sediments for target and analog. Additionally, overlapping log K_{OW} ranges based on empirical evidence for DIDP (8.8–10.36) and DINP (8.8–9.7) were presented in the text of (U.S. EPA, 2024b, e) as well as an estimated log K_{OW} for DINP of 10.21 in (U.S. EPA, 2024b), emphasizing the general similarity in log K_{OW} for DIDP and DINP. Both chemicals exist as a liquid at room temperature and have similar molecular weights.

Table_Apx A-2. Comparison of DIDP and Analog DINP for Several Physical and Chemical and Environmental Fate Properties Relevant to Soil

Property	DIDP (Target)	DINP
Water Solubility	170 ng/L	610 ng/L
Log K_{OW}	10.21 (estimated)	8.8
Log K_{OC}	5.04–5.78	5.5–5.7
Biodegradation in soil (aerobic)	28–52 days (estimated)	28–52 days (estimated)
Biodegradation in soil (anaerobic)	Minimal (0% over 100 days)	No significant change in concentration after 2 years
BAF	0.01–0.02 (*E. fetida*)	0.01–0.02 (*E. fetida*)
Vapor Pressure (mmHg)	5.28E−07	5.40E−07
Molecular Weight	446.7 g/mol	418.62 g/mol
Physical state of the chemical	Clear liquid	Clear liquid

A.3 Ecotoxicological Similarity

For a soil invertebrate hazard quantitative read-across, toxicological similarity between DIDP and DINP was assessed based on empirical benthic invertebrate hazard data with an emphasis on exposures conducted in sediment. Although less relevant than hazard obtained from sediment exposures, toxicological similarity in empirical hazard evidence for aquatic invertebrates exposed to DIDP and DINP in water was also assessed to determine suitability of DINP for read-across of soil invertebrate hazard data to DIDP. Data used in the following comparisons were from studies with overall quality determinations of high and medium. Due to log K_{OW} exceedances of 8 for both target and analog, DIDP

and DINP were considered outside the domain of applicability for generating ECOSAR toxicity predictions for earthworm and aquatic invertebrates as another line of evidence. The ecotoxicological similarity line of evidence had uncertainty in supporting the avian hazard read-across from DEHP to DIDP due to a lack of predictive tools for assessing avian hazard. Therefore, this further supported a qualitative rather than quantitative read-across of avian hazard from DEHP to DIDP.

The empirical hazard data set for benthic and aquatic invertebrates indicates that DIDP and DINP have similar toxicological behavior (Table_Apx A-3).No toxicity was observed in endobenthic and epibenthic invertebrates exposed to DIDP and DINP in sediment at similar levels for 10 days (Call et al., 2001). Similar behavior (entrapment) was observed when neonate *Daphnia magna* were exposed for 21 days to similar levels of DIDP and DINP in water resulting in a reported ChV for survival of 0.042 mg/l and 0.055 mg/l, respectively (Rhodes et al., 1995). When tested with a dispersant, castor oil- 40-ethoxylate, DIDP and DINP concentrations of 1 mg/l show no adverse effects on *D. magna* reproduction, growth, and mortality during a 21-day exposure (Brown et al., 1998). In shorter exposure duration studies, the highest tested concentrations of DIDP and DINP in water did not achieve mortality in 50 percent of exposed larval midges (*P. parthenogenetica*) and *D. magna* neonates when administered at similar levels (Adams et al., 1995; EG & G Bionomics, 1984b; Springborn Bionomics, 1984a). A general lack of toxicity in benthic and aquatic invertebrates is observed when DIDP and DINP are administered at similar levels in the same studies, supporting the suitability of a no-effect hazard in a soil invertebrate (*E. fetida*) exposed to DINP (ExxonMobil, 2010) to quantitatively read-across to DIDP.

Table_Apx A-3. Empirical Hazard Comparison for Benthic and Aquatic Invertebrates Exposed to DIDP or Analog DINP

Species	Endpoint	DIDP (Target)	DINP (Analog)
		Empirical Toxicity	Empirical Toxicity
Midge (*Chironomus tentans*) [a]	10-day NOEC	≥2,630 mg/kg dw sediment	≥2,680 mg/kg dw sediment
Amphipod (*Hyalella azteca*) [a]	10-day NOEC	≥2,090 mg/kg dw sediment	≥2,900 mg/kg dw sediment
Waterflea (*Daphnia magna*) [b]	21-day ChV	0.042 mg/L (entrapment)	0.055 mg/L (entrapment)
Waterflea (*Daphnia magna*) [c]	21-day NOEC	≥1.0 mg/l	≥1.0 mg/l
Midge (*Paratanytarsus parthenogenetica*) [d e]	24–96-hour LC50	>0.64–0.96 mg/L	>0.08–0.12 mg/L
Waterflea (*Daphnia magna*) [f]	48-hour LC50	>0.18 mg/L	>0.089 mg/L
Earthworm (*Eisenia fetida*) [g]	28–56-day NOEL	Read-across	>390–1,052 mg/kg dry soil

dw = dry weight
[a] Data are from (Call et al., 2001) for mortality and growth/development endpoints.
[b] Data are from (Rhodes et al., 1995) for mortality endpoints.
[c] Data are from (Brown et al., 1998) for reproduction, growth, and mortality endpoints in the presence of a surfactant.
[d] Data are from (EG & G Bionomics, 1984b) for 24- to 48-hour mortality endpoints.
[e] Data are from (Adams et al., 1995) for 96-hour mortality endpoints.

Species	Endpoint	DIDP (Target)	DINP (Analog)
		Empirical Toxicity	Empirical Toxicity

[f] Data are from (Springborn Bionomics, 1984a) for mortality endpoints.
[g] Data are from (ExxonMobil, 2010) for mortality, growth/development, and reproductive endpoints.

A.4 Read-Across Weight of Scientific Evidence and Conclusions

DIDP presented with no soil invertebrate or avian hazard data; therefore, analog selection was carried out to address these data gaps. Several phthalates of interest (DINP, DEHP, DIBP, and DBP) were indicated as structurally similar to DIDP. However, DIDP and analog DINP exist as mixtures of isomers which introduces a level of uncertainty in the results generated within a structure program. To address this uncertainty, multiple structural programs were used which have complementary methods of assessing structural similarity between DIDP and its analogs and additional lines of evidence (physical chemical, ecotoxicological) were evaluated in the analog selection. A screening by log K_{OW} values and further comparison of additional physical, chemical, and environmental fate and transport properties indicated that DINP, which has soil invertebrate hazard data, was very similar to DIDP. However, DINP, a preferred analog, did not have avian hazard data to be used in a quantitative read-across to DIDP. DEHP, which has avian hazard data, has a lower log K_{OW} that led to its uncertainty in being used for quantitative read-across. Because of their high log K_{OW} values, DIDP and DINP could not be assessed for predicted earthworm hazard using ECOSAR. However, a comparison of available measured data in related taxa (sediment and aquatic invertebrates) showed almost identical ecotoxicological behavior between DIDP and DINP with generally no effects. Uncertainty in establishing ecotoxicological similarity for avian hazard due to lack of predictive tools further decreased confidence that DEHP could be used in a quantitative read-across for DIDP; therefore, DEHP avian hazard data were used in a qualitative read-across to DIDP. Looking across the multiple lines of evidence (structural, physical and chemical properties, ecotoxicological), DINP is an appropriate analog with high quality soil invertebrate hazard data to be used in a quantitative read-across to DIDP whereas avian hazard data from a less preferred analog, DEHP, was used in a qualitative read-across to DIDP.

Appendix B ENVIRONMENTAL HAZARD DETAILS

B.1 Evidence Integration

Data integration includes analysis, synthesis, and integration of information for the 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, 2021a), 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 (U.S. EPA, 2021a).

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 DIDP, environmental hazard data from toxicology studies identified during systematic review have used evidence that characterizes apical endpoints; that is, endpoints that could have population-level effects such as reproduction, growth, and/or mortality. Mechanistic data, when available, 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, 2021a) 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, 2021a).

EPA used the strength-of-evidence and uncertainties from (U.S. EPA, 2021a) for the hazard assessment to qualitatively rank the overall confidence using evidence Table 5-1 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, 2021a). 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 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 DIDP 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 (Table 5-1):

- *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, 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 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 (2005b) 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 and 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.

B.1.3 Data Integration Considerations Applied to Aquatic and Terrestrial Hazard Representing the DIDP Environmental Hazard Database

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

All of the studies that factored into the confidence section were rated high and medium. Based on systematic review data quality evaluation of studies, 11 studies with an overall quality determination of high and 2 studies with an overall quality determination of medium were used in the aquatic environmental hazard assessment. Studies with an overall quality determination of low or uninformative were not considered in the aquatic or terrestrial compartment. Several aquatic and terrestrial studies evaluated multiple endpoints, species, and durations adding to the overall strength of the database. Confidence in quality of database for acute DIDP hazard to fish and aquatic invertebrates is considered robust; chronic fish and aquatic invertebrate hazard is slight; chronic benthic hazard is moderate; and algal hazard is slight. Confidence in the quality of the database for terrestrial vertebrates (mammals) is considered robust (Table 5-1). Confidence in terrestrial invertebrates was based on read-across from a DINP earthworm study and was considered slight. No reasonably available data were provided to the EPA to assess risk to avian species or terrestrial plants.

Acute fish hazard for DIDP was represented by five species across five studies (Poopal et al., 2020; Chen et al., 2014; Adams et al., 1995; EG & G Bionomics, 1983a, b). Acute aquatic invertebrate hazard was represented by two species across four studies (Adams et al., 1995; EG & G Bionomics, 1984a; Springborn Bionomics, 1984a; Brown and Thompson, 1982). Chronic fish hazard data were identified in one study representing one species (Patyna et al., 2006), and chronic aquatic invertebrate data were identified in one study represented by one species (Rhodes et al., 1995). In each instance, the reported toxicity value exceeded the highest concentration tested. Sediment-dwelling invertebrate hazard data were identified in three studies represented by four species (amphipod [*H. azteca*] and three midges [*C. riparius, C. tentans,* and *P. parthenogenetica*]), with one study being an acute exposure (Call et al., 2001; Brown et al., 1996; Adams et al., 1995). No effects were observed in these four studies. In two algae hazard studies, no effects were seen up to the highest test concentration in the freshwater green algae *S. capricornutum* (Adams et al., 1995; Springborn Bionomics, 1984b).

For the terrestrial assessment, EPA assigned an overall quality determination of high or medium to four acceptable toxicity studies used as surrogates for terrestrial mammals (Cho et al., 2008; Hushka et al., 2001; Waterman et al., 1999; BIBRA, 1986). These studies contained relevant terrestrial toxicity data for Norway rat (*R. norvegicus*) strains F334 and SD (strains Crl:CD BR-VAF/Plus and Crl:CD BR). The terrestrial mammal data suggest potential trends (*e.g.*, sex-specific reproductive effects, strain-specific growth effects, potential route of administration-specific effects on survival); however, the ability to fully assess these trends for consistency is limited by the low number of studies. Additional studies reviewed qualitatively further strengthens the database and brackets the quantitative values in the TRV calculation.

Biological Gradient/Dose-Response

In all aquatic hazard studies, no effects were observed up to the highest DIDP concentration tested. Most of the studies included at least two test concentrations with most studies incorporating four or more test concentrations. One study performed a limit test using one concentration (Adams et al., 1995). It should be noted that the treatment levels in many studies exceeded the water solubility for DIDP (1.7×10^{-4} mg/L) (U.S. EPA, 2024b) suggesting DIDP was not truly solubilized in the test media. Terrestrial hazard for DIDP was represented by four strains of rat across five studies (Cho et al., 2008; Hushka et al., 2001; Waterman et al., 1999; Hellwig et al., 1997; BIBRA, 1986). In those studies, NOAEL/LOAEL values ranged from 38/134 to 128/620 mg/kg-day.

Biological Relevance
The mortality endpoint was evaluated in all acute fish and aquatic invertebrate hazard studies up to 96-hours, which is a relevant endpoint for ecological hazard (Poopal et al., 2020; Chen et al., 2014; Adams et al., 1995; EG & G Bionomics, 1984a; Springborn Bionomics, 1984a; EG & G Bionomics, 1983a, b). Reproduction and mortality (24-hour) was examined in one *D. magna* hazard study, but no effects were observed (Brown and Thompson, 1982). One 96-hour acute toxicity study involving a sediment-dwelling organism (*P. parthenogenetica,* second/third instar) was included with acute aquatic invertebrates since pore water in mg/L was reported and no sediment exposure occurred (Adams et al., 1995).

Mortality was an endpoint evaluated in all three subchronic/chronic benthic hazard studies with development being an additional metric assessed in two of the three studies (Call et al., 2001; Brown et al., 1996; Adams et al., 1995). Bulk sediment concentrations were reported in all subchronic/chronic benthic hazard studies and benthic pore water concentrations were an additionally reported in one study with the amphipod *H. azteca* and midge *C. tentans* (Call et al., 2001).

Chronic fish and aquatic invertebrate hazard studies reported no effects from DIDP exposure. One 140-day chronic hazard study showed no effects on survival, growth, or reproduction to the Japanese medaka *O. latipes* (Patyna et al., 2006). A 21-day flow-through study on *D. magna* reported a film on the test solution surface and subsequent entrapment of daphnids (Rhodes et al., 1995).

Two aquatic algae hazard studies both showed no effects on chlorophyll content in freshwater green algae *S. capricornutum* (Adams et al., 1995; Springborn Bionomics, 1984b).

Endpoints relevant to assessing ecological hazard to terrestrial mammals included studies showing effects on reproduction (Hushka et al., 2001), growth (Cho et al., 2008; Hushka et al., 2001; BIBRA, 1986), and survival (Cho et al., 2008). Other endpoints in these studies were considered qualitatively to support hazard identification but were not used quantitatively for determination of hazard values because they were not considered to be ecologically relevant for population-level effects (*i.e.*, behavior, morphological abnormalities, pathology).

Physical and Chemical Relevance
Most acute fish and aquatic invertebrate hazard studies considered the low solubility/high hydrophobicity of DIDP within the experimental design but did not use a carrier solvent to enhance water solubility. However, without the use of a solvent, the exposure to DIDP more likely reflects the physical and chemical characteristics of the natural environment. Acute hazard studies with the water flea and zebra fish used the solvents acetone and methanol, respectively, as a vehicle for DIDP (Chen et al., 2014; Brown and Thompson, 1982). A solvent was not used for the chronic aquatic invertebrate hazard study (Rhodes et al., 1995) while one was used for the chronic fish study (Patyna et al., 2006).

DIDP is expected to partition to the benthos and impact sediment-dwelling organisms to a greater extent compared to organisms within the water column. In all chronic/subchronic sediment toxicity studies, a solvent (acetone) was included in the experimental design (Call et al., 2001; Brown et al., 1996; Adams et al., 1995).

Environmental Relevance
In the aquatic environment, there is uncertainty regarding the effects of DIDP to the above discussed species because no reasonably available hazard studies demonstrated definitive endpoint values.

However, a solvent was used in some of the aqueous hazard studies that may decrease natural environmental conditions as well as environmental relevance. The database for terrestrial invertebrates consisted of one read-across study (ExxonMobil, 2010) that found no mortality effects of soil DINP on earthworms. EPA has moderate confidence in its relevance (biological, physical and chemical, and environmental) because soil concentrations were analytically verified and earthworms are a relevant representative species. However, one test concentration was used. EPA has moderate confidence in the relevance of the rodent studies and resultant TRV associated with uncertainties between formulated diets vs. natural forage diets for wild mammals.