DIETHYL PHTHALATE

(CAS #84-66-2)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

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GreenScreen® Executive Summary for Diethyl Phthalate (DEP) (CAS #84-66-2)

Diethyl phthalate (DEP) is a colorless to pale yellow liquid at standard temperature and pressure. It is soluble in water (1,080 mg/L). It is not a volatile organic chemical (VOC). It is non-flammable and non-reactive. DEP is used commercially to impart flexibility to plastics (i.e., plasticizer), and can be easily released from these products. It is also used as a denaturant, film forming agent, fragrance, hair conditioning agent, plasticizer, and solvent in cosmetics.

In terms of human toxicity, DEP has moderate hazard concerns for reproductive toxicity, developmental toxicity and endocrine activity. Limited evidence in animals suggests that DEP may be highly irritating to the eyes.

In terms of environmental toxicity, DEP has moderate hazard concerns for acute and chronic aquatic toxicities. DEP is expected to be readily biodegradable, and has very low bioaccumulation potential.

DEP was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2e
    - Moderate Group I Human Toxicity (reproductive toxicity-R, developmental toxicity-D, and endocrine activity-E)

Data gaps (DG) exist for neurotoxicity (single dose-Ns and repeated dose-Nr*). As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), DEP meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if DEP were assigned a High score for the data gap Nr* or a Very High score for Ns, it would still be categorized as a Benchmark 2 Chemical.

GreenScreen® Hazard Summary Table for DEP

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeat*	single	repeat*										
L	**L**	**M**	*M*	**M**	**L**	**L**	**L**	DG	DG	**L**	*L*	**L**	*H*	**M**	**M**	*vL*	**vL**	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Chemical Assessment for Diethyl Phthalate (CAS #84-66-2)

Method Version: GreenScreen® Version 1.4
Assessment Type[1]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.3) Prepared By:
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Date: September 2, 2016

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Date: November 12, 2020, December 14, 2020

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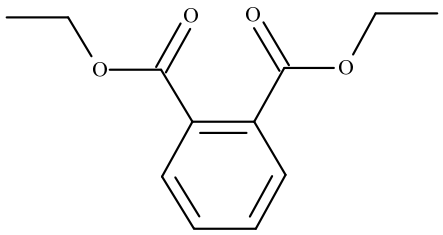
Date: November 12, 2020, December 29, 2020

Expiration Date: December 29, 2025[2]

Chemical Name: Diethyl Phthalate

CAS Number: 84-66-2

Chemical Structure(s):



Also called: 1,2-Benzenedicarboxylic acid, diethyl ester; Diethyl 1,2-benzenedicarboxylate; Diethyl o-phenylenediacetate; Ethyl phthalate; Di-n-ethyl phthalate; 2-Benzenedicarboxylic acid; 1,2-diethyl ester; 1,2-Benzenedicarboxylic acid, diethyl ester; Phthalic acid, diethyl ester (ChemIDplus 2020)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
No surrogates were used in this assessment as a relatively complete dataset sufficient for the assigned benchmark score was identified for DEP, and no appropriate surrogates with relevant data were identified.

[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

Identify Applications/Functional Uses:
1. Plasticizer in plastics and cosmetics (U.S. EPA 2014, EC 2020)
2. Solvent for fragrances and cosmetic ingredients (HSDB 2009, EC 2020)
3. Wetting agent (HSDB 2009)
4. Camphor substitute (HSDB 2009)
5. Alcohol denaturant (HSDB 2009)
6. Film forming agent in cosmetics (EC 2020)
7. Fragrance in cosmetics (EC 2020)
8. Hair conditioning in cosmetics (EC 2020)

Known Impurities[3]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for DEP[4,5 6,7]: DEP was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Toxicity (reproductive toxicity-R, developmental toxicity-D, and endocrine activity-E)

Data gaps (DG) exist for neurotoxicity (single dose-Ns and repeated dose-Nr*). As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), DEP meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if DEP were assigned a High score for the data gap Nr* or a Very High score for Ns, it would still be categorized as a Benchmark 2 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for DEP

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeat*	single	repeat*										
L	**L**	**M**	*M*	**M**	**L**	**L**	**L**	DG	DG	**L**	*L*	**L**	*H*	**M**	**M**	*vL*	**vL**	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[7] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

Environmental Transformation Products

DEP was degraded to ethyl methyl phthalate, dimethyl phthalate, methyl phthalate and ethyl phthalate when co-contaminated with methanol (HSDB 2009). ToxServices did not consider these chemicals feasible environmental transformation products because the presence of methanol is required. DEP hydrolyzes slowly in water (HSDB 2009). However, DEP is predicted to be readily biodegradable and was rapidly degradable in the environment (see Persistence section below); therefore, no degradation products are expected to be persistent enough to be considered relevant transformation products for this assessment. Therefore, the Benchmark Score of DEP is not impacted by its environmental transformation products.

Introduction

DEP (trade names Neantine, Palatinol A, and Solvanol) is used commercially to impart flexibility to plastics, and can be easily released from these products (ATSDR 1995). It is used as a denaturant, film forming agent, fragrance, hair conditioning agent, plasticizer, and solvent in cosmetics (EC 2020). DEP is manufactured by the reaction of phthalic anhydride and ethanol and subsequent purification (HSDB 2009).

ToxServices assessed DEP against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List (SCIL)

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2020a). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

DEP is not listed on the SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2020) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for DEP can be found in Appendix C.

- DEP is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- DEP is not listed on the U.S. DOT list.
- DEP is on the following lists for multiple endpoints.
    - German FEA – Substances Hazardous to Waters
    - GHS – New Zealand – 9.1D (algal) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action

[8] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

  - GHS – New Zealand – 9.1D (crustacean) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action
  - GHS – New Zealand – 9.1D (fish) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

DEP does not have harmonized H Statements in the European Union (EU). It has not been self-classified in the REACH dossier. The majority of REACH notifiers did not classify DEP for any endpoint. H Statements assigned by Japan are listed in Table 1, below.

Table 1: H Statements for DEP (CAS #84-66-2) (NITE 2006, 2018)

H Statement	H Statement Details
H315	Causes skin irritation
H320	Causes eye irritation
H317	May cause an allergic skin reaction
H335	May cause respiratory irritation
H336	May cause drowsiness or dizziness
H401	Toxic to aquatic life

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for DEP (CAS #84-66-2)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Rubber gloves, goggles or face shield, boots	HSDB 2009	ACGIH TLV: 8h TWA = 5 mg/m^3	HSDB 2009
		NIOSH REL: 10h TWA = 5 mg/m^3	HSDB 2009

ACGIH: American Conference of Governmental Industrial Hygienists
REL: Recommended Exposure Limits
TLV: Threshold Limit Value
TWA: Time Weighted Average

Physicochemical Properties of DEP

DEP is a colorless to pale yellow liquid at standard temperature and pressure. It is soluble in water (1,080 mg/L), and its vapor pressure of 2.1×10^3 mm Hg indicates that it is slightly volatile and has the potential for form a vapor. The low partition coefficient (log K_{ow}) of 2.47 indicates that it is more soluble in octanol than in water.

Table 3: Physical and Chemical Properties of DEP (CAS #84-66-2)

Property	Value	Reference
Molecular formula	C12-H14-O4	ChemIDplus 2020
SMILES Notation	CCOC(=O)c1ccccc1C(=O)OCC	ChemIDplus 2020
Molecular weight	222.2386	ChemIDplus 2020
Physical state	Liquid	HSDB 2009
Appearance	Colorless to water-white oily liquid Pale yellow liquid	HSDB 2009 ECHA 2020

Table 3: Physical and Chemical Properties of DEP (CAS #84-66-2)		
Property	**Value**	**Reference**
Melting point	-40.5ºC	HSDB 2009
Boiling point	295ºC	ChemIDplus 2020
Vapor pressure	2.1 x 10^{-3} mmHg	HSDB 2009
Water solubility	1,080 mg/L at 25ºC	HSDB 2009
Dissociation constant	NA	
Density/specific gravity	1.120 at 25ºC	HSDB 2009
Partition coefficient	2.47	HSDB 2009

Toxicokinetics

Following oral administration in rats and mice, DEP is readily and extensively absorbed and rapidly eliminated, with urine being the main elimination pathway. It is widely distributed and does not accumulate in tissue. DEP is primarily metabolized of monoethyl phthalate (MEP). Dermal absorption in animals is significant but dermal absorption through human skin is significantly less (> 10 times) (NICNAS 2008).

- NICNAS 2008
  - *Absorption*
    - *Oral:* Following oral administration of ^{14}C-DEP (doses not reported) in rats and mice, 90% of the administered dose was excreted in the urine within 48 hours, with 82% of it eliminated within the first 24 hours.
    - *Dermal:* Following dermal administration of 5-8 mg/cm^2 ^{14}C-DEP to male rat skin under occlusion, approximately 74% of the dose was absorbed.
    - *Dermal:* In an *in vitro* comparative study of percutaneous absorption of DEP between human and rat skin, DEP was absorbed through rat skin at a higher percentage than through human skin. Approximately 35.9% of the ^{14}C-DEP (dose not reported) was absorbed through male rat dorsal skin, while 3.9% of the ^{14}C-DEP (dose not reported) was absorbed through human breast skin after 72 hours.
    - *Dermal:* A second *in vitro* study also found that the *in vitro* absorption of DEP was significantly higher (37.5%) through rat skin compared to human skin. DEP had a steady state absorption rates of 1.27 µg/cm^2/hour and 41.37 µg/cm^2/hour for human and rat skin, respectively.
  - *Distribution*
    - Following oral administration of ^{14}C-DEP in rats and mice, the highest radioactivity concentrations were measured in the liver and kidney, followed by the blood, spleen, and adipose tissue.
    - Following intraperitoneal injection of ^{14}C-DEP in rats (doses not reported), radioactivity was detected in the amniotic fluid, maternal, placental, and fetal tissues.
  - *Metabolism*
    - The ester hydrolysis product, MEP, was the major metabolite product identified in the urine of rats and mice. Phthalic acid was also identified in the urine.
    - Hydrolysis of DEP to MEP has been demonstrated *in vitro* for rats and humans.
  - *Excretion*
    - As stated previously, following oral administration of ^{14}C-DEP (doses not reported) in rats and mice, 90% of the administered dose was excreted in the urine within 48 hours, with 82% of it eliminated within the first 24 hours. Approximately 3% was identified in the feces within 48 hours.

- In humans, approximately 71% of MEP was excreted in the urine as the free monoester with the remaining excreted as MEP glucuronide.
- Following dermal administration of 5-8 mg/cm^2 ^{14}C-DEP to male rat skin under occlusion, 24% and 1% of the administered dose was excreted in the urine and feces within 24 hours, respectively.
- Following dermal administration of ^{14}C-DEP (doses not reported) to rabbit skin, approximately 49% and 1% of the administered dose was excreted in the urine and feces within 4 days, respectively.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*

DEP was assigned a score of Low for carcinogenicity based on lack of sufficient evidence in dermal studies in rats and mice supported by expert judgments of United States Environmental Protection Agency (U.S. EPA), Dutch National Institute for Public Health and the Environment (RIVM) and International Programme on Chemical Safety (IPCS). GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as equivocal evidence of carcinogenicity was identified in the chronic dermal toxicity study in mice.

- Authoritative and Screening Lists
  - *Authoritative:* U.S. EPA – IRIS Carcinogens – (1986) Group D – Not classifiable as to human carcinogenicity.
  - *Screening:* Not present on any screening lists for this endpoint.
- NTP 1995
  - *Dermal:* F344/N rats (60/sex/dose) were dermally exposed to DEP (>99% purity) at 0, 123, or 369 µg 5 days/week for 103 weeks. Intermediate sacrifice was carried out after 15 months in up to 10 rats per group. Survival in all male groups significantly decreased after 15 months, and there were decreased body weights (slight) in males at the high dose. No adverse clinical signs or evidence of dermatotoxicity were found. There was no evidence of carcinogenicity in this study.
  - *Dermal:* B6C3F$_1$ mice (60/sex/dose) were dermally exposed to DEP (>99% purity) at 0, 9, 19 or 37 µg 5 days/week for 103 weeks followed by a one-week recovery period. Intermediate sacrifice was carried out after 15 months in up to 10 mice per group. Treatment had no effects on survival, body weight, adverse clinical signs or gross evidence of dermatotoxicity. There was an increase in the incidence of liver neoplasms in both sexes with combined incidences of adenoma and carcinoma in the control, low, mid, and high dose groups of 9/50, 14/50, 14/50 and 18/50, respectively, in males and 7/50, 16/51, 19/50 and 12/50, respectively, in females. Statistical significance was reached at the highest dose in males and the two lower doses in females. NTP considered this equivocal evidence of carcinogenicity as these incidences were within the historical range and because there was no clear dose-response in females.
  - DEP did not initiate skin carcinogenesis after chronic dermal exposure and promotion with 12-*O*-tetradecanoylphorbol-13-acetate (TPA), and DEP did not promote skin carcinogenesis in 7,12-dimethylbenz(a)anthracene- (DMBA) initiated CD-1 mice. High incidences of skin cancer were found in DMBA-initiated and TPA-promoted mice.

- ITER 2018
    - The carcinogenicity of DEP has been evaluated by the Agency for Toxic Substances & Disease Registry (ATSDR) (1995 assessment), IPCS (2001 assessment), RIVM (2000 assessment) and U.S. EPA (1998 assessment). U.S. EPA classified it to Group D (not classifiable as a human carcinogen) for all routes of exposure. RIVM concluded that DEP is not genotoxic and developed a risk value based on a threshold approach. IPCS noted that long-term dermal studies on DEP in rats and mice did not demonstrate the carcinogenic potential, and *in vitro* genotoxicity studies provided equivocal results.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

DEP was assigned a score of Low for mutagenicity/genotoxicity based on negative high quality data on gene mutation and chromosomal aberration *in vitro*. Although positive or equivocal results were identified in some bacterial mutagenicity assays and one sister chromatid exchange (SCE) assay, the weight of evidence from well-conducted and reported studies, including several GLP-compliant guideline studies, support a lack of genotoxicity. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as was based on high quality studies reported in the REACH dossier.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020 (only studies specified as "key studies" were described below due to the adequacy of high quality data)
    - *In vitro:* DEP (99.97% purity) in DMSO was negative in a GLP-compliant bacterial reverse mutation assay conducted according to OECD Guideline 471 in *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP_2 *uvr*A at up to 5,000 µg/plate with and without metabolic activation. Cytotoxicity was observed at 1,250 µg/plate and higher in *S. typhimurium* and at 5,000 µg/plate in *E. coli*. Vehicle control, negative control, and positive control were all valid. This study was assigned a Klimisch score of 1 (reliable without restriction) (REACH dossier study 003).
    - *In vitro:* DEP (purity not reported) in DMSO was negative in a bacterial reverse mutation assay conducted in *S. typhimurium* tester strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation. The tested concentrations were not reported. Cytotoxicity and the validity of the vehicle control were not specified. The positive control was valid. No additional details were provided. This study was assigned a Klimisch score of 2 (reliable with restrictions) (REACH dossier study 004).
    - *In vitro:* DEP (99.96% purity, as ester content) in DMSO was negative in a GLP-compliant mammalian cell gene mutation assay conducted according to OECD Guideline 476 in mouse lymphoma L5178Y cells at concentrations of up to 925 µg/mL with and without metabolic activation. Cytotoxicity was observed (details not specified). Vehicle control, negative control and positive control were all valid. This study was assigned a Klimisch score of 1 (reliable without restriction) (REACH dossier study 001).
    - *In vitro:* DEP (99.96% purity, as ester content) in dimethyl sulfoxide (DMSO) was negative in a GLP-compliant *in vitro* chromosomal aberration test conducted according to OECD Guideline 473 in human lymphocytes at concentrations of 104 - 1,780 µg/mL with and without metabolic activation. No cytotoxicity was observed. Vehicle control, negative control, and positive control were all valid. This study was assigned a Klimisch score of 1 (reliable without restriction) (REACH dossier study 002).

- U.S. EPA 2014
    - *In vitro:* Negative results were observed in seven bacterial reverse mutation assays in the presence and absence of metabolic activation in *S. typhimurium* and/or *E.coli.* Positive results were observed for reverse mutation in *S. typhimurium* TA100 in two studies without metabolic activation at 1,000 or 2,000 µg/plate. Cytotoxicity was not measured in one of the studies, and the revertant count was less than twice the control values in the other study. DEP was positive for forward mutation in the absence of metabolic activation in *S. typhimurium* TA100 at 733 µg/mL in an 8-azauanine resistance test in the presence of cytotoxicity.
    - *In vitro:* DEP was negative in an SCE assay when tested at 167 µg/mL in Chinese hamster ovary (CHO) cells without metabolic activation but positive with metabolic activation. DEP was negative for chromosomal aberration in two *in vitro* tests in CHO cells and Chinese hamster fibroblasts with and without metabolic activation when tested at up to 324 and 250 µg/mL, respectively.

Reproductive Toxicity (R) Score (H, M, or L): M

DEP was assigned a score of Moderate for reproductive toxicity based on statistically significant effects on the male reproductive system in rats and mice without affecting fertility and evidence of a relationship between DEP exposure and preterm birth in humans. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity (CPA 2018b). The confidence in the score is high because it is based on well-conducted animal studies.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- NICNAS 2011
    - In a two-generation reproductive toxicity study, CD-1 mice (20/sex/dose) were fed diets containing 0, 0.25, 1.25, or 2.5% DEP (purity not reported) (equivalent to 0, 340, 1,770 or 3,640 mg/kg/day) for 18 weeks; animals were treated one week before cohabitation, during cohabitation (12 weeks), and for 3 weeks after cohabitation. Offspring were removed 12 hours after delivery, except for the final litters which remained with the mother until weaning. At maturity, pups from the same treatment group (20 pairs from 0 and 2.5% dose groups) were mated to produce the F2 generation. F2 litters were examined for litter size, survival, sex, and pup weight. No adverse treatment-related effects on physiology, fertility, or reproductive performance were observed in the F0 generation. Animals in the F1 generation exhibited reduced body weight, decreased number of live pups per litter, decreased sperm concentration, increased prostate weight in males, increased liver weight in females, and decreased pituitary weight in females. The number of pups born alive, pup sex, and pup weight were not affected by treatment. A LOAEL of 3,640 mg/kg/day was identified for maternal toxicity in the F1 generation based on decreased body weight in males and females, increased liver weight in females, and decreased pituitary weight in females. A LOAEL of 3,640 mg/kg/day was assigned for fertility-related parameters based on decreased sperm counts and increased prostate weight in males in the F1 generation. A NOAEL of 3,640 mg/kg/day was assigned for maternal toxicity and fertility-related parameters in the F0 generation. .
    - In a two-generation reproductive study, Sprague-Dawley rats (24/sex/dose) were fed diets containing DEP (purity not reported) at 0, 600, 3,000, or 15,000 ppm (equivalent to 40-56, 197-267, 1,016-1,375 mg/kg/day). Animals were dosed for 15 or 17 weeks (males and

females) beginning 10 weeks prior to mating, throughout mating, gestation, and lactation, until weaning. Pups from the F1 generation were reared for 10 weeks and then mated to produce the F2 generation. Animals in the high dose groups of the F0 and F1 generations exhibited statistically significant increases in absolute and/or relative liver weights. Females in the high dose group of the F1 generation also had significantly increased absolute and relative kidney weights. High dose males in the F0 generation exhibited statistically significant absolute epididymis weight and mid dose group of the same generation exhibited increased number of abnormal and tailless sperms and decreased serum testosterone. In the F1 generation, parental animals in the mid and high dose groups exhibited abnormal and tailless sperm. However, no effect on reproductive organ weight were measured. Number of implants, number of pups born, and pup weights were not affected by treatment. There was no effect on anogenital distance or age of preputial separation, however, the age of onset of vaginal opening was delayed in high dose F1 females. Significant delay in pinna detachment was observed in F1 high dose males. Study investigators concluded delayed pinna detachment and vaginal opening are adverse developmental effects occurring concurrently with increased liver and kidney weights in maternal animals. A NOAEL of 197-267 mg/kg/day and LOAEL of 1,016-1,375 mg/kg/day was assigned for maternal toxicity in males and females based on increased liver weight in the F0 and F1 generations and increased kidney weight in females in the F1 generation. A NOAEL of 40 mg/kg/day and LOAEL of 197 mg/kg/day was assigned in males for fertility-related effects based on decreased serum testosterone in the F0 generation and an increase in abnormal sperm and tailless sperm in the F0 and F1 generation.
    - A number of studies on testes and testicular function are available. Wistar rats, receiving DEP in the diet or by gavage at doses up to 2,000 mg/kg/day for up to 150 days, exhibited decreased testis weight, testicular antioxidant enzymes, serum testosterone, and serum androstenedione, ultrastructural changes in Leydig cells, and decreased sperm counts and motility.
- ATSDR 1995
    - While many phthalates are known to affect the male reproductive system, DEP may produce at most minor adverse effects on male reproductive organ function or morphology in animals. No adverse effects on fertility were observed in a two-generation continuous breeding dietary reproductive toxicity study in CD-1 mice at doses of up to 2.5% (equivalent to 3,250 mg/kg/day, >99% pure), but the total number of live pups per litter born to F1 parental animals significantly reduced at the highest dose (3,250 mg/kg/day). Oral doses up to 1,600 mg/kg/day did not affect the weight and histology of testicular and accessory gland in male rats. Phthalates are known to cause testicular toxicity affected progesterone binding to testis microsomes, testicular CYP450 content, and testicular steroidogenic enzyme activity, but DEP did not have these effects. Ultrastructural Leydig cell changes (mitochondrial swelling with focal dilation of the smooth endoplasmic reticulum) were observed after oral exposure to 2,000 mg/kg DEP in rats. This was considered a less serious effect. DEP adversely affected sperm motility *in vitro* at 0.33 mM and higher concentrations. These data along with data on other phthalates suggest that testicular functional and anatomical changes occur inconsistently at high DEP exposure levels. Limited data were available in females, but indicate that DEP is not reproductively toxic to females.
- Radke et al. 2018
    - A systematic review of epidemiological data evaluated twelve studies describing the association between DEP exposure and sperm parameters. An inverse relationship between

DEP concentration and sperm quality was identified for sperm concentration in four studies, sperm motility in two studies, and sperm morphology in three studies. No association between DEP and sperm quality was identified in the remaining three studies. The authors of the systematic review concluded that the evidence for an effect of DEP on human sperm parameters is indeterminate.

- Radke et al. 2019
    - A systematic review of epidemiological data evaluated studies describing the association between DEP exposure and female pubertal development, primary fecundity outcomes, early or total loss of pregnancy, or preterm birth/gestational duration. The relationships for DEP exposure and female pubertal development, primary fecundity outcomes, and early or total loss of pregnancy are discussed below under the Developmental Toxicity endpoint. The relationship between DEP exposure and preterm birth was considered moderate.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
DEP was assigned a score of Moderate for developmental toxicity based on adverse effects in developmental toxicity studies and two-generation reproductive toxicity studies supported by slight evidence in humans. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity (CPA 2018b). The confidence in the score is reduced as effects were only reported at oral doses exceeding the suggested limit dose of 1,000 mg/kg/day.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020 (only the prenatal developmental toxicity study specified as "key" study are described in detail below)
    - In a GLP-compliant prenatal developmental toxicity study performed in a manner similar to OECD Guideline 414, pregnant Sprague-Dawley rats (25-32/dose) were exposed to 0, 0.25, 2.5 or 5.0% DEP (>99% purity) in the diet during gestational days 6 and 15 and sacrificed on gestational day 20. Reduced body weight and body weight gain were measured in dams at the mid and high doses. Food and water consumption was also reduced in these groups. There was a significant increase in the incidence of skeletal variations due to an increase in rudimentary extra lumbar ribs at the high dose. The study authors identified a NOAEL and LOAEL of 0.25% and 2.5%, respectively, for maternal toxicity based on effects on body weight and body weight gain. A NOAEL and LOAEL of 2.5% and 5.0% were identified for developmental toxicity based on increased incidence of skeletal variations. This study was assigned a Klimisch score of 2 (reliable with restrictions) (REACH dossier study 001).
    - Additional supporting prenatal developmental toxicity studies were also presented in the REACH dossier, and demonstrated a lack of effect on fetal development in rabbits at oral doses up to 1 mL/kg and in mice at dermal doses up to 1,600 mg/kg (maternal toxicity and reduced fetal body weight observed at 5,600 mg/kg/day).
- NICNAS 2011
    - In the previously described two-generation reproductive toxicity study (see the Reproductive Toxicity section, above), CD-1 mice (20/sex/dose) were fed diets containing 0, 0.25, 1.25, or 2.5% DEP (purity not reported) (equivalent to 0, 340, 1,770 or 3,640 mg/kg/day) for 18 weeks; animals were treated one week before cohabitation, during cohabitation (12 weeks), and for 3 weeks after cohabitation. Offspring were removed 12 hours after delivery, except for the final litters which remained with the mother until weaning. At maturity, pups from the same treatment group (20 pairs from 0 and 2.5% dose groups) were mated to produce the

F2 generation. F2 litters were examined for litter size, survival, sex, and pup weight. No adverse treatment-related effects on physiology, fertility, or reproductive performance were observed in the F0 generation. Animals in the F1 generation exhibited reduced body weight, decreased number of live pups per litter, decreased sperm concentration, increased prostate weight in males, increased liver weight in females, and decreased pituitary weight in females. The number of pups born alive, pup sex, and pup weight were not affected by treatment. A LOAEL of 3,640 mg/kg/day was identified for maternal toxicity in the F1 generation based on decreased body weight in males and females, increased liver weight in females, and decreased pituitary weight in females. A LOAEL of 3,640 mg/kg/day was assigned for developmental effects in the F2 generation based on a decrease in the number of live pups per litter. A NOAEL of 3,640 mg/kg/day was assigned for developmental effects in the F1 generation.

- In the previously described two-generation reproductive study (see the Reproductive Toxicity section, above), Sprague-Dawley rats (24/sex/dose) were fed diets containing DEP (purity not reported) at 0, 600, 3,000, or 15,000 ppm (equivalent to 40-56, 197-267, 1,016-1,375 mg/kg/day). Animals were dosed for 15 or 17 weeks (males and females) beginning 10 weeks prior to mating, throughout mating, gestation, and lactation, until weaning. Pups from the F1 generation were reared for 10 weeks and then mated to produce the F2 generation. Animals in the high dose groups of the F0 and F1 generations exhibited statistically significant increases in absolute and/or relative liver weights. Females in the high dose group of the F1 generation also had significantly increased absolute and relative kidney weights. High dose males in the F0 generation exhibited statistically significant absolute epididymis weight and mid dose group of the same generation exhibited increased number of abnormal and tailless sperms and decreased serum testosterone. In the F1 generation, parental animals in the mid and high dose groups exhibited abnormal and tailless sperm. However, no effect on reproductive organ weight were measured. Number of implants, number of pups born, and pup weights were not affected by treatment. There was no effect on anogenital distance or age of preputial separation, however, the age of onset of vaginal opening was delayed in high dose F1 females. Significant delay in pinna detachment was observed in F1 high dose males. Study investigators concluded delayed pinna detachment and vaginal opening are adverse developmental effects occurring concurrently with increased liver and kidney weights in maternal animals. A NOAEL of 197-267 mg/kg/day and LOAEL of 1,016-1,375 mg/kg/day was assigned for maternal toxicity in males and females based on increased liver weight in the F0 and F1 generations and increased kidney weight in females in the F1 generation. A NOAEL of 197-267 mg/kg/day and LOAEL of 1,016-1,3775 mg/kg/day was assigned in males and females for developmental effects based on decreased pup weight on post-natal day (PND) 21 in the F1 and F2 generation and on PNDs 4-21 in females of the F1 generation, delayed pinna detachment in males of the F1 generation, and delayed vaginal opening in females of the F1 generation.

- ATSDR 1995
  - No significant maternal toxicity or developmental toxicity was observed in mice when pregnant mice were administered 4,500 mg/kg DEP on gestational days 6 to 13. This study used a proposed short-term *in vivo* developmental toxicity protocol, and a comparison of this method to conventional assays was not possible. Increased rudimentary (supernumerary) ribs observed at 5.0% (3,210 mg/kg/day) in the rat study described above (under ECHA 2020) has questionable significance because control group had a high incidence of skeletal variations and dams in the high dose group had reduced food and water consumption early in

gestation. The overall weight of evidence indicates that DEP is not a developmental hazard at occupational or environmental concentrations.

- Radke et al. 2018
  - A systematic review of epidemiological five studies evaluated the association between DEP and anogenital distance (AGD). In three medium confidence studies, no evidence of association between DEP and AGD was identified. Discordant results were identified in two different measures of AGD in two studies and one low confidence study identified an inverse association between DEP and AGD. The authors concluded that the evidence is slight.
- Radke et al. 2019
  - A systematic review of epidemiological data evaluated studies describing the association between DEP exposure and female pubertal development, primary fecundity outcomes, early or total loss of pregnancy, or preterm birth/gestational duration. The relationships for DEP exposure and female pubertal development, primary fecundity outcomes, and early or total loss of pregnancy were considered indeterminant or slight. As discussed above, in the Reproductive Toxicity section, the relationship between DEP exposure and preterm birth was considered moderate.
- Radke et al. 2020
  - A systematic review of epidemiological data evaluated studies describing the association between DEP exposure and neurodevelopment.
    - The authors identified nine studies examining exposure to DEP and cognition. Two high confidence studies and one low confidence study identified an inverse relationship between cognition and DEP exposure. The remaining studies found no association between DEP exposure and cognition. The authors concluded that there is only slight evidence for an effect of DEP on neurodevelopmental parameters.
    - The authors identified five studies examining exposure and motor skills. One study identified a non-significant inverse association between DEP exposure and motor activity in one-year-olds. A low confidence study identified a significant association between DEP exposure and motor activity at 6 months. A third study identified an inverse association in 11-year old girls, but not boys. The authors concluded that there is only slight indeterminate evidence of an effect of DEP on motor effects.
    - The authors identified eight studies examining exposure and behavior. One study identified an association between DEP exposure and increased externalizing problems. However, the remaining studies identified no association or inverse associations. The authors concluded that there is only indeterminate evidence of an effect of DEP on behavior.

Endocrine Activity (E) Score (H, M, or L): M

DEP was assigned a score of Moderate for endocrine activity based on endocrine organ weight changes (in the absence of pathological changes), decreased testosterone levels, delayed vaginal opening and pinna detachment, decreased sperm concentration and live pup numbers occurring at high oral doses (> 3,000 mg/kg/day) in rats (the possibility of decreased live pup numbers being mediated through endocrine pathways could not be ruled out), and limited *in vitro* evidence of weak estrogenicity. In addition, DEP is listed as Category 1 endocrine disruptor by the EU, and as an endocrine disruptor by TEDX and SIN lists, all of which are screening lists. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when there is evidence of endocrine activity and they are present on screening lists. The score is raised to High if there is plausibly related adverse effects that result in High scores for other Group I human health endpoints or repeated exposure systemic toxicity (CPA

2018b). As none of the potentially endocrine-related endpoints have High scores, ToxServices kept the score of Moderate for this endpoint. The confidence in the score is high as it is based on *in vivo* evidence from multiple studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* EU – Priority Endocrine Disrupters – Category 1 – *in vivo* evidence of endocrine disruption activity.
  - *Screening:* TEDX – Potential Endocrine Disruptor.
  - *Screening:* ChemSec – SIN List – Endocrine Disruption.
- U.S. EPA 2020b
  - Diethyl phthalate was active in 0/18 estrogen receptor (ER) assays, 0/15 androgen receptor (AR) assays, 2/26 steroidogenesis assays, and 0/2 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century.
- ATSDR 1995
  - No effects on gross pathology or histopathology of pituitary, adrenals, thyroid, or pancreas were found when rats were exposed orally to up to 3,710 mg/kg/day DEP for 2 – 16 weeks. Relative organ weights of adrenals, pituitary, and thyroid increased slightly to moderately at 3,160 mg/kg/day in males in this study.
- ChemSec 2020
  - DEP is on the SIN list due to endocrine disruption based on thyroid and estrogenic activity that affects reproduction, liver, and metabolism.
- TEDX 2017
  - DEP is listed as a potential endocrine disruptor as DEP was weakly estrogenic *in vitro* in yeast cells and increased gene expression in human breast cancer cells (MCF-7 and ZR-75) supported by increased proliferation. DEP inhibited the calcium signaling in human nAChR in SH-SY5Y human neuroblastoma cells, which suggests potential neurological effects. DEP administration to male rats resulted in changes in biochemical parameters, including increased serum ACP, LDH, and ALT enzymes as well as increased glycogen, total cholesterol, total triglycerides and lipid peroxidation, and structural changes in the liver, including vacuolations, fatty degeneration and loss of hepatic architecture.
- EU 2000
  - DEP was listed as having *in vivo* evidence of endocrine disruption activity because of decreased sperm concentration and number of live pups per litter in mice.
- NICNAS 2011
  - A number of studies on testes and testicular function are available. Wistar rats, receiving DEP in the diet or by gavage at doses up to 2,000 mg/kg/day for up to 150 days, exhibited decreased testis weight, testicular antioxidant enzymes, serum testosterone, and serum androstenedione, ultrastructural changes in Leydig cells, and decreased sperm counts and motility.
  - In the previously described two-generation reproductive study, Sprague-Dawley rats (24/sex/dose) were fed diets containing DEP (purity not reported) at 0, 600, 3,000, or 15,000 ppm (equivalent to 40-56, 197-267, 1,016-1,375 mg/kg/day). Animals were dosed for 15 or 17 weeks (males and females) beginning 10 weeks prior to mating, throughout mating, gestation, and lactation, until weaning. Pups from the F1 generation were reared for 10 weeks and then mated to produce the F2 generation. High dose males in the F0 generation exhibited statistically significant absolute epididymis weight and mid dose group of the same generation exhibited increased number of abnormal and tailless sperms and decreased serum testosterone. In the F1 generation, parental animals in the mid and high dose groups

exhibited abnormal and tailless sperm. However, no effect on reproductive organ weight were measured. Number of implants, number of pups born, and pup weights were not affected by treatment. There was no effect on AGD or age of preputial separation, however, the age of onset of vaginal opening was delayed in high dose F1 females. Significant delay in pinna detachment was observed in F1 high dose males. Study investigators concluded delayed pinna detachment and vaginal opening are adverse developmental effects occurring concurrently with increased liver and kidney weights in maternal animals.

- Radke et al. 2018
  - A systematic review of epidemiological studies evaluated the association between DEP and serum testosterone. The authors identified nine studies investigating the association between DEP and testosterone. Of the nine studies, three identified an inverse association between DEP exposure and testosterone levels but none were statistically significant. Some of the remaining studies identified a positive relationship between DEP exposure and testosterone levels. The authors concluded that the evidence is indeterminate.
  - A systematic review of epidemiological five studies evaluated the association between DEP and AGD, as previously described in developmental toxicity section. In three medium confidence studies, no evidence of association between DEP and AGD was identified. Discordant results were identified in two different measures of AGD in two studies and one low confidence study identified an inverse association between DEP and AGD. The authors concluded that the evidence is slight.
- Radke et al. 2019
  - As previously described in reproductive and developmental toxicity sections above, a systematic review of epidemiological data evaluated studies examining the association between DEP exposure and female pubertal development, primary fecundity outcomes, early or total loss of pregnancy, or preterm birth/gestational duration. The relationships for DEP exposure and female pubertal development, primary fecundity outcomes, and early or total loss of pregnancy were considered indeterminant or slight. The relationship between DEP exposure and preterm birth was considered moderate.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): L

DEP was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values of > 2,000 mg/kg and inhalation LC_{50} values > 5 mg/L reported in reliable studies. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values of > 2,000 mg/kg and LC_{50} values > 5 mg/L (dust/mist/fume) are reported (CPA 2018b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* New Zealand – GHS – 6.1D (inhalation and oral) – Acutely toxic (GHS Category 4).
    - Based on an oral LD_{50} of 1,000 mg/kg in rabbits and an inhalation LC_{50} of 4.89 mg/L in mice (CCID 2020).
- ECHA 2020 (only studies with Klimisch scores of 1 (reliable without restrictions) or 2 (reliable with restrictions) are listed below)

  - *Oral:* LD_{50} > 5,591 mg/kg (5 mL/kg) in Wistar rats (OECD Guideline 401)
  - *Oral:* LD_{50} = 9,184 mg/kg (8.2 mL/kg) in rats (strain not reported)
  - *Inhalation:* 6h LC_{50} > 511 ppm (> 4.64 mg/L) in rats (presumably aerosol)
  - *Dermal:* LD_{50} > 11,181 mg/kg (10 mL/kg) in rats (strain not reported)
- SCCNFP 2002
  - *Oral:* LD_{50} = 6,200 mg/kg in mice
  - *Oral:* LD_{50} > 5,600 – 31,000 in rats
  - *Oral:* LD_{50} = 1,000 mg/kg in rabbits
  - *Oral:* LD_{50} = 5,000 mg/kg in dogs
  - *Oral:* LD_{50} > 4,000 – 8,600 mg/kg in guinea pigs
  - *Inhalation:* LC_{50} = 4.9 mg/L in mice
  - *Inhalation:* LC_{50} = 7.5 mg/L in rats
  - *Inhalation:* LC_{50} = 1 mg/L in humans
  - *Dermal:* LD_{50} > 11,000 mg/kg in rats
  - *Dermal:* LD_{50} = 3,000 mg/kg in guinea pigs
- Based on the weight of evidence, a score of Low was assigned. Although DEP is classified as a GHS Category 4 inhalation and oral acute toxicant by New Zealand, which warrants a Moderate score, the weight of evidence indicates that it has low acute oral, dermal, and inhalation toxicity.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score (vH, H, M, or L): L

DEP was assigned a score of Low for systemic toxicity (single dose) based on lack of systemic toxicity observed after acute oral and dermal exposures. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and they are not classified under GHS (CPA 2018b). The confidence in the is high as it is based on reliable studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Japan – GHS – Specific target organ/systemic toxicity following single exposure – Category 3 (respiratory irritation).
    - Based on ACGIH and Patty's Toxicology (4th ed, 1994) describing that vapor stimulates respiratory tract (NITE 2006, 2018).
- ECHA 2020
  - *Oral:* In a pre-GLP acute oral toxicity study performed in a manner similar to OECD Guideline 401, male and female Wistar rats (5/sex/dose) were exposed to a single dose of undiluted DEP (purity not reported) by gavage at 0.5, 1.0, 2.0 or 5.0 mL/kg and observed for 14 days. One male at the high dose was sacrificed due to moribund condition on day 5. Other animals showed no clinical signs of toxicity. There were no treatment-related effects on body weight or gross pathology in surviving animals. This study was assigned a Klimisch score of 2 (reliable with restrictions).
  - *Inhalation:* In an acute inhalation toxicity study in rats (strain not specified) (3/sex/dose) were exposed to aerosolized/vaporized (form not clearly stated) DEP in a whole body inhalation chamber by passing 150ºC air through DEP at 511 ppm (4.64 mg/L) for 6 hours and observed for 14 days. All animals survived the treatment. No other information was reported. This study was assigned a Klimisch score of 2 (reliable with restrictions).
  - *Dermal:* In a pre-GLP acute dermal toxicity study performed according to Hagan EC (Acute toxicity in Appraisal of the Safety of chemicals in foods, drugs and cosmetics), albino rats (strain not reported, 3/sex/dose) were exposed to undiluted DEP (purity not reported) at 1.0, 2.0, 5.0 or 10.0 mL/kg on shaved mildly abraded skin under occlusion for 24 hours and were

observed for 14 days. No mortality occurred. All animals had slightly reddened skin upon patch removal. There were no treatment-related changed in body weight and no gross pathological changes were identified. This study was assigned a Klimisch score of 2 (reliable with restrictions).

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score (H, M, or L): L

DEP was assigned a score of Low for systemic toxicity (repeated dose) based on oral NOAELs ≥ 100 mg/kg/day in subchronic studies in rats, and dermal NOAELs of 700 – 800 mg/kg/day in chronic studies in rats and mice. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate data are available and negative, and they are not classified under GHS (i.e., oral LOAELs > 100 mg/kg/day, and dermal LOAELs > 200 mg/kg/day) (CPA 2018b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020 (only the study with a Klimisch score of 2 were described below. No studies were available with a Klimisch score of 1)
  - *Oral*: In a non-GLP subchronic toxicity study, Sprague-Dawley rats were exposed to DEP (purity >99%) in the diet at 0, 0.2, 1.0 or 5.0% (equivalent to 0, 150, 750 and 3,160 mg/kg/day according to the study author) for 2 (5/sex/dose), 6 (5/sex/dose) or 16 weeks (15/sex/dose). Another two groups of 6 males and 6 females each (pair feeding study) were given 0 or 5% for 16 weeks. The control animals in the pair feeding study were given the same amount of food consumed by the treated animals measured during the previous 24 hours. Parameters examined include body weight, food and water intake, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology. Animals at the mid and high doses consumed significantly less food and gained significantly less weight in one or both sexes. At the high dose, there were statistically significant decreases in the absolute weights of brain, heart, spleen and kidneys in both sexes in the 16-week study, and in the absolute weights of gonads (females) and heart, spleen and kidney (males) in the 2- and 6-week studies. Stomach weight and caecum weight increased in males and/or females in the 16 weeks study. In the mid dose, kidney weight increased and pituitary weights decreased in females after 2 weeks, and gonad weights increased in females after 6 weeks. In terms of relative organ weights, relative weights of brain, kidney, liver, stomach, small intestine and full caecum increased in both sexes and testes weight increased in males at the high dose after 16 weeks, and relative weights of liver, stomach and small intestine also increased at the low and mid doses. However, no corresponding treatment-related histopathological changes were observed in any organs. Therefore, the study authors did not consider organ weight changes as adverse effects. In the pair feeding study, rats treated with 5% DEP lost more weight and gained less weight than pair-fed controls; this effect reached statistical significance in week 16. The authors of the REACH dossier identified a NOAEL of 150 mg/kg/day and a LOAEL of 750 mg/kg/day based on body weight changes observed at mid and high doses. ATSDR (1995) identified the NOAEL at the highest dose (3,160 mg/kg/day). This study was assigned a Klimisch score of 2 (reliable with restrictions) (REACH dossier study 001).
- NTP 1995
  - *Dermal:* In the two previously-described carcinogenicity studies performed in F344/N rats and B5C3F1 mice, no adverse systemic effects were identified, and ATSDR (1995)

identified the highest doses in each study (855 mg/kg/day in rats and 772 mg/kg/day in mice) as the NOAELs.

- ITER 2018
  - According to RIVM, which published their review of DEP in 2000, the NOAEL for peroxisomal proliferation effects is 19 mg/kg/day in rats in subchronic toxicity studies. However, these effects are "of less relevance for humans". Another 16-week oral study identified a NOAEL of 100 mg/kg/day in rats based on liver and testes effects. This NOAEL was used to derive a tolerable daily intake (TDI) for DEP.
  - Several quantitative regulatory values have been established for DEP. IPCS established a tolerable intake (TI) of 5 mg/kg/day for DEP in 2001 based on a NOAEL of 1,600 mg/kg/day for maternal organ weight and fetal body weight changes in a dermal developmental toxicity study in mice. RIVM identified a provisional tolerable daily intake (TDI) of 0.2 mg/kg/day for DEP based on a NOAEL of 100 mg/kg/day for liver and testes effects observed in an oral subchronic study in rats in 2000. Based on the same critical study, the U.S. EPA established an oral reference dose (RfD) of 0.8 mg/kg/day based on a NOAEL of 750 mg/kg/day for effects on organ weights and food intake in rats in 1987.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): DG
DEP was assigned a score of Data Gap for neurotoxicity (single dose) based on lack of sufficient data. While no clinical signs of neurotoxicity were observed in acute oral and dermal toxicity studies, limited information cited by GHS-Japan indicates that inhalation may cause narcotic effects. However, there are no animal or human data that support these statements.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Japan – GHS – Specific target organ/systemic toxicity following single exposure – Category 3 (narcotic effect).
    - Based on giddiness and hypesthesia after inhalation (MOE Risk Assessment, 3rd volume, 2004), and central nervous system restraint as described by Patty's Toxicology (4th ed, 1994) (NITE 2006).
- ECHA 2020
  - In the previously described acute oral and dermal studies in animals, no clinical signs of toxicity were observed.
- SCCNFP 2002
  - In the previously described acute oral toxicity studies in animals, clinical signs included central nervous system depression and convulsion prior to death; however, no other signs of neurotoxicity were identified. *ToxServices noted that central nervous system depression was only observed prior to death, and therefore did not consider it a manifestation of specific neurotoxicity.*

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
DEP was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of sufficient data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ATSDR 1995
  - *Oral:* No data on neurotoxicity were available in humans via the oral route of exposure. Two- to 16-week dietary studies in rats reported no effects on the gross pathology or

histopathology of brain or sciatic nerve at doses up to 3,710 mg/kg/day, although increased relative brain weight was measured at the highest dose (3,160 mg/kg/day in males and 3,710 mg/kg/day in females) in this study.
    - *Dermal:* No data on neurotoxicity were available in humans via the dermal route of exposure. Four-week and 2-year studies in rats and mice did not find any adverse effects on the histopathology or weight of the brain at doses far exceeding GHS guideline values.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L

DEP was assigned a score of Low for skin sensitization based on negative data in animals. While there are a few human case reports, limited details are available and animal data conducted in a controlled environment are considered more reliable than human data for this endpoint. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative, and they are not classified under GHS (CPA 2018b). The confidence in the score is high as it is based on well-conducted studies in animals.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020
    - A non-GLP Buehler test was conducted in a manner similar to OECD Guideline 406. Twelve male guinea pigs were induced with 50% DEP (purity not reported) in water on the back 3 times/week for 6 hours each time for 3 weeks. They were then challenged twice with 50% DEP for presumably 6 hours 2 weeks after the last induction dose. No positive reactions were observed, and the authors concluded that DEP is not sensitizing. This study was assigned a Klimisch score of 2 (reliable with restrictions) (REACH dossier study 001).
    - In a human patch test, 5% DEP (purity not reported) in petrolatum was used to induce and challenge participants (n=309). DEP was applied epicutaneously under occlusive conditions. DEP was not sensitizing to the skin in any participants. Although irritation was observed in 2 participants, no allergic reactions occurred. This study was assigned a Klimisch score of 2 (reliable with restrictions) (REACH dossier study 002).
    - DEP (99% purity) was not sensitizing in a mouse local lymph node assay (LLNA) (GLP status not reported) conducted according to OECD Guideline 429 using female CBA/Ca mice. Mice (4/group) were dermally administered 25 µL of 25, 50 or 100% DEP on the dorsal surface of each ear for 3 consecutive days. Following the final application, the animals were sacrificed and the lymph nodes isolated to perform the proliferation assay. The stimulation indices for the 25, 50, and 100% treatments were 1.0, 1.3 and 1.5, respectively. As all of the stimulation indices were less than 3, DEP was not sensitizing to the skin of mice in this study. This study was assigned a Klimisch score of 2 (reliable with restrictions) (REACH dossier study 003).
    - In a non-GLP skin sensitization study, DEP (purity not reported) was tested in an open epicutaneous test at 0.03 – 100%, a Draize test at 0.1%, a maximization test, and a Freund's complete adjuvant test in Himalayan white spotted guinea pigs (6-8/group). Induction doses in the open epicutaneous test, Draize test, and maximization test were 0.03-100%, 0.1%, and 1.5%, respectively. No positive reactions were found. It was concluded that DEP is not a dermal sensitizer. No additional details were available. This study was assigned a Klimisch score of 2 (reliable with restrictions) (REACH dossier study 004).
- ATSDR 1995
    - Phthalates are contact sensitizers, and DEP may be a contact sensitizer "in a limited number of human receptors".

- NICNAS 2011
    - DEP is not considered a skin sensitizer, though there have been published case reports of sensitization in patients exposed to DEP-containing perfumes and plastic items.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*

DEP was assigned a score of Low for respiratory sensitization based on the absence of structural alerts for respiratory sensitization, negative skin sensitization data, and absence of human evidence of respiratory sensitization . GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020
    - Diethyl phthalate does not contain any structural alerts for respiratory sensitization (Appendix D).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As DEP was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by diethyl phthalate, and as DEP does not contain any structural alerts for respiratory sensitization (OECD 2020), DEP is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L

DEP was assigned a score of Low for skin irritation/corrosivity based on negative data in an animal study. While slight skin irritation was observed in a few human cases, the negative data in rabbits under conservative experimental conditions (24h exposure instead of 4h exposure recommended in OECD guidelines) indicate that DEP is not classifiable under GHS as a skin irritant. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative, and they are not classified under GHS (CPA 2018b). The confidence in the score is high as it is based on a well-conducted study in rabbits.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Japan – GHS – Skin corrosion/irritation – Category 2.
        - Based on 2/143 reactions in a human patch test and dermatitis and eczema observed after adhesion to skin (NITE 2006).
- ECHA 2020
    - A skin irritation study (GLP status not known) was conducted according to the FHSA guideline. Three rabbits (strain not reported) were exposed to 0.5 mL of undiluted DEP (100% purity) on intact and abraded skin under occlusion for 24 hours. Skin reactions were evaluated at 24 and 48 hours after exposure. No skin reactions were observed. Therefore, DEP was concluded to be non-irritating. This study was assigned Klimisch score of 2 (reliable with restrictions) (REACH dossier study 001).

  - DEP (>99% purity) was not irritating to the skin of Fischer 344 rats (10/sex) when applied to the clipped interscapular skin 5 times per week for 4 weeks under occlusive conditions at doses of 0, 37.5, 75, 150, or 300 µL. No edema or erythema was observed at 24, 48, or 72 hours after exposure. This study was assigned Klimisch score of 2 (reliable with restrictions) (REACH dossier study 002).
- HSDB 2009
  - DEP is slightly irritating to the skin.
  - In the previously described chronic dermal carcinogenicity study, minimal to mild epidermal acanthosis were observed at the site of application in both sexes in rats, and was concluded to be a subtle adaptive response to local irritation.
- NICNAS 2008
  - No dermal reactions were reported in an occluded/closed patch test in 576 volunteers treated with undiluted DEP.
- NICNAS 2011
  - DEP causes minimal skin irritation.
  - In an acute skin irritation study, undiluted DEP (purity not reported) was applied to intact and abraded rabbit skin (strain not reported, n=6) in a closed patch test. Exposure duration was not reported. Treatment caused slight to moderate irritation at both test sites at 24 hours and irritation was reduced by 40% at 72 hours. No additional details were provided.
  - Undiluted DEP (0.5 mL) was not irritating in two 4 hour semi-occlusive patch tests in rabbits. No additional details were provided.
- Based on the weight of evidence, a score of Low was assigned. Although DEP is classified as a GHS Category 2 skin irritant by Japan, which warrants a Moderate score, DEP was not irritating to the skin of rabbits in two studies with 4 hour semi-occlusive exposures. Additionally, it was not irritating in one rabbit study with conservative exposure conditions (24 hours exposure under occlusion instead of the 4 hour semi-occlusive exposure recommended in OECD Guideline 404 (OECD 2002)) and was slightly to moderately irritating in a second rabbit study with an occlusive exposure for an unknown period of time. Furthermore, in a human patch test in 576 volunteers no dermal reactions were identified. Therefore, a score of Low was assigned.

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *H*
DEP was assigned a score of High for eye irritation/corrosivity based on being classified to GHS Category 2A. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified to GHS Category 2A (CPA 2018b). The confidence in the score is reduced as the only reliable study available did not test up to 21 days, making it impossible to determine if the effects were reversible in 21 days. In addition, results are not consistent across studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan – GHS – Serious eye damage/eye irritation – Category 2B.
    - Based on slight eye irritation in rabbit and human eyes (NITE 2006).
- ECHA 2020
  - DEP (purity not reported) was not irritating to the eyes of three New Zealand White Rabbits when applied without a solvent vehicle for 48 hours. An overall irritation score of 0 was reported. The scale used for scoring was not specified and no additional study details were available. This study was assigned a Klimisch score of 2 (reliable with restrictions) (REACH dossier study 001).
  - A non-GLP ocular irritation study was conducted according to the FHSA guideline, which is similar to the OECD Guideline 405. Three albino rabbits were exposed to 0.1 mL 12.5%

DEP (purity not reported) in 95% ethanol on the eye and observed for 7 days. Severe conjunctival irritation, including chemosis and discharge, was observed in all three animals. The mean conjunctivae scores over 24 – 72 hours for each animal were 2.3, 2, and 3, and effects were not fully reversible after 7 days. The mean 24 – 72 hours chemosis scores for each animal were 1.3, 1.7 and 1.7, and effects were reversible within 4 days in two animals but not reversible in 7 days in the third animal. The authors of the REACH dossier concluded that DEP is irritating to the eyes (Category 2 under GHS). This study was assigned a Klimisch score of 2 (reliable with restrictions) (REACH dossier study 002).

- According to GHS criteria, conjunctival redness scores of ⩾ 2 in at least 2 of 3 animals, or chemosis scores of ⩾ 2 in at least 2 of three animals, with effects being not fully reversible in 7 days, but reversible in 21 days, warrant classification to GHS Category 2A. It is not clear, if the effects observed in this study were fully reversible in 21 days, as the study only lasted 7 days.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): M

DEP was assigned a score of Moderate for acute aquatic toxicity based on acute aquatic toxicity values ranging from 12 – 86 mg/L in fish, aquatic invertebrates, and algae. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when acute aquatic L/EC_{50} values are between 10 and 100 mg/L (CPA 2018b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan – GHS – Hazardous to the aquatic environment (acute) – Category 2.
    - Based on a 96h LC_{50} of 1.2 mg/L in rainbow trout (NITE 2006).
  - *Screening:* New Zealand – GHS – 9.1D (fish, crustacean and algal) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action (Category 2 or 3).
    - Based on a 96h EC_{50} of 3 – 6.1 mg/L in algae (growth) reported on the IUCLID dataset (CCID 2020).
- ECHA 2020
  - 96h LC_{50} = 29 mg/L in saltwater fish sheepshead minnow (*Cyprinodon variegatus*) (GLP, EPA-660/3-75-009) (Klimisch 2, reliable with restrictions) (REACH dossier study 002)
  - 96h LC_{50} = 12 mg/L in freshwater fish rainbow trout (*Oncorhynchus mykiss*) (GLP, EPA-660/3-75-009) (Klimisch 2, reliable with restrictions) (REACH dossier study 001)
  - 96h LC_{50} = 22 mg/L in freshwater fish bluegill (*Lepomis macrochirus*) (GLP, EPA-660/3-75-009) (Klimisch 2, reliable with restrictions) (REACH dossier study 003)
  - 96h LC_{50} = 17 mg/L in freshwater fish fathead minnow (*Pimephales promelas*) (GLP, EG&G Bionomics protocol for freshwater static acute toxicity test with fish) (Klimisch 2, reliable with restrictions) (REACH dossier study 004)
  - 48h LC_{50} = 90 mg/L in *Daphnia magna* (GLP, EPA-660/3-75-009) (Klimisch 2, reliable with restrictions) (REACH dossier study 001)
  - 48h LC_{50} = 52 mg/L in *D. magna* (EPA-660/3-75-009) (Klimisch 2, reliable with restrictions) (REACH dossier study 002)
  - 72h EC_{50} = 23 mg/L (biomass) and 45 mg/L (growth rate), and 96h EC_{50} = 21 mg/L (biomass) in green algae (*Desmodesmus subspicatus*) (DIN 38 412 Part 1 1982 and DIN 38 42 Part 9 1988, similar to OECD Guideline 201) (Klimisch 2, reliable with restrictions) (REACH dossier study 001)

  - 96h EC_{50} = 85.6 mg/L (cell number) in green algae (*Pseudokirchnerella subcapitata*) (EPA-600/3-83-095) (Klimisch 2, reliable with restrictions) (REACH dossier study 002)
  - 8-day EC_{50} = 30.3 mg/L (cell number) in green algae (*P. subcapitata*) (GLP, similar to OECD Guideline 201) (Klimisch 2, reliable with restrictions) (REACH dossier study 003)
- U.S. EPA 2010
  - 48h EC_{50} = 86 mg/L in *D. magna*
  - 8-day EC_{50} = 16 mg/L (growth) in aquatic plants
- NITE 2018
  - 96h LC_{50} = 1.2 mg/L (*O. mykiss*). No additional data were provided.
- Based on the weight of evidence, a score of Moderate was assigned. DEP is classified as a GHS Category 2 acute aquatic toxicant by GHS Japan based on a 96h LC_{50} of 1.2 mg/L in rainbow trout and as a GHS Category 2 or 3 acute aquatic toxicant by GHS New Zealand based on a 96h EC_{50} of 3 – 6.1 mg/L in algae. These classifications warrant a High score. The weight of evidence of well-conducted studies indicate that a Moderate score is warranted. Studies conducted according to EPA or OECD guidelines and primarily done according to GLP-standards identified acute aquatic toxicity values ranging from 12 – 86 mg/L in fish, aquatic invertebrates, and algae. Therefore, a score of Moderate was assigned based on the lowest acute aquatic toxicity value of 12 mg/L in rainbow trout.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): M

DEP was assigned a score of Moderate for chronic aquatic toxicity based the chronic NOECs of 5 mg/L in fish and 3.8 mg/L in *D. magna*. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when chronic values are between 1 and 10 mg/L (CPA 2018b). The confidence in the score is high as it was based on data from well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020
  - 28-day NOEC = 5 mg/L in adult male common carp (*Cyprinus carpio*) based on behavior in a study designed to examine the endocrine disruption activity of DEP. At 20 mg/L, fish became lethargic starting from day 23, their surface became discolored starting from day 20, and fish were late in response to tapping (external stimuli) (Klimisch 2, reliable with restrictions) (REACH dossier study 001)
  - 21-day NOEC = 25 mg/L (mortality and reproduction) in *D. magna* (GLP, internal EG&G Bionomics protocol 1982 and amendment EGG/CMA-008) (Klimisch 2, reliable with restrictions) (REACH dossier study 001)
  - 21-day NOEC = 13 mg/L (mortality and reproduction) in *D. magna* (non-GLP) (Klimisch 2, reliable with restrictions) (REACH dossier study 002)
  - 72h EC_{10} = 9 mg/L (biomass, growth rate), and 96h EC_{10} = 13 mg/L (biomass) in green algae (*D. subspicatus*) (DIN 38 412 Part 1 1982 and DIN 38 42 Part 9 1988) (Klimisch 2, reliable with restrictions) (REACH dossier study 002)
- NITE 2018
  - 21-day NOEC = 3.8 mg/L (reproduction) in *D. magna*
- Based on the weight of evidence, a score of Moderate was assigned. Chronic NOEC values as low as 5 mg/L and 3.8 mg/L were identified in fish and aquatic invertebrates, respectively. Those NOEC values warrant a Moderate score. Although a chronic NOEC value in algae was not identified, acute aquatic toxicity data indicate that fish are the most sensitive of the three trophic levels and the 72 hour EC_{10} of 9 mg/L in green algae indicates that a chronic NOEC will not warrant a higher score.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *vL*

DEP was assigned a score of Very Low for persistence based on modeling that predicts it is readily biodegradable supported by experimental data. No guideline ready biodegradability studies were identified. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when the chemical is readily biodegradable (i.e. meets the 10-day window) when the major compartment is soil (CPA 2018b). The confidence in the score is reduced because it was based on modeled data, as no reliable ready biodegradability studies were identified.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* EC – CEPA DSL – Persistent.
    - Based on "category" (unspecified), but no experimental biodegradation data were identified in the assessment.
- ECHA 2020
  - In an ultimate biodegradability test similar to EPA560/6-82-003 guideline, DEP reached 94.6% degradation in 28 days based on CO_2 evolution using an adapted activated sludge as the inoculum. The authors of the REACH dossier concluded that DEP was readily biodegradable. This study was assigned a Klimisch score of 2 (reliable with restrictions).
    - ToxServices noted that this study used adapted inoculum, and therefore the results are not sufficient to demonstrate ready biodegradability.
  - DEP was 94.8% degraded after 24 hours under aerobic conditions in a semi-continuous activated sludge test. The study authors concluded that DEP was readily biodegradable. This study was assigned a Klimisch score of 2 (reliable with restrictions).
- NITE 2020
  - DEP was readily biodegradable with 88% degradation (BOD) within 28 days.
- HSDB 2009
  - Complete aerobic degradation of DEP at the initial concentration of 400 mg/L was achieved in 35 hours, at 200 mg/L in 25 hours, at 140 mg/L in 22 hours, and at 75 mg/L in 18 hours using microorganisms isolated from municipal sludge in a shake flask test.
  - In a 3-day die-away test, DEP was completed degraded by Rhine River water at 20ºC.
  - DEP reached 87-92% degradation in 10 – 50 days at 25ºC at the initial concentration of 30 mg/L with activated sludge as the inoculum.
  - DEP has aerobic aquatic half-lives of 0.39 days in a river die-away test, 4.33 days in a MITI test, and 0.71 days with microcosm periphyton. It has an aerobic half-life of 1.83 days in soil in agitated aqueous suspension.
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that DEP is expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 74.8% will partition to water with a half-life of 30 days, 23.2% will partition to water with a half-life of 15 days, and 1.81% will partition to air with a half-life of 3 days (Appendix E).

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL

DEP was assigned a score of Very Low for bioaccumulation based on experimental log K_{ow} values of 2.2 and 2.42 supported by estimated BCF values of 18.35 and 0.770. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are no greater than 4, and BCF values are no greater than 100 (CPA 2018b). The confidence in the score is high as it is based on experimental partition coefficients.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ChemIDplus 2020
  - Log K_{ow} = 2.42 (experimental)
- ECHA 2020
  - Log K_{ow} = 2.2 at 40ºC and pH of 7.5 as determined according to OECD Guideline 117 (non-GLP). This study was assigned a Klimisch score of 1 (reliable without restriction).
- U.S. EPA 2017
  - BCFBAF predicts a BCF of 18.35 using the regression based model based on a measured log K_{ow} of 2.42, and a BCF of 0.770 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix E).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
DEP was assigned a score of Low for reactivity based on lack of structural alerts associated with explosive or oxidizing properties and an NFPA instability score of 0. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when they are not explosive, and there are no other data indicating that they are otherwise reactive (CPA 2018b). The confidence in the score is reduced as it is not based on experimental data or authoritative lists.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020
  - DEP contains no chemical groups associated with explosive or oxidizing properties.
- HSDB 2009
  - Vapors in confined areas may explode in contact with fire.
  - NFPA instability score = 0 (i.e. stable even under fire, and does not react with water)
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of DEP. These procedures are listed in the GHS (UN 2019).
  - Based on the structure of its components or moieties, DEP is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix F).
  - Based on the structure of its components or moieties, DEP is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials.

Flammability (F) Score (vH, H, M, or L): L
DEP was assigned a score of Low for flammability based on a flash point of 170ºC, which is higher than the GHS classification cutoff of 93ºC for flammable liquids (UN 2019). GreenScreen® criteria classify chemicals as a Low hazard for flammability when they are not classified as flammable under GHS (CPA 2018b). The confidence in the score is high because it is based on experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.

- ECHA 2020
    - Flash point = 170ºC following the EU ASTM D93-02 test method. This study was assigned a Klimisch score of 1 (reliable without restriction).

Use of New Approach Methodologies (NAMs)[9] in the Assessment

Table 4: Summary of NAMs Used in the GreenScreen® Assessment		
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	N	Not applicable
Mutagenicity	N	Not applicable
Reproductive toxicity	N	Not applicable
Developmental toxicity	N	Not applicable
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays
Acute mammalian toxicity	N	Not applicable
Single exposure systemic toxicity	N	Not applicable
Repeated exposure systemic toxicity	N	Not applicable
Single exposure neurotoxicity	N	Not applicable
Repeated exposure neurotoxicity	N	Not applicable
Skin sensitization	N	Not applicable
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	Not applicable
Eye irritation	N	Not applicable
Acute aquatic toxicity	N	Not applicable
Chronic aquatic toxicity	N	Not applicable
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: EPA560/6-82-003 Biodegradation test
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

[9] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e. adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Diethyl Phthalate (CAS #84-66-2)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details							S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	Diethyl phthalate	84-66-2	*L*	L	M	*M*	M	L	L	L	DG	DG	L	*L*	L	*H*	M	M	*vL*	vL	*L*	L

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	Yes	No	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Diethyl phthalate	2

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Diethyl phthalate	2

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for Diethyl Phthalate (CAS #84-66-2)

84-66-2
Diethyl phthalate
ALSO CALLED [1431865-87-0] Diethyl phthalate (primary CASRN is 84-66-2), 1,2-benzenedicarboxylic acid diethyl es...
View all synonyms (61)

Share Profile

Hazards | Properties | Functional Uses | Resources

Pharos Hazards View

Download Lists

ENDPOINT	HAZARD LEVEL	HAZARD LIST	HAZARD DESCRIPTION	OTHER LIS
Persistent	High	EC - CEPA DSL	Persistent	
Endocrine	Medium	ChemSec - SIN List	Endocrine Disruption	+2
	Medium	EU - Priority Endocrine Disruptors	Category 1 - In vivo evidence of Endocrine Disruption Activity	
	Medium	TEDX - Potential Endocrine Disruptors	Potential Endocrine Disruptor	
Skin irritation	High	GHS - Japan	Skin corrosion / irritation - Category 2 [H315]	+1
	Potential Concern	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified)	
Skin sensitize	High	GHS - Japan	Skin sensitizer - Category 1 [H317]	
Acute aquatic	High	GHS - Japan	Hazardous to the aquatic environment (acute) - Category 2 [H401]	+3
	Medium	GHS - New Zealand	9.1D (algal) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	
	Medium	GHS - New Zealand	9.1D (crustacean) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	
	Medium	GHS - New Zealand	9.1D (fish) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	
Respiratory	Medium	CHE - Toxicant Database	Asthma - allergen, sensitizer - limited evidence *	+2
	Medium	CHE - Toxicant Database	Asthma - irritant - limited evidence *	
	Medium	CHE - Toxicant Database	Rhinitis - allergic - limited evidence *	
Mammalian	Medium	GHS - New Zealand	6.1D (inhalation) - Acutely toxic	+2
	Medium	GHS - New Zealand	6.1D (oral) - Acutely toxic	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H331 - Toxic if inhaled (unverified)	
Eye irritation	Medium	GHS - Japan	Serious eye damage / eye irritation - Category 2B [H319]	+1
	Potential Concern	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified)	
Organ toxicant	Medium	GHS - Japan	Specific target organs/systemic toxicity following single exposure - Category 3 [H335 or H336]	+2
	Potential Concern	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified)	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H373 - May cause damage to organs through prolonged or repeated exposure (unverified)	
Terrestrial	Medium	GHS - New Zealand	9.3C - Harmful to terrestrial vertebrates	

Restricted list	Potential Concern	CA SCP - Candidate Chemicals	Candidate Chemical List	+18
	Potential Concern	EU - PACT-RMOA Substances	Substances selected for RMOA or hazard assessment	
	Potential Concern	GSPI - Six Classes of Problematic Chemicals	Bisphenols and Phthalates *	
	Potential Concern	Living Building Challenge 4.0 - Red List of Materials & Chemicals	Red List substances to avoid in Living Building Challenge V4.0 projects	
	Potential Concern	Living Future - Living Building Red List 2.1	Red List substance to avoid in Living Building Challenge V2.1 projects *	
	Potential Concern	Living Future - Living Building Red List 3.0	Prospective Red List substances to avoid in Living Building Challenge projects *	
	Potential Concern	Living Future - Living Building Red List 3.0	Red List substances to avoid in Living Building Challenge V3 projects	
	Potential Concern	Living Future - Living Building Red List 3.1	Red List substances to avoid in Living Building Challenge V3.1 projects	
	Potential Concern	MDH - Chemicals of High Concern and Priority Chemicals	Chemicals of High Concern	
	Potential Concern	ME DEP - Chemicals of High Concern and Priority Chemicals	Priority Chemicals	
	Potential Concern	P&W - Precautionary List	Precautionary list of substances recommended for avoidance *	
	Potential Concern	SCHF - Hazardous 100	Chemicals of high concern	
	Potential Concern	Sephora - High Priority Chemicals	High priority chemicals	
	Potential Concern	Target Corp - Formulated Essentials Unwanted Chemical List (UCL)	Unwanted Chemicals	
	Potential Concern	USGBC - LEED Pilot Credits	Substance to avoid to fulfill LEED Pilot Credit 11 *	
	Potential Concern	USGBC - LEED Pilot Credits	Substance to avoid to fulfill LEED Pilot Credit 54 Option 2 *	
	Potential Concern	WA DoE - Chemicals of High Concern to Children	Chemicals of High Concern to Children	
	Potential Concern	ZDHC - MRSL v1.1	ZDHC - MRSL v1.1 for Natural Leather Processing	
	Potential Concern	ZDHC - MRSL v1.1	ZDHC - MRSL v1.1 for Textiles and Synthetic Leather Processing	
Positive list	Low	Cosmetic Ingredient Review (CIR)	Safe as Used	+1
	Low	Inventory of Existing Cosmetic Ingredients in China (IECIC 2015)	Cosmetic Ingredients	
Cancer	Potential Concern	US EPA - IRIS Carcinogens	(1986) Group D - Not classifiable as to human carcinogenicity	
Reproductive	Potential Concern	DK-EPA - Danish Advisory List	Repr. 2; H361 - Suspected of damaging fertility or the unborn child (modeled)	
Multiple	Potential Concern	German FEA - Substances Hazardous to Waters	Class 2 - Hazard to Waters	+1
	Potential Concern	ChemSec - SIN List	Equivalent Concern	

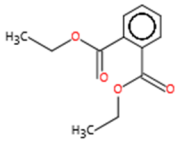
Restricted Substance Lists (19)

- CA SCP - Candidate Chemicals: Candidate Chemical List
- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- GSPI - Six Classes of Problematic Chemicals: Bisphenols and Phthalates *
- Living Building Challenge 4.0 - Red List of Materials & Chemicals: Red List substances to avoid in Living Building Challenge V4.0 projects
- Living Future - Living Building Red List 2.1: Red List substance to avoid in Living Building Challenge V2.1 projects *
- Living Future - Living Building Red List 3.0: Prospective Red List substances to avoid in Living Building Challenge projects *
- Living Future - Living Building Red List 3.0: Red List substances to avoid in Living Building Challenge V3 projects
- Living Future - Living Building Red List 3.1: Red List substances to avoid in Living Building Challenge V3.1 projects
- MDH - Chemicals of High Concern and Priority Chemicals: Chemicals of High Concern
- ME DEP - Chemicals of High Concern and Priority Chemicals: Priority Chemicals
- P&W - Precautionary List: Precautionary list of substances recommended for avoidance *
- SCHF - Hazardous 100: Chemicals of high concern
- Sephora - High Priority Chemicals: High priority chemicals
- Target Corp - Formulated Essentials Unwanted Chemical List (UCL): Unwanted Chemicals
- USGBC - LEED Pilot Credits: Substance to avoid to fulfill LEED Pilot Credit 11 *
- USGBC - LEED Pilot Credits: Substance to avoid to fulfill LEED Pilot Credit 54 Option 2 *
- WA DoE - Chemicals of High Concern to Children: Chemicals of High Concern to Children
- ZDHC - MRSL v1.1: ZDHC - MRSL v1.1 for Natural Leather Processing
- ZDHC - MRSL v1.1: ZDHC - MRSL v1.1 for Textiles and Synthetic Leather Processing

Positive Lists (2)

- Cosmetic Ingredient Review (CIR): Safe as Used
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2015): Cosmetic Ingredients

APPENDIX D: OECD Toolbox Respiratory Sensitization Results for Diethyl Phthalate (CAS #84-66-2)

Filter endpoint tree...	1 [target]
Structure	
⊞ **Structure info**	
⊞ **Parameters**	
⊞ **Physical Chemical Properties**	
⊞ **Environmental Fate and Transport**	
⊞ **Ecotoxicological Information**	
⊞ **Human Health Hazards**	
⊟ **Profiling**	
⊟ **Endpoint Specific**	
Respiratory sensitisation	No alert found

APPENDIX E: EPI Suite™ Modeling Results for Diethyl Phthalate (CAS #84-66-2)

(Estimated values included in the GreenScreen® are highlighted and bolded)

CAS Number: 000084-66-2
SMILES : O=C(OCC)c(c(ccc1)C(=O)OCC)c1
CHEM : DIETHYL PHTHALATE
MOL FOR: C12 H14 O4
MOL WT : 222.24
---------- EPI SUMMARY (v4.11) ----------

Physical Property Inputs:
Log Kow (octanol-water): 2.42
Boiling Point (deg C) : 295.00
Melting Point (deg C) : -40.50
Vapor Pressure (mm Hg) : 0.0021
Water Solubility (mg/L): 1080
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 2.65
Log Kow (Exper. database match) = 2.42
Exper. Ref: ELLINGTON,JT & FLOYD,TL (1996)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 282.13 (Adapted Stein & Brown method)
Melting Pt (deg C): -1.74 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.00254 (Modified Grain method)
VP (Pa, 25 deg C) : 0.339 (Modified Grain method)
MP (exp database): -40.5 deg C
BP (exp database): 295 deg C
VP (exp database): 7.43E-04 mm Hg (9.91E-002 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1044
log Kow used: 2.42 (user entered)
melt pot used: -40.50 deg C
Water Sol (Exper. database match) = 1080 mg/L (25 deg C)
Exper. Ref: HOWARD,PH ET AL. (1985)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 719.88 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Esters

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 3.94E-007 atm-m3/mole (3.99E-002 Pa-m3/mole)

Group Method: 1.12E-007 atm-m3/mole (1.13E-002 Pa-m3/mole)
Exper Database: 2.01E-07 atm-m3/mole (2.04E-002 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 5.686E-007 atm-m3/mole (5.761E-002 Pa-m3/mole)
VP: 0.0021 mm Hg (source: User-Entered)
WS: 1.08E+003 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 2.42 (user entered)
Log Kaw used: -5.085 (exp database)
Log Koa (KOAWIN v1.10 estimate): 7.505
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.9901
Biowin2 (Non-Linear Model) : 0.9997
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.9885 (weeks)
Biowin4 (Primary Survey Model) : 3.9850 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.8002
Biowin6 (MITI Non-Linear Model): 0.8870
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.6909
Ready Biodegradability Prediction: YES

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 0.28 Pa (0.0021 mm Hg)
Log Koa (Koawin est): 7.505
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 1.07E-005
Octanol/air (Koa) model: 7.85E-006
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.000387
Mackay model : 0.000856
Octanol/air (Koa) model: 0.000628

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 3.4658 E-12 cm3/molecule-sec
Half-Life = 3.086 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 37.034 Hrs
Ozone Reaction:
No Ozone Reaction Estimation

Fraction sorbed to airborne particulates (phi):
0.000622 (Junge-Pankow, Mackay avg)
0.000628 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 104.9 L/kg (MCI method)
Log Koc: 2.021 (MCI method)
Koc : 135.7 L/kg (Kow method)
Log Koc: 2.132 (Kow method)
Experimental Log Koc: 1.84 (database)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 7.551E-002 L/mol-sec
Kb Half-Life at pH 8: 106.231 days
Kb Half-Life at pH 7: 2.908 years
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.264 (BCF = 18.35 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.7079 days (HL = 0.01959 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.770 (BCF = 5.889)
Log BAF Arnot-Gobas method (upper trophic) = 0.770 (BAF = 5.889)
log Kow used: 2.42 (user entered)

Volatilization from Water:
Henry LC: 2.01E-007 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 4344 hours (181 days)
Half-Life from Model Lake : 4.751E+004 hours (1980 days)

Removal In Wastewater Treatment:
Total removal: 2.90 percent
Total biodegradation: 0.10 percent
Total sludge adsorption: 2.79 percent
Total to Air: 0.01 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**1.81**	**74.1**	**1000**
Water	**23.2**	**360**	**1000**
Soil	**74.8**	**720**	**1000**
Sediment	**0.14**	**3.24e+003**	**0**

Persistence Time: 571 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)

Air	1.81	74.1	1000
Water	23.2	360	1000
water	(23.2)		
biota	(0.000306)		
suspended sediment	(0.00366)		
Soil	74.8	720	1000
Sediment	0.14	3.24e+003	0

Persistence Time: 571 hr

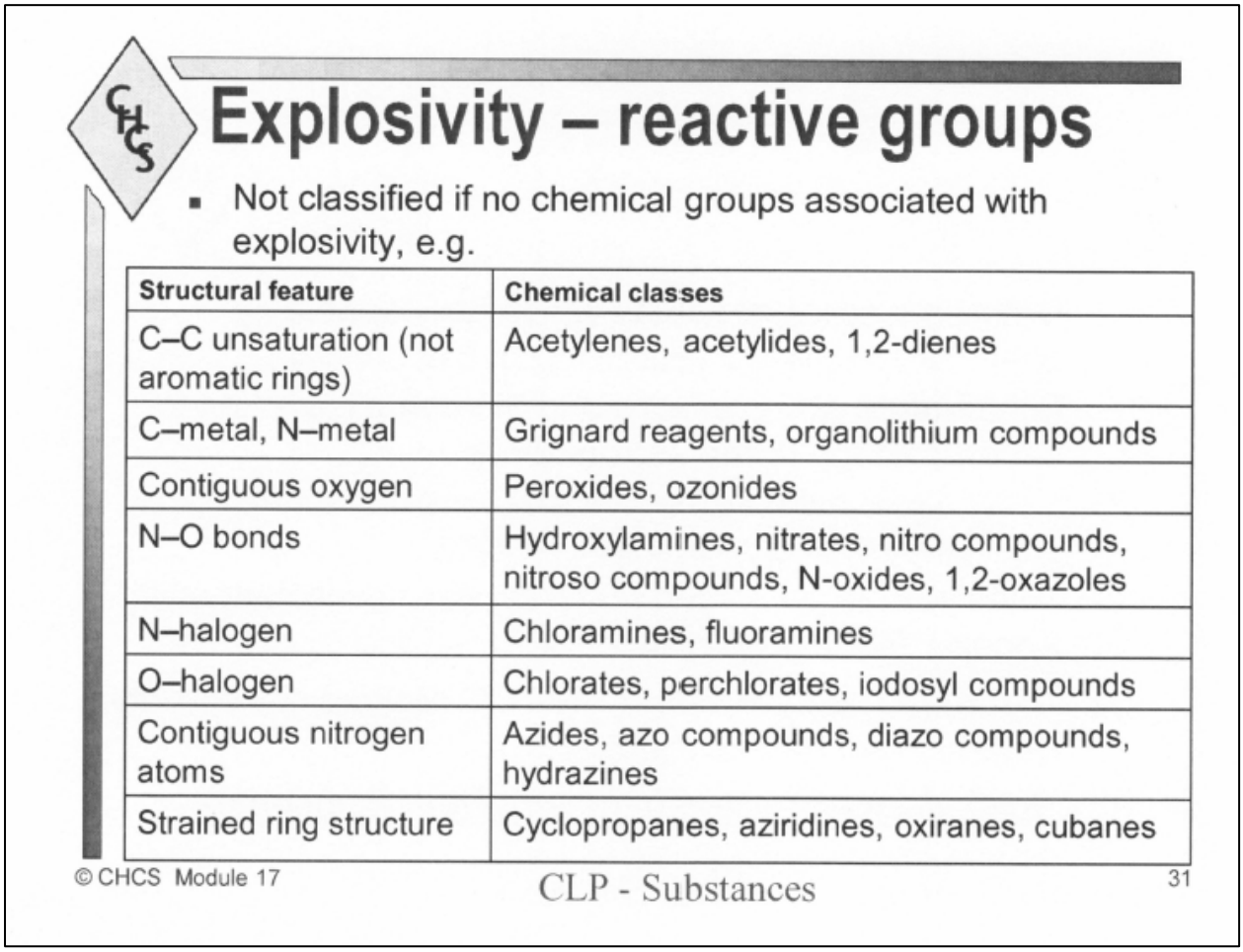
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.8	74.1	1000
Water	23.2	360	1000
water	(23.2)		
biota	(0.000305)		
suspended sediment	(0.00375)		
Soil	74.9	720	1000
Sediment	0.142	3.24e+003	0

Persistence Time: 572 hr

APPENDIX F: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

- Not classified if no chemical groups associated with explosivity, e.g.

Structural feature	Chemical classes
C–C unsaturation (not aromatic rings)	Acetylenes, acetylides, 1,2-dienes
C–metal, N–metal	Grignard reagents, organolithium compounds
Contiguous oxygen	Peroxides, ozonides
N–O bonds	Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles
N–halogen	Chloramines, fluoramines
O–halogen	Chlorates, perchlorates, iodosyl compounds
Contiguous nitrogen atoms	Azides, azo compounds, diazo compounds, hydrazines
Strained ring structure	Cyclopropanes, aziridines, oxiranes, cubanes

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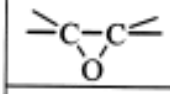
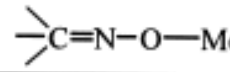
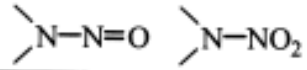
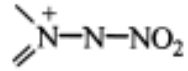
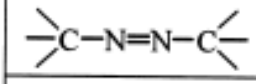
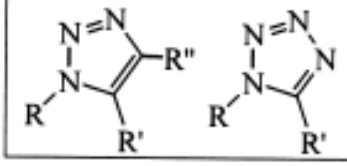
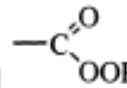
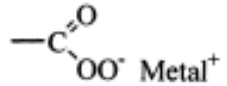
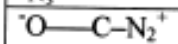
Explosivity – Full List

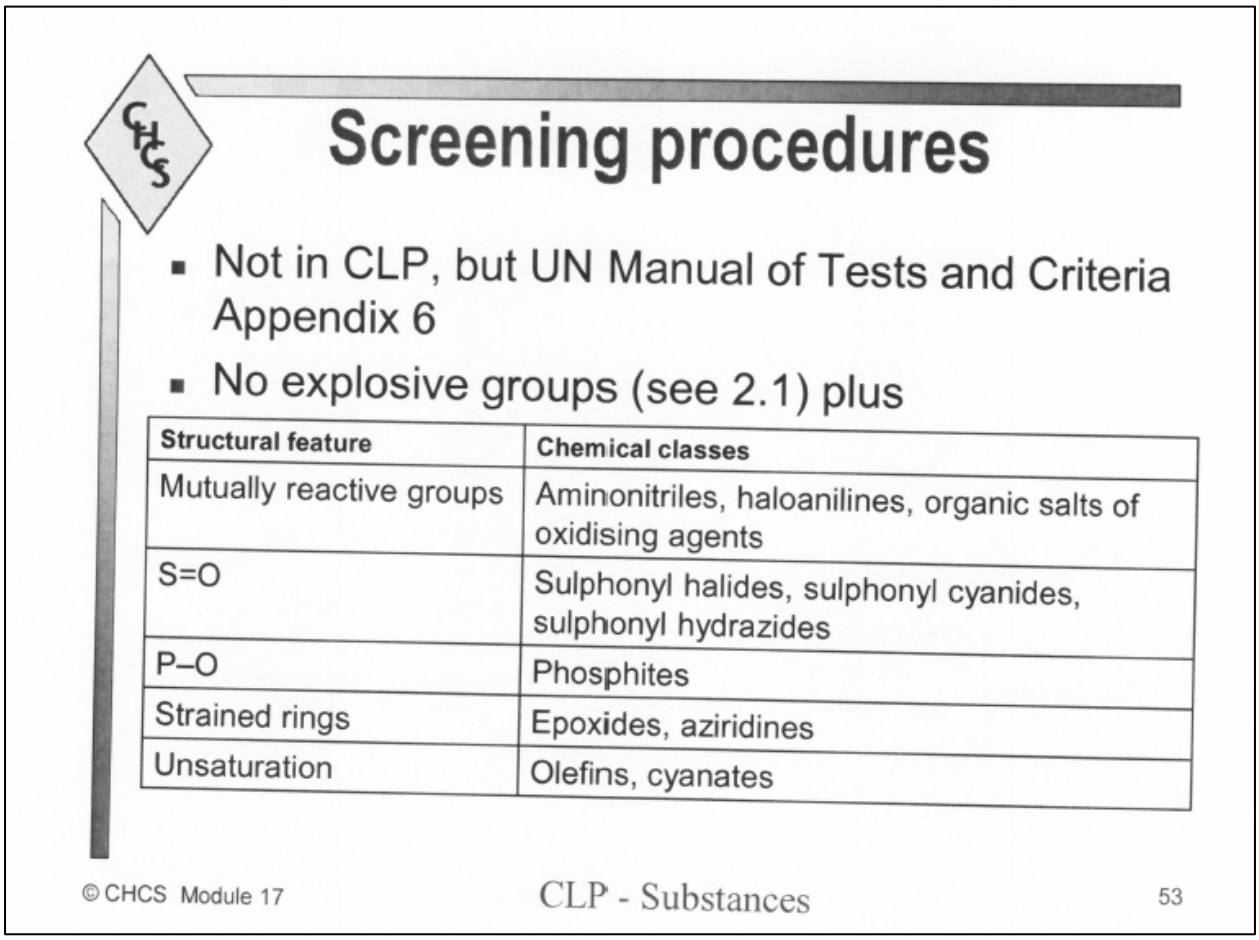
Table R.7.1-28 Chemical groups associated with explosive properties

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO_2	Acyl or Alkyl Nitrites and Nitrates
	1,2-Epoxides
	Metal Fulminates or *aci*-Nitro Salts
	N-Metal Derivatives (especially heavy metals)
	N-Nitroso and N-Nitro Compounds
	N-Azolium Nitroimidates
	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
$(ArN=N)_2O$, $(ArN=N)_2S$	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. $NC1_3$, $RNC1_2$	N-Halogen Compounds

Adapted from Bretherick (Bretherick's Handbook of Reactive Chemical Hazards 6th Ed., 1999, Butterworths, London)

Self-Reactive Substances



Licensed GreenScreen® Profilers

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