Supporting Information for Low-Priority Substance
Propanedioic Acid, 1,3-Diethyl Ester
(CASRN 105-53-3)
(Diethyl Malonate)
Final Designation

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Office of Pollution Prevention and Toxics
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1. Introduction

The Lautenberg amendments to the Toxic Substances Control Act (TSCA) require EPA to designate chemical substances as either High-Priority Substances for risk evaluation, or Low-Priority Substances for which risk evaluations are not warranted at this time (section 6(b)(1)(B) and implementing regulations (40 CFR 702.3)). A high-priority substance is defined as a chemical substance that the Administrator concludes, without consideration of costs or other non-risk factors, may present an unreasonable risk of injury to health or the environment because of a potential hazard and a potential route of exposure under the conditions of use, including an unreasonable risk to potentially exposed or susceptible subpopulations identified as relevant by the Administrator. If the Administrator concludes, based on information sufficient to establish, without consideration of costs or other non-risk factors, that the high-priority standard is not met, then the substance must be designated as a low-priority substance. Propanedioic acid, 1,3-diethyl ester, referenced as diethyl malonate for the remainder of this document, is one of the 40 chemical substances initiated for prioritization as referenced in a March 21, 2019 notice (84 FR 10491)[1] and one of the 20 proposed as low-priority substances in an August 15, 2019 notice (84 FR 41712).[2]

As described under EPA's regulations at 40 CFR 702.9[3] and pursuant to section 6(b)(1)(A) of the statute, EPA generally used reasonably available information to screen the chemical substance, or conduct a screening review, under its conditions of use against the following criteria and considerations:

- the hazard and exposure potential of the chemical substance;
- persistence and bioaccumulation;
- potentially exposed or susceptible subpopulations;
- storage near significant sources of drinking water;
- conditions of use or significant changes in the conditions of use of the chemical substance;
- the chemical substance's production volume or significant changes in production volume; and
- other risk-based criteria that EPA determines to be relevant to the designation of the chemical substance's priority.

Designation of a low-priority substance is not a finding that the chemical substance does not present an unreasonable risk, but rather that the chemical does not meet the statutory criteria for a high-priority substance and that a risk evaluation is not warranted at the time. As explained in the preamble to the Prioritization Rule, "low-priority substance designations give the public notice of chemical substances for which the hazard and/or exposure potential is anticipated to be low or nonexistent and provides some insight into which chemical substances are likely not to need additional evaluation and risk management under TSCA." 82 FR 33753 at 33755. EPA is not precluded from later revising the designation based on reasonably available information, if warranted. 40 CFR 702.13; 702.15.

[1] https://www.federalregister.gov/documents/2019/03/21/2019-05404/initiation-of-prioritization-under-the-toxic-substances-control-act-tsca

[2] https://www.federalregister.gov/documents/2019/08/15/2019-17558/proposed-low-priority-substance-designation-under-the-toxic-substances-control-act-tsca-notice-of

[3] The prioritization process is explained in the *Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act* (82 FR 33753).

The screening review is not a risk evaluation, but rather a review of reasonably available information on the chemical substance that relates to the specific criteria and considerations in TSCA section 6(b)(1)(A) and 40 CFR 702.9. This paper documents the results of the screening review which supports the final designation of diethyl malonate as a low-priority substance. EPA has also prepared a general response to comments and, as applicable, chemical-specific responses to comments.

EPA's risk-based, screening-level review is organized as follows:

- *Section 1 (Introduction):* This section explains the requirements of the Lautenberg amendments to the Toxic Substances Control Act (TSCA) and implementing regulations – including the criteria and considerations -- pertinent to prioritization and designation of low-priority substances.

- *Section 2 (Background on the Low-Priority Substance):* This section includes information on attributes of the chemical substance, including its structure, and relates them to its functionality.

- *Section 3 (Physical-Chemical Properties):* This section includes a description of the physical-chemical properties of the chemical substance and explains how these properties lead to the chemical's fate, transport, and exposure potential.

- *Section 4 (Relevant Assessment History):* This section includes an overview of the outcomes of other governing entities' assessments of the chemical substance.

- *Section 5 (Conditions of Use):* This section presents the chemical substance's known, intended, and reasonably foreseen conditions of use under TSCA.

- *Section 6 (Hazard Characterization):* This section summarizes the reasonably available hazard information and screens the information against low-concern benchmarks.

- *Section 7 (Exposure Characterization):* This section includes a qualitative summary of potential exposures to the chemical substance.

- *Section 8 (Summary of Findings):* In this section, EPA presents information pertinent to prioritization against each of the seven statutory and regulatory criteria and considerations, and makes a conclusion based on that evidence.

- *Section 9 (Final Designation):* In this section, EPA presents the final designation for this chemical substance.

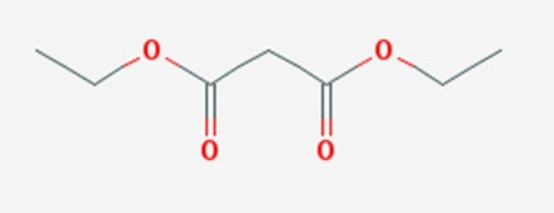
- *Appendix A (Conditions of Use Characterization):* This appendix contains a comprehensive list of TSCA and non-TSCA uses for the chemical substance from publicly available databases.

- *Appendix B (Hazard Characterization):* This appendix contains information on each of the studies used to support the hazard evaluation of the chemical substance.

- *Appendix C (Literature Search Outcomes):* This appendix includes literature search outcomes and rationales for studies that were identified in initial literature screening but were found to be off-topic or unacceptable for use in the screening-level review.

2. Background on Diethyl Malonate

Table 1 below provides the CAS number, synonyms, and other information on diethyl malonate.

Table 1: Diethyl Malonate at a Glance	
Chemical Name	Diethyl Malonate
CASRN	105-53-3
Synonyms	Ethyl Malonate; Diethyl Propanedioate; Malonic Ester; Propanedioic acid, diethyl ester; Dicarbethoxymethane; Carbethoxyacetic ester;
Trade Name(s)	
Molecular Formula	$C_7H_{12}O_4$
Representative Structure	

Diethyl malonate is a diester derivative of malonic acid, a dicarboxylic acid with two carboxyl groups (-COO-) separated by one methylene group (-CH2-). Diethyl malonate is formed by the replacement of the hydroxyl groups (-OH) of malonic acid with ethoxy groups (-OCH2CH3). The hydrogen atoms on the methylene carbon between the two carboxyl groups make this compound acidic. Because of its unique structure, diethyl malonate is reactive and functions as a reagent for organic synthesis and to make products such as barbiturates, pigments, and agrochemicals. Volatile esters are known to have fruity scents and are often used as fragrances and flavorings. Diethyl malonate is a volatile diester that occurs naturally in fruits such as grapes, strawberries, guava, melon, pineapple, and blackberries. Section 5 includes conditions of use for this chemical.

3. Physical-Chemical Properties

Table 2 lists physical-chemical properties for diethyl malonate. A chemical's physical-chemical properties provide a basis for understanding a chemical's behavior, including in the environment and in living organisms. These endpoints provide information generally needed to assess potential environmental release, exposure, and partitioning as well as insight into the potential for adverse toxicological effects.

Table 2: Physical-Chemical Properties for Diethyl Malonate

Source/ Model	Data Type	Endpoint	Endpoint value	Notes
PubChem 2019	Experimental	State at room temperature	Liquid	
ChemIDPlus 2019; OECD SIDS 2005; Reported to the ECHA database 2019; EPISuite v.4.11[4]	Estimated	Molecular weight	160 g/mol	
EPISuite v.4.11	Calculated	Molecular weight	160.17 g/mol	
Lyman et al. 1990	Estimated	Molar volume	183 cm^3/mol	
ChemIDPlus 2019	Experimental	Melting Point	-50 °C	
ChemIDPlus 2019; EPISuite v.4.11	Experimental	Boiling Point	200 °C	
OECD SIDS 2005	Experimental	Water solubility	2.00E+04 mg/L	
ChemIDPlus 2019; Reported to the ECHA database 2019; EPISuite v.4.11	Experimental	Water solubility	2.32 E+04 at 37 °C mg/L	
EPISuite v.4.11	Estimated	Water solubility	2.97E+04 mg/L	K_{ow} method
David et al., 2012	Experimental	Vapor pressure	1 mm Hg at 40 °C	
ChemIDPlus 2019; OECD SIDS 2005; Reported to the ECHA database 2019	Experimental	Vapor pressure	0.27 mm Hg (0.36 hPa) at 25 °C	
EPISuite v.4.11	Estimated	Vapor pressure	3.61E-01 mm Hg	

[4] All EPI Suite estimates used the following physical property inputs: BP = 200 deg C, MP = -50 deg C, VP = 0.269 mm Hg, WS = 23,200 mg/L, log P = 0.96; SMILES: O=C(OCC)CC(=O)OCC

Table 2: Physical-Chemical Properties for Diethyl Malonate				
Source/ Model	**Data Type**	**Endpoint**	**Endpoint value**	**Notes**
EPISuite v.4.11	Experimental	Henry's Law constant	2.1E-06 atm-m^3/mol	Experimental value identified in EPISuite's internal database
ChemIDPlus 2019; OECD SIDS 2005; Reported to the ECHA database 2019; EPISuite v.4.11	Experimental	Log K_{ow}	0.96	
EPISuite v.4.11	Estimated	Log K_{ow}	0.9	
EPISuite v.4.11	Estimated	Log K_{oa}	5.026	
EPISuite v.4.11	Estimated	Log K_{oc}	1 (MCI); 1.325 (Kow)	
Cataldo et al. 1990; Fellows et al. 1990	Experimental	Volatilization (T ½)	From soil: 1.2-2 hours	
Cataldo et al. 1990; Fellows et al. 1990	Experimental	Volatilization (T ½)	From foliar surfaces: 1.3 – 242 hours	• Foliar surface composition affects sorption and volatilization
EPISuite v.4.11	Estimated	Volatilization ($T_{1/2}$)	From river: 14.76 days; from lake: 165.4 days	
OECD SIDS 2005	Experimental	Photolysis ($T_{1/2}$)	35 minutes	
EPISuite v.4.11	Estimated	Indirect photolysis ($T_{1/2}$)	3.13 days	• From OH rate constant 3.41E-12 cm^3/molecules-second (12 hour day; 1.5E6 OH/cm^3)
EPISuite v.4.11	Estimated	Hydrolysis ($T_{1/2}$)	Half-life at pH=7: 16.198 days Half-life at pH=8: 1.620 days	
EPISuite v.4.11	Estimated	BAF	1.058	
EPISuite v.4.11	Estimated	BCF	3.162	
EPISuite v.4.11	Estimated	Biodegradability	Ready biodegradability prediction: Yes	
EPISuite v.4.11	Estimated	Wastewater treatment plant removal	93.5% Total Removal (93.2% biodegradation, 0.3% sludge, 0.02% air)	Input parameters: BioP = 4, BioA = 1 and BioS = 1 based on 98% degradation in 28 days with 92% in 10 days in OECD 301A test

Based on its reported physical form (PubChem, 2019) and measured melting point (ChemIDPlus, 2019), diethyl malonate is a liquid under ambient conditions. Liquids have the potential for exposure via direct dermal contact with the substance, and through ingestion or by inhalation of aerosols if they are generated. Exposure through direct dermal contact with this substance is expected to result in poor to moderate dermal absorption based on experimental data (discussed further in Section 6.1.1) and its molecular weight, water solubility and log K_{OW}. Based on its measured vapor pressure (ChemIDPlus, 2019), diethyl malonate is expected to volatilize at ambient temperatures, and therefore has the potential for inhalation exposure to vapor-phase material. The estimated Henry's Law constant (EPI Suite, 2019) for diethyl malonate indicates slow volatilization from water and aqueous solutions, which can also result in inhalation exposure to volatilized material. Based on measured solubility data (ChemIDPlus, 2019), diethyl malonate is considered water soluble, indicating the potential for this substance to dissolve in water and form an aqueous solution. Water soluble substances have an increased potential for absorption through the lungs; therefore, if inhalation of vapors or aerosols occurs, absorption through the lungs is likely. Based on its estimated log K_{ow} (EPI Suite, 2019), diethyl malonate is unlikely to cross lipid membranes. Absorption and sequestration in fatty tissues are unlikely, as reflected in the estimated BCF and BAF values for this compound (EPI Suite, 2019). The estimated log K_{oc} (EPISuite) indicates diethyl malonate is highly mobile in soils, increasing its potential for leaching into groundwater, including groundwater sources of drinking water. If oral exposure occurs via ingestion of contaminated drinking water absorption through the gastrointestinal tract is expected to be poor based on the log K_{OW} (EPI Suite, 2019). Measured and estimated data (discussed further in Section 6.3.1) indicate diethyl malonate is readily biodegradable, meaning that it has the potential to break down in the environment into carbon dioxide and water.

3.1 References

Cataldo, D. A., Ligotke, M. W., Harvey, S. D., Fellows, R. J., Li, S. W. (1990). Acute environmental toxicity and persistence of DEM, a chemical agent simulant: Diethyl malonate. Final report. Technical Report, Department of Energy

ChemIDplus. (2019). Diethyl malonate. Retrieved from https://chem.nlm.nih.gov/chemidplus/rn/112-92-5

David, R. M., Bachman, A. N., Butala, J. H., Piper, J. T. (2012) Esters of Mono-, Di-, and Tricarboxylic Acids. Patty's Toxicology, Sixth Edition. Volume 4, John Wiley & Sons, Chapter 58, Page 147.

European Chemicals Agency (ECHA). (2019). Diethyl malonate. Retrieved from https://echa.europa.eu/substance-information/-/substanceinfo/100.003.006

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Lyman, Warren J., Reehl, W. F., Rosenblatt, D. H. (1990). Handbook of chemical property estimation methods: environmental behavior of organic compounds. American Chemical Society

OECD (2005). Malonic acid diesters. Retrieved from https://heronet.epa.gov/heronet/index.cfm/reference/download/reference_id/4935263

PubChem. (2019). Diethyl malonate. Retrieved from https://pubchem.ncbi.nlm.nih.gov/compound/8221

U.S. EPA. (2019). Estimation Programs Interface Suite, v 4.11. United States Environmental Protection Agency, Washington, DC, USA

4. Relevant Assessment History

EPA assessed the toxicological profile of diethyl malonate and added the chemical to the Safer Choice Program's Safer Chemical Ingredients List (SCIL) in July 2013 under the functional class of fragrances. The SCIL[5] is a continuously updated list of chemicals that meet low-concern Safer Choice criteria.[6]

EPA also reviewed international assessments of diethyl malonate. EPA identified assessments by the Organisation for Economic Co-operation and Development (OECD) and Canadian, Germany, and New Zealand government agencies.

The OECD SIAM discussed the SIDS Initial Assessment Report (SIAR) on malonic acid diesters, including diethyl malonate, in April 2005. The SIAM determined this chemical to be "low priority for further work" for human health and the environment.[7]

The Canadian Government, through an assessment of toxicity and exposure as part of its categorization of the Domestic Substance List, found that diethyl malonate did not meet its criteria for further attention.[8]

The German Environment Agency (UBA) designated diethyl malonate as "low hazard to waters" in August 2017 based on an assessment of ecotoxicity and environmental fate.[9]

New Zealand's Environmental Protection Authority lists diethyl malonate in its Chemical Classification and Information Database (CCID), which includes hazard and physical information about single chemicals for use in hazard classifications and safety information. For diethyl malonate, the CCID includes the classification description "acutely toxic."[10] This classification is based on information in Chemwatch[11] from 2006 that classified this chemical as R65, "Harmful: may cause lung damage if swallowed." Section 6.1 of this screening review contains a summary of the reasonably available information on acute toxicity in 2019 and an explanation of why EPA does not believe acute toxicity is a concern for this chemical.

[5] https://www.epa.gov/saferchoice/safer-ingredients
[6] https://www.epa.gov/sites/production/files/2013-12/documents/dfe_master_criteria_safer_ingredients_v2_1.pdf
[7] https://hpvchemicals.oecd.org/ui/handler.axd?id=66A562AA-27EC-4A1B-B87D-637A7DA9E162
[8] https://canadachemicals.oecd.org/ChemicalDetails.aspx?ChemicalID=8443FA36-2730-44AE-AD1E-EDD461C2026F
[9] https://webrigoletto.uba.de/rigoletto/public/searchDetail.do?kennummer=1188
[10] https://www.epa.govt.nz/database-search/chemical-classification-and-information-database-ccid/view/14427
[11] https://www.chemwatch.net

5. Conditions of Use

Per TSCA section 3(4), the term "conditions of use" means the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of. EPA assembled information on all uses of diethyl malonate (Appendix A) to determine conditions of use.[12] One source of information that EPA used to help determine conditions of use is 2016 Chemical Data Reporting (CDR). The CDR rule (previously known as the Inventory Update Rule, or IUR), under TSCA section 8, requires manufacturers (including importers) to report information on the chemical substances they produce domestically or import into the U.S., generally above a reporting threshold of 25,000 lb. per site per year. CDR includes information on the manufacturing, processing, and use of chemical substances with information dating to the mid-1980s. CDR may not provide information on other life-cycle phases such as the chemical substance's end-of-life after use in products (i.e., disposal).

According to CDR, diethyl malonate is manufactured domestically and imported. It is used in processing (incorporation into formulation, mixture or reaction and processing as a reactant) for construction, odor agents manufacturing, and other applications. Industrial uses include automotive paint and cleaning and washing agents. Consumer and commercial uses include washing and cleaning products, polishes and wax blends, and air care products, among others. Based on the known manufacturing, processing, and uses of this chemical substance, EPA assumes distribution in commerce. According to CDR, five facilities reported that the chemical substance was not recycled (e.g., not recycled, remanufactured, reprocessed, or reused). For another three facilities, this information was withheld. For an additional facility, information was not known or reasonably ascertained. No information on disposal is found in CDR or through EPA's Toxics Release Inventory (TRI) Program[13] since diethyl malonate is not a TRI-reportable chemical. Although reasonably available information did not specify additional types of disposal, for purposes of this prioritization designation, EPA assumed end-of-life pathways that include releases to air, wastewater, surface water, and land via solid and liquid waste based on the conditions of use (e.g., incineration, landfill).

To supplement CDR, EPA conducted research through the publicly available databases listed in Appendix A (Table A.2) and performed additional internet searches to clarify conditions of use or find additional occupational[14] and consumer uses. This research improved the Agency's understanding of the conditions of use for diethyl malonate. Although EPA identified uses of diethyl malonate in personal care products, the screening review covered TSCA conditions of use for the chemical substance and personal care products were not considered in EPA's assessment. Exclusions to TSCA's regulatory scope regarding "chemical substance" can be found at TSCA section 3(2). Table 3 lists the conditions of use for diethyl malonate considered for chemical substance prioritization, per TSCA section 3(4). Table 3 reflects the TSCA uses determined as conditions of use listed in Table A.3 (Appendix A).

[12] The prioritization process, including the definition of conditions of use, is explained in the *Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act* (82 FR 33753).

[13] https://www.epa.gov/toxics-release-inventory-tri-program

[14] Occupational uses include industrial and/or commercial uses

Table 3: Conditions of Use for Diethyl Malonate			
Life Cycle Stage	**Category**	**Subcategory of Use**	**Source**
Manufacturing	Domestic manufacture	Domestic manufacture – information on whether domestically manufactured was not reported	EPA (2017b)
	Import	Import- multiple sites report import	
Processing	Processing- incorporation into formulation, mixture or reaction	Other-construction	EPA (2017b)
		Pharmaceutical and medicine manufacturing	
		Odor agents-miscellaneous manufacturing	EPA (2017b), CPCat (2019)
	Processing as a reactant	Other-pharmaceutical and medicine manufacturing	EPA (2017b)
	Other	Automotive manufacturing	CPCat (2019)
		Chemical manufacturing	CPCat (2019), Reported to the ECHA database (2018)
		Toilet preparation manufacturing	CPCat (2019)
	Recycling	Recycling	EPA (2017b)[15]
Distribution	Distribution	Distribution	EPA (2017b)
Industrial Uses	Other	Automotive paint	CPCat (2019)
		Chemical warfare agents	CPCat (2019)
		Cleaning and washing agents	CPCat (2019), Reported to the ECHA database (2018)
		Motor vehicle care	CPCat (2019)
		Isocyanate blocking agent	Synapse Information Resources (n.d.); Special Chem (2018)
		Paints, lacquers, varnishes – possibly industrial/consumer/ commercial.	CPCat (2019)
		Absorbents and adsorbents---possibly industrial/commercial/consumer	CPCat (2019)

[15] In the 2016 CDR, five facilities reported that the chemical substance was not recycled (e.g., not recycled, remanufactured, reprocessed, or reused). For three facilities, this information was withheld. For one facility, information was not known or reasonably ascertained. No further information about recycling or disposal was found.

Table 3: Conditions of Use for Diethyl Malonate			
Life Cycle Stage	**Category**	**Subcategory of Use**	**Source**
Commercial/ Consumer	Building/construction materials not elsewhere covered		EPA (2017b)
	Washing and cleaning products		Reported to the ECHA database (2018)
	Polishes and wax blends		Reported to the ECHA database (2018)
Commercial	Coatings		Reported to the ECHA database (2018)
Consumer	Air care products	Air fresheners (oil diffusion, pluggable aerosol, pluggable liquid dispenser, scented candle, wax melts	EPA (2017b), CPCat (2019), P&G (2015), DeLima Associates (2015a,b), DeLima Associates (2016a,b)
		Car air freshener	P&G (2016), CPCat (2019)
	Cleaning and washing agents		Specific proprietary uses identified in Safer Choice program's Salesforce database
Disposal	Releases to air, wastewater, solid and liquid wastes		Though not explicitly identified, releases from disposal were assumed to be reasonably foreseen[16]

[16] See Section 5 for a discussion on why releases were assumed to be reasonably foreseen for purposes of this prioritization designation.

6. Hazard Characterization

EPA reviewed primary literature and other data sources to identify reasonably available information. This literature review approach[17] is tailored to capture the reasonably available information associated with low-hazard chemicals. EPA also used this process to verify the reasonably available information for reliability, completeness, and consistency. EPA reviewed the reasonably available information to identify relevant, quality studies to evaluate the hazard potential for diethyl malonate against the endpoints listed below. EPA's New Chemicals Program has used these endpoints for decades to evaluate chemical substances under TSCA[18] and EPA toxicologists rely on these endpoints as key indicators of potential human health and environmental effects. These endpoints also align with internationally accepted hazard characterization criteria, such as the Globally Harmonized System of Classification and Labelling of Chemicals[19] as noted above in Section 4 and form the basis of the comparative hazard assessment of chemicals.

Human health endpoints evaluated: Acute mammalian toxicity, repeated dose toxicity, carcinogenicity, mutagenicity/genotoxicity, reproductive and developmental toxicity, neurotoxicity, skin sensitization, respiratory sensitization, immunotoxicity and eye and skin irritation.

Environmental fate and effects endpoints evaluated: Aquatic toxicity, environmental persistence, and bioaccumulation.

The low-concern criteria used to evaluate both human health and environmental fate and effects are included in Table 4 below.

Table 4: Low concern Criteria for Human Health and Environmental Fate and Effects

Human Health				
Acute Mammalian Toxicity[20]	**Very High**	**High**	**Moderate**	**Low**
Oral LD50 (mg/kg)	≤ 50	> 50 – 300	> 300 - 2000	> 2000
Dermal LD50 (mg/kg)	≤ 200	> 200 – 1000	> 1000 - 2000	> 2000
Inhalation LC50 (vapor/gas) (mg/L)	≤ 2	> 2 – 10	> 10 - 20	> 20
Inhalation LC50 (dust/mist/fume) (mg/L)	≤ 0.5	> 0.5 - 1.0	> 1.0 - 5	> 5

[17] Discussed in the document "Approach Document for Screening Hazard Information for Low-Priority Substances Under TSCA," which can be found at https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0450-0002.

[18] https://www.epa.gov/sustainable-futures/sustainable-futures-p2-framework-manual

[19] https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev07/English/ST_SG_AC10_30_Rev7e.pdf

[20] Values derived from GHS criteria (*Chapter 3.1: Acute Toxicity.* 2009, United Nations).

Table 4: Low concern Criteria for Human Health and Environmental Fate and Effects				
Repeated Dose Toxicity, Neurotoxicity, and Immunotoxicity (90-day study)[21]		**High**	**Moderate**	**Low**
Oral (mg/kg-bw/day)		< 10	10 - 100	> 100
Dermal (mg/kg-bw/day)		< 20	20 - 200	> 200
Inhalation (vapor/gas) (mg/L/6h/day)		< 0.2	0.2 - 1.0	> 1.0
Inhalation (dust/mist/fume) (mg/L/6h/day)		< 0.02	0.02 - 0.2	> 0.2
Reproductive and Developmental Toxicity[22]		**High**	**Moderate**	**Low**
Oral (mg/kg/day)		< 50	50 - 250	> 250
Dermal (mg/kg/day)		< 100	100 - 500	> 500
Inhalation (vapor, gas, mg/L/day)		< 1	1 - 2.5	> 2.5
Inhalation (dust/mist/fume, mg/L/day)		< 0.1	0.1 - 0.5	> 0.5
Mutagenicity/ Genotoxicity[23]	**Very High**	**High**	**Moderate**	**Low**
Germ cell mutagenicity	GHS Category 1A or 1B: Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans.	GHS Category 2: Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans.	Evidence of mutagenicity support by positive results *in vitro* OR *in vivo* somatic cells of humans or animals	Negative for chromosomal aberrations and gene mutations, or no structural alerts.
Mutagenicity and Genotoxicity in Somatic Cells		OR Evidence of mutagenicity supported by positive results in *in vitro* AND		

[21] Values from GHS criteria for Specific Target Organ Toxicity Repeated Exposure (*Chapter 3.9: Specific Target Organ Toxicity Repeated* Exposure. 2009, United Nations).

[22] Values derived from the US EPA's Office of Pollution Prevention & Toxics criteria for HPV chemical categorizations (*Methodology for Risk-Based Prioritization Under ChAMP*), and the EU REACH criteria for Annex IV (2007).

[23] From GHS criteria (*Chapter 3.5: Germ Cells Mutagenicity.* 2009, United Nations) and supplemented with considerations for mutagenicity and genotoxicity in cells other than germs cells.

Table 4: Low concern Criteria for Human Health and Environmental Fate and Effects				
		in vivo somatic cells and/or germ cells of humans or animals.		
Carcinogenicity[24]	**Very High**	**High**	**Moderate**	**Low**
	Known or presumed human carcinogen (GHS Category 1A and 1B)	Suspected human carcinogen (GHS Category 2)	Limited or marginal evidence of carcinogenicity in animals (and inadequate[25] evidence in humans)	Negative studies or robust mechanism-based SAR
Sensitization[26]		**High**	**Moderate**	**Low**
Skin sensitization		High frequency of sensitization in humans and/or high potency in animals (GHS Category 1A)	Low to moderate frequency of sensitization in human and/or low to moderate potency in animals (GHS Category 1B)	Adequate data available and not GHS Category 1A or 1B
Respiratory sensitization		Occurrence in humans or evidence of sensitization in humans based on animal or other tests (equivalent to GHS Category 1A or 1B)	Limited evidence including the presence of structural alerts	Adequate data available indicating lack of respiratory sensitization
Irritation/ Corrosivity[27]	**Very High**	**High**	**Moderate**	**Low**
Eye Irritation/ Corrosivity	Irritation persists for >21 days or corrosive	Clearing in 8-21 days, severely irritating	Clearing in 7 days or less, moderately irritating	Clearing in less than 24 hours, mildly irritating
Skin Irritation/ Corrosivity	Corrosive	Severe irritation at 72 hours	Moderate irritation at 72 hours	Mild or slight irritation at 72 hours

[24] Criteria mirror classification approach used by the IARC (*Preamble to the IARC Monographs: B. Scientific Review and Evaluation: 6. Evaluation and rationale.* 2006*)* and incorporate GHS classification scheme (*Chapter 3.6: Carcinogenicity.* 2009, United Nations).

[25] EPA's approach to determining the adequacy of information is discussed in the document "Approach Document for Screening Hazard Information for Low-Priority Substances Under TSCA", also released at proposal.

[26] Incorporates GHS criteria (*Chapter 3.4: Respiratory or Skin Sensitization.* 2009, United Nations).

[27] Criteria derived from the Office of Pesticide Programs Acute Toxicity Categories (US EPA. *Label Review Manual.* 2010).

Table 4: Low concern Criteria for Human Health and Environmental Fate and Effects			
Environmental Fate and Effects			
Acute Aquatic Toxicity Value (L/E/IC50)[28]	**Chronic Aquatic Toxicity Value (L/E/IC50)**[28]	**Persistence (Measured in terms of level of biodegradation)**[29]	**Bioaccumulation Potential**[30]
May be low concern if ≤10 ppm…	…and ≤1 ppm…	…and the chemical meets the 10-day window as measured in a ready biodegradation test…	…and BCF/BAF < 1000.
Low concern if >10 ppm and <100 ppm…	…and >1 ppm and <10 ppm…	…and the chemical reaches the pass level within 28 days as measured in a ready biodegradation test	
Low concern if ≥100 ppm…	…and ≥ 10 ppm…	… and the chemical has a half-life < 60 days…	

6.1 Human Health Hazard

Below is a summary of the reasonably available information that EPA included in the hazard evaluation of diethyl malonate. In many cases, EPA used analogous chemicals to make findings for a given endpoint. Where this is the case, use of the analog is explained. If the chemical studied is not named, the study is for diethyl malonate. Appendix B contains more information on each study.

EPA used best professional judgement to select analogs for diethyl malonate based on similarity in structure, physical-chemical properties, and functionality, with the assumption that these chemicals will have similar environmental transport and persistence characteristics, bioavailability and toxicity profiles. Diethyl malonate is the diethyl ester of propanedioic acid. EPA is using two analogs for diethyl malonate. The first is dimethyl malonate, the dimethyl ester of propanedioic acid. The second is dimethyl glutarate, which varies from dimethyl malonate by only its carbon chain length.

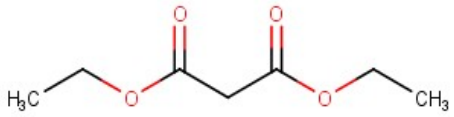
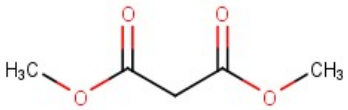
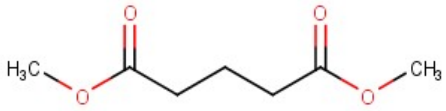
Other possible analogs for diethyl malonate are dimethyl succinate (DMS, CASRN 106-65-0) and dimethyl adipate (DMA, CASRN 627-93-0). These are all aliphatic diesters like diethyl malonate, except that the aliphatic chain lengths separating the esters groups are longer. There is a large amount of data available for the commercial mixture commonly known as dibasic esters (DBE- mixture of DMS, DMA and DMG, CASRN 95481-62-2); however, this CASRN was excluded as a potential analog based on its variable composition. EPA did not identify relevant, quality studies[31] for these other possible analogs, resulting in the selection of dimethyl malonate and dimethyl glutarate as appropriate analogs for this screening review.

[28] Derived from GHS criteria (*Chapter 4.1: Hazards to the Aquatic Environment.* 2009, United Nations), EPA OPPT New Chemicals Program (*Pollution Prevention (P2) Framework,* 2005*)* and OPPT's criteria for HPV chemical categorization (*Methodology for Risk Based Prioritization Under ChAMP. 2009).*

[29] Derived from OPPT's New Chemicals Program and DfE Master Criteria, and reflects OPPT policy on PBTs (*Design for the Environment Program Master Criteria for Safer Chemicals, 2010)*.

[30] Derived from OPPT's New Chemicals Program and Arnot & Gobas (2006) [Arnot, J.A. and F.A. Gobas, *A review of bioconcentration factor (BCF) and bioaccumulation factor (BAF) assessments for organic chemicals* in aquatic organisms. Environmental Reviews, 2006. 14: p. 257-297.]

[31] The literature search and review process to determine studies of adequate quality for inclusion in the screening review is further discussed in the document "The Approach Document for Screening Hazard Information for Low-Priority Substances under TSCA." https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0450-0002.

Table 5: Diethyl Malonate and Analog Structures		
CASRN	**Name**	**Structure**
105-53-3	Diethyl malonate	
108-59-8	Dimethyl malonate	
1119-40-0	Dimethyl glutarate	

6.1.1 Absorption, Distribution, Metabolism, and Excretion

To review absorption, distribution, metabolism and excretion (ADME) endpoints without adequate quality[31] experimental data, EPA used widely accepted new approach methodologies (NAMs), such as modeling and estimation tools often based on physical-chemical properties, which provided information sufficient to fill these endpoints.

Absorption

To assess the substance's dermal absorption potential, EPA relied on experimental data. An *in vivo* dermal absorption study using diethyl malonate showed that approximately 2.5% to 15% of the applied dose penetrated through the skin of several animal species (mice, human or pig skin grafted on mice, pig, and dog) following a 24- to 48-hour exposure period (Reifenrath et al., 1984). Another study indicated approximately 16% of the applied dose penetrated through human cadaver skin following a 24-hour exposure period, with a maximum penetration rate of approximately 350 µg/cm^2/hour (CIR Expert Panel, 2010; OECD, 2005). In one study using pig skin, approximately 3% to 10% of the applied dose was absorbed or found in the receptor fluid and approximately 8% to 30% of the applied dose remained in the skin following a 50-hour exposure period (CIR Expert Panel, 2010; OECD, 2005). In another study using pig skin, approximately 0.2 to 1.6% of the applied dose was found in the receptor fluid, 0.2-0.9% of the applied dose remained in the skin, and 0.2 to 0.7% of the applied dose remained on the skin surface following a 24-hour exposure period (CIR Expert Panel, 2010; OECD, 2005; Chellquist and Reifenrath, 1988). These results demonstrate poor to moderate dermal absorption of diethyl malonate.

If ingested orally, diethyl malonate is expected to have poor absorption from the gastrointestinal tract based on its molecular weight, water solubility, and log K_{ow} (Section 3).

If inhaled as a vapor or aerosol, absorption from the lungs is likely based on diethyl malonate's water solubility (Section 3).

Distribution

Based on its water solubility and log K_{ow} (Section 3), diethyl malonate is likely to be distributed mainly in aqueous compartments of an organism, and absorption and sequestration in fatty tissues is unlikely.

Metabolism

Experimental data determined to be of adequate quality[32] on diethyl malonate metabolite formation were not reasonable available for the assessment of metabolism. The Quantitative Structure-Activity Relationship (QSAR) toolbox[33] was used to run the rat liver S9 metabolism simulator, the skin metabolism simulator, and the *in vivo* rat metabolism simulator. The QSAR toolbox was used to identify putative diethyl malonate metabolites. All three metabolism simulators predicted ethanol and 2-ethoxycarbonyl-acetic acid as metabolites of diethyl malonate. The rat liver S9 and *in vivo* rat metabolism simulators predicted acetic acid, acetaldehyde and malonic acid as metabolites of diethyl malonate.

Excretion

Based on diethyl malonate's lower molecular weight and high water solubility, it is likely to be excreted via urine. Because of its low vapor pressure, excretion via gas exchange is unlikely.

6.1.2 Acute Toxicity

EPA assessed toxicity from acute exposures to diethyl malonate using read-across from dimethyl malonate. A study on rats exposed to dimethyl malonate in their diet reported no effects at the single dose tested (2000 mg/kg), resulting in an LD_{50} greater than 2000 mg/kg (Reported to the ECHA database, 1992b). Another study on rats exposed to dimethyl malonate by oral gavage also reported an LD_{50} greater than 2000 mg/kg (OECD, 2005; Reported to the ECHA database, 1992c). These results provide sufficient information to indicate low concern for acute toxicity from oral exposures with LD_{50}s exceeding the low-concern benchmark of 2000 mg/kg.

A study on rats exposed to dimethyl malonate via dermal application for 24 hours demonstrated no effects at the single dose tested (2000 mg/kg), resulting in an LD_{50} greater than 2000 mg/kg (OECD, 2005; Reported to the ECHA database, 1992a). This result provides sufficient information to indicate low concern for acute toxicity from dermal exposure based on the LD_{50} exceeding the low-concern benchmark of 2000 mg/kg.

6.1.3 Repeated Dose Toxicity

EPA assessed the potential for mammalian toxicity from repeated exposures to diethyl malonate using read-across from dimethyl malonate. In an OECD Guideline 422 study, rats were exposed to dimethyl

[32] The literature search and review process to determine studies of adequate quality for inclusion in the screening review is further discussed in the document "The Approach Document for Screening Hazard Information for Low-Priority Substances under TSCA." https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0450-0002

[33] https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

malonate via oral gavage for 39 days for males and 51 days for females (OECD, 2005; Reported to the ECHA database, 2003). A no observed adverse effect level (NOAEL) of 300 mg/kg-day and a lowest observed adverse effect level (LOAEL) of 1000 mg/kg-day based on hepatocellular hypertrophy were reported. EPA considered this effect reversible because there was not a significant increase in hypertrophy in the recovery groups. The results provide sufficient information to indicate low-concern for toxicity from repeated exposures because the effects were reversible and the reported NOAEL and LOAEL meet the low-concern benchmark of 300 mg/kg-day for a ~30-day repeated dose study.

To review the potential for inhalation repeated dose toxicity for diethyl malonate, EPA used route-to-route extrapolation, which is the prediction of the amount of substance administered by one route that would produce the same responses as that obtained by a given amount of the substance administered by another route.[34] EPA performed route-to-route extrapolation using the oral combined repeated dose study with reproduction/developmental toxicity screening (OECD Guideline 422) for dimethyl malonate that demonstrated a lowest observed adverse effect level (LOAEL) of 1000 mg/kg/day based on hepatocellular hypertrophy discussed in the preceding paragraph. However, EPA considered this effect reversible because there was not a significant increase in hypertrophy in the recovery groups. No effects on the other measured repeated dose parameters (e.g., clinical signs, body weight gain, food and water consumption, clinical chemistry, hematology parameters, organ weights, or functional observation battery tests) or reproductive and developmental parameters (discussed below in Section 6.1.4) were observed. Therefore, EPA considers 1000 mg/kg-day to be the NOAEL. This NOAEL value is also the highest dose tested in the study. Extrapolation of the oral value of 1000 mg/kg-day, with consideration of the standard respiratory volume and percent absorption using EPA's Exposure Factors Handbook, [35] results in a prediction of inhalation toxicity observed at concentrations greater than 0.44 mg/m^3 (see Appendix B for calculation information). Because the dose extrapolation was performed on the highest dose tested, which EPA determined did not cause an adverse effect, the predicted inhalation toxicity value represents a dose at which EPA does not expect adverse effects to occur. While this value technically falls within the moderate concern benchmarks outlined in Table 4, because of the study's dosing limitations, there is uncertainty in the dose level at which adverse effects may occur following repeated inhalation exposures. This predicted inhalation value is an artifact of study dose limitations, based on a conservative approach for route-to-route extrapolation, and does not provide evidence of moderate concern. This estimation technique provides sufficient information to screen the potential for inhalation repeated dose toxicity.

6.1.4 Reproductive and Developmental Toxicity

EPA assessed the potential for diethyl malonate to induce developmental toxicity using read-across from dimethyl malonate. In the same OECD Guideline 422 study described in Section 6.1.3, male and female rats exposed to dimethyl malonate via oral gavage were also tested for reproductive and developmental outcomes (OECD, 2005; Reported to the ECHA database, 2003). Reproductive and developmental parameters including fertility indices, duration of gestation, number of corpora lutea, pre and post-implantation loss, numbers of pups born and live litters, mean litter size, sex, ratio, pup

[34] https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258

[35] 2011 Edition. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

viability, and pup survivability were recorded. Pups from each litter were examined for external deformities, malformations and gross pathologies. No adverse effects were noted on any of these parameters, resulting in a NOAEL of 1000 mg/kg-day. This result, taken with the low-concern criteria oral benchmark of 250 mg/kg-day, provides sufficient information to indicate low concern for reproductive and developmental toxicity.

EPA also used read-across from an analog to assess developmental toxicity from inhalation exposures. A study in rabbits exposed to vapors of the analog dimethyl glutarate from gestation day 7 to 28 reported a no observed adverse effect concentration (NOAEC) of 1.0 mg/L (the highest dose tested) based on no adverse effects noted related to developmental toxicity (Munley, 2003). While the NOAEC of 1.0 mg/L technically falls below the low-concern benchmark of 2.5 mg/L, this is an artifact of the study dosing and does not indicate moderate concern for this endpoint. Because no adverse effects were observed, these results indicate developmental toxicity from inhalation exposures are unlikely. EPA applied expert scientific judgement based on the reasonably available information to conclude that these results provide sufficient information to indicate low concern for developmental toxicity for diethyl malonate.

6.1.5 Genotoxicity

EPA assessed diethyl malonate's potential to induce genotoxicity using experimental data and read-across from analogs. Diethyl malonate was negative for inducing gene mutations in bacteria in two studies (OECD, 2005). EPA used read-across from dimethyl malonate to assess genotoxicity through chromosomal aberrations. Human peripheral lymphocytes exposed to dimethyl malonate were negative for chromosomal aberrations with and without metabolic activation (OECD, 2005; Reported to the ECHA database, 2003). An *in vivo* study on rats exposed to dimethyl glutarate also reported negative results for chromosomal aberrations (SOCMA, 2002). These results provide sufficient information to indicate low concern for genotoxicity.

6.1.6 Carcinogenicity

Because experimental carcinogenicity studies determined to be of adequate quality[31] for diethyl malonate were not reasonably available, EPA used widely accepted NAMs, such as publicly available quantitative structure activity relationship (QSAR) models and structural alerts (SA) to assess the carcinogenic potential for diethyl malonate. Structural alerts represent molecular functional groups or substructures that are known to be linked to the carcinogenic activity of chemicals. The most common structural alerts are those for electrophiles (either direct acting or following activation). Modulating factors that will impact the carcinogenic potential of a given electrophile will include its relative hardness or softness, its molecular flexibility or rigidity, and the balance between its reactivity and stability.[36] For this chemical and its metabolites, there is an absence of the types of reactive structural features that are present in genotoxic carcinogens. Diethyl malonate is not an electrophile. ISS

[36] "Fundamental and Guiding Principles for (Q)SAR Analysis of Chemical Carcinogens with Mechanistic Considerations: Series on Testing and Assessment, No. 229." 2015. Environment Directorate, Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.

profiler, a QSAR model[37], did not identify any structural alerts for diethyl malonate. However, an aldehyde alert is flagged for an aldehyde metabolite. This aldehyde metabolite is transient, as it is further oxidized to a ketone and then conjugated to form a glucuronide metabolite (see Figure 2 (metabolic tree) in the Metabolic Pathway Trees Supplemental Document[38]). Also, diethyl malonate goes through multiple other detoxification pathways, including ester hydrolysis and amino acid conjugation transformations that do not lead to an aldehyde metabolite (see Figure 2 in the Metabolic Pathway Trees Supplemental Document). Further, the Virtual models for property Evaluation of chemicals within a Global Architecture (VEGA) models'[39] results indicate diethyl malonate has low potential to be carcinogenic or mutagenic with moderate reliability.

Applying expert judgement based on the reasonably available information and weight of the scientific evidence, EPA finds that diethyl malonate's transformation profile, predictions by QSAR modeling, absence of structural alerts in the parent chemical substance, and experimental genotoxicity results provide sufficient information to indicate this chemical is unlikely to be carcinogenic or mutagenic.

6.1.7 Neurotoxicity

EPA assessed the potential for neurotoxicity using relevant endpoints measured in repeated dose studies, reasonably available information from mechanistic studies, and searching accepted NAMs, such as predictions by U.S. EPA's ToxCast.[40]

No treatment-related effects in functional observation battery tests were reported in a combined repeated dose and reproduction/developmental screening test in rats exposed to the analog dimethyl malonate at gavage doses up to 1000 mg/kg-day (OECD, 2005).

EPA also considered mechanistic studies to assess neurotoxicity. Dimethyl malonate was not cytotoxic to striatal neurons in an *in vitro* cytotoxicity study in primary culture neurons from the fetal rat ganglionic eminence (Mclaughlin et al., 1998). In another study, dimethyl malonate exposure caused selective motor neuron death to primary neuronal cells isolated from rat spinal cord tissue (Kanki et al., 2004). Other mechanistic studies indicate malonate salt (CASRN 108-59-8) may be involved in oxidative stress through the involvement of glutamate receptors, and induce dopamine efflux (Moy et al., 2007; Zeevalk et al., 1998). However, these effects do not appear to translate into adverse outcomes, as noted in the functional observation battery results. Further, ToxCast results for diethyl malonate included 15 *in vitro* high-throughput biochemical and cell-based assays related to neurological functions.[41] Diethyl malonate did not induce bioactivity in any of these assays.

[37] Carcinogenicity alerts by ISS 2.4 profiler as encoded in the QSAR Toolbox 4.3 (qsartoolbox.org) and the 4 carcinogenicity models housed within the VEGA 1.1.4 software tool available from https://www.vegahub.eu. A summary of the results from these models is provided in Appendix B.

[38] The metabolic tree was generated using the in vivo rat metabolism simulator (v07.12) within TIMES V2.29.1.88.

[39] There are four carcinogenicity models housed within the VEGA 1.1.4 software tool available from https://www.vegahub.eu. A summary of the results from these models is provided in Appendix B.

[40] https://comptox.epa.gov/dashboard/. Chemical specific assay list can be found at https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID7021863#invitrodb.

[41] Identified by supplemental information in Chushak Y., Shows H., Gearhart J., Pangburn H. 2018. In silico identification of protein targets for chemical neurotoxins using Toxcast in vitro data and read-across within the QSAR toolbox. Toxicology Research issue 3. Supplemental files: https://pubs.rsc.org/en/content/articlelanding/2018/tx/c7tx00268h#!divAbstract.

Based on the absence of effects in the functional observation battery tests, negative results for bioactivity in ToxCast assays, mechanistic study results, and low-concern results for other endpoints, including acute, reproductive and developmental toxicity, EPA has sufficient information to indicate low concern for neurotoxicity.

6.1.8 Skin Sensitization

EPA assessed diethyl malonate's potential to act as a skin sensitizer using read-across from dimethyl malonate. An OECD Guideline 406 study in guinea pigs exposed to dimethyl malonate reported it as negative for inducing skin sensitization (Reported to the ECHA database, 1992g). These results provide sufficient information to indicate low concern for skin sensitization.

6.1.9 Respiratory Sensitization

Experimental data determined to be of adequate quality[42] on diethyl malonate or closely related analogs were not reasonably available for the assessment of respiratory sensitization potential. To model respiratory sensitization for diethyl malonate, EPA used NAMs, such as the QSAR Toolbox, version 4.2 models[43] for keratinocyte gene expression; protein binding potency h-CLAT; protein binding potency cysteine; protein binding potency lysine; and respiratory sensitization. No structural alerts were identified for diethyl malonate. The results from NAMs and weight of the scientific evidence provide sufficient information to indicate low concern for respiratory sensitization.

6.1.10 Immunotoxicity

EPA reviewed the literature for immunotoxicity endpoints such as lymphoid organ weight, histopathology, and immune function. Specific endpoints included immune system function (e.g., T-cell dependent antibody response), immunophenotyping (e.g., changes in cell types), natural killer cell activity, host resistance assays, macrophage neutrophil function, and cell-mediated immunity assays. Experimental data determined to be of adequate quality[44] on diethyl malonate or closely related analogs were not reasonably available for the assessment of immunotoxicity potential.

Repeated dose testing is designed to be comprehensive in nature and is intended to address a wide range of possible impacts, including, but not limited to immunotoxicity. The testing required to address repeated dose toxicity typically includes routine clinical observations, hematology and clinical biochemistry, body weight/food and water consumption, as well as both gross necropsy and histopathology involving organs and organ systems. For example, repeated dose studies can evaluate changes to the spleen or thymus, which with accompanying histological changes or changes in hematological parameters can indicate potential for immunological toxicity. Where immune system-related endpoints were measured in repeated dose studies, any adverse effects would be incorporated

[42] The literature search and review process to determine studies of adequate quality for inclusion in the screening review is further discussed in the document "The Approach Document for Screening Hazard Information for Low-Priority Substances under TSCA." https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0450-0002.

[43] The OECD QSAR Toolbox is one of EPA's listed new approach methodologies under TSCA 4(h)(2), available at https://www.epa.gov/sites/production/files/2019-12/documents/alternative_testing_nams_list_first_update_final.pdf

[44] The literature search and review process to determine studies of adequate quality for inclusion in the screening review is further discussed in the document "The Approach Document for Screening Hazard Information for Low-Priority Substances under TSCA." https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0450-0002.

into the lowest observed adverse effect level used against the low-concern benchmarks. Therefore, EPA relied on this information from repeated dose studies when it was reasonably available. For diethyl malonate, the included repeated dose study on the analog dimethyl malonate did not report changes in lymphoid organ weights (thymus, spleen, lymph nodes), with accompanying histopathology, or hematological changes at concentrations up to the highest dose of 1000 mg/kg/day in rats. These results provide sufficient information to indicate low concern for immunotoxicity potential from diethyl malonate.

6.1.11 Skin Irritation

EPA assessed diethyl malonate's potential to act as a skin irritant using read-across from dimethyl malonate. In a study following OECD Guideline 404, rabbits exposed dermally to dimethyl malonate had slight erythema 30 to 60 minutes after the patch was removed, but there were no other signs of irritation (OECD, 2005; Reported to the ECHA database, 1992f). Dimethyl malonate was considered to be non-irritating. These results provide sufficient information to indicate low concern for skin irritation.

6.1.12 Eye Irritation

EPA assessed diethyl malonate's potential to act as an eye irritant using experimental data. In a study following OECD Guideline 405, rabbits exposed to diethyl malonate displayed slight to moderate chemosis, irritation of the conjunctivae and iris, and cornea opacity with all effects reversible within 21 days (OECD, 2005). Despite the fact that the effects observed were considered slight to moderate, because the study design demonstrates reversibility within 21 days, EPA interprets the results against the eye irritation benchmarks in Table 4 to indicate diethyl malonate has high potential for eye irritation. The weight of the scientific evidence for these results is discussed in Section 8.1.

6.1.13 Hazards to Potentially Exposed or Susceptible Subpopulations

The above information supports a low human health hazard finding for diethyl malonate based on low-concern criteria. This finding includes considerations such as the potential for developmental toxicity, reproductive toxicity, and acute or repeated dose toxicity that may impact potentially exposed or susceptible subpopulations. Based on the hazard information discussed in Section 6, EPA did not identify populations with greater susceptibility to diethyl malonate.

6.2 Environmental Hazard

To review environmental hazard endpoints without adequate quality[31] experimental data, EPA used widely accepted new approach methodologies (NAMs), such as modeling and estimation tools often based on physical-chemical properties, which provided information sufficient to fill these endpoints and form the basis for designation. EPA assessed environmental hazard for diethyl malonate based on available acute experimental data and estimated chronic toxicity values using the Ecological Structure Active Relationships (ECOSAR) predictive model.[45] Appendix B contains a summary of the reasonably available environmental hazard data.

[45] https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model

6.2.1 Acute Aquatic Toxicity

EPA assessed environmental hazard from acute exposures using experimental data. Five studies in aquatic vertebrates exposed to diethyl malonate resulted in LC_{50}s ranging from 11.8 mg/L to 17 mg/L (OECD, 2005; Geiger et al., 1986; Call et al., 1981). Invertebrates exposed to diethyl malonate had an EC_{50} of 202 mg/L (OECD, 2005) and algae had an EC_{50} greater than 800 mg/L (OECD, 2005). For a chemical with acute aquatic toxicity values between 10 ppm to 100 ppm to be considered low concern for environmental hazard, the chemical must reach 60% degradation within 28 days. These results provide sufficient information to indicate low concern for acute aquatic exposure due to aquatic toxicity values greater than 10 mg/L coupled with biodegradation (discussed in Section 6.3.1).

6.2.2 Chronic Aquatic Toxicity

Chronic toxicity values were estimated using the ECOSAR predictive model. Chronic effects are predicted to occur at 8.1 mg/L for aquatic vertebrates, 190 mg/L for aquatic invertebrates, and 18 mg/L for algae. For a chemical with chronic aquatic toxicity values between 1 ppm and 10 ppm to be considered low concern for environmental hazard, the chemical must reach 60% degradation with 28 days. Given the toxicity values estimated for diethyl malonate's and its ability to biodegrade within 28 days (Section 6.3.1), EPA has sufficient information to indicate this chemical is expected to have low concern for chronic aquatic toxicity.

6.3 Persistence and Bioaccumulation Potential

6.3.1 Persistence

EPA assessed environmental persistence for diethyl malonate using an experimental study following OECD Guideline 301A (OECD, 2005). Diethyl malonate degraded 92% in 7 days and 98% in 28 days. These results indicate low concern for persistence based on the benchmark of aerobic ready biodegradation occurring within 28 days given the aquatic toxicity values (discussed in Section 6.2). Furthermore, a microbial inhibition test indicates diethyl malonate is non-toxic to microbial populations found in sewage treatment plants (Fellows et al., 1990). These results, in addition to the predicted wastewater treatment removal in Table 2, indicate diethyl malonate is expected to undergo extensive removal through wastewater treatment plants prior to release in the environment.

EPA predicted anaerobic biodegradation for diethyl malonate using BioWin[46] models which predicted diethyl malonate will degrade quickly in anaerobic environments.

No degradation products of concern were identified for this chemical substance. The aerobic and anaerobic biodegradation results provide sufficient information to indicate this chemical will have low persistence.

6.3.2 Bioaccumulation Potential

Based on the estimated bioaccumulation factor (BAF) value of 1.06, using the Estimation Programs Interface (EPI) Suite models,[47] EPA has sufficient information that diethyl malonate is expected to

[46] https://envirosim.com/products/biowin
[47] https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

have low potential for bioaccumulation in the environment based on the low-concern benchmark of less than 1000.

7. Exposure Characterization

EPA considered reasonably available information on exposure for diethyl malonate. In general, there is limited information on exposure for low-hazard chemicals. EPA determined the CDR database and certain other sources of diethyl malonate use information are sources of information relevant to diethyl malonate's exposure potential. Of these sources, EPA determined that the CDR database contained the primary source of information on the conditions of use for this exposure characterization. EPA also consulted sources of use information from other databases and public sources (listed in Table A.2). EPA used these sources only where they augmented information from the CDR database to inform intended, known, or reasonably foreseen uses (Section 5).

As shown in Tables 3 and A.3, diethyl malonate is used as a processing aid for construction and other applications, as well as in various industrial, commercial, and consumer uses. Non-TSCA uses, including those excluded under TSCA section 3(2), are beyond the scope of this assessment (See Table A.3).

Under the conditions of use identified in Table 3, EPA assessed the potential exposure to the following categories: the environment, the general population, and potentially exposed or susceptible subpopulations including workers and consumers.

7.1 Production Volume Information

Production volume information for diethyl malonate is based on an analysis of CDR data reported from 1986 to 2015.[48] The CDR database indicates that for reporting year 2015, 15 companies manufactured or imported diethyl malonate at 16 sites. In 1986, 1990, 1998, and 2006 reporting years, aggregate production volume for diethyl malonate was between 500,000 and 1,000,000 lbs. In the 1994 reporting year, aggregate production volume was between 1,000,000 and 10,000,000 lbs., and in the 2002 reporting year was between 10,000 and 500,000 lbs. For the 2012 to 2015 reporting years aggregate production volume was between 100,000 and 500,000 lbs., and for 2011, the exact amount was reported at 385,876 lbs. In general, since 2011, production volume has remained relatively stable.

7.2 Exposures to the Environment

EPA expects most exposures to the environment to occur during the manufacture, processing, import, and industrial, commercial, and consumer use of diethyl malonate. Exposure is also possible from other uses, such as distribution and disposal. These activities could result in releases of diethyl malonate to media including surface water, landfills, and air.

EPA expects high levels of removal of diethyl malonate during wastewater treatment (either directly from the facility or indirectly via discharge to a municipal treatment facility or Publicly Owned Treatment Works (POTW), Table 2). Further, diethyl malonate is expected to have low persistence (aerobic and anaerobic biodegradation are discussed in Section 6.3.1) and has the potential to

[48] The CDR requires manufacturers (including importers) to report information on the chemical substances they produce domestically or import into the U.S. above 25,000 lb. per site per year.

breakdown in the environment to carbon dioxide and water. Therefore, any release of this chemical is expected to break down, reducing exposure to aquatic organisms in the water column and groundwater sources of drinking water, including well water. Based on the estimated log K_{oc} (Section 3), diethyl malonate is expected to have negligible adsorption to sediment, reducing the potential for toxicity to benthic organisms. Diethyl malonate's biodegradability and removal during treatment processes will reduce the exposure potential to aquatic organisms.

If disposed of in a landfill, this chemical is expected to degrade under aerobic and anaerobic conditions (aerobic and anaerobic biodegradation are discussed in Section 6.3.1).

If incineration releases during manufacturing and processing occur, EPA expects significant degradation of diethyl malonate to the point that it will not be present in air.

7.3 Exposures to the General Population

EPA expects the general population is unlikely to be exposed to diethyl malonate from the potential environmental releases described above. Air exposure is unlikely from incineration. If diethyl malonate is present in the air from volatilization, it is expected to be reduced significantly by photolysis, with a half-life of 35 minutes (see Table 2 in Section 3). Diethyl malonate is also unlikely to be present in surface water because it will degrade, reducing the potential for the general population to be exposed by oral ingestion or dermal exposure. Given the low bioaccumulation and bioconcentration potential of diethyl malonate, oral exposure to diethyl malonate via fish ingestion is unlikely.

7.4 Exposures to Potentially Exposed or Susceptible Subpopulations

EPA identified workers as a potentially exposed or susceptible subpopulation based on greater exposure to diethyl malonate than the general population during manufacturing, processing, distribution, use, and disposal. EPA also identified consumers as a population that may experience greater exposure to diethyl malonate than the general population through use of washing and cleaning products, polishes and wax blends, and air care products, for example.

7.4.1 Exposures to Workers

Based on its reported physical form and measured melting point (Table 2), diethyl malonate is a liquid under ambient conditions. Based on diethyl malonate's conditions of use (Table 3), workers may be exposed to liquids through direct dermal contact with the substance and inhalation of aerosols if generated. Based on its measured vapor pressure, diethyl malonate is expected to be volatile at ambient temperatures, and therefore workers may be exposed through inhalation of vapors. If diethyl malonate is in a dilute form, the estimated Henry's Law constant for diethyl malonate indicates volatilization from water and aqueous solutions is possible. Workers may be exposed to diethyl malonate in manufacturing, processing, distribution, use, and disposal.

7.4.2 Exposures to Consumers

Consumers may be exposed to diethyl malonate through the use of washing and cleaning products, polishes and wax blends, and air care products, for example. For all these uses, if dermal contact does occur, diethyl malonate is expected to have poor to moderate absorption through the skin based on its

molecular weight, water solubility and partitioning coefficients (Section 3) and on experimental dermal absorption studies (Section 6). If the chemical is in an aerosol product and inhalation exposure occurs, diethyl malonate's absorption from the lungs is likely. EPA does not include intentional misuse, such as people drinking products containing this chemical, as part of the known, intended, or reasonably foreseen conditions of use that could lead to an exposure (82 FR 33726). Diethyl malonate's metabolism and excretion is expected to further reduce the duration of exposure.

8. Summary of Findings

EPA has used reasonably available information on the following statutory and regulatory criteria and considerations to screen diethyl malonate against each of the priority designation considerations in 40 CFR 702.9(a), discussed individually in this section, under its conditions of use:

- the hazard and exposure potential of the chemical substance (See Sections 6 and 7);
- persistence and bioaccumulation (See Section 6.3);
- potentially exposed or susceptible subpopulations (See Section 7.4);
- storage near significant sources of drinking water (See Section 8.4);
- conditions of use or significant changes in the conditions of use of the chemical substance (See Section 5);
- the chemical substance's production volume or significant changes in production volume (See Section 7.1); and
- other risk-based criteria that EPA determines to be relevant to the designation of the chemical substance's priority.

EPA conducted a risk-based screening-level review based on the criteria and other considerations above and other relevant information described in 40 CFR 702.9(c) to inform the determination of whether the substance meets the standard of a high-priority substance. High-priority substance means a chemical substance that EPA determines, without consideration of costs or other non-risk factors, may present an unreasonable risk of injury to health or the environment because of a potential hazard and a potential route of exposure under the conditions of use, including an unreasonable risk to potentially exposed or susceptible subpopulations identified as relevant by EPA (40 CFR 702.3). Designation of a low-priority substance is not a finding that the chemical substance does not present an unreasonable risk, but rather that the chemical does not meet the statutory criteria for a high-priority substance and that a risk evaluation is not warranted at the time. This section explains the basis for the final designation and how EPA applied statutory and regulatory requirements, addressed rationale, and reached conclusions.

8.1 Hazard and Exposure Potential of the Chemical Substance

Approach: EPA evaluated the hazard and exposure potential of diethyl malonate. EPA used this information to inform its determination of whether diethyl malonate meets the statutory criteria and considerations for final designation as a low-priority substance.

- **Hazard potential:**

For diethyl malonate's hazard potential, EPA gathered information for a broad set of human health and environmental endpoints described in detail in Section 6 of this document. EPA screened this information against low-concern benchmarks. EPA found that diethyl malonate is of low concern for human health and environmental hazard across the range of endpoints in this low-concern criteria.

- **Exposure potential:**

To understand exposure potential, EPA gathered information on physical-chemical properties, production volumes, and the types of exposures likely to be faced by workers, the general population,

consumers, and children (discussed in Sections 3 and 7). EPA also gathered information on environmental releases. EPA identified the general population, workers, consumers, and the environment as most likely to experience exposures. EPA determined that while the general population, workers, and consumers may be exposed to diethyl malonate, exposure by the dermal and ingestion pathways are limited by diethyl malonate's physical-chemical properties. If inhalation occurs, diethyl malonate is expected to be metabolized and excreted, reducing the duration of exposure. If diethyl malonate is released into the environment, its exposure potential will be reduced through biodegradation under aerobic and anaerobic conditions.

Rationale: Although diethyl malonate may have high potential to cause eye irritation, the effects are reversible, thereby reducing concern for longer-term effects. TSCA conditions of use would be unlikely to result in frequent eye exposure because use patterns do not involve intentional eye exposure. Workers could be exposed during manufacturing, processing, distribution, use, and disposal, splashing of solutions, or hand-to-face and eye contact. Other uses covered under TSCA, especially consumer uses in washing and cleaning products, would be unlikely to result in more than incidental eye exposure. Eye irritation resulting from exposure in occupational and consumer settings is mitigated by the reversible nature of the effect and furthermore by the strong likelihood that any exposures would be self-limiting, especially by those who experience eye irritation from eye exposure.

In addition, EPA estimated repeated dose inhalation toxicity using route-to-route extrapolations from available oral hazard data. Because the dose extrapolation was performed on the highest dose tested, which EPA determined did not cause an adverse effect, this predicted inhalation toxicity value represents a dose at which EPA does not expect adverse effects to occur. While this value technically falls within the moderate concern benchmarks outlined in Table 4, the study's dosing limitations do not allow for EPA to determine the dose level at which adverse effects may occur following repeated inhalation exposures. In other words, any repeated dose effects from this chemical substance would be seen at doses higher than those found through the route-to-route extrapolation. The predicted inhalation value is an artifact of study dosing limitations, based on conservative approaches for route-to-route extrapolation, and does not provide evidence of moderate concern. As part of the weight of scientific evidence, EPA notes that the OECD Screening Information Dataset (SIDS) Initial Assessment Meeting (SIAM) reached a similar conclusion in April 2005 stating "the chemicals of this category are currently of low priority for further work due to their hazard profile" for human health (discussed further in Section 4 of the chemical's screening review). Based on the weight of scientific evidence and reasonably available information, EPA has sufficient information that diethyl malonate does not meet the standard for a high-priority substance and does not consider animal testing necessary to support this finding.

Conclusion: Based on an initial analysis of reasonably available hazard and exposure information, EPA concludes that the risk-based, screening-level review under 40 CFR 702.9(a)(1) does not support a finding that diethyl malonate meets the standard for a high-priority substance. The reasonably available hazard and exposure information described above provides sufficient information to support this finding. Even if the unlikely, infrequent, and temporary occurrence of potential high eye irritation were to occur, EPA does not find that this potential eye irritation rises to the significance of the standard for a high-priority substance (i.e., that the substance "may present an unreasonable risk of

injury to health"). Further, the route-to-route dose extrapolation prediction for inhalation toxicity does not alter EPA's conclusion that diethyl malonate does not meet the standard for a high-priority substance given that this prediction represents a dose level at which EPA does not expect adverse effects to occur.

8.2 Persistence and Bioaccumulation

Approach: EPA has evaluated both the persistence and bioaccumulation potential of diethyl malonate based on a set of EPA and internationally accepted measurement tools and benchmarks that are indicators of persistence and bioaccumulation potential (described in Section 6). These endpoints are key components in evaluating a chemical's persistence and bioaccumulation potential.

Rationale: EPA review of experimental data indicates diethyl malonate is biodegradable under aerobic conditions and predicted to be degradable under anaerobic conditions (discussed in Section 6.3.1). EPA's EPI Suite models indicate a low potential for bioaccumulation and bioconcentration (Section 6.3.2).

Conclusion: Based on an initial screen of reasonably available information on persistence and bioaccumulation, EPA concludes that the screening-level review under 40 CFR 702.9(a)(2) does not support a finding that diethyl malonate meets the standard for a high-priority substance. The reasonably available persistence and bioaccumulation information described above provides sufficient information to support this finding.

8.3 Potentially Exposed or Susceptible Subpopulations

Approach: TSCA Section 3(12) states that the "term 'potentially exposed or susceptible subpopulation' means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, consumers, or the elderly." EPA identified workers engaged in the manufacturing, processing, distribution, use, and disposal of diethyl malonate as a potentially exposed or susceptible subpopulation (described in more detail in Section 7). Consumers are also a potentially exposed subpopulation because of their use of products such as washing and cleaning products, polishes and wax blends, and air care products, as shown in Table 3.

Rationale: EPA did not identify hazard effects for this chemical that would make any population susceptible. EPA expects workers and consumers to have a higher exposure to diethyl malonate than the general population. Because of the chemical's low-concern hazard properties and reversibility of effects, exposure does not pose a significant increase in risk for consumers or workers.

Conclusion: Based on the Agency's understanding of the conditions of use and expected users such as potentially exposed or susceptible subpopulations, EPA concludes that the screening-level review under 40 CFR 702.9(a)(3) does not support a finding that diethyl malonate meets the standard for a high-priority substance. The conditions of use could result in increased exposures to certain populations. Even in light of this finding, the consistently low-concern hazard profile of diethyl malonate provides sufficient evidence to support a finding of low concern. The reasonably available

information on conditions of use, hazard, and exposure described above provides sufficient information to support this finding.

8.4 Storage near Significant Sources of Drinking Water

Approach: In Sections 6 and 7, EPA explains its evaluation of the elements of risk relevant to the storage of diethyl malonate near significant sources of drinking water. For this criterion, EPA focused primarily on the chemical substance's potential human health hazards, including to potentially exposed or susceptible subpopulations, and environmental fate properties, and explored a scenario of a release to a drinking water source. EPA also investigated whether the chemical substance was monitored for and detected in a range of environmental media. The requirement to consider storage near significant sources of drinking water is unique to prioritization under TSCA Section 6(b)(1)(A).

Rationale: In terms of health hazards, diethyl malonate is expected to present low concern to the general population, including susceptible subpopulations, across a spectrum of health endpoints.

In the event of an accidental release into a surface drinking water source, diethyl malonate is expected to be water soluble (see Section 3) and not expected to persist (see Section 6) in the drinking water supply. In the event of an accidental release to land, the estimated log K_{oc} indicates this substance is highly mobile in soils, increasing its potential for leaching into groundwater, including well water. The fate and transport evaluation indicates diethyl malonate is unlikely to partition into sediment, predicted to biodegrade under aerobic and anaerobic conditions (see Section 3), and unlikely to bioaccumulate (see Section 6), minimizing the likelihood that the chemical would be present in sediment or groundwater to pose a longer-term drinking water contamination threat.

A sudden release of large quantities of the chemical near a drinking water source could have immediate effects on the usability of a surface drinking water source. If such a release were to occur, two primary factors would operate together to reduce concern. First, the chemical would be expected to present low concern to the general population, including susceptible subpopulations, across a spectrum of health endpoints (see Section 6). Second, diethyl malonate would degrade in aerobic and anaerobic environments (see Section 6). Together, these factors mean that any exposures to this chemical through drinking water sources would be short-lived, and that if ingestion were to take place, concern for adverse health effects would be low.

EPA also explored whether the chemical had been identified as a concern under U.S. environmental statutes in the past. EPA searched lists of chemicals and confirmed that diethyl malonate does not appear on these lists. The lists reviewed include EPA's List of Lists (https://www.epa.gov/sites/production/files/2015-03/documents/list_of_lists.pdf). EPA also searched the lists of chemicals included in the National Primary Drinking Water Regulations and the Unregulated Contaminant Monitoring Rule (UCMR) under the Safe Drinking Water Act (SDWA).

Conclusion: Based on a qualitative review of a potential release near a significant source of drinking water, EPA concludes that the screening-level review of diethyl malonate under 40 CFR 702.9(a)(4) does not support a finding that diethyl malonate meets the standard for a high-priority substance. The reasonably available information on storage near significant sources of drinking water described above provides sufficient information to support these findings.

8.5 Conditions of Use or Significant Changes in Conditions of Use of the Chemical Substance

Approach: EPA evaluated the conditions of use for diethyl malonate and related potential exposures and hazards.

Rationale: EPA evaluated the conditions of use of diethyl malonate (see Section 5 and Appendix A) and found it to have a narrow range of conditions of use. EPA expects that even if the conditions of use were to expand beyond activities that are currently known, intended, or reasonably foreseen, the exposure outcome of the screening review would likely not change and would not alter the Agency's conclusion of low concern. EPA bases this expectation on diethyl malonate's consistently low-concern hazard characteristics across the spectrum of hazard endpoints and regardless of a change in the nature or extent of its use and resultant increased exposures.

Conclusion: EPA's qualitative evaluation of potential risk does not support a finding that diethyl malonate meets the standard for a high-priority substance, based on its low-hazard profile under the current conditions of use. EPA concludes that even if conditions of use broaden, resulting in an increase in the frequency or amount of exposures, the analysis conducted to support the screening-level review under 40 CFR 702.9(a)(5) would not change significantly. In particular, the analysis of concern for hazard, which forms an important basis for EPA's findings, would not be impacted by a change in conditions of use. Therefore, such changes would not support a finding that diethyl malonate meets the standard for a high-priority substance. The reasonably available information on conditions of use or significant changes in conditions of use described above provides sufficient information to support this finding.

8.6 The Volume or Significant Changes in Volume of the Chemical Substance Manufactured or Processed

Approach: EPA evaluated the current production volumes of diethyl malonate (Section 7.1) and related potential exposures (Sections 7.2 through 7.4).

Rationale: EPA used reasonably available information on production volume (see Appendix A) in considering potential risk. It is possible that designation of diethyl malonate as a low-priority substance could result in increased use and higher production volumes. EPA expects, however, that any changes in diethyl malonate's production volume would not alter the Agency's assessment of low concern given the chemical's low-hazard profile. EPA bases this expectation on diethyl malonate's consistently low-concern hazard characteristics across the spectrum of hazard endpoints. This expectation would apply, even with a significant change in the volume of the chemical manufactured or processed and resultant increased exposures.

Conclusion: Based on this screening criteria under 40 CFR 702.9(a)(6), EPA concludes that even if production volumes increase, resulting in an increase in the frequency or level of exposure, diethyl malonate does not meet the standard for a high-priority substance. The reasonably available information on production volume or significant changes in production volume described above provides sufficient information to support this finding.

8.7 Other Considerations

EPA did not identify other considerations for the screening review to support the final designation of diethyl malonate as a low-priority substance.

9. Final Designation

Based on a risk-based screening-level review of the chemical substance and relevant information received from the public and other information as appropriate and consistent with TSCA section 26(h), (i) and (j), EPA concludes that diethyl malonate does not meet the standard for a high-priority substance. The reasonably available information described above provides sufficient information to support this finding. Accordingly, EPA is designating diethyl malonate as a low-priority substance.

Appendix A: Conditions of Use Characterization

EPA gathered information on and related to conditions of use including uses of the chemical, products in which the chemical is used, types of users, and status (e.g., known, regulated).

A.1 CDR Manufacturers and Production Volume

The Chemical Data Reporting (CDR) rule (previously known as the Inventory Update Rule, or IUR), under TSCA section 8, requires manufacturers (including importers) to report information on the chemical substances they produce domestically or import into the U.S., generally above a reporting threshold of 25,000 lb. per site per year. According to the 2016 CDR database, 9 companies manufactured or imported diethyl malonate at 9 sites for reporting year 2015. Individual production volumes were withheld, but may be available in later releases of the 2016 CDR.

Table A.1 presents the historic production volume of diethyl malonate from the CDR (previously known as the Inventory Update Rule, or IUR) from 1986-2015. In 1986, 1990, 1998, and 2006 reporting years, aggregate production volume for diethyl malonate was between 500,000 and 1,000,000 lbs. In the 1994 reporting year, aggregate production volume was between 1,000,000 and 10,000,000 lbs., and in the 2002 reporting year was between 10,000 and 500,000 lbs. For the 2012 to 2015 reporting years aggregate production volume was between 100,000 and 500,000 lbs., and for 2011, the exact amount was reported at 385,876 lbs. In general, since 2011, production volume has remained relatively stable without significant increases or decreases.

Table A.1: 1986-2015 National Production Volume Data for Diethyl Malonate (Non-Confidential Production Volume in Pounds)

1986	1990	1994	1998	2002	2006	2011	2012	2013	2014	2015
500 K – 1 M	500 K – 1 M	1 M – 10 M	500 K – 1 M	10 K – 500K	500 K – 1M	385,876	100 K – 500 K	100 K – 500 K	100 K – 500 K	100 K – 500 K

Source(s):
EPA (2018a; 2017b; 2006; 2002)

Note(s):
K = Thousand; M = Million

A.2. Uses

A.2.1 Methods for Uses

Section A.2 provides a list of known uses of diethyl malonate, organized by category of use. To compile the uses, EPA searched publicly available databases listed in Tables A.2 and conducted additional internet searches to clarify uses. Search terms differed among databases because of different search term requirements for each database (i.e., some databases search by CASRN while others search by chemical name).

Table A.2: Sources Searched for Uses of Diethyl Malonate

Title	Author and Year	Search Term(s)	Found Use Information? [1]
Sources searched for all use reports			
California Links to Pesticides Data	California Dept of Pesticide Regulation (2013)	105-53-3	No
Canada Chemicals Management Plan information sheets	Government of Canada (2018)	105-53-3	No
Chemical and Product Categories (CPCat)	CPCat (2019)	105-53-3	Yes
ChemView [2]	EPA (2018a)	105-53-3	Yes
Children's Safe Product Act Reported Data	Washington State Dept. of Ecology (2018)	105-53-3	No
Consumer Product Information Database (CPID)	DeLima Associates (2018)	105-53-3	Yes
Danish surveys on chemicals in consumer products	Danish EPA (2018)	Diethyl malonate	No
Datamyne	Descartes Datamyne (2018)	Diethyl malonate	No
DrugBank	DrugBank (2018)	105-53-3; Diethyl malonate	No
European Chemicals Agency (ECHA) Registration Dossier	ECHA (2018)	105-53-3	Yes
eChemPortal [2]	OECD (2018)	105-53-3	Yes
Envirofacts [2]	EPA (2018b)	105-53-3	No
Functional Use Database (FUse)	EPA (2017a)	105-53-3	Yes
Kirk-Othmer Encyclopedia of Chemical Technology	Kirk-Othmer (2006)	Diethyl malonate	No
Non-Confidential 2016 Chemical Data Reporting (CDR)	EPA (2017b)	105-53-3	Yes
PubChem Compound	Kim et al. (2016)	105-53-3	Yes
Safer Chemical Ingredients List (SCIL)	EPA (2018d)	105-53-3	Yes

Table A.2: Sources Searched for Uses of Diethyl Malonate			
Title	**Author and Year**	**Search Term(s)**	**Found Use Information?** [1]
Synapse Information Resources [2]	Synapse Information Resources (2009)	Diethyl malonate	Yes
Resource Conservation and Recovery Act (RCRA)	EPA (2018c)	Diethyl malonate	No
Scorecard: The Pollution Information Site	GoodGuide (2011)	105-53-3	No
Skin Deep Cosmetics Database	EWG (2018)	105-53-3	No
Toxics Release Inventory (TRI)	EPA (2018e)	Diethyl malonate	No
TOXNET [2]	NLM (2018a)	105-53-3	Yes
Ullmann's Encyclopedia of Industrial Chemistry	Ullmann's (2000)	Diethyl malonate	No
Additional sources identified from reasonably available information			
Procter & Gamble	P&G (2015)	Incidentally identified while researching into details of this chemical's uses and products.	Yes
Special Chem	Special Chem (2018)		
Note(s): 1. If use information was found in the resource, it will appear in Table 3 unless otherwise noted. 2. This source is a group of databases; thus, the exact resource(s) it led to will be cited instead of the database as whole.			

The U.S. Patent and Trademark Office has an online database that shows 6,038 patents referencing "diethyl malonate" (USPTO 2018). Although patents could be useful in determining reasonably foreseen uses, it is difficult to confirm whether any of the patented technologies are currently in use. Uses inferred from patents containing diethyl malonate were not included in Table A.3. Note that the uses in Table A.3 that are covered under TSCA are included in Section 5, Table 3 of this document.

A.2.2 Uses of Diethyl Malonate

Table A.3: Uses of Diethyl Malonate		
Use	**Expected Users**	**Description of Use and References**
TSCA Conditions of Use: Air Scent and Fragrance Products		
Air care products	Consumer	EPA (2017b); CPCat (2019); Reported to the ECHA database (2018) CDR identified the use of diethyl malonate in air care products. CDR does not provide further details, however, this category generally includes products such as air fresheners, candles, and scented gels. Air care products currently available for use are listed elsewhere in this report, but CDR does not state the manufacturers of these products. CPCat lists the use of diethyl malonate in "air fresheners and deodorizer." The ECHA registration dossier reports the use of diethyl malonate in European countries in air care products. Expected users are based on CDR's consumer/commercial classification.
Air freshener (oil diffusion)	Consumer	P&G (2015) Diethyl malonate is listed as an ingredient for one oil diffusing air freshener product. The product releases scent by exposing scented oil to open air. Expected users are consumer as the product is intended for consumer use only.
Air freshener refills (pluggable aerosol)	Consumer	DeLima Associates (2015b) Air freshener pluggable aerosol products are devices that contain refillable aerosol inserts, which plug into wall outlets and automatically releases aerosol scented spritzes. CPID generally includes products for consumer use; therefore, the expected user is a consumer.
Air freshener refills (pluggable liquid dispenser)	Consumer	DeLima Associates (2015a) Air freshener pluggable liquid products are devices that contain scented liquid, which plug into wall outlets and automatically releases liquid scented spritzes. CPID generally includes products for consumer use; therefore, the expected user is a consumer.

Table A.3: Uses of Diethyl Malonate		
Use	**Expected Users**	**Description of Use and References**
Aroma chemicals	Consumer, commercial	EPA (2017b) CDR identified the use of diethyl malonate in aroma chemicals used in various products using fragrance. Expected users are based on CDR's consumer/commercial classification.
Car air freshener	Consumer	P&G (2016); CPCat (2019) Diethyl malonate is listed as an ingredient for one car air freshener product. CPCat lists the use of diethyl malonate in a car air freshener product. Expected users are consumer as the product is intended for consumer use only.
Perfumes	Industrial	CPCat (2019) CPCat lists the use of diethyl malonate in industrial perfumes. Expected users are industrial based on CPCat's user classification.
Scented candle	Consumer	DeLima Associates (2016a) CPID generally includes products for consumer use; therefore, the expected user is a consumer.
Wax melts (scented)	Consumer	DeLima Associates (2016b) Wax melts are used to insert into devices that heat and melt the wax pellets to release scent. CPID generally includes products for consumer use; therefore, the expected user is a consumer.
TSCA Conditions of Use: Industrial Uses		
Adhesive	Consumer, industrial	CPCat (2019); Reported to the ECHA database (2018) CPCat lists the use of diethyl malonate as a resin for industrial adhesive hardener, a type of bonding agent and an adhesive for consumer use. The ECHA registration dossier reports the use of diethyl malonate in adhesives. Expected users are industrial based on CPCat's user classification, and inclusion in ECHA's uses at industrial sites.

Table A.3: Uses of Diethyl Malonate		
Use	**Expected Users**	**Description of Use and References**
Automotive paint	Industrial	CPCat (2019) CPCat lists the use of diethyl malonate in paint for automotive care including “bodywork repair.” Expected users are industrial based on CPCat’s user classification.
Chemical warfare agents	Industrial	CPCat (2019) CPCat lists the use of diethyl malonate in chemical warfare agents. No further information could be found on the use of diethyl malonate in chemical warfare agent. Expected user is not stated, but it is most likely industrial for use of chemical warfare agents.
Cleaning and washing agents	Industrial	CPCat (2019); Reported to the ECHA database (2018) CPCat lists the use of diethyl malonate in industrial cleaning and washing. No further information could be found on this use. The ECHA registration dossier reports the use of diethyl malonate in European countries in industrial washing and cleaning products. Expected users are industrial based on inclusion in ECHA’s uses at industrial sites.
Construction/ building materials	Consumer, commercial, industrial	EPA (2017b) CDR identified the use of diethyl malonate in processing – incorporation into formulation, mixture, or reaction product in construction, and in “building/ construction materials not covered elsewhere.” CPCat lists the use of diethyl malonate in the “building of complete construction and parts thereof civil.” Expected users are consumer, commercial, and industrial based on identification in CDR’s consumer/commercial classification and industrial processing and use report.
Motor vehicle care	Industrial	CPCat (2019) CPCat lists the use of diethyl malonate in the “maintenance and repair of motor vehicles” and “other motor vehicle services.” Other automotive uses in automotive paint, car air fresheners, and automotive manufacturing are recorded elsewhere. Expected users are industrial based on CPCat’s user classification.

Table A.3: Uses of Diethyl Malonate		
Use	**Expected Users**	**Description of Use and References**
TSCA Conditions of Use: Manufacturing		
Automotive manufacturing	Industrial	CPCat (2019] CPCat lists the use of diethyl malonate in the "manufacture of motor vehicles, trailers, and semi-trailers." Expected users are industrial based on CPCat's user classification.
Chemical manufacturing	Industrial	CPCat (2019); Reported to the ECHA database (2018) CPCat lists the use of diethyl malonate in the "manufacture of chemicals and chemical products." The ECHA registration dossier reports the use of diethyl malonate in European countries as an intermediate in chemical synthesis. Expected users are industrial based on CPCat's user classification, and inclusion in ECHA"s uses at industrial sites.
Isocyanate blocking agent	Industrial	Synapse Information Resources (2009); Special Chem (2018) Synapse Information Resources lists use of diethyl malonate as an isocyanate blocking agent. One press release from a materials science company reports the development of a diethyl malonate-based isocyanates, which allows "a significant reduction in the curing temperature of powder coatings formulated with it." This allows for easier coating of wood and plastic objects in the manufacturing process. Current use of this method is unknown. Expected users are unknown but are likely industrial for using an isocyanate blocking agent.
Odor agent in manufacturing	Industrial	EPA (2017b); CPCat (2019) CDR identified the use diethyl malonate as an odor agent in "miscellaneous manufacturing." CPCat lists the use diethyl malonate as an odor agent "to change the way a product smells." Expected users are industrial based on identification in CDR's industrial processing and use report.
Toilet preparation manufacturing	Industrial	CPCat (2019) CPCat lists the use of diethyl malonate in the "manufacturing of perfumes and toilet preparations." Expected users are industrial based on CPCat's user classification.

Table A.3: Uses of Diethyl Malonate		
Use	**Expected Users**	**Description of Use and References**
TSCA Conditions of Use: Cleaning Products		
Washing and cleaning products	Consumer, commercial	Reported to the ECHA database (2018) The ECHA registration dossier reports the use of diethyl malonate in European countries in washing, cleaning, and maintenance products. No further information about this specific use could be found and it is unknown whether this is an ongoing use in the United States. Expected users are consumer and commercial based on inclusion in ECHA's consumer uses and uses by professional workers.
TSCA Conditions of Use: Paints and Coatings		
Coatings	Commercial	Reported to the ECHA database (2018) The ECHA registration dossier reports the use of diethyl malonate in European countries in coatings. No further information about this specific use could be found and it is unknown whether this is an ongoing use in the United States. Expected users are commercial based on inclusion in ECHA's uses by professional workers.
Paints, lacquers, and varnishes	Industrial	CPCat (2019) CPCat lists the use diethyl malonate in paints, lacquers, and varnishes, and in paint primers. Use of paint for vehicles is listed elsewhere. Expected users are assumed to be industrial.
Polishes and wax blends	Consumer, commercial	Reported to the ECHA database (2018) The ECHA registration dossier reports the use of diethyl malonate in European countries in polish and wax blend products. No further information about this specific use could be found and it is unknown whether this is an ongoing use in the United States. Expected users are consumer and commercial based on inclusion in ECHA's consumer uses and uses by professional workers.

Table A.3: Uses of Diethyl Malonate		
Use	**Expected Users**	**Description of Use and References**
TSCA Conditions of Use: Miscellaneous		
Absorbents and adsorbents	Industrial	CPCat (2019) CPCat lists the use of diethyl malonate as absorbent and adsorbent. No further information could be found on this use. Expected users are assumed to be industrial.
Non-TSCA Uses		
Barbiturates	Unknown	Synapse Information Resources (2009) Synapse Information Resources lists use of diethyl malonate as an intermediate in barbiturates. Barbiturates refer to any sedatives derived from barbituric acid. Expected users are unknown, due to the limited availability of information.
Biocides	Unknown	Reported to the ECHA database (2018) The ECHA registration dossier reports the use of diethyl malonate in European countries in biocides. No further information about this specific use could be found and it is unknown whether this is an ongoing use in the United States. Expected users are consumer based on inclusion in ECHA's consumer uses.
Cigarettes	Unknown	CPCat (2019) CPCat lists the use diethyl malonate as an additive in cigarettes. No further information could be found on this use. Expected users are unknown, due to the limited availability of information.
Flavoring agent in pharmaceuticals	Industries	Synapse Information Resources (2009) Synapse Information Resources lists the use of diethyl malonate as a synthetic flavoring agent in pharmaceuticals. Expected users are unknown but are likely industrial for use of a flavoring agent in pharmaceuticals.

Table A.3: Uses of Diethyl Malonate		
Use	**Expected Users**	**Description of Use and References**
Fragrance in cosmetics and personal care products	Consumer, commercial	Synapse Information Resources (2009); CPCat (2019); Reported to the ECHA database (2018) Synapse Information Resources lists the use of diethyl malonate as a fragrance in cosmetics. CPCat lists the use diethyl malonate as a fragrance in personal care products. The ECHA registration dossier reports the use of diethyl malonate in European countries in cosmetics as a perfume/ fragrance. Expected users are consumer and commercial based on inclusion in ECHA's consumer uses and uses by professional workers.
Perfume/ fragrance in pharmaceuticals	Consumer	Reported to the ECHA database (2018) The ECHA registration dossier reports the use of diethyl malonate in European countries in pharmaceuticals as a perfume/ fragrance. No further information about this specific use could be found and it is unknown whether this is an ongoing use in the United States. Expected users are consumer based on inclusion in ECHA's consumer uses.
Pharmaceutical and medicine manufacturing	Industrial	EPA (2017b); CPCat (2019); Reported to the ECHA database (2018) CDR identified the use diethyl malonate as an intermediate for pharmaceuticals in pharmaceutical and medicine manufacturing. CPCat lists the use diethyl malonate in drug manufacturing. The ECHA registration dossier reports the use of diethyl malonate in European countries as an intermediate in pharmaceuticals. Expected users are industrial based on identification in CDR's industrial processing and use report.
Synthetic flavoring agent in foods[49]	Unknown	Synapse Information Resources (2009); CPCat (2019) Synapse Information Resources lists the use of diethyl malonate as a synthetic flavoring agent in foods, described as a "fruity flavor". CPCat lists the use of diethyl malonate as a food additive flavoring. Expected users are unknown, due to the limited availability of information.

[49] EPA notes that Federal Drug Administration (FDA) has a process to assess chemicals that are used as flavoring agents or are allowed for food contact. In the case of diethyl malonate, the Joint FAO and WHO Expert Committee on Food Additives (JECFA) reached the conclusion that "the safety of flavouring agents in this group would not raise concern when they were used at the current levels of estimated intake." Source: http://www.inchem.org/documents/jecfa/jecmono/v44jec10.htm

Table A.3: Uses of Diethyl Malonate		
Use	**Expected Users**	**Description of Use and References**
Children's Products		
CDR reports did not include any uses in children's products.		
Recycling and Disposal		
In the 2016 CDR, five facilities reported that the chemical was not recycled (e.g., not recycled, remanufactured, reprocessed, or reused). For three facilities, this information was withheld. For one facility, information was not known or reasonably ascertained. No further information about recycling or disposal was found.		

A.3 References

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Appendix B: Hazard Characterization

Table B.1: Human Health Hazard

ADME

Source	Exposure Route	Species & Strain (if available)	Duration	Doses and Replicate Number	Effect	Study Details
1141389, 4939812	Dermal (*in vitro*)	Human cadaver	24 hours	**Dose:** 4 uL/0.8 cm^2 skin	16% of applied dose penetrated through skin	**Method:** • Test substance reported as CASRN 105-53-3 • Purity: 99% • Guideline study and GLP not reported **Results:** • Mean penetration rate: 120 µg/cm^2/hour; max flux rate: 350 µg/cm^2/hour • 45-50% of applied substance evaporated, and 34-39% remained on skin
1141389, 4939812	Dermal (*in vitro*)	Yorkshire pig	50 hours	**Dose:** 100µg/cm^2; 100µg diluted in ethanol (12.5 mg/mL) /cm^2; 4µg in ethanol (0.5 mg/mL)/cm^2	3-10% of applied dose was absorbed; 8-30% of applied dose remained in skin	**Method:** • Test substance reported as CASRN 105-53-3 • Purity > 95% • Method and GLP not reported **Results:** • 100 µg group: 3% ± 1% of dose was absorbed with 8% ± 0.5% remained in skin • 100 µg diluted group: 6% ± 3% of dose was absorbed with 13% ± 2% remaining in skin • 4 µg diluted group: 10 ± 3% of dose was absorbed with 30 ± 10% remaining in skin • 25-50% loss of radioactivity due to evaporation

Table B.1: Human Health Hazard						
1141389, 4923746	Dermal (*in vitro*)	Yorkshire pigs	24 hours	**Dose:** 1 mg/cm^2 in 10 µL acetone	0.2-16% applied dose in acceptor cell, 0.2-0.9% in skin, and 0.6-0.7% on surface	**Method:** • Test substance reported as CASRN 105-53-3 (DEM) • Purity: 98% • Method and GLP compliance not reported **Results:** • Radiolabeled hydrolysis products (monomethyl malonate and malonic acid) were 15-35% (total) with 20-21% in the acceptor cell, 3-5% in the skin, and 2-4% on the surface • Heat treated skin samples had increased absorption of radiolabeled DEM and decreased hydrolysis products • Total recovery of radiolabel was 50-80%; some radiolabel lost to volatilization
94897	Dermal	• Athymic nude mice • Yorkshire pigs • Hairless dog • Human skin grafted on athymic nude mice • Pig skin grafted on athymic nude mice	24-48 hours	**Dose:** 0.1 mg/cm^2	2.5% to 15% penetration of the applied dose	**Method:** • Test substance reported as CASRN 105-53-3 • Purity > 98% • Method and GLP compliance not reported **Results:** • Athymic nude mice: 15 ± 2% penetration • Yorkshire pigs: 2.5 ± 0.2% penetration • Hairless dog: 4 ± 2% penetration • human skin grafted on athymic nude mice: 4 ± 2% penetration • Pig skin grafted on athymic nude mice: 6 ± 1% penetration

Table B.1: Human Health Hazard						
Acute Mammalian Toxicity						
Source	**Exposure Route**	**Species & Strain (if available)**	**Duration**	**Doses and Replicate Number**	**Effect**	**Study Details**
4940215	Oral (feed)	WISW rats	Single exposure	**Dose:** 2000 mg/kg **Replicates:** 5 per sex	**LD_{50}** > 2000 mg/kg	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity not reported • OECD Guideline 401 • GLP compliant
4940413, 1141389	Oral (gavage)	WISW rats	Single exposure, observed for 14 days	**Dose:** 2000 mg/kg **Replicates:** 5 per sex	**LD_{50}** > 2000 mg/kg	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity: 99% • OECD Guideline 401 • GLP compliant
1141389, 4940412	Dermal	WISW rats	24 hour exposure, observed up to 14 days	**Dose:** 2000 mg/kg **Replicates:** 5 per sex	**LD_{50}** > 2000 mg/kg	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity: 99% • OECD Guideline 402 • GLP compliant
Repeated Dose Toxicity						
Source	**Exposure Route**	**Species & strain (if available)**	**Duration**	**Doses and replicate number**	**Effect**	**Study Details**
1141389, 4940227	Oral (gavage)	Wistar rats	39 days (males), 51 days (females)	**Doses:** 0, 100, 300, and 1000 mg/kg-day **Replicates:** 10 per sex per group in main group, 5 per sex per dose in recovery group	**NOAEL:** 300 mg/kg-day; **LOAEL:** 1000 mg/kg-day based on hepatocellular hypertrophy	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity 99.8% • OECD Guideline 422 • GLP compliant **Results:** • Significantly increased incidences of hepatocellular hypertrophy in highest dose. The effect was reversible as the effect was not increased in recovery group animals

Table B.1: Human Health Hazard						
Reproductive Toxicity						
Source	**Exposure Route**	**Species & Strain (if available)**	**Duration**	**Doses and replicate number**	**Effect**	**Study Details**
1141389, 4940227	Oral (gavage)	Wistar rats	39 days (males), 51 day (females)	**Doses:** 0, 100, 300, and 1000 mg/kg-day **Replicates:** 10 per sex per group in main group, 5 per sex per dose in recovery group	**NOAEL:** 1000 mg/kg-day	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity 99.8% • OECD Guideline 422 • GLP compliant
Developmental Toxicity						
Source	**Exposure Route**	**Species & Strain (if available)**	**Duration**	**Doses and replicate number**	**Effect**	**Study Details**
1141389, 4940227	Oral (gavage)	Wistar rats	39 days (males), 51 day (females)	**Doses:** 0, 100, 300, and 1000 mg/kg-day **Replicates:** 10 per sex per group in main group, 5 per sex per dose in recovery group	**NOAEL:** 1000 mg/kg-day	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity 99.8% • OECD Guideline 422 • GLP compliant
5097463	Inhalation	Hra(NZW) SPF rabbits	Gestation Day 7 to 28	**Doses:** 0, 0.03, 0.10, 0.30, and 1 mg/L-day **Replicates:** 22 per group	**NOAEC:** 1 mg/L-day	**Methods:** • Test substance reported as CASRN 1119-40-0 • Purity 99.61% • OPPTS 870.3700 • GLP compliant
Cancer						
Source	**Effect**	**Study Details**				
OncoLogic v8.0	OncoLogic currently has no assessment criteria regarding diesters.	Structure could not be evaluated by Oncologic				

Table B.1: Human Health Hazard						
ISS v2.4[50]	Negative (estimated) Diethyl malonate does not contain any structural features indicative of electrophilic potential.					**Methods:** Carcinogenicity alerts by ISS profiler **Results:** No alerts were identified for the parent structure (an aldehyde alert is flagged for its primary aldehyde metabolite). This is further oxidized and then conjugated to form a glucuronide (Figure 2 metabolic tree in Metabolic Pathway Trees Supplemental Document[51]
VEGA 1.1.4[52]	Diethyl malonate was processed through all 4 models. IRFMN/ISSCAN-GX 1.0.0 predicted it to be a non-carcinogenic with moderate reliability.					**Methods:** VEGA 1.1.4 contains 4 models for carcinogenicity – CAESAR 2.1.9, ISS 1.0.2, IRFMN/Antares 1.0.0, IRFMN/ISSCAN-GX 1.0.0 **Results:** • CAESAR 2.1.9: Low reliability (diethyl malonate lies outside of the applicability domain (AD) of the model) • ISS 1.0.2: Low reliability (diethyl malonate lies outside of the AD) • IRFMN/Antares 1.0.0: Low reliability (diethyl malonate lies outside of the AD) • IRFMN/ISSCAN-GX 1.0.0: Moderate reliability (diethyl malonate could be outside of the AD)
Genotoxicity						
Source	**Exposure Route**	**Species & Strain (if available)**	**Duration**	**Doses and replicate number**	**Effect**	**Study Details**
1141389	Gene mutation (*in vitro*)	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538	With and without	**Doses:** 8, 40, 200, 1000, and 5000 µg/plate	Negative	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity not reported • Directive 84/449/EEC B.14 • GLP compliant

[50] Carcinogenicity alerts by ISS profiler comprises 55 structural alerts for genotoxic and non-genotoxic carcinogenicity. The alerts have been compiled upon existing knowledge of the mechanism of action of carcinogenic chemicals that have been published elsewhere (Benigni and Bossa (2011) *Chem Rev* 111: 2507-2536 and Benigni R et al. (2013) *Chem Rev.* 113: 2940-2957).

[51] The metabolic tree was generated using the in vivo rat metabolism simulator (v07.12) within TIMES v2.29.1.88.

[52] VEGA 1.1.4 contains 4 different models to facilitate an *in silico* assessment of carcinogenicity potential. The models are summarized in Golbamaki et al. (2016) J Environ Sci and Health Part C http://dx.doi.org/10.1080/10590501.2016.1166879 as well as in documentation that is downloadable from within the VEGA tool itself (https://www.vegahub.eu/).

- CAESAR 2.1.9 is a classification model for carcinogenicity based on a neural network.
- ISS 1.0.2 is a classification model based on the ISS ruleset (as described above for the OECD Toolbox).
- IRFMN/Antares 1.0.0 and IRFMN/ISSCAN-GX 1.0.0 are classification models based on a set of rules built with SARpy software (part of the same suite of VEGA tools https://www.vegahub.eu/) extracted from the Antares and ISSCAN-CGX datasets respectively.

Table B.1: Human Health Hazard						
1141389	Gene mutation (*in vitro*)	*Salmonella typhimurium* strains TA97, TA98, TA100	With and without	**Doses:** up to 5000 µg/plate	Negative	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity not reported • GLP compliance not reported
1141389, 4940224	Chromosomal aberrations (*in vitro*)	Human peripheral lymphocytes	With and without	**Doses:** 0, 312.5, 625, 1250, 2500, and 5000 µg/mL	Negative	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity: 99.8% • OECD Guideline 473 • GLP compliant
5097466	Chromosomal aberrations (*in vivo*), inhalation	Fischer 344 Albino Rats	With	**Doses:** 0, 0.5, 1.0, and 2.0 mg/L **Replicates:** 5 per sex per dose	Negative	**Methods:** • Test substance reported as CASRN 1119-40-0 • Purity: 99.61% • OECD Guideline 474 • GLP compliant
Sensitization						
Source	**Exposure Route**	**Species & Strain (if available)**	**Duration**	**Doses and replicate number**	**Effect**	**Study Details**
4940214	Dermal	Dunkin Hartley guinea pigs	Observed for 72 hours	**Doses:** 0.4 to 0.46 g of test substance **Replicates:** 10 animals per dose	Negative	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity not reported • OECD Guideline 406 • GLP compliant

Table B.1: Human Health Hazard						
Irritation						
Source	**Exposure Route**	**Species & Strain (if available)**	**Duration**	**Doses and replicate number**	**Effect**	**Study Details**
1141389	Ocular	White Russian rabbits	Observed for 21 days	**Dose:** 0.1 mL of undiluted substance **Replicates:** 6 total rabbits	Positive	**Methods**: • Test substance reported as CASRN 105-53-3 • Purity not reported • GLP compliant **Results:** • Average irritation scores for cornea, iris, conjunctivae redness and chemosis were 0.6, 0.8, 1.7, and 1.3, respectively, with an overall irritation (Draize) score of 25.8 out of 110 • All effects were fully reversible within 21 days
4940225, 1141389	Ocular	White Russian rabbits	Single exposure, observed for 8 days	**Dose:** 0.1 mL undiluted substance **Replicates:** 3 males	Positive (slightly irritating)	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity: 99% • OECD Guideline 405 • GLP compliant **Results:** • Mean irritation scores (for 24, 48, and 72-hour observations) for each animal: • Cornea opacity: 1.67/4, 1.33/4, 1/4 • Iris: 1/2, 0.33/2, 0.67/2 • Conjunctivae: 2/3, 2/3, 2/3 • Chemosis: 1.67/4, 1.33/4, 1.33/4 • All effects were reversible within 8 days

Table B.1: Human Health Hazard						
1141389, 4940218	Dermal	White Russian rabbits	4 hour exposure, observed for 72 hours	**Dose:** 0.5 mL of undiluted substance **Replicates:** 1 mal e and 2 females	Negative	**Methods**: • Test substance reported as CASRN 108-59-8 • Purity: 99% • OECD Guideline 404 • GLP compliant **Results:** • Slight erythema was observed in all animals 30-60 minutes after removal of the patch, but no other signs of irritation • Considered to be non-irritating
Neurotoxicity						
Source	**Exposure Route**	**Species & Strain (if available)**	**Duration**	**Doses and replicate number**	**Effect**	**Study Details**
1141389, 4940227	Oral (gavage)	Wistar rats	39 days (males), 51 days (females)	**Doses:** 0, 100, 300, and 1000 mg/kg-day **Replicates:** 5 per sex per dose	**NOAEL:** 1000 mg/kg-day	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity 99.8% • OECD Guideline 422 • GLP compliant **Endpoints:** • No effects were noted for functional observational battery test
4923714	Neuron cytotoxicity (*In vitro*)	Fetal Sprague-Dawley rat primary culture neurons	72 hours	**Dose:** 50 µM	Negative	**Methods**: • Test substance reported as CASRN 108-59-8 • Purity not reported • GLP compliance not reported
4933586	Electron transport chain assays	Wistar rat cerebral cortex homogenates	Single exposure	**Doses:** 1, 2.5, and 5 mM	Significant inhibition of Complex I, Complex II, Complex I+III, and Complex II+III activities, but not Complex III or Complex IV activities	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity not reported • GLP compliance not reported

Table B.1: Human Health Hazard						
4926318	Neuron cytotoxicity (*In vitro*)	Primary neuronal cells isolated from rat spinal cord tis sue	48 hours	**Doses:** 0, 10, 20, 30, 50, and 100 mM	Causes selective motor neuron death at lower doses. The toxicity is mediated by ionotropic glutamate receptors	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity not reported • GLP compliance not reported
4931886	Neuron cytotoxicity (*In vitro*)	Mesencephalic culture from embryonic day 15 rats	24 hours	**Dose:** 50 µM	Suggests that glutamate receptors become involved after the interruption of energy metabolism and contributes to irreversible cell damage	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity not reported • GLP compliance not reported
4933534	Neuron, IP injection	Male Swiss Webster mice	15 minutes Via striatal microdialysis, 24 hour observation	**Doses:** 4 µM to 2.67 M	Suggests that dopamine efflux via the dopamine transporter plays a role in neuronal cell damage	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity not reported • GLP compliance not reported
4933481	Mechanistic neurological	Brain homogenate from adult Wistar rats		**Doses:** 1, 2 and 4 mmol/L	Direct interactions of malonate with NMDA receptors are not involved in malonate pro-oxidative activity *in vitro*	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity not reported • GLP compliance not reported
Immunotoxicity						
Source	**Exposure Route**	**Species & Strain (if available)**	**Duration**	**Doses and replicate number**	**Effect**	**Study Details**
1141389, 4940227	Oral (gavage)	Wistar rats	39 days (males), 51 days (females)	**Doses:** 0, 100, 300, and 1000 mg/kg-day **Replicates:** 5 per sex per dose	**NOAEL:** 1000 mg/kg-day	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity 99.8% • OECD Guideline 422 • GLP compliant **Endpoints:** • No effects were noted for hematology, clinical chemistry, and lymphoid organ weight.

Table B.2: Route to Route Extrapolation Information for Oral to Inhalation Exposures for Diethyl Malonate		
Formula[53]: Corrected inhalation NOAEL = ($NOAEL_{ORAL}$ or $LOAEL_{ORAL}$) x ($1/sRV_{rat}$) x ($ABS_{oral\text{-}rat}/ABS_{inh\text{-}human}$) x ($sRV_{human}/wRV_{human}$)		
Variable	**Units**	**Value Used**
Corrected inhalation NOAEL	Predicted NOAEL for inhalation exposure to humans, mg/m^3	0.440
$NOAEL_{ORAL}$	No observed adverse effect level from oral exposure, mg/kg-bw/day	1000
sRV_{RAT}	Rat standard respiratory volume for 8-hours, m^3/kg-bw	0.38
$ABS_{ORAL\text{-}RAT}$	Percent absorption by the oral route in rats, based on "poor to moderate" absorption, %	15
$ABS_{INHAL\text{-}HUMAN}$	Percent absorption by inhalation in humans, based on "good" absorption, %	60
sRV_{HUMAN}	Human standard respiratory volume for 8-hours, m^3	6.7
wRV_{HUMAN}	Worker respiratory volume for 8-hours, m^3	10

Table B.3: Environmental Hazard					
Aquatic Toxicity: Experimental					
Source	**Species & strain (if available)**	**Duration**	**Doses and replicate number**	**Effect**	**Study Details**
4939286	*Pimephales promelas*	96 hours	**Doses:** 0, 5.06, 9.51, 17.2, 34.3, and 64.1 mg/L	**LC_{50}**: 14.9 mg/L	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity: 99% • GLP compliant **Results:** • EC_{50}: 14.8 mg/L
4939288	*Pimephales promelas*	96 hours	**Doses:** 0.22, 6.78, 9.59, 16.3, 24.6, and 33.5 mg/L (measured)	**LC_{50}**: 11.8 mg/L	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity: 99% • GLP compliant
4935263	*Pimephales promelas*	96 hours	**Doses:** 2.8, 10.4, 13.2, 20.6, 33.3, and 54.6 mg/L (measured)	**LC_{50}**: 17 mg/L	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity: 99% • OECD Guideline 203

[53] ECHA (European Chemicals Agency). 2012. *Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterization of dose [concentration]-response for human health.* Available at: https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258. See example B.3.

Table B.3: Environmental Hazard					
					• GLP compliance not reported
4935263	*Pimephales promelas*	96 hours	**Doses:** 0, 5.1-5.4, 9.0-10.4, 17.4-18.3, 33.2-37.5, and 63.6-67.5 mg/L (measured)	**LC_{50}**: 15.4 mg/L	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity: 99% • OECD Guideline 203 • GLP compliance not reported
4935263	*Pimephales promelas*	96 hours	**Doses:** 0, 6.78, 9.59, 16.3, 24.6, and 33.5 mg/L (measured)	**LC_{50}**: 12 mg/L	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity not reported • GLP compliance not reported
4935263	*Daphnia magna*	48 hours	**Doses:** 0, 100, 140, 200, 280, 400, 560, and 800 mg/L (nominal)	**EC_{50}:** 202 mg/L, 95% confidence limit: 175.2 - 233.6	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity: 99.5% • Test method 84/449/EC C.2 • GLP compliant **Results:** • EC_0: 100 mg/L (nominal • EC_{100}: 400 mg/L (nominal)
4935263	*Scenedesmus subspicatus*	72 hours	**Doses:** 0, 12.5, 25, 50, 100, 200, 400, and 800 mg/L (nominal)	**EC_{50}** > 800 mg/L	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity not reported • Guideline 88/302/EEC • GLP compliance not reported **Results:** • EC_{10}: 115 mg/L (nominal) • NOEC: 25 mg/L (nominal)
Aquatic Toxicity: Estimated					
Model	**Endpoint**	**Species**	**Predicted Effect Level**	**Notes**	
ECOSAR v2.0 (Class: Esters)	Estimated	Freshwater fish	8.1 mg/L	• Input SMILES: O=C(OCC)CC(=O)OCC. Experimental input values: logKow = 0.96; WS = 23200 mg/L; MP = -50°C.	
ECOSAR v2.0 (Class: Esters)	Estimated	Daphnia magna	190 mg/L	• Input SMILES: O=C(OCC)CC(=O)OCC. Experimental input values: logKow = 0.96; WS = 23200 mg/L; MP = -50°C.	

Table B.3: Environmental Hazard				
ECOSAR v2.0 (Class: Esters)	Estimated	Green algae	18 mg/L	• Input SMILES: O=C(OCC)CC(=O)OCC. Experimental input values: logKow = 0.96; WS = 23200 mg/L; MP = -50°C.

Table B.4: Fate					
Environmental Fate: Experimental					
Source	**Endpoint**	**Duration**	**Doses and number of replicates**	**Results**	**Study Details**
4935263	Biodegradation	28 days	**Dose:** 9.56 mg/L	Readily biodegradable	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity > 99% • OECD Guideline 301A • GLP compliant **Biodegradation kinetics:** • 92% in 7 days • 98% in 28 days
4935263	Photolysis	35 minutes	**Dose:** 5 mg/L	Readily photolyzes	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity not reported • Photolytic Ozonation • GLP compliance not reported **Results:** • 100% in 35 minutes
4923463	Photooxidation	N/A.	**Doses:** 5-7 µL	Rate coefficient (k) (3.75 ± 0.4) × 10−12 cm^3/molecules-second	**Methods:** • Test substance reported as CASRN 108-59-8 • Purity: 98% • GLP compliance not reported
4924633	Toxicity to microorganisms	3 and 28 days	**Doses:** 0-2500 µg/g (nominal)	Negative; EC_{50} > 2500 µg/g	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity not reported • GLP compliance not reported
4924617, 4924633	Volatilization (soil)		**Doses:** 150 mg/m^3 and 1500 mg/m^3	$T_{1/2}$: 1.2 – 2 hours	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity not reported • GLP compliance not reported

Table B.4: Fate					
4924617, 4924633	Volatilization (foliar surfaces)		**Doses:** 150 mg/m^3 and 1500 mg/m^3	$T_{1/2}$: 1.29 to 242.5 hours	**Methods:** • Test substance reported as CASRN 105-53-3 • Purity not reported • GLP compliance not reported **Results:** • Foliar surface composition is likely to affect sorption and volatilization
Environmental Fate: Modelled					
Model	**Data Type**	**Endpoint**	**Predicted Endpoint**	**Notes**	
EPISuite v.4.11	Estimated	BAF	1.058		
EPISuite v.4.11	Estimated	BCF	3.162		
EPISuite v.4.11 (BIOWIN 7)	Estimated	Anaerobic biodegradation	Predicted to biodegrade quickly under anaerobic conditions	Predicted probability of 1.0986. Fragment representation is valid. Fast degradation is defined as predicted probability > 0.5.	

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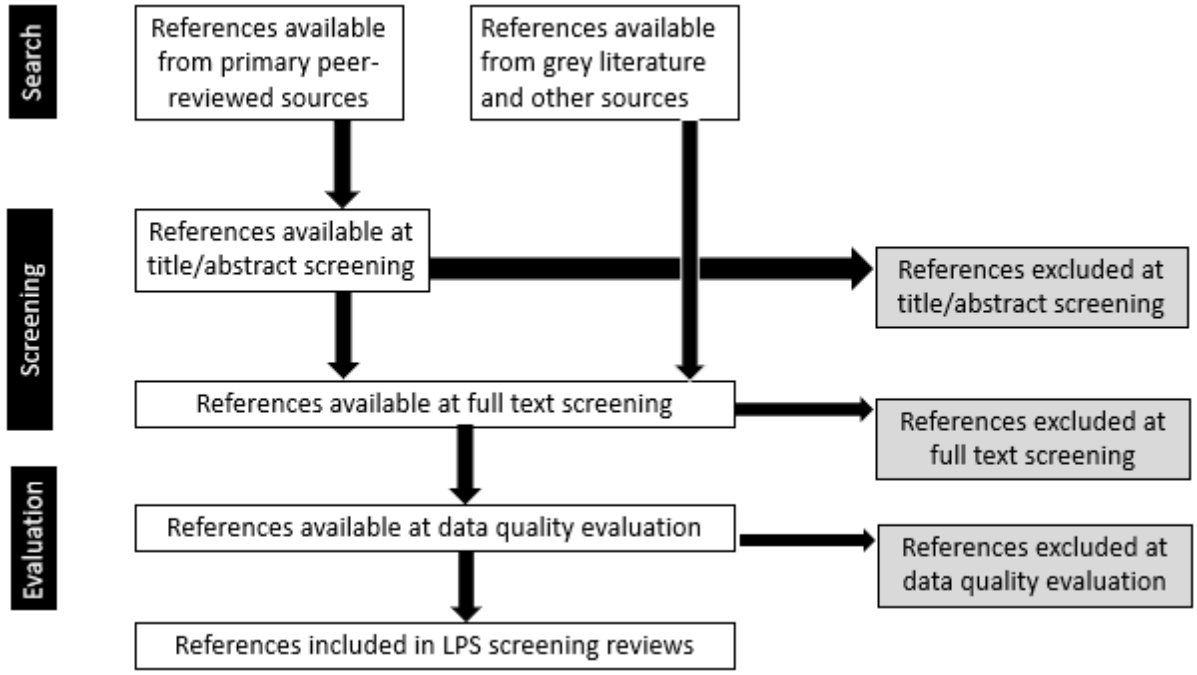
Appendix C: Literature Search Outcomes

C.1 Literature Search and Review

This section briefly describes the literature search and review process, search terms, and search outcomes for the hazard and fate screening of diethyl malonate. Search outcomes and reference details are provided on the candidate's HERO[54] project page.

EPA created a fit-for-purpose process to transparently document the literature search and review[55] of available hazard and fate information for low-priority substance (LPS) candidates. References from peer-reviewed primary sources, grey sources,[56] and other sources were identified, screened at the title/abstract and full text level, and evaluated for data quality based on discipline-specific criteria. An overview of the literature search and review process is illustrated in Figure C1.

Figure C.1: Overview of the Literature Search and Review Process



C.1.1 Search for Analog Data

To supplement the information on the candidate chemical, diethyl malonate, EPA identified dimethyl glutarate (CASRN 1119-40-0) as an analog. For more details and justification on analogs, see section

[54] The HERO low-priority substance candidate project pages are accessible to the public at https://hero.epa.gov/hero/.

[55] Discussed in the document "Approach Document for Screening Hazard Information for Low-Priority Substances Under TSCA."

[56] Grey literature and additional sources are the broad category of studies not found in standard, peer-reviewed literature database searches. This includes U.S. and international government agency websites, non-government organization (NGO) websites, and data sources that are difficult to find, or are not included, in the peer-reviewed databases, such as white papers, conference proceedings, technical reports, reference books, dissertations, and information on various stakeholder websites.

6.1.1. Analogs were used to fill data gaps on endpoints for which diethyl malonate lacked quality data, such as acute, repeated dose, and developmental toxicity, and to add to the weight of the scientific evidence. EPA collected reasonably available information for these endpoints by searching specific grey literature and other secondary sources, listed on Table C.1. If information related to the identified analogs were available in these sources, the references were screened and evaluated using the same process as references on diethyl malonate described above.[55] EPA also used read-across from the LPS candidate, dimethyl malonate (CASRN 108-59-8). Both chemicals along with the analog mentioned above fall under the malonates cluster in HERO.

Table C.1: Sources Used for Analog Search

Resource	URL
ATSDR	http://www.atsdr.cdc.gov/toxprofiles/index.asp
ChemID (EPA – HPVIS via ChemID)	http://chem.sis.nlm.nih.gov/chemidplus/
CIR	http://www.cir-safety.org/ingredients
ECHA	http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances
ECOTOX	https://cfpub.epa.gov/ecotox/quick_query.htm
EPA – ChemView (incl. TSCATS, RBP/HC, and HPV/HPVIS)	https://chemview.epa.gov/chemview
European Food Safety Authority (EFSA)	http://www.efsa.europa.eu/
FDA	https://www.fda.gov/default.htm
HERA	http://www.heraproject.com/RiskAssessment.cfm
NICNAS	http://www.nicnas.gov.au/
NITE (J-CHECK)	http://www.safe.nite.go.jp/jcheck/search.action?request_locale=en
NTP	https://ntpsearch.niehs.nih.gov/home
OECD/SIDS	https://hpvchemicals.oecd.org/UI/Search.aspx; http://webnet.oecd.org/hpv/ui/SponsoredChemicals.aspx

C.1.2 Search Terms and Results

EPA began the literature review process for the hazard screening of diethyl malonate by developing search terms. To gather publicly available information, specific search terms were applied for each discipline and across databases and grey literature sources. Table C.2 lists the search terms used in the database search of peer -reviewed literature for the malonates cluster including diethyl malonate. For grey literature and other secondary sources, Table C.3 lists the search terms used for the LPS malonates and analogs.

Table C.2: Search Terms Used in Peer Reviewed Databases

Discipline	Database	Search terms[57]
Human health	PubMed	108-59-8[rn] OR 105-53-3[rn] OR "Carbethoxyacetic ester"[tw] OR "Dicarbethoxymethane"[tw] OR "Diethyl malonate"[tw] OR "Diethyl propane-1,3-dioate"[tw] OR "Diethyl propanedioate"[tw] OR "diethylmalonate"[tw] OR "Dimethyl 1,3-propanedioate"[tw] OR "Dimethyl malonate"[tw] OR "Dimethyl propanedioate"[tw] OR "Ethyl malonate"[tw] OR

[57] Additional language or syntax such as [tw], [rn], [org], and [nm] were added to search terms. These are unique to individual databases and must be applied to search terms so that the query can run properly.

Table C.2: Search Terms Used in Peer Reviewed Databases		
		"Ethyl methanedicarboxylate"[tw] OR "Ethyl propanedioate"[tw] OR "MALONATE, DIETHYL"[tw] OR "Malonate diethyl ester"[tw] OR "Malonic acid, diethyl ester"[tw] OR "Malonic acid, dimethyl ester"[tw] OR "Malonic ester"[tw] OR "Methanedicarboxylic acid diethyl ester"[tw] OR "Methanedicarboxylic acid, diethyl ester"[tw] OR "Methyl malonate"[tw] OR "PROPANEDIOATE, DIETHYL"[tw] OR "PROPANEDIOATE, DIMETHYL"[tw] OR "Propanedioic acid diethyl ester"[tw] OR "Propanedioic acid dimethyl ester"[tw] OR "Propanedioic acid, 1,3-diethyl ester"[tw] OR "Propanedioic acid, 1,3-dimethyl ester"[tw] OR "Propanedioic acid, diethyl ester"[tw] OR "Propanedioic acid, dimethyl ester"[tw]
	Toxline	(108-59-8 [rn] OR 105-53-3 [rn] OR "carbethoxyacetic ester" OR "dicarbethoxymethane" OR "diethyl malonate" OR "diethyl propane-1 3-dioate" OR "diethyl propanedioate" OR "diethylmalonate" OR "dimethyl 1 3-propanedioate" OR "dimethyl malonate" OR "dimethyl propanedioate" OR "ethyl malonate" OR "ethyl methanedicarboxylate" OR "ethyl propanedioate" OR "malonate diethyl" OR "malonate diethyl ester" OR "malonic acid diethyl ester" OR "malonic acid dimethyl ester" OR "malonic ester" OR "methanedicarboxylic acid diethyl ester" OR "methanedicarboxylic acid diethyl ester" OR "methyl malonate" OR "propanedioate diethyl" OR "propanedioate dimethyl" OR "propanedioic acid diethyl ester" OR "propanedioic acid dimethyl ester" OR "propanedioic acid 1 3-diethyl ester" OR "propanedioic acid 1 3-dimethyl ester" OR "propanedioic acid diethyl ester" OR "propanedioic acid dimethyl ester") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HAPAB [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	TSCATS 1	108-59-8[rn] OR 105-53-3[rn]
	WOS	TS=("108-59-8" OR "105-53-3" OR "Carbethoxyacetic ester" OR "Dicarbethoxymethane" OR "Diethyl malonate" OR "Diethyl propane-1,3-dioate" OR "Diethyl propanedioate" OR "diethylmalonate" OR "Dimethyl 1,3-propanedioate" OR "Dimethyl malonate" OR "Dimethyl propanedioate" OR "Ethyl malonate" OR "Ethyl methanedicarboxylate" OR "Ethyl propanedioate" OR "MALONATE, DIETHYL" OR "Malonate diethyl ester" OR "Malonic acid, diethyl ester" OR "Malonic acid, dimethyl ester" OR "Malonic ester" OR "Methanedicarboxylic acid diethyl ester" OR "Methanedicarboxylic acid, diethyl ester" OR "Methyl malonate" OR "PROPANEDIOATE, DIETHYL" OR "PROPANEDIOATE, DIMETHYL" OR "Propanedioic acid diethyl ester" OR "Propanedioic acid dimethyl ester" OR

Table C.2: Search Terms Used in Peer Reviewed Databases		
		"Propanedioic acid, 1,3-diethyl ester" OR "Propanedioic acid, 1,3-dimethyl ester" OR "Propanedioic acid, diethyl ester" OR "Propanedioic acid, dimethyl ester") AND ((WC=("Toxicology" OR "Endocrinology & Metabolism" OR "Gastroenterology & Hepatology" OR "Gastroenterology & Hepatology" OR "Hematology" OR "Neurosciences" OR "Obstetrics & Gynecology" OR "Pharmacology & Pharmacy" OR "Physiology" OR "Respiratory System" OR "Urology & Nephrology" OR "Anatomy & Morphology" OR "Andrology" OR "Pathology" OR "Otorhinolaryngology" OR "Ophthalmology" OR "Pediatrics" OR "Oncology" OR "Reproductive Biology" OR "Developmental Biology" OR "Biology" OR "Dermatology" OR "Allergy" OR "Public, Environmental & Occupational Health") OR SU=("Anatomy & Morphology" OR "Cardiovascular System & Cardiology" OR "Developmental Biology" OR "Endocrinology & Metabolism" OR "Gastroenterology & Hepatology" OR "Hematology" OR "Immunology" OR "Neurosciences & Neurology" OR "Obstetrics & Gynecology" OR "Oncology" OR "Ophthalmology" OR "Pathology" OR "Pediatrics" OR "Pharmacology & Pharmacy" OR "Physiology" OR "Public, Environmental & Occupational Health" OR "Respiratory System" OR "Toxicology" OR "Urology & Nephrology" OR "Reproductive Biology" OR "Dermatology" OR "Allergy")) OR (WC="veterinary sciences" AND (TS="rat" OR TS="rats" OR TS="mouse" OR TS="murine" OR TS="mice" OR TS="guinea" OR TS="muridae" OR TS=rabbit* OR TS=lagomorph* OR TS=hamster* OR TS=ferret* OR TS=gerbil* OR TS=rodent* OR TS="dog" OR TS="dogs" OR TS=beagle* OR TS="canine" OR TS="cats" OR TS="feline" OR TS="pig" OR TS="pigs" OR TS="swine" OR TS="porcine" OR TS=monkey* OR TS=macaque* OR TS=baboon* OR TS=marmoset*)) OR (TS=toxic* AND (TS="rat" OR TS="rats" OR TS="mouse" OR TS="murine" OR TS="mice" OR TS="guinea" OR TS="muridae" OR TS=rabbit* OR TS=lagomorph* OR TS=hamster* OR TS=ferret* OR TS=gerbil* OR TS=rodent* OR TS="dog" OR TS="dogs" OR TS=beagle* OR TS="canine" OR TS="cats" OR TS="feline" OR TS="pig" OR TS="pigs" OR TS="swine" OR TS="porcine" OR TS=monkey* OR TS=macaque* OR TS=baboon* OR TS=marmoset* OR TS="child" OR TS="children" OR TS=adolescen* OR TS=infant* OR TS="WORKER" OR TS="WORKERS" OR TS="HUMAN" OR TS=patient* OR TS=mother OR TS=fetal OR TS=fetus OR TS=citizens OR TS=milk OR TS=formula OR TS=epidemio* OR TS=population* OR TS=exposure* OR TS=questionnaire OR SO=epidemio*)) OR TI=toxic* OR TS=metaboli* OR TS=biotransform* OR ((TS="breakdown" OR TS="break-down") AND (TS=product OR TS=products)))

Table C.2: Search Terms Used in Peer Reviewed Databases		
Environmental hazard fate	WOS	TS=("108-59-8" OR "105-53-3" OR "Carbethoxyacetic ester" OR "Dicarbethoxymethane" OR "Diethyl malonate" OR "Diethyl propane-1,3-dioate" OR "Diethyl propanedioate" OR "diethylmalonate" OR "Dimethyl 1,3-propanedioate" OR "Dimethyl malonate" OR "Dimethyl propanedioate" OR "Ethyl malonate" OR "Ethyl methanedicarboxylate" OR "Ethyl propanedioate" OR "MALONATE, DIETHYL" OR "Malonate diethyl ester" OR "Malonic acid, diethyl ester" OR "Malonic acid, dimethyl ester" OR "Malonic ester" OR "Methanedicarboxylic acid diethyl ester" OR "Methanedicarboxylic acid, diethyl ester" OR "Methyl malonate" OR "PROPANEDIOATE, DIETHYL" OR "PROPANEDIOATE, DIMETHYL" OR "Propanedioic acid diethyl ester" OR "Propanedioic acid dimethyl ester" OR "Propanedioic acid, 1,3-diethyl ester" OR "Propanedioic acid, 1,3-dimethyl ester" OR "Propanedioic acid, diethyl ester" OR "Propanedioic acid, dimethyl ester") AND ((WC=("Agriculture, Dairy & Animal Science" OR "Biodiversity Conservation" OR "Biology" OR "Developmental Biology" OR "Ecology" OR "Entomology" OR "Environmental Sciences" OR "Environmental Studies" OR "Fisheries" OR "Forestry" OR "Limnology" OR "Marine & Freshwater Biology" OR "Microbiology" OR "Mycology" OR "Oceanography" OR "Ornithology" OR "Plant Sciences" OR “Reproductive Biology” OR "Zoology")) OR (SU=("Agriculture" OR "Biodiversity & Conservation" OR “Developmental Biology” OR "Entomology" OR "Environmental Sciences & Ecology" OR "Fisheries" OR "Forestry" OR "Marine & Freshwater Biology" OR "Microbiology" OR "Mycology" OR "Plant Sciences" OR “Reproductive Biology” OR "Zoology" OR "Oceanography")) OR (TI=toxic*) OR (TS=(ecotox* OR environment* OR phytotox* OR pollut* OR "A. platyrhynchos" OR "agnatha" OR "agnathan" OR "alligator" OR "alligators" OR "amphibian" OR "amphibians" OR "amphipod" OR "amphipoda" OR "amphipods" OR "Anas platyrhynchos" OR "annelid" OR "annelida" OR "annelids" OR "Antilocapridae" OR "apidae" OR "Aplodontidae" OR "Apoidea" OR "aquatic" OR "archiannelid" OR "archiannelida" OR "Arvicolinae" OR "aves" OR "avian" OR "avians" OR "badger" OR "badgers" OR "barnacle" OR "barnacles" OR "bass" OR "bear" OR "bears" OR "beaver" OR "beavers" OR "bee" OR "bees" OR "bird" OR "birds" OR "bivalve" OR "bivalves" OR "bleak" OR "bluegill" OR "bluegills" OR "bluehead" OR "bobwhite" OR "bobwhites" OR "Bovidae" OR "C. carpio" OR "caiman" OR "Canidae" OR "carp" OR "Castoridae" OR "catfish" OR "cephalopod" OR "cephalopoda" OR "cephalopods" OR "Cervidae" OR "chicken" OR "chickens" OR "chiselmouth" OR "clam" OR "clams" OR "cockle" OR "cockles" OR "cod" OR "copepod" OR "copepoda" OR "copepods" OR "coturnix" OR "crab" OR "crabs" OR "crappie"

Table C.2: Search Terms Used in Peer Reviewed Databases		
		OR "crappies" OR "crayfish" OR "croaker" OR "crocodile" OR "crocodiles" OR "crustacea" OR "crustacean" OR "crustaceans" OR "Cyprinus carpio" OR "D. magna" OR "D. rerio" OR "dace" OR "Danio rerio" OR "daphnia" OR "Daphnia magna" OR "darter" OR "darters" OR "Dasypodidae" OR "Dicotylidae" OR "Didelphidae" OR "Dipodidae" OR "dog" OR "dogs" OR "dogfish" OR "duck" OR "duckling" OR "ducklings" OR "ducks" OR "earthworm" OR "earthworms" OR "ec50" OR "ec50s" OR "echinoderm" OR "echinoderms" OR "eel" OR "eels" OR "elasmobranch" OR "Equidae" OR "Erethizontidae" OR "Felidae" OR "ferret" OR "fish" OR "fisher" OR "fishers" OR "fishes" OR "flagfish" OR "flatworm" OR "flatworms" OR "flounder" OR "frog" OR "frogs" OR "galaxias" OR "gallus" OR "gastropod" OR "gastropoda" OR "gastropods" OR "Geomyidae" OR "goldfish" OR "gourami" OR "gouramy" OR "Green Algae" OR "grunion" OR "guppies" OR "guppy" OR "haddock" OR "hagfish" OR "haplodrili" OR "Harvest mice " OR "Harvest mouse" OR "herring" OR "Heteromyidae" OR "honeybee" OR "honeybees" OR "hooknose" OR "inanga" OR "killifish" OR "L. idus" OR "L. macrochirus" OR "lamprey" OR "lampreys" OR "lc50" OR "lc50s" OR "leech" OR "lemming" OR "Lepomis macrochirus" OR "Leporidae" OR "lethal concentration" OR "Leuciscus idus" OR "lizard" OR "lizards" OR "lobster" OR "lobsters" OR "macroinvertebrate" OR "macroinvertebrates" OR "mallard" OR "mallards" OR "marten" OR "medaka" OR "menhaden" OR "Microtus" OR "milkfish" OR "mink" OR "minnow" OR "minnows" OR "mollusc" OR "molluscs" OR "mollusk" OR "mollusks" OR "molly" OR "mrigal" OR "mudfish" OR "mudsucker" OR "mulles" OR "mullet" OR "mummichog" OR "mummichogs" OR "mussel" OR "mussels" OR "Mustelidae" OR "Myocastoridae" OR "Mysid shrimp" OR "newt" OR "newts" OR "northern pike" OR "O. latipes" OR "O. mykiss" OR "Ochotonidae" OR "octopi" OR "octopus" OR "oligochaeta" OR "oligochaete" OR "Oncorhynchus mykiss" OR "Onychomys" OR "opossum" OR "Oryzias latipes" OR "oyster" OR "oysters" OR "P. promelas" OR "P. reticulata" OR "P. subcapitata" OR "perch" OR "Peromyscus" OR "Pimephales promelas" OR "pinfish" OR "pinfishes" OR "planaria" OR "planarian" OR "Poecilia reticulata" OR "polychaeta" OR "polychaete" OR "polychaetes" OR "Procyonidae" OR "Pseudokirchneriella subcapitata" OR "puffer" OR "puffers" OR "pumpkinseed" OR "pumpkinseeds" OR "pupfish" OR "quahog" OR "quahogs" OR "quail" OR "quails" OR "rasbora" OR "rasboras" OR "Reithrodontomys" OR "reptile" OR "reptiles" OR "rohu" OR "S. erythrophthalmus" OR "S. quadricauda" OR "S. subspicatus" OR "salamander" OR "salamanders" OR "salmon" OR "scallop" OR "scallops" OR "Scardinius erythrophthalmus" OR "Scenedesmus quadricauda " OR "Scenedesmus subspicatus" OR "Sciuridae"

Table C.2: Search Terms Used in Peer Reviewed Databases		
		OR "sea anemone" OR "sea anemones" OR "sea cucumber" OR "sea cucumbers" OR "sea urchin" OR "sea urchins" OR "seabass" OR "seabream" OR "shark" OR "sharks" OR "shiner" OR "shiners" OR "shrimp" OR "Sigmodon" OR "Sigmodontinae" OR "silverside" OR "silversides" OR "skunk" OR "skunks" OR "snake" OR "snakehead" OR "snakes" OR "songbird" OR "songbirds" OR "Soricidae" OR "squid" OR "starfish" OR "stickleback" OR "sticklebacks" OR "sting ray" OR "sting rays" OR "sucker" OR "suckers" OR "Suidae" OR "sunfish" OR "Talpidae" OR "teleost" OR "teleostei" OR "teleosts" OR "terrapin" OR "terrapins" OR "tilapia" OR "tilapiaz" OR "toad" OR "toadfish" OR "toadfishes" OR "toads" OR "tortoise" OR "tortoises" OR "trout" OR "tubificid" OR "tubificidae" OR "tubificids" OR "turkey" OR "turkeys" OR "turtle" OR "turtles" OR "Ursidae" OR "vole" OR "walleye" OR "walleyes" OR "water flea" OR "water fleas" OR "waterbird" OR "waterbirds" OR "waterfowl" OR "waterfowls" OR "weakfish" OR "weasel" OR "whelk" OR "whelks" OR "wildlife")))
	Toxline	Same as human health strategy synonyms only
	TSCATS 1	Same as human health strategy CASRN only
	Proquest	Title=("108-59-8" OR "105-53-3" OR "Carbethoxyacetic ester" OR "Dicarbethoxymethane" OR "Diethyl malonate" OR "Diethyl propane-1,3-dioate" OR "Diethyl propanedioate" OR "diethylmalonate" OR "Dimethyl 1,3-propanedioate" OR "Dimethyl malonate" OR "Dimethyl propanedioate" OR "Ethyl malonate" OR "Ethyl methanedicarboxylate" OR "Ethyl propanedioate" OR "MALONATE, DIETHYL" OR "Malonate diethyl ester" OR "Malonic acid, diethyl ester" OR "Malonic acid, dimethyl ester" OR "Malonic ester" OR "Methanedicarboxylic acid diethyl ester" OR "Methanedicarboxylic acid, diethyl ester" OR "Methyl malonate" OR "PROPANEDIOATE, DIETHYL" OR "PROPANEDIOATE, DIMETHYL" OR "Propanedioic acid diethyl ester" OR "Propanedioic acid dimethyl ester" OR "Propanedioic acid, 1,3-diethyl ester" OR "Propanedioic acid, 1,3-dimethyl ester" OR "Propanedioic acid, diethyl ester" OR "Propanedioic acid, dimethyl ester") Abstract=("108-59-8" OR "105-53-3" OR "Carbethoxyacetic ester" OR "Dicarbethoxymethane" OR "Diethyl malonate" OR "Diethyl propane-1,3-dioate" OR "Diethyl propanedioate" OR "diethylmalonate" OR "Dimethyl 1,3-propanedioate" OR "Dimethyl malonate" OR "Dimethyl propanedioate" OR "Ethyl malonate" OR "Ethyl methanedicarboxylate" OR "Ethyl propanedioate" OR "MALONATE, DIETHYL" OR "Malonate diethyl ester" OR "Malonic acid, diethyl ester")

Table C.2: Search Terms Used in Peer Reviewed Databases		
		Abstract=("Malonic acid, dimethyl ester" OR "Malonic ester" OR "Methanedicarboxylic acid diethyl ester" OR "Methanedicarboxylic acid, diethyl ester" OR "Methyl malonate" OR "PROPANEDIOATE, DIETHYL" OR "PROPANEDIOATE, DIMETHYL" OR "Propanedioic acid diethyl ester" OR "Propanedioic acid dimethyl ester" OR "Propanedioic acid, 1,3-diethyl ester" OR "Propanedioic acid, 1,3-dimethyl ester" OR "Propanedioic acid, diethyl ester" OR "Propanedioic acid, dimethyl ester") Subject=("108-59-8" OR "105-53-3" OR "Carbethoxyacetic ester" OR "Dicarbethoxymethane" OR "Diethyl malonate" OR "Diethyl propane-1,3-dioate" OR "Diethyl propanedioate" OR "diethylmalonate" OR "Dimethyl 1,3-propanedioate" OR "Dimethyl malonate" OR "Dimethyl propanedioate" OR "Ethyl malonate" OR "Ethyl methanedicarboxylate" OR "Ethyl propanedioate" OR "MALONATE, DIETHYL" OR "Malonate diethyl ester" OR "Malonic acid, diethyl ester" OR "Malonic acid, dimethyl ester" OR "Malonic ester" OR "Methanedicarboxylic acid diethyl ester" OR "Methanedicarboxylic acid, diethyl ester" OR "Methyl malonate" OR "PROPANEDIOATE, DIETHYL" OR "PROPANEDIOATE, DIMETHYL" OR "Propanedioic acid diethyl ester" OR "Propanedioic acid dimethyl ester" OR "Propanedioic acid, 1,3-diethyl ester" OR "Propanedioic acid, 1,3-dimethyl ester" OR "Propanedioic acid, diethyl ester" OR "Propanedioic acid, dimethyl ester")
Fate	WOS	TS=("108-59-8" OR "105-53-3" OR "Carbethoxyacetic ester" OR "Dicarbethoxymethane" OR "Diethyl malonate" OR "Diethyl propane-1,3-dioate" OR "Diethyl propanedioate" OR "diethylmalonate" OR "Dimethyl 1,3-propanedioate" OR "Dimethyl malonate" OR "Dimethyl propanedioate" OR "Ethyl malonate" OR "Ethyl methanedicarboxylate" OR "Ethyl propanedioate" OR "MALONATE, DIETHYL" OR "Malonate diethyl ester" OR "Malonic acid, diethyl ester" OR "Malonic acid, dimethyl ester" OR "Malonic ester" OR "Methanedicarboxylic acid diethyl ester" OR "Methanedicarboxylic acid, diethyl ester" OR "Methyl malonate" OR "PROPANEDIOATE, DIETHYL" OR "PROPANEDIOATE, DIMETHYL" OR "Propanedioic acid diethyl ester" OR "Propanedioic acid dimethyl ester" OR "Propanedioic acid, 1,3-diethyl ester" OR "Propanedioic acid, 1,3-dimethyl ester" OR "Propanedioic acid, diethyl ester" OR "Propanedioic acid, dimethyl ester") AND TS=(adsorp* OR aerob* OR anaerob* OR bioaccumulat* OR bioavail* OR bioconcentrat* OR biodegrad* OR biomoni* OR biotrans* OR degrad* OR dispers* OR fish* OR hydroly* leach* OR migrat* OR partic* OR partition* OR persisten* OR photoly* OR volatil* OR abiotic OR absorb OR absorption OR accumulation-rate

Table C.2: Search Terms Used in Peer Reviewed Databases		
		OR aerosol OR aerosols OR air OR anoxic OR atm-m3/mol OR biomagnification OR biosolids OR biota OR breakdown-product OR breakdown-products OR chelation OR coagulation complexation OR decay-rate OR diffusion-coefficient OR dissolution OR dust OR effluent OR environmental-fate OR evaporation-from-water OR excretion OR flocculation OR flux OR fugacity OR gas-phase-mass-transfer OR ground-water OR groundwater OR half-life OR henry's-law OR incinerate OR incineration OR indoor-outdoor-ratio OR influent OR ingestion OR intake OR kinetics OR liquid-phase-mass-transfer OR mass-transfer-coefficient OR microcosm OR modified-state-space OR particle-size OR particulate OR pathway OR pathways OR penetration-factor OR penetration-ratio OR photostability OR placenta OR plasma OR plume OR point-source OR point-sources OR pore-water OR pretreatment-program OR redox OR sediment OR serum OR sewage-treatment OR sludge OR soil OR subsurface-intrusion OR surface-water-concentration OR time-weighted-average OR transfer OR transformation OR trophic-magnification OR vapor OR wait-time OR wastewater-treatment OR weight-fraction OR wildlife OR BAF OR BCF OR BSAF OR BSAFs OR KAW OR Kd OR KOA OR KOC OR POTW OR SES OR WWTP OR ((OECD OR OPPTS OR OCSPP) AND (Guideline OR guidelines)))

Table C.3: Search Terms Used in Grey Literature and Additional Sources	
Chemical	**Search terms**
Malonates (dimethyl malonate; diethyl malonate)	Searched as a string or individually depending on source: 108-59-8" OR "105-53-3" OR "Carbethoxyacetic ester" OR "Dicarbethoxymethane" OR "Diethyl malonate" OR "Diethyl propane-1,3-dioate" OR "Diethyl propanedioate" OR "Dimethyl 1,3-propanedioate" OR "Dimethyl malonate" OR "Dimethyl propanedioate" OR "Ethyl malonate" OR "Ethyl malonate (VAN)" OR "Ethyl methanedicarboxylate" OR "Ethyl propanedioate" OR "MALONATE, DIETHYL" OR "Malonate diethyl ester" OR "Malonic acid, diethyl ester" OR "Malonic acid, dimethyl ester" OR "Malonic ester" OR "Methanedicarboxylic acid diethyl ester" OR "Methanedicarboxylic acid, diethyl ester" OR "Methyl malonate" OR "PROPANEDIOATE, DIETHYL" OR "PROPANEDIOATE, DIMETHYL" OR "Propanedioic acid diethyl ester" OR "Propanedioic acid dimethyl ester" OR "Propanedioic acid, 1,3-diethyl ester" OR "Propanedioic acid, 1,3-dimethyl ester" OR "Propanedioic acid, diethyl ester" OR "Propanedioic acid, dimethyl ester" OR "diethylmalonate"
Analogs searched	dimethyl succinate (106-65-0); dimethyl adipate (627-93-0); dimethyl glutarate (1119-40-0); diethyl succinate (123-25-1); dibasic esters (95481-62-2)

After the search terms were applied, more than 1,150 references were returned by all search efforts across peer-reviewed databases and grey literature sources. The total number of references include database results, additional strategies, and analog searches for the malonate cluster including diethyl malonate. All references from the search efforts were screened and evaluated through the LPS literature search and review process.[55] Of these, 30 references were included for data evaluation and used to support the designation of diethyl malonate as LPS. The included hazard and fate references are listed in the bibliography of Appendix B.

C.2 Excluded Studies and Rationale

This section lists the excluded references, by HERO ID, found to be off-topic or unacceptable for use in the hazard screening of diethyl malonate. The excluded references are organized by discipline (human health hazard, environmental hazard, and fate), presented along with a rationale based on exclusion criteria. The criteria[55] was used to determine off-topic references in the title/abstract or full text screening and to determine unacceptable references in the data quality evaluation are provided in the form of questions.

C.2.1 Human Health Hazard Excluded References

For the screening review of diethyl malonate, EPA excluded a total of 540 references when assessing human health hazard. Off-topic references (e.g., studies that did not contain information relevant to human health) were excluded at either title/abstract screening (see Table C.4), or full-text screening (see Table C.5). Unacceptable references (e.g., studies that did not meet data quality metrics) were excluded at full-text screening (see Tables C.6 and C.7). Off-topic and unacceptable references are displayed next to the corresponding exclusion criteria.

Table C.4: Off-Topic References Excluded at Title/Abstract Screening for Human Health Hazard

Reference excluded (HERO ID) because the reference did NOT contain information needs[58] relevant to human health hazard									
1022206	4929206	4923743	4923477	4923618	3053987	4935828	4923841	4923552	4923669
1040619	4931325	4923744	4923478	4923619	3120733	4935831	4923843	4923553	4923670
1042992	4931453	4923747	4923479	4923620	3163278	4935835	4923844	4923554	4923671
1048932	4931491	4923750	4923480	4923622	3186448	4935836	4923845	4923555	4923672
1104864	4931882	4923751	4923481	4923623	3233658	4935837	4923846	4923557	4923673
1149967	4932500	4923752	4923482	4923625	3235030	4935838	4923847	4923558	4923674
1315937	4932525	4923753	4923483	4923626	3438987	4935839	4923848	4923559	4923675
1378092	4932620	4923754	4923484	4923627	3537907	4935842	4924289	4923560	4923676
1441881	4932898	4923756	4923485	4923628	3538154	4935845	4924291	4923562	4923678
1449817	4932902	4923757	4923486	4923629	3538342	4935846	4924292	4923563	4923679
1460212	4932934	4923758	4923487	4923630	3603771	4935847	4924293	4923566	4923680
1525969	4933183	4923760	4923488	4923631	3653305	4935851	4924294	4923567	4923681
1529848	4933274	4923761	4923489	4923633	3691713	4935855	4924295	4923568	4923682
1538279	4933275	4923764	4923490	4923634	3716147	4935856	4924296	4923569	4923683
1610851	4933315	4923765	4923491	4923635	3732842	4935857	4924297	4923570	4923684
1752669	4933402	4923788	4923492	4923636	3738490	4935858	4924298	4923571	4923702
1793913	4933404	4923790	4923493	4923637	3758890	4935859	4924299	4923572	4923703
1794243	4933405	4923792	4923494	4923638	3812332	4935860	4924300	4923573	4923705
1799722	4933410	4923796	4923495	4923639	3824612	4935865	4924301	4923574	4923706
1806144	4933412	4923798	4923496	4923640	3831063	4935868	4924302	4923575	4923707
184678	4933425	4923800	4923497	4923641	4034025	4935869	4924303	4923576	4923709
2115081	4933434	4923802	4923498	4923642	4045028	4935870	4924304	4923577	4923710
2241931	4933436	4923806	4923518	4923643	4076914	4935881	4924306	4923578	4923711

[58] The information needs for human health hazard includes a list of study characteristics pertaining to the study population/test organism, types of exposures and routes, use of controls, type and level of effects. A complete list of the information needs is provided in Table A1 of the "Approach Document for Screening Hazard Information for Low-Priority Substances Under TSCA". These information needs helped guide the development of questions for title/abstract and full-text screening.

Table C.4: Off-Topic References Excluded at Title/Abstract Screening for Human Health Hazard									
2302911	4933480	4923807	4923519	4923644	4228731	4935883	4924307	4923579	4923713
2302941	4933489	4923809	4923520	4923645	4298108	4935884	4924308	4923580	4923715
2302995	4933492	4923810	4923521	4923646	4386903	4935886	4924309	4923581	4923717
2369325	4933539	4923811	4923522	4923647	4442437	4935889	4924310	4923582	4923718
2545667	4933543	4923812	4923523	4923650	4453116	4935890	4924311	4923583	4923719
2718695	4933553	4923813	4923524	4923651	4559723	4935893	4924313	4923584	4923721
2777734	4933555	4923814	4923525	4923652	4567745	4935894	4924314	4923585	4923724
2779458	4933559	4923815	4923526	4923653	466056	4935896	4924316	4923586	4923725
2789619	4933560	4923816	4923527	4923654	4865076	4935899	4924317	4923587	4923726
2792326	4933563	4923817	4923528	4923655	4923443	4935900	4924318	4923588	4923727
2794054	4933582	4923818	4923529	4923656	4923445	4935902	4924319	4923589	4923728
2810456	4933596	4923833	4923530	4923657	4923446	4935905	4924320	4923590	4923729
2810786	4933643	4923834	4923531	4923658	4923447	4935908	4924322	4923591	4923730
2823794	4935814	4923835	4923532	4923659	4923448	4935909	4924323	4923592	4923731
2861807	4935818	4923836	4923533	4923660	4923449	4935910	4924325	4923593	4923732
2892878	4935823	4923837	4923547	4923661	4923451	4935912	4924326	4923594	4923734
2898376	4935824	4923838	4923548	4923663	4923452	4935915	4924327	4923595	4923736
2907621	4935825	4923839	4923550	4923664	4923454	4935919	4924345	4923596	4923737
2913951	4935826	4923840	4923551	4923666	4923455	4935925	4924388	4923597	4923738
4923465	4936877	4929173	4923605	659685	4923457	4935927	4924389	4923598	4923739
4923466	4936893	4929174	4923606	660376	4923459	4935928	4924390	4923599	4923741
4923467	4936899	4929192	4923607	661835	4923460	4935929	4924391	4923600	4923742
4923468	4937069	4929193	4923608	4923474	4923461	4936097	4924392	4923601	4923614
4923469	4937115	4929194	4923610	4923475	4923462	4936265	4924617	4923602	4923615
4923470	4937116	4929198	4923611	4923476	4923463	4936853	4924618	4923603	4923616
4923471	4937118	4929201	4923612	4929204	4923464	4936866	4924633	4923604	4923617
4923472	4937119	4929202	4923613	4937473	4923473				
Reference excluded (HERO ID) because the reference primarily contained *in silico* data									
2777734									

Table C.5: Screening Questions and Off-Topic References Excluded at Full Text Screening for Human Health Hazard		
Question	**Off-topic if answer is:**	**References excluded (HERO ID)**
Does the reference contain information pertaining to a low- priority substance candidate?	No	2282023 2791394 4923720 4931349 4933541 4933573 4939813 4940067 4940209 4940210 4940211 4923677 4923716 4923735 4940224 4940226

Table C.5: Screening Questions and Off-Topic References Excluded at Full Text Screening for Human Health Hazard		
What type of source is this reference?	Review article or book chapter that contains only citations to primary literature sources	4923458 4935830
What kind of evidence does this reference primarily contain?	*In silico* studies that DO NOT contain experimental verification	4931349
The following question apply to HUMAN evidence only		
Does the reference report an exposure route that is or is presumed to be by an inhalation, oral, or dermal route?	No	N/A.
Does the reference report both test substance exposure(s) AND related health outcome(s)?	No	N/A.
If the reference reports an exposure to a chemical mixture, are measures of the test substance or related metabolite(s) reported independently of other chemicals?	No	N/A.
Note: If the paper does not pertain to mixtures, choose "Not Applicable".	No	N/A.
The following question apply to ANIMAL evidence only		
Does the reference report an exposure route that is by inhalation, oral, or dermal route?	No	4733654 4933474 4933486 4933488 4933535 4933550 4935815
Does the reference report both test substance-related exposure(s) AND related health outcome(s)?	No	N/A.
Does the reference report the duration of exposure?	No	2282023
Does the reference report an exposure to the test substance only (i.e. no mixtures with the exception of aqueous solutions and reasonable impurities and byproducts)?	No	2282023
Does the paper report a negative control that is a vehicle control or no treatment control?	No[59]	2282023 4933550
The following questions apply to MECHANISTIC/ALTERNATIVE TEST METHODS evidence only		
Does the reference report a negative control that is a vehicle control or no treatment control?	No	1060760 4935815 4935882 4940221 4940211

[59] Except for acute mammalian toxicity and skin and eye irritation studies, where the use of a negative control may not be required (e.g., OECD 403 Acute Inhalation Toxicity Guidelines).

Table C.5: Screening Questions and Off-Topic References Excluded at Full Text Screening for Human Health Hazard		
Does the reference report an exposure to the test substance only (i.e. no mixtures with the exception of aqueous solutions and reasonable impurities and byproducts)?	No	1060760 4935815 4935882
For genotoxicity studies only: Does the study use a positive control?	No	1060760 4940211

Table C.6: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Human Health Hazard – Animal		
Data Quality Metric	**Unacceptable if:**	**References excluded (HERO ID)**
Metric 1: Test substance identity	• The test substance identity cannot be determined from the information provided (e.g., nomenclature was unclear and CASRN or structure were not reported). **OR** • For mixtures, the components and ratios were not characterized or did not include information that could result in a reasonable approximation of components.	N/A.
Metric 2: Negative and vehicle controls	A concurrent negative control group was not included or reported. **OR** The reported negative control group was not appropriate (e.g., age/weight of animals differed between control and treated groups).	N/A.
Metric 3: Positive controls	When applicable, an appropriate concurrent positive control (i.e., inducing a positive response) was not used.	N/A.
Metric 4: Reporting of doses/concentrations	Doses/concentrations were not reported and could not be calculated using default or reported estimates of body weight and diet/water intake (e.g., default intake values are not available for pregnant animals).	4939812 4940213 4940223
Metric 5: Exposure duration	The duration of exposure was not reported. **OR** The reported exposure duration was not suited to the study type and/or outcome(s) of interest (e.g., <28 days for repeat dose).	4939812 4940229

Table C.6: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Human Health Hazard – Animal		
Data Quality Metric	**Unacceptable if:**	**References excluded (HERO ID)**
Metric 6: Test Animal characteristics	The test animal species was not reported. **OR** The test animal (species, strain, sex, life-stage, source) was not appropriate for the evaluation of the specific outcome(s) of interest (e.g., genetically modified animals, strain was uniquely susceptible or resistant to one or more outcome of interest).	N/A.
Metric 7: Number of animals per group	The number of animals per study group was not reported. **OR** The number of animals per study group was insufficient to characterize toxicological effects (e.g., 1-2 animals in each group).	4939812
Metric 8: Outcome assessment methodology	The outcome assessment methodology was not sensitive for the outcome(s) of interest (e.g., evaluation of endpoints outside the critical window of development, a systemic toxicity study that evaluated only grossly observable endpoints, such as clinical signs and mortality, etc.).	4939812 4940229
Metric 9: Reporting of data	Data presentation was inadequate (e.g., the report does not differentiate among findings in multiple exposure groups). **OR** Major inconsistencies were present in reporting of results.	4939812 4940227

Table C.7: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Human Health Hazard – In Vitro		
Data Quality Metric	**Unacceptable if:**	**References excluded (HERO ID)**
Metric 1: Test substance identity	The test substance identity or description cannot be determined from the information provided (e.g., nomenclature was unclear and CASRN or structure were not reported). **OR** For mixtures, the components and ratios were not characterized or did not include information that could	1141389 4923763

Table C.7: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Human Health Hazard – In Vitro		
Data Quality Metric	**Unacceptable if:**	**References excluded (HERO ID)**
	result in a reasonable approximation of components.	
Metric 2: Negative controls	A concurrent negative control group was not included or reported. **OR** The reported negative control group was not appropriate (e.g., different cell lines used for controls and test substance exposure).	651740 1141389 4929197 4940222
Metric 3: Positive controls	A concurrent positive control or proficiency group was not used.	1141389 4940222
Metric 4: Assay type	The assay type was not reported. **OR** The assay type was not appropriate for the study type or outcome of interest (e.g., *in vitro* skin corrosion protocol used for *in vitro* skin irritation assay).	N/A.
Metric 5: Reporting of concentration	The exposure doses/concentrations or amounts of test substance were not reported.	625777 1141389 4935924
Metric 6: Exposure duration	No information on exposure duration(s) was reported. **OR** The exposure duration was not appropriate for the study type and/or outcome of interest (e.g., 24 hours exposure for bacterial reverse mutation test).	625777 1141389 4929197 4933481 4935924 4940217 4940222
Metric 7: Metabolic activation	No information on the characterization and use of a metabolic activation system was reported. **OR** The exposure duration was not appropriate for the study type and/or outcome of interest (e.g., 24 hours exposure for bacterial reverse mutation test).	1141389 4929197
Metric 8: Test model	The test model was not reported **OR** The test model was not routinely used for evaluation of the specific outcome of interest.	N/A.
Metric 9: Outcome assessment methodology	The outcome assessment methodology was not reported. **OR**	1141389 4933534 4935924

Table C.7: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Human Health Hazard – In Vitro		
Data Quality Metric	**Unacceptable if:**	**References excluded (HERO ID)**
	The assessment methodology was not appropriate for the outcome(s) of interest (e.g., cells were evaluated for chromosomal aberrations immediately after exposure to the test substance instead of after post-exposure incubation period).	

C.2.2 Environmental Hazard

For the screening review of LPS candidate diethyl malonate, EPA excluded a total of 466 references when assessing environmental hazard. Off-topic environmental hazard references excluded at title/abstract screening are listed in Table C.8, and those excluded at full-text screening are listed in Table C.9. References in Table C.10 represent unacceptable studies based on specific data quality metrics for environmental hazard. Off-topic and unacceptable references are displayed next to the corresponding exclusion criteria.

Table C.8: Off-Topic References Excluded at Title/Abstract Screening for Environmental Hazard									
Reference excluded (HERO ID) because the reference did NOT contain information needs[60] relevant to environmental hazard									
94897	4936806	4936221	4933099	4923806	4246082	4933547	4936269	4933345	4931453
184678	4936815	4936227	4933101	4923810	4332446	4933550	4936270	4933348	4931491
625777	4936817	4936228	4933105	4923838	4381738	4933552	4936271	4933350	4931879
651740	4936820	4936229	4933106	4923841	4386903	4933553	4936273	4933352	4931880
660376	4936840	4936231	4933175	4923845	4422413	4933555	4936274	4933397	4931881
922459	4936844	4936232	4933180	4924292	4442437	4933557	4936275	4933398	4931882
1040619	4936849	4936233	4933181	4924297	4482713	4933558	4936781	4933399	4931883
1042992	4936853	4936236	4933182	4924298	4482800	4933559	4936785	4933400	4931884
1048932	4936854	4936237	4933183	4924301	4499033	4933560	4936790	4933402	4931886
1060760	4936858	4936238	4933186	4924311	4607184	4933563	4936791	4933403	4931888
1149967	4936863	4936239	4933187	4924313	4671024	4933565	4936792	4933404	4931889
1315937	4936864	4936240	4933189	4924318	4720648	4933566	4936794	4933405	4931891
1441881	4936866	4936241	4933191	4924322	4923443	4933567	4933661	4933406	4931892
1448620	4936867	4936242	4933264	4924325	4923445	4933570	4933662	4933410	4932219
1538279	4936871	4936243	4933265	4924388	4923448	4933571	4933663	4933411	4932490
1616838	4936873	4936244	4933270	4924389	4923449	4933573	4933665	4933412	4932491
1794239	4936877	4936245	4933271	4924617	4923452	4933577	4933667	4933413	4932494
2235088	4936892	4936246	4933272	4924618	4923460	4933578	4933669	4933414	4932495
2324664	4936893	4936247	4933275	4926318	4923464	4933580	4935815	4933415	4932500
2545667	4936895	4936248	4933279	4929173	4923468	4933582	4935818	4933418	4932502
2777734	4936898	4936249	4933283	4929174	4923469	4933583	4935825	4933420	4932503
2779458	4936899	4936251	4933284	4929192	4923470	4933586	4935828	4933421	4932513

[60] The information needs for environmental hazard includes a list of study characteristics pertaining to the test organism/species, type and level of effects, and use of controls. A complete list of the information needs is provided in Table A2 of the "Approach Document for Screening Hazard Information for Low-Priority Substances Under TSCA". These information needs helped guide the development of questions for title/abstract and full-text screening.

Table C.8: Off-Topic References Excluded at Title/Abstract Screening for Environmental Hazard									
2789619	4937069	4936252	4933285	4929193	4923471	4933587	4935831	4933422	4932520
2792326	4937146	4936253	4933286	4929194	4923475	4933588	4935835	4933423	4932620
2810786	4937172	4936254	4933313	4929196	4923478	4933590	4935836	4933425	4932621
2823794	4937173	4936255	4933315	4929197	4923479	4933591	4935837	4933427	4932688
3120733	4937174	4936259	4933321	4929198	4923488	4933595	4935839	4933429	4932890
3163278	4937480	4936260	4933324	4929200	4923492	4933596	4935857	4933431	4932892
3235030	4933535	4936262	4933329	4929201	4923498	4933597	4935865	4933432	4932894
3438987	4933537	4936263	4933331	4929202	4923522	4933598	4935869	4933433	4932896
3538154	4933539	4936264	4933332	4929204	4923524	4933602	4935881	4933434	4932898
3603771	4933541	4936265	4933333	4929205	4923526	4933604	4935886	4933436	4932900
3653305	4933542	4936266	4933338	4929206	4923527	4933606	4935889	4933474	4932901
3732842	4933543	4936267	4933342	4931325	4923529	4933632	4935905	4933475	4932906
4079158	4933545	4936268	4933343	4931349	4923530	4933633	4935908	4933476	4932907
4923640	4933652	4935969	4933493	4932987	4923552	4933634	4935909	4933479	4932936
4923646	4933653	4935984	4933494	4932992	4923553	4933635	4935910	4933480	4932937
4923660	4933655	4936018	4933495	4932993	4923557	4933637	4935912	4933481	4932944
4923672	4933656	4936097	4933497	4932995	4923562	4933638	4935919	4933483	4932945
4923676	4933657	4936137	4933522	4933000	4923581	4933640	4935925	4933485	4932950
4923678	4933658	4936138	4933527	4933090	4923584	4933641	4935927	4933486	4932951
4923682	4933660	4936142	4933528	4933092	4923587	4933642	4935928	4933488	4932953
4923702	4923743	4936200	4933530	4933093	4923589	4933643	4935929	4933489	4932978
4923703	4923748	4923727	4933533	4923726	4923604	4933645	4935949	4933490	4932982
4923710	4923751	4923728	4933534	4923715	4923605	4933648	4935953	4933492	4932985
4923713	4923757	4923742	4923714	4923792					
Reference excluded (HERO ID) because the reference did NOT present quantitative environmental hazard data									
N/A.									

Table C.9: Screening Questions and Off-Topic References Excluded at Full Text Screening for Environmental Hazard		
Question	**Off-topic if answer is:**	**References excluded (HERO ID)**
Does the reference contain information pertaining to a low- priority substance candidate?	No	4939897 4951381 4939518
What type of source is this reference?	Review article or book chapter that contains only citations to primary literature sources	N/A.
Is quantitative environmental hazard data presented?	No	N/A.
Is this primarily a modeling/simulation study? [Note: select "No" if experimental verification was included in the study]	Yes	N/A.
Is environmental hazard data presented for standard or non-standard aquatic or terrestrial species (fish, invertebrates, microorganisms, non-mammalian terrestrial species)?	No	N/A.
Is exposure measured for the target substance or is the test substance a	Mixture	N/A.
	Formulated Product	N/A.

Table C.9: Screening Questions and Off-Topic References Excluded at Full Text Screening for Environmental Hazard		
Question	**Off-topic if answer is:**	**References excluded (HERO ID)**
mixture (except for reasonable impurities, byproducts, and aqueous solutions) or formulated product?		
Does the reference report a duration of exposure?	No	N/A.
Does the reference report a negative control that is a vehicle control or no treatment control?	No	4939816 4939817 4940066
Does the reference include endpoints in the information needs?	No	N/A.

Table C.10: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Environmental Hazard		
Question	**Unacceptable if:**	**References excluded (HERO ID)**
Metric 1: Test substance identity	The test substance identity or description cannot be determined from the information provided (e.g., nomenclature was unclear, CASRN or structure were not reported, substance name/ description does not match CASRN). **OR** For mixtures, the components and ratios were not characterized or did not include information that could result in a reasonable approximation of components.	4935613 4939694
Metric 2: Negative controls	A concurrent negative control group was not included or reported.	4935263 4939694
Metric 3: Experimental system	The experimental system (e.g., static, semi-static, or flow-through regime) was not described.	4935263 4939287 4939484 4939694
Metric 4: Reporting of concentrations	Test concentrations were not reported.	4935263
Metric 5: Exposure duration	The duration of exposure was not reported. **OR** The reported exposure duration was not suited to the study type and/or outcome(s) of interest (e.g., study intended to assess effects on reproduction did not expose organisms for an acceptable period of time prior to mating).	4935263
Metric 6: Test organism characteristics	The test species was not reported. **OR** The test species, life stage, or age was not appropriate for the outcome(s) of interest.	N/A.
Metric 7:	The outcome assessment methodology was not reported.	4935263 4939694

Table C.10: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Environmental Hazard		
Question	**Unacceptable if:**	**References excluded (HERO ID)**
Outcome assessment methodology		
Metric 8: Reporting of data	Data presentation was inadequate. **OR** Major inconsistencies were present in reporting of results.	4935263

C.2.3 Fate

For the screening review of LPS candidate diethyl malonate, EPA excluded a total of 469 references when assessing environmental fate. Off-topic fate references excluded at title/abstract screening are listed in Table C.11, and those excluded at full-text screening are listed in Table C.12. References in Table C.13 represent unacceptable studies based on specific data quality metrics for fate. Off-topic and unacceptable references are displayed next to the corresponding exclusion criteria.

Table C.11: Off-Topic References Excluded at Initial Screening for Fate									
Reference excluded (HERO ID) because the reference did NOT contain information needs[61] relevant to environmental fate									
4924311	4936179	4936039	4935967	4923550	4033388	4937141	4936111	4936159	4935825
4931883	4936180	4936040	4935969	4923557	4089130	4937142	4936112	4936160	4935826
448349	4936181	4936042	4935971	4923575	4096023	4937143	4936114	4936161	4935828
466056	4936182	4936045	4935972	4923579	4142764	4937144	4936115	4936162	4935838
488729	4936184	4936046	4935975	4923580	4182651	4937145	4936116	4936164	4935845
651740	4936185	4936047	4935977	4923581	4228731	4937146	4936117	4936165	4935886
659685	4936186	4936048	4935978	4923584	4238775	4937148	4936118	4936167	4935896
922459	4936190	4936049	4935979	4923585	4238776	4937149	4936120	4936169	4935899
1160162	4936191	4936050	4935981	4923589	4275273	4937150	4936121	4936170	4935925
1166560	4936193	4936051	4935982	4923599	4298108	4937152	4936122	4936171	4935929
1181656	4936194	4936052	4935983	4923604	4419091	4937153	4936123	4936172	4935931
1182264	4936195	4936053	4935985	4923610	4419092	4937154	4936124	4936174	4935933
1190450	4936196	4936055	4935987	4923613	4419093	4937155	4936125	4936175	4935935
1204263	4936198	4936056	4935988	4923629	4422413	4937156	4936126	4936176	4935936
1449817	4936199	4936057	4935989	4923638	4422447	4937157	4936127	4936177	4935937
1452087	4936200	4936059	4935990	4923640	4453116	4937159	4936129	4936178	4935938
1453426	4936201	4936060	4935991	4923642	4559723	4937160	4936132	4923457	4935939
1610186	4936204	4936061	4935992	4923643	4607184	4937161	4936133	4923459	4935940
1610851	4936205	4936064	4935993	4923645	4665778	4937162	4936134	4923468	4935941
1611653	4936206	4936065	4935995	4923647	4708473	4937163	4936135	4923471	4935943
1752669	4936207	4936066	4935996	4923664	4709249	4937164	4936136	4923473	4935944
1792712	4936209	4936067	4935998	4923670	4711360	4937165	4936137	4923475	4935945
1793863	4936210	4936068	4935999	4923671	4720648	4937166	4936138	4923477	4935948
1794382	4936211	4936070	4936000	4923682	4721999	4937167	4936139	4923480	4935949

[61] The information needs for fate includes a list of study characteristics pertaining to the associated media and exposure pathways, associated processes, and use of controls. A complete list of the information needs is provided in Table A3 of the "Approach Document for Screening Hazard Information for Low-Priority Substances Under TSCA". These information needs helped guide the development of questions for title/abstract and full-text screening.

Table C.11: Off-Topic References Excluded at Initial Screening for Fate									
1941474	4936212	4936071	4936001	4923703	4722919	4937169	4936140	4923482	4935950
1949851	4936213	4936072	4936002	4923706	4761067	4937170	4936141	4923486	4935952
1950394	4936216	4936073	4936003	4923711	4789294	4937474	4936142	4923487	4935953
1951869	4936218	4936074	4936004	4923715	4830553	4937475	4936144	4923488	4935954
1954812	4936220	4936075	4936006	4923725	4866723	4937476	4936146	4923489	4935955
1965772	4936221	4936076	4936007	4923726	4882194	4937477	4936148	4923491	4935957
1967704	4936222	4936077	4936010	4923730	4923449	4937478	4936149	4923493	4935958
2241931	4936223	4936078	4936012	4923732	4923451	4937479	4936150	4923498	4935959
2324664	4936225	4936079	4936013	4923743	4923525	4935964	4935961	4923519	4935960
2369325	4936226	4936081	4936014	4923845	4923527	4935965	4935962	4923522	4923523
2791394	4936249	4936083	4936016	4924292	3738367	4937127	4936094	4936030	4929194
2792326	4936251	4936084	4936017	4924296	3751974	4937128	4936096	4936032	4931453
2810786	4936259	4936085	4936018	4924297	3753346	4937129	4936097	4936033	4932990
2879557	4936271	4936086	4936022	4924306	3754273	4937131	4936100	4936035	4933315
2904592	4936864	4936087	4936023	4924308	3757714	4937132	4936101	4936036	4933411
3002189	4937121	4936089	4936024	4924313	3758839	4937133	4936102	4936037	4933577
3537907	4937122	4936090	4936025	4924318	3763886	4937134	4936103	4936151	4933632
3538342	4937124	4936091	4936026	4924388	3765216	4937135	4936104	4936154	4933633
3603771	4937125	4936092	4936028	4924618	3830431	4937136	4936107	4936156	4933634
3705115	4937126	4936093	4936029	4929193	3830766	4937138	4936108	4936157	4935814
4923533	4033387	4937140	4936110	4936158	4935815				
Reference excluded (HERO ID) because the reference did NOT present quantitative environmental fate data									
N/A.									

Table C.12: Screening Questions and Off-Topic References Excluded at Full Text Screening for Fate		
Question	**Off-topic if answer is:**	**References excluded (HERO ID)**
Does the reference contain information pertaining to a low-priority substance candidate?	No	4935968 4935984 1448620 2545667 4935968 4935984
What type of source is this reference?	Review article or book chapter that contains only citations to primary literature sources	N/A.
Is quantitative fate data presented?	No	N/A.
Is this primarily a modeling/simulation study? [Note: Select "Yes" only if there is no experimental verification]	Yes	N/A.

Table C.13: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Fate		
Data quality metric	**Unacceptable if:**	**References excluded (HERO ID)**
Metric 1: Test substance identity	The test substance identity or description cannot be determined from the information provided (e.g., nomenclature was unclear and CASRN or structure were not reported). **OR**	4931884

Table C.13: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Fate		
Data quality metric	**Unacceptable if:**	**References excluded (HERO ID)**
	For mixtures, the components and ratios were not characterized or did not include information that could result in a reasonable approximation of components.	
Metric 2: Study controls	The study did not include or report crucial control groups that consequently made the study unusable (e.g., no positive control for a biodegradation study reporting 0% removal). **OR** The vehicle used in the study was likely to unduly influence the study results.	4935263 4939814
Metric 3: Test substance stability	There were problems with test substance stability, homogeneity, or preparation that had an impact on concentration or dose estimates and interfered with interpretation of study results.	4935263
Metric 4: Test method suitability	The test method was not reported or not suitable for the test substance. **OR** The test concentrations were not reported. **OR** The reported test concentrations were not measured and the nominal concentrations reported greatly exceeded the substances water solubility, which would greatly inhibit meaningful interpretation of the outcomes.	4935263
Metric 5: Testing conditions	Testing conditions were not reported and the omission would likely have a substantial impact on study results. **OR** Testing conditions were not appropriate for the method (e.g., a biodegradation study at temperatures that inhibit the microorganisms).	4935263 4939814
Metric 6: System type and design-partitioning	Equilibrium was not established or reported, preventing meaningful interpretation of study results. **OR** The system type and design (e.g. static, semi-static, and flow-through; sealed, open) were not capable of appropriately maintaining substance concentrations, preventing meaningful interpretation of study results.	N/A.
Metric 7: Test organism-degradation	The test organism, species, or inoculum source were not reported, preventing meaningful interpretation of the study results.	N/A.
Metric 8: Test organism-partitioning	The test organism information was not reported. **OR** The test organism is not routinely used and would likely prevent meaningful interpretation of the study results.	N/A.
Metric 9: Outcome assessment methodology	The assessment methodology did not address or report the outcome(s) of interest.	2545667 4935263

Table C.13: Data Quality Metrics and Unacceptable References Excluded at Data Quality Evaluation for Fate		
Data quality metric	**Unacceptable if:**	**References excluded (HERO ID)**
Metric 10: Data reporting	Insufficient data were reported to evaluate the outcome of interest or to reasonably infer an outcome of interest. **OR** The analytical method used was not suitable for detection or quantification of the test substance. **OR** Data indicate that disappearance or transformation of the parent compound was likely due to some other process.	4935263
Metric 11: Confounding variables	There were sources of variability and uncertainty in the measurements and statistical techniques or between study groups.	4935263 4939814
Metric 12: Verification or plausibility of results	Reported value was completely inconsistent with reference substance data, related physical chemical properties, or otherwise implausible, suggesting that a serious study deficiency exists (identified or not).	N/A.