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Draft Environmental Hazard Assessment for Diisodecyl Phthalate (DIDP)

Technical Support Document for the Draft Risk Evaluation

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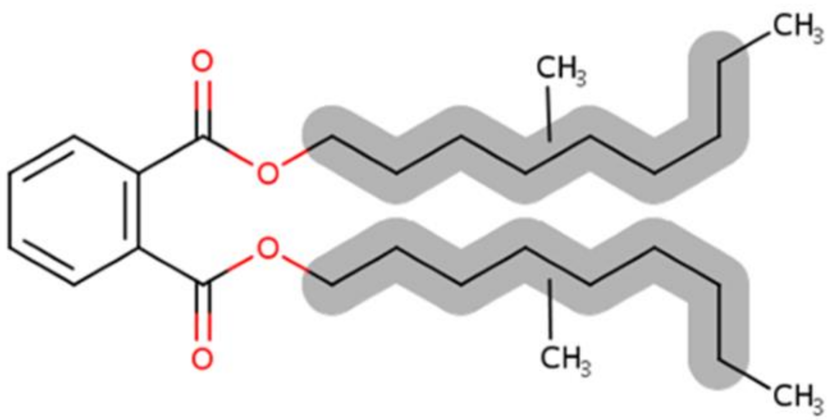

(Representative Structure)

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ABBREVIATIONS AND ACRONYMS

AF	Assessment factor
COC	Concentration(s) of concern
EC50	Effect concentration at which 50 percent of test organisms exhibit an effect
EPA	Environmental Protection 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
LOAEL	Lowest-observable-adverse-effect level
NOAEL	No-observable-adverse-effect level
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

Di-isodecyl Phthalate (DIDP) – Environmental Exposures:
Key Points

EPA considered all reasonably available information identified by the Agency through its systematic review process under TSCA to characterize environmental hazard endpoints for DIDP. The following bullets summarize key points of this risk evaluation section:

1 Aquatic species:
- 1.1 Hazard data for fish and aquatic invertebrates indicated no acute or chronic toxicity up to and exceeding the limit of water solubility.
- 1.2 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.
- 1.3 No toxicity was observed in two species of algae up to the highest tested concentration.

2 Terrestrial species:
- 2.1 Terrestrial hazard data for DIDP were not available for birds or mammalian wildlife species, so studies in laboratory rodents were used to derive hazard values for mammalian species.
- 2.2 DINP was considered appropriate for use as an analog for read-across to DIDP for earthworm (*Eisenia fetida*) hazard based on structural similarity, similar physical, chemical, environmental fate and transport behavior in soil, and similar toxicological behavior in other invertebrates (sediment-dwelling and aquatic).
- 2.3 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

Diisodecyl phthalate (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, narcotic mode of toxic action (Parkerton and Konkel, 2000); however, previous assessments have found few to no effects of DIDP on organism survival and fitness (EC/HC, 2015; ECJRC, 2003). EPA 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. EPA identified sources of environmental hazard data shown in Figure 2-10 of the *Final Scope of the Risk Evaluation for Di-isodecyl Phthalate (DIDP), CASRN 26761-40-0 and 68515-49-1* (Final Scope for the Risk Evaluation of DIDP) *Scope of the Risk Evaluation for 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* (U.S. EPA, 2021a) and *Draft Risk Evaluation for Diisodecyl Phthalate (DIDP) – Systematic Review Protocol* (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 toxicity reference value (TRV), which is expressed as a dose in units of mg/kg-bw/day. 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 the DIDP Ecological Risk Characterization module.

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 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). 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 studies summarized in Table 3-1 as the most relevant for quantitative assessment. Several studies evaluated multiple endpoints, species, and test durations.

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 NOEC 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 studies, mortality in 50 percent of the test organisms was not achieved up to the highest concentrations tested, resulting in LC50s ranging from greater than 0.37 to greater than 1.0 mg/L.

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 exceeded the highest concentration 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 phthlate (Springborn Bionomics, 1984a).

Chronic invertebrate hazard data for DIDP were identified in one acceptable study evaluating mortality and reproduction represented by one freshwater species over the course of 21-day (water flea [*D.*

magna]) (Rhodes et al., 1995). The study reported entrapment at the two highest concentrations and no effects on mortality and reproduction at the lower concentrations. The investigators attributed the apparent mortality to this surface entrapment or through a mechanism not related to the chemical. Therefore, this study was not used for quantitative hazard determination.

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 dry weight (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 and inconsistent effects of DIDP on mechanistic endpoints such as gene expression and protein synthesis. Therefore, EPA has moderate confidence in the studies that describe the potential effects of chronic dietary DIDP exposure to fish populations.

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

Duration	Test Organism	Endpoint	Hazard Value	Effect	Citation (Study Quality)
Aquatic vertebrates					
Acute	Fathead minnow (*Pimephales promelas*)	96-hour LC50	>0.66 mg/L	Mortality	(EG & G Bionomics, 1983a) (high)
	Fathead minnow (*Pimephales promelas*)	96-hour LC50	>0.47 mg/L	Mortality	(Adams et al., 1995) (high)
	Fathead minnow (*Pimephales promelas*)	96-hour LC50	>1.0 mg/L	Mortality	(Adams et al., 1995) (high)
	Bluegill (*lepomis macrochirus*)	96-hour LC50	>0.55 mg/L	Mortality	(EG & G Bionomics, 1983b) (high)
	Bluegill (*lepomis macrochirus*)	96-hour LC50	>0.37 mg/L	Mortality	(Adams et al., 1995) (high)
	Sheepshead minnow (*Cyprinodon variegatus*)	96-hour LC50	>0.47 mg/L	Mortality	(Adams et al., 1995) (high)
	Rainbow trout (*Oncorhynchus mykiss*)	96-hour LC50	>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	>500 mg/L	Mortality	(Chen et al., 2014) (medium)
Subchronic/ Chronic	Japanese medaka (*Oryzias latipes*)	42,81-day LOEC	>1 mg/kg bw/day	Post-hatch survival	(Patyna et al., 2006) (high)
	Japanese medaka (*Oryzias latipes*)	140-day LOEC	>1 mg/kg bw/day	Survival/ growth	(Patyna et al., 2006) (high)
Aquatic invertebrates					
Acute	Water flea (*Daphnia magna*)	48-hour LC50	>0.18 mg/L	Mortality	(Springborn Bionomics, 1984a) (high)
	Water flea (*Daphnia magna*)	48-hour LC50	>0.02 mg/L	Mortality	(Adams et al., 1995) (high)
	Water flea (*Daphnia magna*)	48-hour LC50	>0.32 mg/L	Mortality	(Brown and Thompson, 1982) (medium)
	Mysid shrimp (*Americamysis bahia*)	96-hour LC50	>0.08 mg/L	Mortality	(Adams et al., 1995) (high)
	Mysid shrimp (*Americamysis bahia*)	96-hour LC50	>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)
Benthic invertebrates					
Acute	Midge (*Paratanytarsus parthenogenica*)	96-hour LC50	>0.64 mg/L	Mortality	(Adams et al., 1995) (high)

Subchronic/ Chronic	Amphipod Crustacean (*Hyalella azteca*)	10-day LC50	>0.931 mg/L PW; >2,090 mg/kg BS	Mortality	(Call et al., 2001) (high)
	Midge (*Chironomus tentans*)	10-day LC50	>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)
Aquatic plants and algae					
Acute	Freshwater green algae (*Selenastrum capricornutum*)	96-hour LC50	>0.80 mg/L	Chlorophyll [a] increase	(Adams et al., 1995) (high)
Subchronic/ Chronic	Freshwater green algae (*Selenastrum capricornutum*)	8-day EC50	>1.3 mg/L	Chlorophyll [a] increase	(Springborn Bionomics, 1984b) (high)

DS = dry sediment; PW = pore water; BS = bulk sediment
[a] Feed study.
[b] Study authors indicate that the observed toxicity may be due to entrapment within the surface layer of the test chamber.

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 read-across to DIDP (Table 4-1).

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 EPA'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 no-observable-adverse-effect level (NOAELs) ranged from 38 to 1,000 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 SD 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 two 2-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). 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-observable-adverse-effect level (LOAEL) of 253 mg/kg-day and 508 mg/kg-day. 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. 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. F2 female body weight in Study B was also significantly decreased at sexual maturation. Studies are described further detail in the DIDP Human Health Hazard Assessment (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 two 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-day and 427 mg/kg-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-day and 508 mg/kg-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-day and 229 mg/kg-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-day and 414 mg/kg-day).

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

In the two-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-day for male and female rats, respectively (Cho et al., 2008).

Terrestrial Invertebrates

No terrestrial invertebrate studies were reasonably available to assess potential hazards from DIDP exposure. However, a 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 examining four replicates of 10 earthworms (*E. fetida*) *each* in artificial soil, which were exposed to DINP in concentrations of 925.2, 971.2, 981.2, and 1,052 mg/kg-dw for 28 days (ExxonMobil, 2010). Although it was reported that there was a significant increase in numbers of juvenile worms at study termination, no difference in mortality was observed in earthworms exposed to 1,000 mg DINP/kg-dw (nominal) soil (ExxonMobil, 2010).

Avian

No avian studies were available to assess potential hazards from DIDP exposure.

Terrestrial Plants

No terrestrial plants studies were available to assess potential hazards from DIDP exposure.

4.1 Terrestrial Organism Hazard Conclusions

Overall, EPA has moderate confidence in the evidence that DIDP has hazard to terrestrial mammals, but robust confidence that DIDP poses no hazard to soil invertebrates (Table 5-1). No studies on DIDP exposure to wild mammals, birds, or plants were available to assess DIDP hazard, indicating that no hazard has been observed in these groups under realistic exposure conditions. EPA reviewed studies of laboratory rodents to derive a TRV of 128 mg/kg-bw/day dietary DIDP exposure. This TRV represents the potential chronic exposure dose at which the dietary effects of DIDP may affect a general mammal. Thus, EPA has only 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.

Table 4-1. Terrestrial Organisms Environmental Hazard Studies Used for DIDP

Study Design	Test Organism	NOAEL/LOAEL (mg/kg-day)	Effect	Citation (Study Quality)
Terrestrial vertebrates				
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	Sprague-Dawley Rats (*Rattus norvegicus*)	500/1,000	Growth: ↓maternal body weight gain and food consumption at 1,000 mg/kg-day	(Waterman et al., 1999) (High)
Rats (30/sex/dose) fed diets containing 0, 0.2, 0.4, 0.8% DIDP continuously for two-generations (Study A). Received doses in units of mg/kg-day shown in Table 3-7 of the Human Health technical package (U.S. EPA, 2024d)	Sprague-Dawley Crl:CD BR-VAF/Plus Rat (*Rattus norvegicus*)	None/ 135[c] ↓ F2 survival on PND 1 and 4	Reproduction: ↓ F1/F2 percent live births at 0.8% (524/574 mg/kg-day) ↓ F1 survival on PND 4 (0.8%; 524 mg/kg-day); ↓ F2 survival on PND 1 and 4 (≥0.2%; 135 mg/kg-day), and PND 7 (0.8%; 574 mg/kg-day)	(Hushka et al., 2001) (Medium)
		117/229 ↓Body weight in P2 males	Growth/development: ↓ body weight at ≥0.4% in P2 males (≥229 mg/kg-day) and at 0.8% in P1 both sexes (427/508 mg/kg-day) and P2 females (566 mg/kg-day); ↓ F1 and F2 pup body weight and body weight gain at 0.8% (641/637 mg/kg-day) ↑ age (≤2 days) of vaginal patency for F1 females at ≥0.4% (359 mg/kg-day)	
Rats (30/sex/dose) fed diets containing 0, 0.02, 0.06, 0.2, 0.4% DIDP continuously for two-generations (Study B). Received doses in units of mg/kg-day shown in Table 3-10. of the Human Health technical package (U.S. EPA, 2024d)	Sprague-Dawley Crl:CD BR Rat (*Rattus norvegicus*)	38/ 134[a]	Reproduction: ↓survival of F2 pups on PND 1 and 4 at ≥0.2% (134 mg/kg-day)	(Hushka et al., 2001) (Medium)
		178/356	Growth/development: ↑ age at preputial separation (↑1.2 day) in F2 males at 0.4% (356 mg/kg-day)	
Rats (5/sex/dose) fed diets containing 0, 0.3, 1.2, or 2.5% DIDP for 21 days (equivalent to 0/0, 304/264, 1134/1042, 2100/1972 mg/kg-day for males/females	Fischer 344 Rat (*Rattus norvegicus*)	1042/1972	Growth: Body weight gain and terminal body weight decreased by 20 to 32% at high dose in both sexes (2100/1972 mg/kg-day)	(BIBRA, 1986) (High)

Rats fed diets containing 0, 400, 2000, or 8000 ppm (0/0, 22/23, 110/128, 479/620 mg/kg-day for males/females) for 2 years	Fischer 344 Rat (*Rattus norvegicus*)	128/620	Growth: Terminal body weight decreased by 14% in males and 18% in females at high dose (479/620 mg/kg-day in males/females)	(Cho et al., 2008) (Medium)
Terrestrial invertebrates				
Chronic exposure of DINP on the earthworm in artificial soil	Earthworm (*Eisenia fetida*)	None/1,000 mg/kg-dw soil	No difference in mortality between earthworms in the control soil and those exposed to 1,000 mg DINP/kg-dw soil	(ExxonMobil, 2010)
[a] 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. Mean measured doses of DIDP for Study A and B are provided in the human health hazard assessment (U.S. EPA, 2024d).				

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 Supporting TSCA Risk Evaluations for Chemical Substances* (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 moderate 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 EPA 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	Hazard Confidence
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	++	++	++	++	+++	Moderate
Terrestrial invertebrate assessment	+	Not applicable	+	+	++	Moderate
Terrestrial plant assessment	ND	ND	ND	ND	ND	Indeterminate

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

6 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 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 Kow 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) when enough data are available and deterministic approaches (*e.g.*, deriving a geometric mean of several comparable values) when more limited data are available. A Species Sensitivity Distribution (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 used an HC05 (a Hazardous Concentration threshold for 5% of species) to estimate a concentration that would protect 95% of species. This HC05 can then be used to derive a concentration of concern (COC), and the lower bound of the 95 percent confidence interval (CI) 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.

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

1. 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). EPA 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, EPA 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 227 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 6-2).

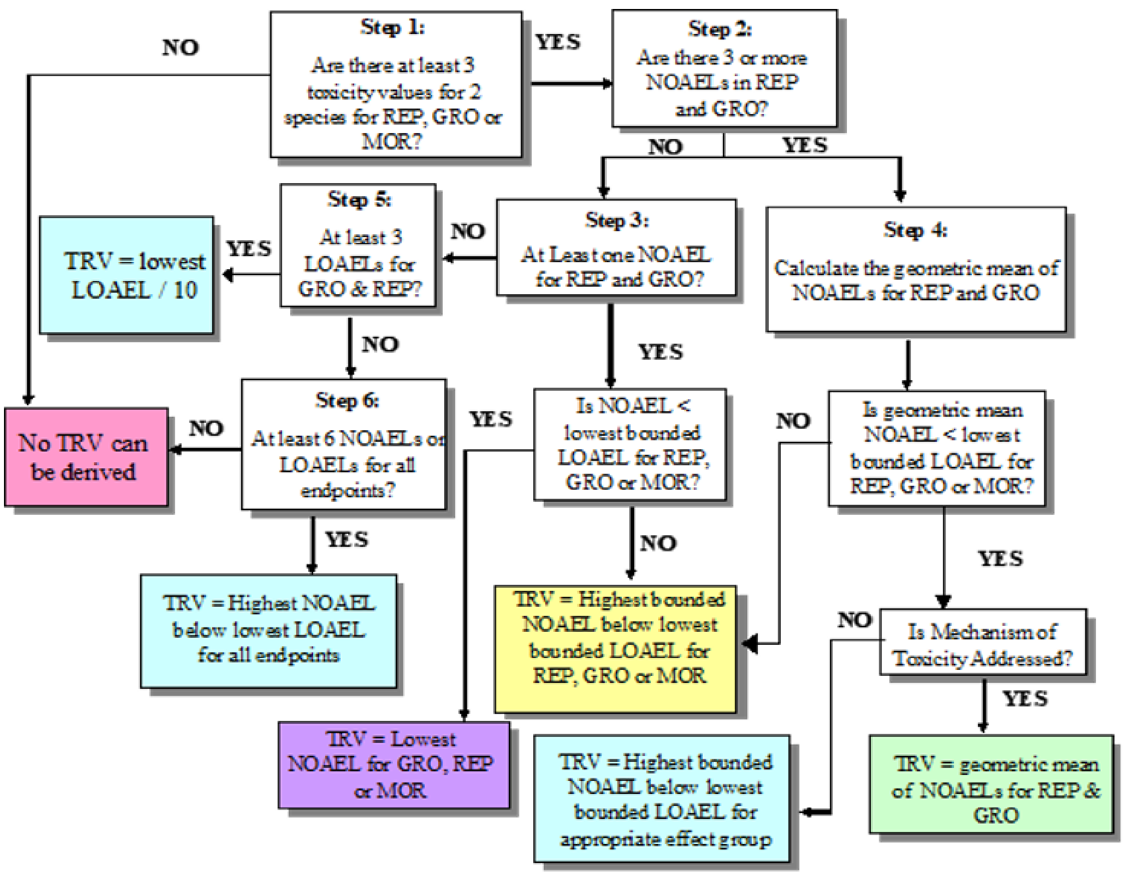
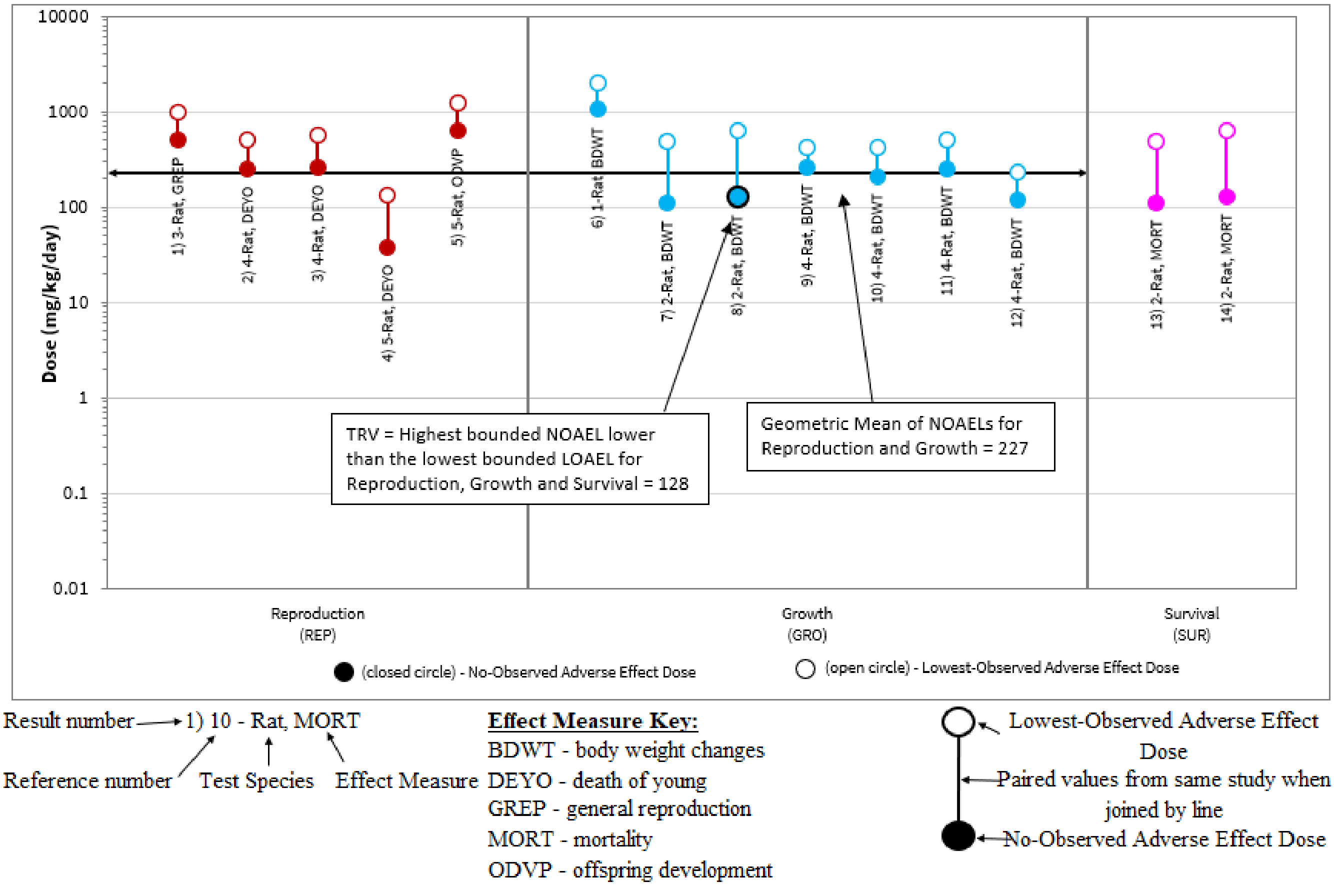


Figure 6-1. Terrestrial Mammal TRV Flow Chart



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 227 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 6-2. Mammalian TRV Derivation for DIDP

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/chemical/environmental fate and transport properties, and toxicity. This study found no difference in mortality between earthworms exposed to 1000 mg DINP/kg dw soil compared to control worms. However, the study found a statistically significant difference between the number of juveniles found in 1,000 mg DINP/kg dw soil compared to controls.

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: Terrestrial hazard data for DIDP were not available for birds, terrestrial plants, or terrestrial mammalian wildlife species, so 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 of 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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Appendix A ANALOG SELECTION FOR ENVIRONMENTAL HAZARD

No hazard data were identified for DIDP for soil invertebrates. Analog selection was performed to identify an appropriate analog to read-across to DIDP. Diisononyl phthalate (DINP) was selected as an analog 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 benthic and aquatic invertebrates. The DINP soil invertebrate hazard data to be used as analog data for DIDP received an overall quality determination of high (ExxonMobil, 2010). The similarities between DIDP and analog DINP 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 an EPA Office of Research product (Search Module within the Cheminformatics Modules) 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). Chemical Morgan fingerprints for DIDP (CASRN 28553-12-0) and DINP (CASRN 26761-40-0) could not be obtained using the U.S. EPA program, GenRA. 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. Analogs that appeared in two out of three programs were identified as potential analog candidates. Using these parameters, 57 analogs were identified as potentially suitable analog candidates for DIDP based on structural similarity. Only the results for structural comparison of DINP to DIDP is shown below because DINP was ultimately selected for read-across of soil invertebrate hazard to DIDP based on the additional lines of evidence (physical, chemical, and environmental fate and transport similarity and toxicological similarity) and having completed data evaluation and extraction.

DINP was indicated as structurally similar to DIDP in AIM (1st pass), OECD QSAR Toolbox (PubChem features = 1.00), in the Cheminformatics Search Module (Tanimoto coefficient = 1.00, Table_Apx A-1). The structural similarity of DIDP to DINP indicated in these tools supported the selection of DINP in the read-across to DIDP soil invertebrate hazard.

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

Phthalate	AIM	OECD QSAR Toolbox	Cheminformatics
DIDP (target)	Exact Match	1.00	1.00
DINP	1st pass	1.00	1.00

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 and DINP values were obtained from the *Scope of the Risk Evaluation for Di-isodecyl Phthalate DIDP* and *Final Scope of the Risk Evaluation for Di-isononyl Phthalate (DINP)* (U.S. EPA, 2021b, 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 57 candidate analogs to 6 candidate analogs. Two of the six candidate analogs represented DINP (CASRNs 28553-12-0 and 68515-48-0). Because DINP was ultimately selected for read-across of soil invertebrate hazard to DIDP based on the additional line of evidence (toxicological similarity) and having completed data evaluation and extraction, 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 *Chemistry and Fate Technical Support Packages Physical and Chemical Property Assessment [Draft] Risk Evaluation for Di-isodecyl Phthalate (DIDP)* (U.S. EPA, 2024e), *Fate and Transport Assessment [Draft] Risk Evaluation for Di-isodecyl Phthalate (DIDP)* (U.S. EPA, 2024b), *Physical and Chemical Property Assessment [Draft] Risk Evaluation for Di-isononyl Phthalate (DINP)* (U.S. EPA, 2024f), and *Fate and Transport Assessment [Draft] Risk Evaluation for Di-isononyl 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} mmHg and 5.40×10^{-7} mmHg, respectively), indicating both target and analog are highly insoluble in water and not volatile.

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 to 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 KOW 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, 2024d, e) as well as an estimated log KOW for DINP of 10.21 in (U.S. EPA, 2024b), emphasizing the general similarity in log KOW for DIDP and DINP. Both chemicals exist as a liquid at room temperature and have similar molecular weights. The similarity in the properties described in Table_Apx A-2 support the ability to read-across to DIDP from DINP soil invertebrate hazard data.

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 Toxicological Similarity

For a soil invertebrate hazard 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 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 *D. magna* were exposed for 21 days to similar levels of DIDP and DINP in water (Rhodes et al., 1995). 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 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)
Midge (*Paratanytarsus parthenogenetica*) [c d]	24-96-hour LC50	>0.64-0.96 mg/L	>0.08-0.12 mg/L
Waterflea (*Daphnia magna*) [e]	48-hour LC50	>0.18 mg/L	>0.089 mg/L
Earthworm (*Eisenia fetida*)[f]	28-56-day NOEL	Read-across	>389.6-1052 mg/kg dry soil

[a] Data are from (Call et al., 2001) for mortality and growth/development endpoints.
[b] Data are from (Rhodes et al., 1995) for mortality and reproductive endpoints.
[c] Data are from (EG & G Bionomics, 1984b) for 24- to 48-hour mortality endpoints.
[d] Data are from (Adams et al., 1995) for 96-hour mortality endpoints.
[e] Data are from (Springborn Bionomics, 1984a) for mortality endpoints.
[f] Data are from (ExxonMobil, 2010) for mortality, growth/development, and reproductive endpoints.

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 the scientific evidence. As stated in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (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. Additionally, mechanistic data that can be linked to apical endpoints will add to the weight of the 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 the scientific evidence and uncertainties was completed to support EPA's decisions. The weight of the scientific evidence fundamentally means that the evidence is weighed (*i.e.*, ranked) and weighted (*i.e.*, a piece or set of evidence or uncertainty may have more importance or influence in the result than another). Based on the weight of the scientific evidence and uncertainties, a confidence statement was developed that qualitatively ranks (*i.e.*, robust, moderate, slight, or indeterminate) the confidence in the hazard threshold. The qualitative confidence levels are described below.

The evidence considerations and criteria detailed within (U.S. EPA, 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 the scientific evidence and uncertainties that are described in the narrative and may or may not be equal. Therefore, the overall score is not necessarily a mean or defaulted to the lowest score. The confidence levels and uncertainty type examples are described below.

Confidence Levels

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

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

811 **Table_Apx B-1. Considerations that Inform Evaluations of the Strength of the Evidence within an Evidence Stream (*i.e.*, Apical
812 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/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.		

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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 two 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*], midge [*C. riparius*], midge [*C. tentans*], and midge [*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 five acceptable toxicity studies used as surrogates for terrestrial mammals (Hushka, 2001, 1336376; Cho et al, 2008, 698194; Waterman, 1999, 680201; Hellwig, 1997, 674193; BIBRA, 1986, 1325511). 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 x 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-hour, 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-h) was examined in one *D. magna* hazard study, but no effects were observed (Brown and Thompson, 1982). One 96-h 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, 2001, 1336376), growth (Hushka, 2001, 1336376; BIBRA, 1987, 1325511; Cho, 2008, 698194), and survival (Cho, 2008, 698194). 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/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 since no reasonably available hazard studies demonstrated definitive endpoint values. However, a solvent was used in some of the aqueous hazard studies which may decrease natural environmental conditions and environmental relevance. In the terrestrial environment, there is uncertainty regarding the exposure of DIDP to avian taxa and terrestrial plants. Exposure to these taxa via atmospheric deposition or other airborne release is unknown.