

**SCREENING LEVEL HAZARD CHARACTERIZATION
OF HIGH PRODUCTION VOLUME CHEMICALS**

CHEMICAL CATEGORY NAME

Diesters

SPONSORED CHEMICALS

Maleic acid, bis(1,3-dimethylbutyl)ester (CAS No. 105-52-2)
[9th CI Name: 2-Butenedioic acid (2Z)-, bis(1,3-dimethylbutyl) ester]
Maleic acid, bis(2-ethylhexyl)ester (CAS No. 142-16-5)
[9th CI Name: 2-Butenedioic (2Z)-, bis(2-ethylhexyl) ester]
Adipic acid, diisopropyl ester (CAS No. 6938-94-9)
[9th CI Name: Hexanedioic acid, bis(1-methylethyl) ester]
Adipic acid, diisooctyl ester (CAS No. 1330-86-5)
[9th CI Name: Hexanedioic acid, diisooctyl ester]
Adipic acid, bis(1-methylheptyl)ester (CAS No. 108-63-4)
[9th CI Name: Hexanedioic acid, bis(1-methylheptyl) ester]
Adipic acid, diisononyl ester (CAS No. 33703-08-1)
[9th CI Name: Hexanedioic acid, diisononyl ester]
Adipic acid, diisodecyl ester (CAS No. 27178-16-1)
[9th CI Name: Hexanedioic acid, diisodecyl ester]
Adipic acid, ditridecyl ester (CAS No. 16958-92-2)
[9th CI Name: Hexanedioic acid, ditridecyl ester]
Azelaic acid, bis(2-ethylhexyl)ester (CAS No. 103-24-2)
[9th CI Name: Nonanedioic acid, bis(2-ethylhexyl) ester]
Azelaic acid, diisodecyl ester (CAS No. 28472-97-1)
[9th CI Name: Nonanedioic acid, diisodecyl ester]
Sebacic acid, dimethyl ester (CAS No. 106-79-6)
[9th CI Name: Decanedioic acid, dimethyl ester]
Sebacic acid, bis(2-ethylhexyl)ester (CAS No. 122-62-3)
[9th CI Name: Decanedioic acid, bis(2-ethylhexyl) ester]

SUPPORTING CHEMICALS

Maleic acid, dibutyl ester (CAS No. 105-76-0)
[9th CI Name: 2-Butanedioic acid (2Z)-, dibutyl ester]
Adipic acid, dibutyl ester (CAS No. 105-99-7)
[9th CI Name: Hexanedioic acid, dibutyl ester]
Adipic acid, di-C7-9 branched and linear alkyl ester (CAS NO. 68515-75-3)
[9th CI Name: Hexanedioic acid, di-C7-9 branched and linear alkyl esters]
Adipic acid, bis(2-ethylhexyl) ester (CAS No. 103-23-1)
[9th CI Name: Hexanedioic acid, bis(2-ethylhexyl) ester]

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INTERIM

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SCREENING LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program¹ is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1,400 sponsored chemicals. OPPT is using a hazard-based screening process to prioritize review of the submissions. The hazard-based screening process consists of two tiers described below briefly and in more detail on the Hazard Characterization website³.

Tier 1 is a computerized sorting process whereby key elements of a submitted data set are compared to established criteria to “bin” chemicals/categories for OPPT review. This is an automated process performed on the data as submitted by the sponsor. It does not include evaluation of the quality or completeness of the data.

In Tier 2, a screening-level hazard characterization is developed by EPA that consists of an objective evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. The evaluation is performed according to established EPA guidance^{2,4} and is based primarily on hazard data provided by sponsors. EPA may also include additional or updated hazard information of which EPA, sponsors or other parties have become aware. The hazard characterization may also identify data gaps that will become the basis for a subsequent data needs assessment where deemed necessary. Under the HPV Challenge Program, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. This approach often significantly reduces the need for conducting tests for all endpoints for all category members. As part of Tier 2, evaluation of chemical category rationale and composition and data extrapolation(s) among category members is performed in accord with established EPA² and OECD⁵ guidance.

The screening-level hazard characterizations that emerge from Tier 2 are important contributors to OPPT’s existing chemicals review process. These hazard characterizations are technical documents intended to support subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public. The public, including sponsors, may offer comments on the hazard characterization documents.

The screening-level hazard characterizations, as the name indicates, do not evaluate the potential risks of a chemical or a chemical category, but will serve as a starting point for such reviews. In 2007, EPA received data on uses of and exposures to high-volume TSCA existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule. For the chemicals in the HPV Challenge Program, EPA will review the IUR data to evaluate exposure potential. The resulting exposure information will then be combined with the screening-level hazard characterizations to develop screening-level risk characterizations^{4,6}. The screening-level risk characterizations will inform EPA on the need for further work on individual chemicals or categories. Efforts are currently underway to consider how best to utilize these screening-level risk characterizations as part of a risk-based decision-making process on HPV chemicals which applies the results of the successful U.S. High Production Volume Challenge Program and the IUR to support judgments concerning the need, if any, for further action.

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. HPV Chemicals Hazard Characterization website (<http://www.epa.gov/hpvis/abouthc.html>).

⁴ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

⁵ OECD. Guidance on the Development and Use of Chemical Categories; <http://www.oecd.org/dataoecd/60/47/1947509.pdf>.

⁶ U.S. EPA. Risk Characterization Program; <http://www.epa.gov/osa/spc/2riskchr.htm>.

SCREENING LEVEL HAZARD CHARACTERIZATION

Diesters Category

Introduction

The sponsor, the American Chemistry Council's Aliphatic Esters Panel, submitted a Test Plan and Robust Summaries to EPA for the Aliphatic Esters category on December 20, 2001. EPA posted the submission on the ChemRTK Web site on February 20, 2002 (<http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm>). EPA comments on the original submission were posted to the website on August 28, 2002. The sponsor submitted updated/revised documents for five separate aliphatic ester categories based on EPA's comments on the original submission. The sponsor submitted the Diesters category on November 14, 2003 that was posted to the ChemRTK website on January 6, 2004. EPA comments on the Diesters category revision were posted to the website on May 1, 2006. The Diesters category consists of the following compounds:

Sponsored Chemicals

Maleic acid, bis(1,3-dimethylbutyl)ester	CAS No. 105-52-2
Maleic acid, bis(2-ethylhexyl)ester	CAS No. 142-16-5
Adipic acid, diisopropyl ester	CAS No. 6938-94-9
Adipic acid, diisooctyl ester	CAS No. 1330-86-5
Adipic acid, bis(1-methylheptyl)ester	CAS No. 108-63-4
Adipic acid, diisononyl ester	CAS No. 33703-08-1
Adipic acid, diisodecyl ester	CAS No. 27178-16-1
Adipic acid, ditridecyl ester	CAS No. 16958-92-2
Azelaic acid, bis(2-ethylhexyl)ester	CAS No. 103-24-2
Azelaic acid, diisodecyl ester	CAS No. 28472-97-1
Sebacic acid, dimethyl ester	CAS No. 106-79-6
Sebacic acid, bis(2-ethylhexyl)ester	CAS No. 122-62-3

Supporting Chemicals

Maleic acid, dibutyl ester	CAS No. 105-76-0
Adipic acid, dibutyl ester	CAS No. 105-99-7
Adipic acid, di-C7-9 branched and linear alkyl ester	CAS NO. 68515-75-3
Adipic acid, bis(2-ethylhexyl) ester	CAS No. 103-23-1

This screening-level hazard characterization is based primarily on the review of the Test Plan and Robust Summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. The structures of the sponsored chemical(s) are included in Appendix 1, and the structure of the excluded chemical is in Appendix 2. Summary tables of SIDS endpoint data are included in the document. The screening-level hazard characterization for environmental and human health toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Category Justification

The sponsor submitted the diesters category in response to EPA's comments on the original aliphatic esters category. The original category contained 45 category members divided into five groups (monoesters, diesters, glycol esters, sorbitan esters, and polyol esters). The thirteen chemicals in the diesters category include diesters of maleic (C4), adipic (C6), azelaic (C9), and sebacic (C10) acids. Total carbon numbers for the category members range from C12 to C32. The sponsor justified the category based on structural and molecular weight similarities and carbon numbers. Representative structures of diesters category members are depicted in the appendix.

In the revised submission, the sponsor included adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester (CAS No. 141-17-3) as an additional category member. However, EPA considered that the chemical structure and physical-chemical properties of this chemical are different from the other category members. In addition, the sponsor did not submit toxicity data to compare it with the other category members. EPA requested further justification or removal of this chemical from the category. The sponsor has not yet submitted the requested information to justify the inclusion of this chemical in the category, therefore, EPA did not consider this chemical in this hazard characterization document.

Supporting Chemicals Justification

The sponsor provided data using the following supporting substances for several SIDS endpoints:

<u>Supporting Chemicals</u>	<u>CAS No.</u>	<u>Endpoint(s) Supporting</u>
Maleic acid, dibutyl ester	105-76-0	Aquatic toxicity to fish, daphnia and algae; Repeated-dose/reproductive/developmental and genetic toxicity
Adipic acid, dibutyl ester	105-99-7	Aquatic toxicity to fish, daphnia and algae
Adipic acid, di-C7-9 branched and linear alkyl ester	68515-75-3	Reproductive/developmental toxicity and gene mutation; Not used in hazard characterization
Adipic acid, bis(2-ethylhexyl) ester	103-23-1	Biodegradation; not used in this hazard characterization since biodegradation was addressed adequately by the other category members.

EPA agreed that these chemicals, which range in carbon number from C12 to C22, are appropriate supporting chemicals based on similarities in chemical structure and physical-chemical properties. Maleic acid, dibutyl ester and adipic acid, dibutyl ester were assessed under the OECD HPV Chemicals Program and the assessments have been published on the UNEP website (<http://www.chem.unep.ch/irptc/sids/OECD/SIDS/105760.pdf>) and (<http://www.chem.unep.ch/irptc/sids/OECD/SIDS/105997.pdf>). Adipic acid, di-C7-9 branched and linear alkyl ester was submitted to the U.S. EPA HPV Chemicals Program on November 20, 2002 and revised on June 11, 2003 (<http://www.epa.gov/chemrtk/pubs/summaries/hexanedi/c14079tc.htm>).

Summary-Conclusion

The log K_{ow} values for three category members (adipic acid, diisopropyl ester; sebacic acid, dimethyl ester and sebacic acid, bis(2-ethylhexyl)ester) indicate that their potential to bioaccumulate is expected to be low. The log K_{ow} values for the remaining category members are high. However, their low water solubility (10^{-4} to 10^{-9} mg/L) suggests the potential of these chemicals to bioaccumulate is expected to be low. The diesters category members are readily biodegradable, indicating that they are not expected to persist in the environment

The aquatic toxicity data for category members with low solubility were generated using Water Accommodated Fractions or dispersion by propeller techniques. The evaluation of available toxicity data indicates that the potential acute hazard to fish is high for maleic acid esters and moderate for C12 esters and low for esters above C20 (due to low water solubility). The potential acute hazard of the diester category members to aquatic invertebrates is low and to aquatic plants is moderate in the C12 to C20 range and low above C20.

Acute oral toxicity for the diesters category members is low. Acute dermal toxicity studies for two category members also indicate low toxicity. Maleic acid, dibutyl ester is a strong sensitizer. Repeated exposures to several category members via the dietary and dermal routes resulted in effects including increased relative kidney weights, histopathological changes in the kidney and liver, changes in enzyme activities, peroxisome proliferation, decreased triglycerides, renal tubular lesions, and heart, kidney and liver lesions. In rats, reproductive toxicity was evident for the supporting chemical, maleic acid, dibutyl ester, which showed pup deaths and a lack of nursing behavior. Evaluation of gonad showed no effects in the repeated-dose toxicity studies with adipic acid, ditridecylester and adipic acid, di-C7-9 branched and linear alkyl ester. Developmental effects included increased incidence of levocardia (adipic acid ditridecyl ester) and decreased fetal body weight and skeletal anomalies (presence of rudimentary structures) (adipic acid, di-C7-9 branched and linear alkyl ester) at high doses. Increased pup deaths were seen in a study with maleic acid, dibutyl ester. The tested category members or supporting chemicals did not induce gene mutation or chromosomal aberrations.

The potential hazard of the diesters category members is moderate based on concern for reproductive/developmental toxicity.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

A summary of physical-chemical properties and environmental fate data submitted is provided in Table 1. For the purpose of the screening-level hazard characterization, the review and summary of these data was limited to the octanol-water partition coefficient and biodegradation endpoints as indicators of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

Adipic acid, diisopropyl ester (CAS No. 6938-94-9) (C12)

Log K_{ow}: 3.2 (estimated)

Sebacic acid, dimethyl ester (CAS No. 106-79-6) (C12)

Log K_{ow}: 3.4 (estimated)

Sebacic acid, bis(2-ethylhexyl)ester (CAS No. 122-62-3) (C26)

Log K_{ow}: 3.74 (measured)

Maleic acid, bis(1,3-dimethylbutyl)ester (CAS No. 105-52-2)

Log K_{ow}: 5.8 (estimated)

Maleic acid, bis(-ethylhexyl)ester (CAS No. 142-16-5)

Log K_{ow}: 7.9 (estimated)

Adipic acid, diisooctyl ester CAS No. 1330-86-5

Log K_{ow}: 8.1 (estimated)

Adipic acid, bis(1-methylheptyl)ester CAS No. 108-63-4

Log K_{ow}: 8.1 (estimated)

Adipic acid, diisononyl ester CAS No. 33703-08-1

Log K_{ow}: 9.2 (estimated)

Adipic acid, diisodecyl ester CAS No. 27178-16-1

Log K_{ow}: 10.1 (estimated)

Adipic acid, ditridecyl ester CAS No. 16958-92-2

Log K_{ow}: 13.2 (estimated)

Azelaic acid, bis(2-ethylhexyl)ester CAS No. 103-24-2

Log K_{ow}: 9.6 (estimated)

Azelaic acid, diisodecyl ester CAS No. 28472-97-1

Log K_{ow}: 11.6 (estimated)

The model used to estimate the K_{ow} submitted (KOWWIN v.1.66) has been demonstrated to be accurate in predicting log K_{ow} between -4 and 10. Given the estimates for adipic acid, diisodecyl ester; adipic acid, ditridecyl

ester and azelaic acid, diisodecyl ester are outside this range, the absolute value may not be accurate. Nonetheless, it is reasonable to conclude that this prediction is indicative that the log K_{ow} for this chemical is high (> 4).

Biodegradation

Adipic acid, bis(2-ethylhexyl) ester (CAS No. 103-23-1; supporting chemical)

(1) In a Modified MITI test, 67-74% of adipic acid, bis(2-ethylhexyl) ester had degraded after 28 days.

Adipic acid, bis(2-ethylhexyl) ester is readily biodegradable.

(2) In a CO₂ Evolution test, 94% of adipic acid, bis(2-ethylhexyl) ester had degraded after 35 days.

Adipic acid, bis(2-ethylhexyl) ester is readily biodegradable.

Adipic acid, diisooctyl ester (CAS No. 1330-86-5) (C22)

In a Shake Flask method using activated domestic sludge as the inoculum, 86.8% adipic acid, diisooctyl ester had degraded after 28 days.

Adipic acid, diisooctyl ester is readily biodegradable.

Adipic acid, diisononyl ester (CAS No. 33703-08-1) (C24)

In a Manometric Respirometry test using domestic activated sludge as the inoculum, 73% of adipic acid, diisononyl ester had degraded after 28 days.

Adipic acid, diisononyl ester is readily biodegradable.

Adipic acid, diisodecyl ester (CAS No. 27178-16-1) (C26)

In a Manometric Respirometry test using domestic activated sludge as the inoculum, 76.5% of adipic acid, diisodecyl ester had degraded after 28 days.

Adipic acid, diisodecyl ester is readily biodegradable.

Adipic acid, ditridecyl ester (CAS No. 16958-92-2) (C32)

In two Shake Flask methods using unacclimated activated domestic sludge as inoculum, 57 and 60% adipic acid, ditridecyl ester had degraded after 28 days.

Adipic acid, ditridecyl ester is readily biodegradable.

Azelaic acid, bis(2-ethylhexyl)ester (CAS No. 103-24-2) (C25)

In a Shake Flask method using activated sludge from a municipal sewage treatment plant as inoculum, 81% of azelaic acid, bis(2-ethylhexyl)ester had degraded after 28 days.

Azelaic acid, bis(2-ethylhexyl)ester is readily biodegradable.

Sebacic acid, bis(2-ethylhexyl)ester (CAS No. 122-62-3) (C26)

In a Manometric Respirometry method using activated sludge from a municipal sewage treatment plant as inoculum, 65% of sebacic acid, bis(2-ethylhexyl)ester had degraded after 28 days.

Sebacic acid, bis(2-ethylhexyl)ester is readily biodegradable.

Conclusion: The log K_{ow} values for three category members (adipic acid, diisopropyl ester; sebacic acid, dimethyl ester and sebacic acid, bis(2-ethylhexyl)ester) indicate that their potential to bioaccumulate is expected to be low. The log K_{ow} values for the remaining category members are high. However, their low water solubility (10^{-4} to 10^{-9} mg/L) suggests the potential of these chemicals to bioaccumulate is expected to be low. The diesters category members are readily biodegradable, indicating that they are not expected to persist in the environment

Table 1. Summary of Physical-chemical Properties and Environmental Fate Data¹

Endpoints	Maleic acid, bis(1,3-dimethylbutyl) ester (C16) (105-52-2)	Maleic acid, bis(2-ethylhexyl) ester (C20) (142-16-5)	Adipic acid, diisopropyl ester (C12) (6938-94-9)	Sebacic acid, dimethyl ester (C12) (106-79-6)	Adipic acid, diisooctyl ester (C22) (1330-86-5)	Adipic acid, bis (1-methyl heptyl) ester (C22) (108-63-4)	Adipic acid, diisononyl ester (C24) (33703-08-1)	Azelaic acid, bis(2-ethylhexyl) ester (C25) (103-24-2)	Adipic acid, diisodecyl ester (C26) (27178-16-1)	Sebacic acid, bis (2-ethylhexyl) ester (C26) (122-62-3)	Azelaic acid, diisodecyl ester (C29) (28472-97-1)	Adipic acid, dodecyl ester (C32) (16958-92-2)
Melting Point (°C)	-28 (e)	-60 (m)	-1 (m)	38 (m)	-70 (m)	–	-60 (m)	-78 (m)	-71 (m)	-48 (m)	–	–
Boiling Point (°C)	292 (e)	164 (m)	120 (m)	175 (m)	205 - 220 (m)	175 (m)	233 (m)	237 (m)	239 - 246 (m)	212 & 256(m)	460 (e)	509 (e)
Vapor Pressure (hPa)	–	–	–	–	< 0.16 at 150°C (m)	–	1.2 at 200°C (m)	–	1.7 × 10 ⁻³ at 20°C (m)	–	–	–
Log K _{ow}	5.8 (e)	7.9 (e)	3.2 (e)	3.4 (e)	8.12 (e)	8.12 (e)	9.24 (e)	9.6 (e)	10.1 (e)	3.74 (m) 10.1 (e)	11.6 (e)	13.17 (e)
Water Solubility (mg/L)	–	0.00117 (e)	–	120 (m)	5.45 × 10 ⁻⁴ (e)	–	2.2 × 10 ⁻⁴ (m)	1.65 × 10 ⁻⁵ (e)	4.4 × 10 ⁻⁵ (m)	1.5 × 10 ⁻⁷ (e)	1.54 × 10 ⁻⁷ (e)	3.43 × 10 ⁻⁹ (e)
Direct Photodegradation	–	–	–	–	–	–	–	–	–	–	–	–
Indirect Photodegradation (t _{1/2})(days)	0.23 (e)	0.19 (e)	1.03 (e)	1.1 (e)	0.45 (e)	0.42 (e)	0.40 (e)	0.36 (e)	0.36 (e)	0.35 (e)	0.32 (e)	0.28 (e)
Stability in Water (Hydrolysis)(t _{1/2})(yrs)	12.2 (e)	0.52 (e)	2.33 (e)	3.6 (e)	2.07 (e)	2.33 (e)	4.64 (e)	3.22 (e)	2.07 (e)	7.1 (e)	2.1 (e)	4.64 (e)
Fugacity (Level III Model)												
Air (%)	0.9	1.1	2.7	2.5	0.3	1.2	0.6	0.6	0.2	0.5	0.2	0.4
Water (%)	16.4	11.2	38.0	36.7	3.5	11.1	7.2	7.2	3.4	7.2	3.4	7.0
Soil (%)	37.3	29.6	58.8	60.1	27.3	29.5	28.8	28.4	28.5	28.7	29.8	61.7
Sediment (%)	45.3	58.1	0.6	0.7	69.0	58.2	63.4	63.8	67.9	63.6	66.6	61.7
Biodegradation at 28 days (%)	67 – 94 ² Readily biodegradable	67 – 94 ² Readily biodegradable	No data 87 (RA) Readily biodegradable	No data 87 (RA) Readily biodegradable	87 (m) Readily biodegradable	No data 87 (RA) Readily biodegradable	73 (m) Readily biodegradable	81 (m) Readily biodegradable	76 (m) Readily biodegradable	65 (m)	No data 57-65 (RA) Not readily biodegradable	57-60 (m)

(RA) = Read Across; (m) = measured data; (e) = estimated data; – indicates endpoint was not addressed for this chemical. ¹Compounds arranged according to carbon number except for the maleic acid ester compounds, which are expected to exhibit higher toxicity; ²Data for supporting chemical, adipic acid, bis(2-ethylhexyl) ester (CAS No. 103-23-1).

2. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 2. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Toxicity to Fish

Maleic acid, dibutyl ester (CAS No. 105-76-0; supporting chemical) (C12)

Rainbow trout (*Oncorhynchus mykiss*) were exposed to maleic acid, dibutyl ester at 0, 1.0, 1.7, 3.0, 5.2 and 9.0 mg/L for 96 hours. At 48 hours, the concentration of the test substance had decreased to 33% of nominal concentration; therefore, the concentrations were readjusted to 100%. By 96 hours, the concentrations had again decreased to 35% of nominal. Behavioral changes (incoordination of movements during swimming) and darker color were seen at the two highest concentrations five hours after exposure and later at all concentrations. Mortality was seen at all concentrations at 96 hours. Although the OECD SIDS documents reported the nominal LC₅₀ value, the robust summary also reported an LC₅₀ of 0.6 mg/L, based on the geometric mean of the nominal and measured concentrations.

96-h LC₅₀ = 0.6 mg/L

Dibutyl adipate (CAS No. 105-99-7; supporting chemical) (C14)

Medaka (*Oryzias latipes*) were exposed to dibutyl adipate at five nominal concentrations from 1.0 – 10 mg/L under semi-static conditions for 96 hours. DMSO:HC 40 (9:1) (dimethylsulfoxide:hydrogenated castor oil 40) was used as a vehicle. No additional information was provided.

96-h LC₅₀ = 3.7 mg/L

Adipic acid, diisononyl ester (CAS No. 33703-08-1) (C24)

Rainbow trout (*Oncorhynchus mykiss*) were exposed to adipic acid, diisononyl ester as a water accommodated fraction (WAF) at a loading rate of 100 mg/L (measured concentration of 2.6 mg/L) under semi-static conditions for 96 hours. No effects were noted at the WAF loading rate. EPA does not consider the loading rate as the no effect concentration when the concentration exceeds the water solubility of the substance. Assuming exposure concentration in the WAF is the water solubility limit (saturation) which for adipic acid, diisononyl ester, the no effect concentration would be approximately 2.2×10^{-4} mg/L.

No effects at saturation

Sebacic acid, bis(2-ethylhexyl)ester (CAS No. 122-62-3)(C26)

Golden orfe (*Leuciscus idus*) were exposed to sebacic acid, bis(2-ethylhexyl)ester as a WAF at a loading rate of 1,000 mg/L under semi-static conditions for 96 hours. No analytical measurements were made on the WAFs. No mortality was seen. EPA does not consider the loading rate as the no effect concentration when the concentration exceeds the water solubility of the substance. Assuming exposure concentration in the WAF is the water solubility limit (saturation), which for sebacic acid, bis(2-ethylhexyl)ester, the no effect concentration would be approximately 1.5×10^{-7} mg/L.

No effects at saturation

Adipic acid, ditridecyl ester (CAS No. 16958-92-2) (C32)

Sheepshead minnow (*Cyprinodon variegates*, 20/concentration) were exposed to adipic acid, ditridecyl ester at nominal concentrations of 0, 500, 1000, 2500 and 5000 mg/L under static conditions for 96 hours. No analytical measurements were made. Five fish died at 2500 mg/L and 20 fish died at 5000 mg/L (possibly due to physical toxicity). The results of this test are difficult to interpret because the substance was tested considerably above its water solubility limit (3.4×10^{-9} mg/L).

LC₅₀ at or below water solubility limit

Acute Toxicity to Aquatic Invertebrates

Maleic acid, dibutyl ester (CAS No. 105-76-0; supporting chemical) (C12)

Daphnia magna (20/concentration) were exposed to maleic acid, dibutyl ester at 0, 10, 18, 32, 56 and 100 mg/L under static conditions for 48 hours. Measured concentrations were 95% and 91% of the initial concentrations at 24 and 48 hours, respectively.

48-h EC₅₀ = 21 mg/L

Dibutyl adipate (CAS No. 105-99-7; supporting chemical) (C14)

Daphnia magna were exposed to dibutyl adipate at five nominal concentrations from 5.6 – 56 mg/L for 24 hours. DMSO:HC 40 (9:1) was used as a vehicle. No additional information was provided.

24-h EC₅₀ = 17 mg/L

Sebacic acid, bis(2-ethylhexyl)ester (CAS No. 122-62-3)(C26)

Daphnia magna were exposed to sebacic acid, bis(2-ethylhexyl)ester as a WAF using a loading rate of 1000 mg/L under static conditions for 48 hours. No immobilization was observed. No analytical measurements were made on the WAFs. EPA does not consider the loading rate as the no effect concentration when the concentration exceeds the water solubility of the substance. Assuming exposure concentration in the WAF is the water solubility limit (saturation) which for sebacic acid, bis(2-ethylhexyl)ester, the no effect concentration would be approximately 1.5×10^{-7} mg/L.

No effects at saturation

Toxicity to Aquatic Plants

Maleic acid, dibutyl ester (CAS No. 105-76-0; supporting chemical) (C12)

Green algae (*Scenedesmus subspicatus*) were exposed to maleic acid, dibutyl ester at nominal concentrations ranging from 0.4 – 12.8 mg/L under static condition for 72 hours. At the end of the test, measured concentrations decreased to 43.4% at lower concentrations. Because of the poor recovery at low concentrations, the only nominal concentrations were reported. Although 43% recovery of the test substance at lower concentrations recommends against use of nominal concentrations, this study was accepted in the OECD HPV Chemicals Program and published on the UNEP website.

72-h EC₅₀ = 6.2 mg/L

Dibutyl adipate (CAS No. 105-99-7; supporting chemical) (C14)

Green algae (*Pseudokirchneriella supcapitata*) were exposed to dibutyl adipate at 5 nominal concentrations from 1 – 5 mg/L for 72 hours. No additional information was provided.

72-h EC₅₀ (biomass) = 2.8 mg/L

Sebacic acid, bis(2-ethylhexyl)ester (CAS No. 122-62-3) (C26)

Green algae (*Scenedesmus subspicatus*) were exposed to sebacic acid, bis(2-ethylhexyl)ester as WAF a loading rate of 1000 mg/L for 72 hours. Although percent inhibition (according to biomass/AUC) was 1%, the sponsor concluded that there was no inhibition of algae growth. No analytical measurements were made on the WAFs. EPA does not consider the loading rate as the no effect concentration when the concentration exceeds the water solubility of the substance. Assuming exposure concentration in the WAF is the water solubility limit (saturation) which for sebacic acid, bis(2-ethylhexyl)ester, the no effect concentration would be approximately 1.5×10^{-7} mg/L.

No effects at saturation

Chronic Toxicity to Aquatic Organisms

In comments on the revised test plan (May 2006), EPA stated that the submitter needed to provide measured data on a low- (C12) and mid- (C14-16) molecular weight category member. In-depth review of the category chemicals and the supporting chemicals revealed that the use of maleic acid, dibutyl ester (C12; CAS No. 105-76-0) as supporting for the two maleic acid category members is appropriate because they are all predicted by ECOSAR to be toxic via acrylate-type toxicity and the toxicity of the C16 and C20 maleates will likely be limited by solubility. The use of dibutyl adipate (C14; CAS No. 105-99-7) is a reasonable analog to support the other C12 category members (adipic acid, diisopropyl ester, CAS No. 6938-94-9 and sebacic acid, dimethyl ester, CAS No. 106-79-6) because they are all predicted by ECOSAR to be toxic via ester-type toxicity and the analog is expected to be the most toxic of the

three. Considering this information and that all category members are expected to be readily biodegradable, chronic toxicity testing is not deemed necessary at this time.

Conclusion: The aquatic toxicity data for category members with low solubility were generated using Water Accommodated Fractions or dispersion by propeller techniques. The evaluation of available toxicity data indicates that the potential acute hazard to fish is high for maleic acid esters and moderate for C12 esters and low for esters above C20 (due to low water solubility). The potential acute hazard of the diester category members to aquatic invertebrates is low and to aquatic plants is moderate in the C12 to C20 range and low above C20.

Table 2. Summary of Environmental Effects – Aquatic Toxicity Data¹

Endpoints	Maleic acid, bis(1,3-di methyl butyl) ester (C16) (105-52-2) ²	Maleic acid, bis(2-ethylhexyl) ester (C20) (142-16-5) ²	Adipic acid, diisopropyl ester (C12) (6938-94-9) ³	Sebacic acid, dimethyl ester (C12) (106-79-6) ³	Adipic acid, bis (1-methyl heptyl) ester (C22) (108-63-4)	Adipic acid, diisooctyl ester (C22) (1330-86-5)	Adipic acid, diisononyl ester (C24) (33703-08-1)	Azelaic acid, bis(2-ethylhexyl) ester (C25) (103-24-2)	Adipic acid, diisodecyl ester (C26) (27178-16-1)	Sebacic acid, bis(2-ethylhexyl) ester (C26) (122-62-3)	Azelaic acid, diisodecyl ester (C29) (28472-97-1)	Adipic acid, dodecyl ester (C32) (16958-92-2)
Fish 96-h LC ₅₀ (mg/L)	0.6	0.6	3.7	3.7	No data NES (RA)	No data NES (RA)	NES⁴ (~2.2 x 10 ⁻⁴)	No data NES (RA)	No data NES (RA)	NES⁴ (~1.5 x 10 ⁻⁷)	No data NES (RA)	NES⁴ (~3.4 x 10 ⁻⁹)
Aquatic Invertebrates 48-h EC ₅₀ (mg/L)	21	21	17	17	No data NES (RA)	No data NES (RA)	No data NES (RA)	No data NES (RA)	No data NES (RA)	NES⁴ (~1.5 x 10 ⁻⁷)	No data NES (RA)	No data NES (RA)
Aquatic Plants 72-h EC ₅₀ (mg/L)	6.2	6.2	2.8	2.8	No data NES (RA)	No data NES (RA)	No data NES (RA)	No data NES (RA)	No data NES (RA)	NES⁴ (~1.5 x 10 ⁻⁷)	No data NES (RA)	No data NES (RA)

Measured data (bold); (RA) = Read Across; ¹Compounds arranged according to carbon number except for the maleic acid compounds, which are expected to exhibit higher toxicity; ²Data for supporting chemical: maleic acid, dibutyl ester (CAS No. 105-76-0); ³Data for supporting chemical: dibutyl adipate (CAS No. 105-99-7); ⁴NES = No effects at saturation (water solubility limit).

3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 3. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Oral Toxicity

For the category members, the LD₅₀ values range from > 2000 (Azelaic acid, diisodecyl ester, CAS No. 28472-97-1) to > 64,000 mg/kg-bw (Adipic acid, bis(1-methylheptyl) ester, CAS No. 108-63-4). Individual LD₅₀ values are provided in Table 3.

Acute Dermal Toxicity

Adipic acid, diisononyl ester (CAS No. 33703-08-1) (C24)

Rabbits (4/dose, strain not stated) were administered undiluted adipic acid, diisononyl ester dermally at 50, 200, 794 and 3,160 mg/kg-bw to clipped, abraded abdominal skin for 24 hours and observed for 14 days. No mortality was seen. Slight irritation (slight edema and slight to moderate erythema) was seen at the application site.

LD₅₀ > 3160 mg/kg-bw

Adipic acid, ditridecyl ester (CAS No. 16958-92-2) (C32)

New Zealand white rabbits (10 animals, sex not stated) were administered undiluted adipic acid, ditridecyl ester dermally at 5000 mg/kg-bw to abraded skin under semi-occlusive conditions for 24 hours and observed for 14 days. No mortality was seen. Clinical signs consisted of edema, erythema, bloated abdomen, diarrhea, emaciation and lethargy.

LD₅₀ > 5000 mg/kg-bw

Repeated-Dose Toxicity

Maleic acid, dibutyl ester (CAS No. 105-76-0; supporting chemical) (C12)

In a combined repeated-dose/reproductive/developmental toxicity screening study, Wistar rats (12/sex/dose) were administered maleic acid, dibutyl ester in arachis oil via gavage at 0, 30, 95 and 300 mg/kg-bw/day during the pre-mating (2 weeks) and mating periods (10 days). Females were then allowed to litter normally and sacrificed with the offspring on day 4 of lactation. Dosing of both sexes continued until the end of the study. Parental toxicity was determined by evaluation of body weight and food consumption changes, necropsy and organ weight analyses, and histopathology of selected tissues. Males were also evaluated for changes in hematology and clinical chemistry. At 300 mg/kg-bw/day, the rats of both sexes had unspecific signs of 'reduced well-being' and increased absolute and/or relative liver and kidney weights. Also at this dose, males showed a higher incidence of dermal hyperemia, lower body weights, higher albumin, higher total protein, higher bilirubin and decreased mean corpuscular hemoglobin and renal tubular lesions (dilation, epithelial basophilia, and epithelial proliferation and karyomegaly). One high-dose female had heart, kidney and liver lesions and lost its litter due to lack of nursing.

LOAEL = 300 mg/kg-bw/day (based on multiple effects with the kidney and liver as the main target organs)

NOAEL = 95 mg/kg-bw/day

Adipic acid, diisononyl ester (CAS No. 33703-08-1) (C24)

(1) Rats (10/sex/dose, strain not indicated) were administered adipic acid, diisononyl ester in the diet at 0, 50, 150 or 500 mg/kg-bw/day for 13 weeks. Clinical observations, body weights and food consumption were recorded weekly. Hematology, blood chemistry and urinalysis were evaluated at weeks 4 and 13. A complete necropsy was performed after 13 weeks. Tissues were examined microscopically. A statistically significant (p-level not provided) increase in the kidney weight relative to body weight was seen at 500 mg/kg-bw/day; however, there was no increase in the absolute kidney weights and no histopathological changes were observed.

LOAEL = 500 mg/kg-bw/day (based on increased relative kidney weights)

NOAEL = 150 mg/kg-bw/day

(2) Beagle dogs (4/sex/dose) were administered adipic acid, diisononyl ester in the diet at 0, 0.3, 1.0 and 3.0 percent (approximately 82.2, 274 and 822 mg/kg-bw/day) for 13 weeks. The high dose was adjusted to 6.0 percent (1644 mg/kg-bw/day) during weeks 9 – 13. Animals were observed daily and body weights and food consumption determined weekly. Hematology, blood chemistry and urinalysis were performed at the start of the study and at weeks 4 and 13, with a complete necropsy after 13 weeks. Organ weights were taken and tissues/organs were examined microscopically. Decreased food consumption and body weight, increased liver weight and enzyme activities, discoloration of liver and kidney and histopathological changes in the liver and kidneys were seen at the high dose.

LOAEL ~ 822/1644 mg/kg-bw/day (based on decreased body weights and food consumption increased liver weight and enzyme levels and histopathological changes in the liver and kidneys)

NOAEL ~ 274 mg/kg-bw/day

Sebacic acid, bis(2-ethylhexyl) ester (CAS No. 122-62-3) (C26)

Fischer 344 rats (males; 4 treated and 13 control) were administered sebacic acid, bis(2-ethylhexyl) ester in the diet at 2% (~1000 mg/kg-bw/day) for 3 weeks. The study focused on measuring peroxisome proliferation. Liver size and weight were measured and sections of liver were examined for peroxisome proliferation. Cholesterol and triglycerides levels and carnitine acetyltransferase and catalase activities in serum were measured. Results showed that hepatic peroxisome proliferation had occurred and liver weight and hepatic peroxisomal enzymes were increased. Decreases in triglycerides were also seen.

LOAEL = 1,000 mg/kg-bw/day (based on peroxisome proliferation and related effects)

NOAEL = Not established

Adipic acid, ditiidecyl ester (CAS No. 16958-92-2) (C32)

Sprague-Dawley rats (10/sex/dose) were administered undiluted adipic acid, ditiidecyl ester dermally at 0, 800 or 2000 mg/kg-bw for 5 days/week for 13 weeks. Mortality, clinical observations, body weights, hematology, serum chemistry, necropsy and gross and microscopic evaluations were conducted. Sperm morphology was evaluated. Dermal absorption was determined to be 10% as measured using ¹⁴C-radiolabeled compound in a separate group of rats. The study authors concluded that test substance did not cause systemic toxicity. No treatment-related effects were seen on sperm morphology, uterus or epididymides weights, urinalysis or macroscopic evaluation. Increased liver and kidney weights were considered as adaptive responses and not a reflection of toxicity. Histopathological examination did not reveal treatment-related changes in the kidneys or liver. Slight erythema and flaking of the skin were observed at the application sites. The study authors concluded that NOAEL and LOAEL could not be estimated from this study. No other method details were available.

Reproductive Toxicity

Maleic acid, dibutyl ester (CAS No. 105-76-0; supporting chemical) (C12)

In the combined repeated-dose/reproductive/developmental toxicity screening study in Wistar rats described previously, fertility parameters, gestation parameters and reproductive organ toxicity were evaluated. A single female exhibited heart, kidney and liver lesions at the high dose. The number of dead pups was statistically significantly higher (p level not given) in the mid- and high-dose groups. One female in the high dose group (that also showed lesions in the heart, liver, and kidney) lost its entire litter due to lack of nursing behavior; excluding this loss, one additional pup died at the highest dose.

LOAEL (reproductive toxicity) = 95 mg/kg-bw/day (based on pup deaths)

NOAEL (reproductive toxicity) = 30 mg/kg-bw/day

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3; supporting chemical) (C22)

In the 90-day study in Sprague-Dawley rats described previously, gonad weights, examination of testes, seminal vesicles, ovary, prostate, and uterus was conducted at the high dose and histopathological examination of the testes and ovaries was conducted at all dose levels. No adverse effects on reproductive organs were observed.

Adipic acid, ditiidecyl ester (CAS No. 16958-92-2)(C32)

In the 13-week repeated-dose dermal toxicity study in Sprague-Dawley rats described previously, approximately 10% of the compound was absorbed through the skin. No treatment-related effects were seen in sperm morphology, uterus or epididymides weights or histopathology. No additional details were provided about which tissues were examined.

Developmental Toxicity

Maleic acid, dibutyl ester (CAS No. 105-76-0; supporting chemical) (C12)

In the combined repeated-dose and reproductive/developmental toxicity screening study in Wistar rats described previously, measurements in the offspring included clinical signs, litter weight, number, sex, viability and necropsy. At 300 mg/kg-bw/day, in the parental generation, rats of both sexes had unspecific signs of ‘reduced well-being’ and increased absolute and/or relative liver and kidney weights. A single female also exhibited heart, kidney and liver lesions at this dose. The number of dead pups was statistically significantly higher (p-level not provided) in the mid and high doses. One female at the high dose (that also showed lesions in the heart, liver, and kidney) lost its entire litter due to lack of nursing behavior; excluding this loss, one additional pup died at the highest dose.

LOAEL (maternal toxicity) = 300 mg/kg-bw/day (based on increased kidney and liver weights and general decreased health status)

NOAEL (maternal toxicity) = 95 mg/kg-bw/day

LOAEL (developmental toxicity) = 95 mg/kg-bw/day (based on increased pup deaths)

NOAEL (developmental toxicity) = 30 mg/kg-bw/day

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3; supporting chemical)(C20)

Sprague-Dawley rats were administered adipic acid, di-C7-9 branched and linear alkyl ester at 0, 1000, 4000 and 7000 mg/kg-bw/day during gestation days (GD) 6 – 19. Clinical signs and body weights were recorded on GD 0, 6, 15 and 20. On GD 20, the dams were sacrificed and uteri were removed and weighed. Fetuses were weighed and examined for external, skeletal and soft tissue defects. Sex ratios of fetuses were determined and numbers of implantations, live fetuses, resorptions and corpora lutea were evaluated. The maternal body weights were significantly decreased ($p < 0.01$) at 7000 mg/kg-bw/day. Although fetal body weights were slightly lower than the control at 7000 mg/kg-bw/day, the difference was not statistically significant. The incidence of rudimentary structures (unilateral/bilateral and adjacent to the last thoracic or first lumbar vertebral transverse process) was higher in the high-dose fetuses compared with other doses. There was no indication as to whether this effect was statistically significant.

LOAEL (maternal toxicity) = 7,000 mg/kg-bw/day (based on decreased maternal weight)

NOAEL (maternal toxicity) = 4,000 mg/kg-bw/day

LOAEL (developmental toxicity) = 7,000 mg/kg-bw/day (based on skeletal anomalies and decreased fetal weight)

NOAEL (developmental toxicity) = 4,000 mg/kg-bw/day

Adipic acid, ditridecyl ester (16958-92-2)(C32)

(1) Mated females (15/dose) were administered undiluted adipic acid, ditridecyl ester dermally at 0, 800 or 2,000 mg/kg-bw/day from gestation day 0 – 19. Dams were examined daily for mortality and clinical signs of toxicity. Body weights and food consumption were measured throughout gestation and all females were sacrificed and examined macroscopically on day 20. Uteri were weighed, examined for number of corpora lutea, number of implantation sites, and number/location of fetuses and resorptions. Number, sex, weight, length, and defects (external, visceral, and skeletal) were recorded. Blood chemistry was evaluated at gestation day 20. No other study details were available. In fetuses, visceral anomalies (increased incidence of levocardia) were seen at 2,000 mg/kg-bw/day. Levocardia is a reversal of the placement of abdominal and thoracic organs other than the heart and almost always indicates presence of congenital heart disease

NOAEL (maternal toxicity) = 2,000 mg/kg-bw/day (based on no effects at the highest dose tested)

LOAEL (developmental toxicity) = 2,000 mg/kg-bw/day (based on increased incidence of levocardia)

NOAEL (developmental toxicity) = 800 mg/kg-bw/day

(2) Pregnant female rats (25/dose) were administered 0 or 2,000 mg/kg-bw of undiluted adipic acid, ditridecyl ester dermally from day 0 – 19 of gestation. Dams were examined daily for mortality and clinical signs of toxicity. Body weights and food consumption were measured throughout gestation and all females were sacrificed and examined macroscopically on day 20. Uteri were weighed, examined for number of corpora lutea, number of implantation sites, and number/location of fetuses and resorptions. Number, sex, weight, and defects (external, visceral, and skeletal) were recorded. No maternal or developmental effects were observed. No other study details were available.

NOAEL (maternal/developmental toxicity) = 2,000 mg/kg-bw/day (based on no effects at the only dose tested)

Genetic Toxicity – Gene Mutations

In vitro

Maleic acid, dibutyl ester (CAS No. 105-76-0; supporting chemical) (C12)

Salmonella typhimurium strains TA97a, TA98, TA100 and TA1535A were exposed to maleic acid, dibutyl ester at concentrations up to 500 µg/plate with and without metabolic activation. Positive and negative controls were used and yielded the expected results. Toxicity was observed at 500 µg/plate. The test compound did not show increased mutations in any strain or at any concentration.

Maleic acid, dibutyl ester was not mutagenic in this assay.

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3; supporting chemical) (C22)

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to adipic acid, di-C7-9 branched and linear alkyl ester up to 10 µl/plate (with 25 µL/plate as a spot test) with and without metabolic activation. Positive controls were used, with ethanol as the solvent control. No mutagenicity was observed up to 25 µL/plate. Decreased solubility was observed at 3 and 10 µL in the plate incorporation method.

Adipic acid, di-C7-9 branched and linear alkyl ester was not mutagenic in this assay.

(2) Mouse lymphoma L5178Y TK+/- cells were exposed to adipic acid, di-C7-9 branched and linear alkyl ester up to 3000 µg/mL without metabolic activation and up to 4000 µg/mL with metabolic activation. Cytotoxicity occurred at 500 µg/mL and higher without activation and at 4000 µg/mL with activation. None of the concentrations yielded higher mutation frequencies than the solvent controls.

Adipic acid, di-C7-9 branched and linear alkyl ester was not mutagenic in this assay.

Adipic acid, diisononyl ester (33703-08-1) (C24)

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to adipic acid, diisononyl ester at concentrations up to 1,000 µg/plate with and without metabolic activation. Revertant colonies were scored at 72 hours. The positive and negative controls gave expected responses. There was no increase in revertant colonies with or without metabolic activation.

Adipic acid, diisononyl ester was not mutagenic in this assay.

(2) Mouse lymphoma L5178Y cells were exposed to adipic acid, diisononyl ester at 5.6 – 100 µL/mL with metabolic activation and 7.5 – 100 µL/mL without metabolic activation. Mutant colonies per total colony counts were determined using triplicate plates. The positive and negative controls gave expected responses. The compound was negative for mutagenicity both with and without metabolic activation.

Adipic acid, diisononyl ester was not mutagenic in this assay.

Sebacic acid, bis(2-ethylhexyl)ester (CAS No. 122-62-3)(C26)

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to sebacic acid, bis(2-ethylhexyl) ester at concentrations up to 10,000 µg/plate, with and without metabolic activation. The positive and negative controls gave expected responses. Precipitate was observed at 3,333 and 10,000 µg/plate with TA1535, but no toxicity was observed. The compound was negative for mutagenicity both with and without metabolic activation.

Sebacic acid, bis(2-ethylhexyl) ester was not mutagenic in this assay.

Adipic acid, ditridecyl ester (16958-92-2)(C32)

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to adipic acid, ditridecyl ester at concentrations up to 10 µL/plate with and without metabolic activation. The positive and negative controls gave expected responses. The compound was negative for mutagenicity both with and without metabolic activation.

Adipic acid, ditridecyl ester was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo

Maleic acid, dibutyl ester (CAS No. 105-76-0; supporting chemical) (C12)

Three groups of NMRI mice (5/sex) were administered maleic acid, dibutyl ester via gavage at 2,000 mg/kg-bw/day and were sacrificed at 24, 48 and 72 hours and micronucleated erythrocytes were evaluated in the bone marrow. The ratio of polychromatic erythrocytes (PCEs) to total erythrocytes was not changed by the treatment. Slight increases in micronucleated erythrocytes were observed but were not statistically significant; results at 24 and 48 hours were slightly higher than historical controls. Based on these results, the authors indicated the results as negative, but also stated that a slight clastogenic effect could not be excluded.

Maleic acid, dibutyl ester did not induce chromosomal aberrations in this assay.

Adipic acid, ditridecyl ester (16958-92-2) (C32)

Male and female Sprague-Dawley rats were administered undiluted adipic acid, ditridecyl ester dermally at 0, 800 and 2000 mg/kg-bw to clipped dorsal skin for 5 days/week for 13 weeks. Normochromatic and polychromatic erythrocytes (NCEs and PCEs) were evaluated for cytotoxicity and micronuclei formation using bone marrow and peripheral blood cells. The ratio of PCE to NCE and numbers of micronucleated PCEs per 1000 PCEs and micronucleated NCEs per 1000 NCEs were determined. No positive controls were used. No animals died and no cytotoxicity of peripheral red blood cells was observed. No increases in micronucleated NCEs/PCEs and no other effects were observed.

Adipic acid, ditridecyl ester did not induce chromosomal aberrations in this assay.

Additional Information

Skin Sensitization

Maleic acid, dibutyl ester (CAS No. 105-76-0; supporting chemical) (C12)

Albino guinea pigs were administered maleic acid, dibutyl ester in a Magnusson-Kligman guinea pig maximization test. Six injections were given to 10 control (corn oil) and 20 test animals (10% test substance in corn oil and Freund's adjuvant) at different locations. After one and two weeks intervals, 100% of the test substance was administered topically for 24 hours. Eighty percent of the test animals showed erythema at 24 hours after the 2-week challenge versus no response in control animals. The study authors concluded that the test substance exhibited a strong sensitizing effect.

Maleic acid, dibutyl ester was a strong sensitizer in this assay.

Conclusion: Acute oral toxicity for the diesters category members is low. Acute dermal toxicity studies for two category members also indicate low toxicity. Maleic acid, dibutyl ester is a strong sensitizer. Repeated exposures to several category members via the dietary and dermal routes resulted in effects including increased relative kidney weights, histopathological changes in the kidney and liver, changes in enzyme activities, peroxisome proliferation, decreased triglycerides, renal tubular lesions, and heart, kidney and liver lesions. In rats, reproductive toxicity was evident for the supporting chemical, maleic acid, dibutyl ester, which showed pup deaths and a lack of nursing behavior. Evaluation of gonad showed no effects in the repeated-dose toxicity studies with adipic acid, ditridecylester and adipic acid, di-C7-9 branched and linear alkyl ester. Developmental effects included increased incidence of levocardia (adipic acid ditridecyl ester) and decreased fetal body weight and skeletal anomalies (presence of rudimentary structures) (adipic acid, di-C7-9 branched and linear alkyl ester) at high doses. Increased pup deaths were seen in a study with maleic acid, dibutyl ester. The tested category members or supporting chemicals did not induce gene mutation or chromosomal aberrations.

The potential hazard of the diesters category members is moderate based on concern for reproductive/developmental toxicity.

Table 3. Summary of Human Health Data

Endpoints	Maleic acid, bis(1,3di-methylbutyl) ester (C16) (105-52-2)	Maleic acid, bis(2ethylhexyl) ester (C20) (142-16-5)	Adipic acid, diisopropyl ester (C12) (6938-94-9)	Sebacic acid, dimethyl ester (C12) (106-79-6)	Adipic acid, diisooctyl ester (C22) (1330-86-5)	Adipic acid, bis(1-methyl heptyl)ester (C22) (108-63-4)	Adipic acid, diisononyl ester (C24) (33703-08-1)	Azelaic acid, bis(2-ethylhexyl) Ester (C25) (103-24-2)	Adipic acid, diisodecyl ester (C26) (27178-16-1)	Sebacic acid, bis(2-ethylhexyl) ester (C26) (122-62-3)	Azelaic acid, diisodecyl ester (C29) (28472-97-1)	Adipic acid, ditiidecyl ester (C32) (16958-92-2)
Acute Oral Toxicity LD ₅₀ (mg/kg-bw, unless noted)	7460	> 9440 mg/kg-bw ⁵	> 3110	No data > 3,110 (RA)	> 4,650 (ml/kg-bw)	> 64,000	> 10,000	7980 ⁵	20,500	> 12,800	> 2000	> 16,000
Acute Dermal Toxicity LD ₅₀ (mg/kg-bw)	—*	—*	—*	—*	—*	—*	> 3160	—*	—*	—*	—*	5000
Repeated-dose Toxicity (mg/kg-bw/day)	No data	No data	No data	No data	No data	No data	(Rat) 150 500	No data (Rat) 150 500	No data (Rat) 150 500	NE 1000	No data NE 1000	No data NE 1000
NOAEL	95	95	95	95	150	150	(Dog) 274	150	150	NE	1000	NE
LOAEL	300 (RA) ²	300 (RA) ²	300 (RA) ²	300 (RA) ²	500 (RA)	500 (RA)	822/1,644	500 (RA)	500 (RA)	1000 (RA)	1000 (RA)	1000 (RA)
Reproductive/Developmental Toxicity (mg/kg-bw/day)	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Maternal NOAEL	95	95	95	95	4000	4000	2,000 (hdt)	2,000 (hdt)	2,000 (hdt)	2,000 (hdt)	2,000 (hdt)	2,000 (hdt)
Maternal LOAEL	300	300	300	300	7000	7000						
Developmental NOAEL	30	30	30	30	4000	4000	800	800	800	800	800	800
Developmental LOAEL	95 (RA) ²	95 (RA) ²	95 (RA) ^{2,3}	95 (RA) ^{2,3}	7000 (RA) ³	7000 (RA) ³	2000 (RA)	2000 (RA)	2000 (RA)	2000 (RA)	2000 (RA)	2000 (RA)
Genetic Toxicity – Gene Mutations <i>In vitro</i>	No data Negative (RA) ²	No data Negative (RA) ²	No data Negative (RA) ²	No data Negative (RA) ²	No data Negative (RA)	No data Negative (RA)	Negative	No data Negative (RA)	No data Negative (RA)	Negative	No data Negative (RA)	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	No data Negative (RA) ²	No data Negative (RA) ²	No data Negative (RA) ²	No data Negative (RA) ²	No data Negative (RA)	No data Negative (RA)	No data Negative (RA)	No data Negative (RA)	No data Negative (RA)	No data Negative (RA)	No data Negative (RA)	Negative
Additional Information – Sensitization	Positive (RA) ²	Positive (RA) ²	—*	—*	—*	—*	—*	—*	—*	—*	—*	—*

Measured data (bold); (RA) = Read Across; — indicates endpoint was not addressed for this chemical; * indicates endpoint not necessary for this chemical; hdt = highest dose tested²Supporting chemical: maleic acid, dibutyl ester (CAS No. 105-76-0);³ Supporting chemical: adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3).

4. Hazard Characterization

The log K_{ow} values for three category members (adipic acid, diisopropyl ester; sebacic acid, dimethyl ester and sebacic acid, bis(2-ethylhexyl)ester) indicate that their potential to bioaccumulate is expected to be low. The log K_{ow} values for the remaining category members are high. However, their low water solubility (10^{-4} to 10^{-9} mg/L) suggests the potential of these chemicals to bioaccumulate is expected to be low. The diesters category members are readily biodegradable, indicating that they are not expected to persist in the environment

The aquatic toxicity data for category members with low solubility were generated using Water Accommodated Fractions or dispersion by propeller techniques. The evaluation of available toxicity data indicates that the potential acute hazard to fish is high for maleic acid esters and moderate for C12 esters and low for esters above C20 (due to low water solubility). The potential acute hazard of the diester category members to aquatic invertebrates is low and to aquatic plants is moderate in the C12 to C20 range and low above C20.

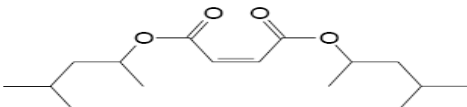
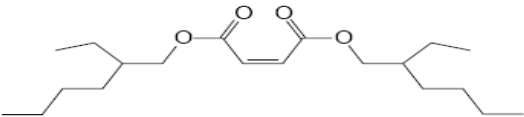
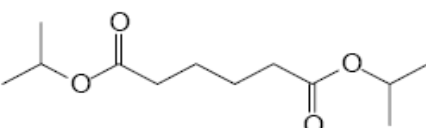
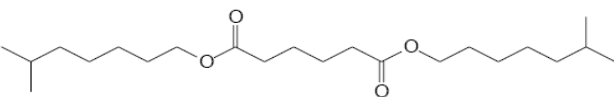
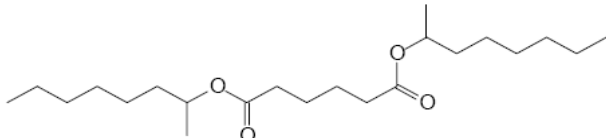
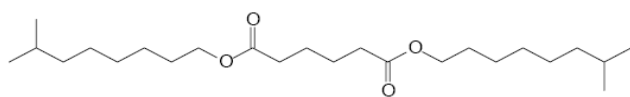
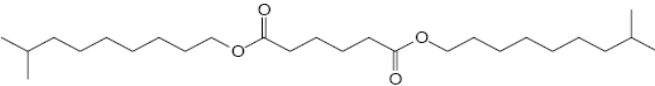
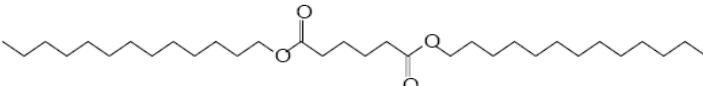
Acute oral toxicity for the diesters category members is low. Acute dermal toxicity studies for two category members also indicate low toxicity. Maleic acid, dibutyl ester is a strong sensitizer. Repeated exposures to several category members via the dietary and dermal routes resulted in effects including increased relative kidney weights, histopathological changes in the kidney and liver, changes in enzyme activities, peroxisome proliferation, decreased triglycerides, renal tubular lesions, and heart, kidney and liver lesions. In rats, reproductive toxicity was evident for the supporting chemical, maleic acid, dibutyl ester, which showed pup deaths and a lack of nursing behavior. Evaluation of gonad showed no effects in the repeated-dose toxicity studies with adipic acid, ditridecylester and adipic acid, di-C7-9 branched and linear alkyl ester. Developmental effects included increased incidence of levocardia (adipic acid ditridecyl ester) and decreased fetal body weight and skeletal anomalies (presence of rudimentary structures) (adipic acid, di-C7-9 branched and linear alkyl ester) at high doses. Increased pup deaths were seen in a study with maleic acid, dibutyl ester. The tested category members or supporting chemicals did not induce gene mutation or chromosomal aberrations.

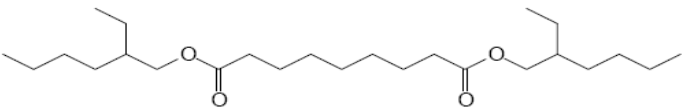
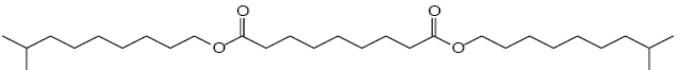
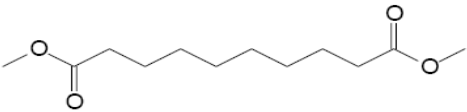
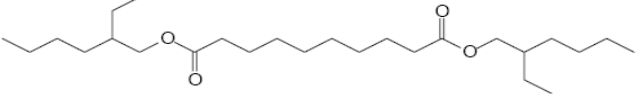
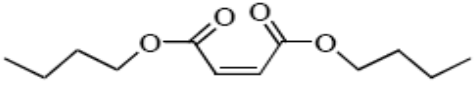
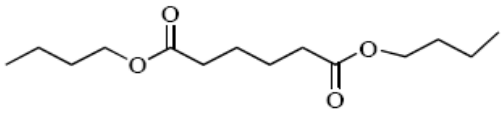
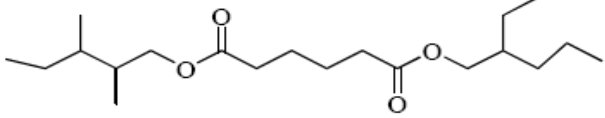
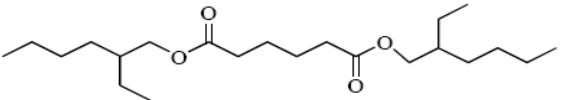
The potential hazard of the diesters category members is moderate based on concern for reproductive/developmental toxicity.

5. Data Gaps

No data gaps were identified under the HPV Challenge Program.

Appendix

Diesters Category		
CAS No.	Chemical Name	Structure
SPONSORED CHEMICALS		
105-52-2	Maleic, acid, bis(1,3-dimethylbutyl)ester	 <chem>CC(C)CC(C)OC(=O)/C=C/C(=O)OC(C)CC(C)C</chem> $C_{16}H_{28}O_4$
142-16-5	Maleic acid, bis(2-ethylhexyl) ester	 <chem>CCCCC(CC)COOC(=O)/C=C/C(=O)OCCCC(CC)C</chem> $C_{20}H_{36}O_4$
6938-94-9	Adipic acid, diisopropyl ester	 <chem>CC(C)OC(=O)CCCCC(=O)OC(C)C</chem> $C_{12}H_{22}O_4$
1330-86-5	Adipic acid, diisooctyl ester	 <chem>CC(C)CCCCCOOC(=O)CCCCC(=O)OCCCC(C)C</chem> $C_{22}H_{42}O_4$
108-63-4	Adipic acid, bis(1-methylheptyl) ester	 <chem>CCCCC(C)COOC(=O)CCCCC(=O)OC(C)CCCC</chem> $C_{22}H_{42}O_4$
33703-08-1	Adipic acid, diisononyl ester	 <chem>CC(C)CCCCCOOC(=O)CCCCC(=O)OCCCC(C)C</chem> $C_{24}H_{46}O_4$
27178-16-1	Adipic acid, diisodecyl ester	 <chem>CCCCC(C)COOC(=O)CCCCC(=O)OCCCC(C)C</chem> $C_{26}H_{50}O_4$
16958-92-2	Adipic acid, ditridecyl ester	 <chem>CCCCCCCCCOOC(=O)CCCCC(=O)OCCCC(C)C</chem> $C_{32}H_{62}O_4$

Diesters Category		
CAS No.	Chemical Name	Structure
103-24-2	Azelaic acid, bis(2-ethylhexyl) ester	 C ₂₅ H ₄₈ O ₄
28472-97-1	Azelaic acid, diisodecyl ester	 C ₂₉ H ₅₆ O ₄
106-79-6	Sebacic acid, bis(2-ethylhexyl) ester	 C ₁₂ H ₂₂ O ₄
122-62-3	Sebacic acid, bis(2-ethylhexyl) ester	 C ₂₆ H ₅₀ O ₄
SUPPORTING CHEMICALS		
105-76-0	Maleic acid, dibutyl ester	 C ₁₂ H ₂₀ O ₄
105-99-7	Adipic acid, dibutyl ester	 C ₁₄ H ₂₆ O ₄
68515-75-3	Adipic acid, di-C7-9 branched and linear alkyl ester	 C ₂₀ H ₃₈ O ₄
103-23-1	Adipic acid, bis(2-ethylhexyl) ester	 C ₂₂ H ₄₂ O ₄