Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals

Sponsored Chemical

Adipic acid, di-C7-9 branched and linear alkyl ester (CASRN 68515-75-3)
(9th CI and CA Index Name: Hexanedioic acid, di-C7-9-branched and linear alkyl esters)

Supporting Chemicals

Di(n-hexyl) adipate (CASRN 110-33-8)
(CA Index Name: Hexanedioic acid, 1,6-dihexyl ester)
(9th CI Name: Hexanedioic acid, diheyxl ester)

Adipic acid, bis(2-ethylhexyl) ester (CASRN 103-23-1)
(CA Index Name: Hexanedioic acid, 1,6-bis(2-ethylhexyl) ester)
(9th CI Name: Hexanedioic acid, bis(2-ethylhexyl) ester)

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BACKGROUND

Screening-level hazard, exposure and risk characterizations for high production volume chemicals (HPV) are important contributions to the chemicals cooperation work being done in North America[1] through the EPA Chemical Assessment and Management Program (ChAMP)[2]. These screening-level characterizations are developed by EPA for individual chemicals or chemical categories to support initial Risk-Based Prioritizations (RBPs) for HPV chemicals. These screening-level characterizations are technical documents intended primarily to inform the Agency's internal decision-making process. Accordingly, they are written for assessment professionals and assume a degree of technical understanding. Each of the support documents is described below.

The Risk-Based Prioritizations are found in an accompanying document and are written for a general audience. They present EPA's initial thinking regarding the potential risks presented by these chemicals and future possible actions that may be needed.

Hazard Characterizations for HPV Chemicals

EPA's screening-level hazard characterizations are based primarily on the review of the summaries of studies and other information submitted by the chemical sponsor(s) under the HPV Challenge Program[3]. These studies included in the scope of the HPV Challenge comprise the Screening Information Data Set (SIDS) of the Organization for Economic Cooperation and Development (OECD)[4], an internationally recognized battery of tests that provides the basic data necessary to make an initial evaluation of a chemical's hazards and fate. In preparing the initial hazard characterizations, EPA also consulted a variety of reliable sources[5] for additional relevant information and 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. In order to determine whether any new hazard information was developed since the time of an HPV submission, EPA also searched publicly available databases[6] for information entered from one year prior to the HPV submission through May 2008. The screening-level hazard characterization is performed according to established EPA guidance[7]. A more detailed description of the hazard characterization process is available on the EPA website[8].

With respect to chemicals for which internationally-accepted OECD SIDS Initial Assessment Profiles (SIAP) and Initial Assessment Reports (SIAR) were available, EPA did not generate its own screening-level hazard characterization, but did check for and incorporate updated information in the risk characterization.

Exposure Characterizations for HPV Chemicals

EPA recently received exposure-related data on chemicals submitted in accordance with the requirements of Inventory Update Reporting (IUR)[9]. The 2006 IUR submissions pertain to chemicals manufactured in

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[1] U.S. EPA – U.S. Commitments to North American Chemicals Cooperation: http://www.epa.gov/hpv/pubs/general/sppframework.htm.
[2] U.S. EPA – ChAMP information: http://www.epa.gov/champ/.
[3] U.S. EPA – HPV Challenge Program information: http://www.epa.gov/hpv.
[4] U.S. EPA – Technical Guidance Document, OECD SIDS Manual Sections 3.4 and 3.5: http://www.epa.gov/chemrtk/pubs/general/sidsappb.htm.
[5] U.S. EPA – Public Database Hazard Information: http://www.epa.gov/hpvis/hazardinfo.htm.
[6] U.S. EPA – Public Database Update Information: http://www.epa.gov/chemrtk/hpvis/updateinfo.htm.
[7] U.S. EPA – Risk Assessment Guidelines: http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[8] U.S. EPA – About HPV Chemical Hazard Characterizations: http://www.epa.gov/hpvis/abouthc.htm.
[9] U.S. EPA – Basic IUR Information: http://www.epa.gov/opptintr/iur/pubs/guidance/basic-information.htm.

(including imported into) the U.S. during calendar year 2005 in quantities of 25,000 pounds or more at a single site. The reports include the identity, the quantity, and the physical form of the chemical manufactured or imported, and the number of workers reasonably likely to be exposed during manufacture of the chemical. For chemicals manufactured or imported in quantities of 300,000 pounds or more at a single site, additional reported information includes: the industrial processing and uses of the chemical; the number of industrial processing sites and workers reasonably likely to be exposed to the chemical at those sites; the consumer and commercial uses of the chemical; and an indication whether the chemical was used in products intended for use by children under 14 years of age.

EPA's screening-level exposure characterizations are based largely on the information submitted under the IUR reporting, although other exposure information submitted to the Agency (for example, in HPV submissions) or readily available through a limited set of publicly accessible databases[10] was also considered. The screening-level exposure characterizations identify a potential (high, medium, or low) that each of five populations – the environment, the general population, workers, consumers, and children – might be exposed to the chemical. In most cases, this potential doesn't address the quantity, frequency, or duration of exposure, but refers only to the likelihood that an exposure could occur.

In many instances EPA is not able to fully disclose to the public all the IUR exposure-related data reviewed or relied upon in the development of the screening-level documents because some of the material was claimed as confidential business information (CBI) when it was submitted to the Agency. These CBI claims do limit the Agency's ability to be completely transparent in presenting some underlying exposure and use data for chemicals in public documents. EPA does consider all data, including data considered to be CBI, in the screening-level exposure and risk characterization process, and endeavors whenever possible to broadly characterize supporting materials claimed as confidential in ways that do not disclose actual CBI.

Risk Characterizations for HPV Chemicals

EPA combines the information from the screening-level exposure characterization with the screening-level hazard characterization to develop a qualitative screening-level risk characterization, as described in the Agency's guidance on drafting risk characterizations[11]. These screening-level risk characterizations are technical documents intended to support subsequent priority-setting decisions and actions by OPPT. The purpose of the qualitative screening-level risk characterization is two-fold: to support initial risk-based decisions to prioritize chemicals, identify potential concerns, and inform risk management options; and to identify data needs for individual chemicals or chemical categories.

These initial characterization and prioritization documents do not constitute a final Agency determination as to risk, nor do they determine whether sufficient data are available to characterize risk. Recommended actions reflect EPA's relative judgment regarding this chemical or chemical category in comparison with others evaluated under this program, as well as the uncertainties presented by gaps that may exist in the available data.

[10] U.S. EPA – Summary of Public Databases Routinely Searched: http://www.epa.gov/chemrtk/hpvis/pubdtsum.htm.
[11] U.S. EPA – Risk Characterization Program: http://www.epa.gov/osa/spc/2riskchr.htm

QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

CHEMICAL NAME

SPONSORED CHEMICAL

Adipic Acid, di-C7-C9 Branched and Linear Alkyl Ester (CAS No. 68515-75-3)
(9th CI Name: Hexanedioic acid, di-C7 – C9 branched and linear alkyl ester)

SUPPORTING CHEMICALS

Di(n-hexyl) adipate (CAS No. 110-33-8)
(9th CI Name: Hexanedioic acid, dihexyl ester)
Adipic Acid, bis(2-ethylhexyl) Ester (CAS No. 103-23-1)
(9th CI Name: Hexanedioic acid, bis(2-ethylhexyl) ester)

September 2008

Prepared by
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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Adipic Acid, di-C7-C9 Branched and Linear Alkyl Ester (CAS No. 68515-75-3)
(9th CI Name: Hexanedioic acid, di-C7 – C9 branched and linear alkyl ester)

SUPPORTING CHEMICALS

Di(n-hexyl) adipate (CAS No. 110-33-8)
(9th CI Name: Hexanedioic acid, dihexyl ester)
Adipic Acid, bis(2-ethylhexyl) Ester (CAS No. 103-23-1)
(9th CI Name: Hexanedioic acid, bis(2-ethylhexyl) ester)

1. Physical-Chemical Properties and Environmental Fate

Hexanedioic Acid, diC7 – C9 branched and linear alkyl ester (C20) is a viscous liquid or solid. Supporting chemicals, hexanedioic acid, dihexyl ester and hexanedioic acid, bis(2-ethylhexyl) ester (C22) are liquids with low to moderate water solubility and low vapor pressures. They are expected to have low to moderate mobility in soil. The rate of volatilization of these chemicals is considered low to moderate based on their Henry's Law constants. The rate of hydrolysis is considered negligible for these chemicals. The rate of atmospheric photooxidation is considered rapid. These chemicals are expected to have low persistence (P1) and low bioaccumulation potential (B1).

2. Hazard Characterization

Aquatic Organism Toxicity: Adequate acute toxicity data for fish, aquatic invertebrates, and aquatic plants were not submitted. EPA used ECOSAR estimates and the hazard information available in the Diesters Category to conclude that acute toxicity of hexanedioic Acid, diC7 – C9 branched and linear alkyl ester (C20) to aquatic organisms is low. The evaluation of chronic toxicity data for aquatic invertebrates for the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, indicates that the potential chronic hazard of hexanedioic Acid, diC7 – C9 branched and linear alkyl ester to aquatic organisms is low.

Human Health Toxicity: The acute oral toxicity in rats and the acute dermal toxicity in rabbits for adipic acid, di-C7-9 branched and linear alkyl ester is low. Adipic acid, di-C7-9 branched and linear alkyl ester is slightly irritating to rabbit skin and eye. A repeated-dose oral toxicity study on adipic acid, di-C7-9 branched and linear alkyl ester showed no systemic toxicity. Two separate one-generation reproductive toxicity studies with the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, showed no reproductive toxicity. Likewise, numerous repeated-dose toxicity studies in rats on adipic acid, di-C7-9 branched and linear alkyl ester, as well as the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, with examination of various

reproductive organs and endpoints showed either no reproductive toxicity or low reproductive toxicity. A prenatal developmental toxicity study on adipic acid, di-C7-9 branched and linear alkyl ester showed low maternal and developmental toxicity. A prenatal developmental toxicity study on the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, that included an assessment of postnatal growth and development, also showed low maternal and developmental toxicity. Adipic acid, di-C7-9 branched and linear alkyl ester did not induce gene mutation, and the supporting chemicals, di(n-hexyl) adipate and adipic acid, bis(2-ethylhexyl) ester, did not induce chromosomal aberrations *in vitro* or *in vivo*. IARC has classified the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, into Group 3 (substances not classifiable as to its carcinogenicity to humans).

3. Exposure Characterization

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS# 68515-75-3) has an aggregated production and/or import volume in the range of 500,000 to 1 million pounds. Non-confidential IUR information reported processing activities in various industrial sectors but didn't specify the function. IUR information also indicated its use in commercial settings or consumer products as a component of transportation products. Information submitted as part of the High Production Volume (HPV) Challenge Program indicates that this chemical is used as a plasticizer to give PVC film, sheet and coatings low-temperature flexibility. It is also used as a plasticizer in rubber formulations.

Potential Exposures to the General Population and the Environment: There is potential for environmental release to water during industrial processing and use, as well as during commercial/consumer use, based on the IUR use information and other data sources. Based on the information considered, including information found from non-confidential public sources, EPA identifies, for the purposes of risk-based prioritization, a high potential that the general population and the environment might be exposed.

Persistence and bioaccumulation ratings for this chemical are P1 and B1. These ratings indicate that this chemical is not persistent in the environment and is not bioaccumulative.

Potential Exposures to Workers: Based on the information considered including IUR data, and from the HPV Challenge Program, and in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a medium relative ranking for potential worker exposure. The medium relative ranking is based on the potential dermal exposure during industrial processing and use activities and commercial uses, as well as potential inhalation exposure to particulates, and the number of workers potentially exposed.

Potential Exposures to Consumers: EPA identifies, for the purposes of risk-based prioritization, a high potential that consumers might be exposed based on the use of products containing this chemical. IUR submissions indicate uses in commercial settings or consumer uses. The non-confidential commercial/consumer uses for this chemical are as transportation products. The specifics as to whether this is a commercial use as well as a consumer use are not defined. Other IUR submissions reported consumer uses as Not Readily Obtainable (NRO). There is also potential for exposure to consumers based on information from public data sources. This

chemical is contained in fabrics used in raingear and luggage, as well as in food-contact packaging, a non-TSCA use.

Potential Exposures to Children: The IUR reported that information on products intended for use by children is NRO. No uses in products intended to be used by children are found in any other data sources. Based on this uncertainty (NRO), and that there may be potential exposure of children through the use of some consumer products, EPA identifies, for the purposes of risk-based prioritization, a high potential that children might be exposed.

4. Risk Characterization

The statements and rationale provided below are intended solely for the purpose of this qualitative screening-level risk characterization and will be used for prioritizing substances for future work in the Chemical Assessment Management Program (ChAMP).

Risk Statement and Rationale

Potential Risk to Aquatic Organisms from Environmental Releases (LOW CONCERN). EPA identifies a high potential that aquatic organisms might be exposed from environmental releases. Adipic acid, di-C7-9 branched and linear alkyl ester has low persistence and low bioaccumulation. Although adequate acute toxicity data for adipic acid, di-C7-C9 branched and linear alkyl ester was not submitted, EPA used ECOSAR estimates and hazard information available in the Diesters Category to conclude that acute toxicity is expected to be low. The evaluation of chronic toxicity data for aquatic invertebrates for the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, indicates that the potential chronic hazard of hexanedioic Acid, diC7 – C9 branched and linear alkyl ester to aquatic organisms is low. The combination of low toxicity, low persistence and low bioaccumulation potential suggest a low concern for potential risk to aquatic organisms.

Potential Risk to the General Population from Environmental Releases (LOW CONCERN). EPA identifies a high potential that the general population might be exposed from environmental releases. The potential human health hazard is expected to be low due to the lack of specific toxicity to animals following exposure to high doses. The low hazard and the environmental fate characteristics of low persistence and low bioaccumulation together suggest a low concern for potential risk to the general population from environmental releases.

Potential Risk to Workers (LOW CONCERN). EPA identifies a medium relative ranking for potential exposure to workers. The potential human health hazard is expected to be low due to the lack of specific toxicity to animals following exposure to high doses. Therefore, taken together, the available information suggests a low concern for potential risks to workers.

Potential Risk to Consumers from Known Uses (LOW CONCERN). Available IUR data indicate that there is a high potential that consumers might be exposed based on the use of products containing this chemical. The potential human health hazard is expected to be low due to the lack of specific toxicity to animals following exposure to high doses. Taken together, the available information suggests a low concern for potential risks to consumers.

Potential Risk to Children (LOW CONCERN). EPA identifies a high potential that children might be exposed. Postnatal animal toxicity data indicated a low concern for potential toxicity to young animals. Taken together, the available information suggests a low concern for potential risks to children.

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Adipic Acid, di-C7-C9 Branched and Linear Alkyl Ester (CAS No. 68515-75-3)
(9th CI Name: Hexanedioic acid, di-C7 – C9 branched and linear alkyl ester)

SUPPORTING CHEMICALS

Di(n-hexyl) adipate (CAS No. 110-33-8)
(9th CI Name: Hexanedioic acid, dihexyl ester)
Adipic Acid, bis(2-ethylhexyl) Ester (CAS No. 103-23-1)
(9th CI Name: Hexanedioic acid, bis(2-ethylhexyl) ester)

September 2008

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SCREENING-LEVEL HAZARD CHARACTERIZATION
Hexanedioic Acid, Di-C7 – C9 Branched and Linear Alkyl Ester (CAS No. 68515-75-3)

Introduction

The sponsor, Solutia Inc., submitted a Test Plan and Robust Summaries to EPA for hexanedioic acid, di-C7 – C9 branched and linear alkyl ester[12] (CAS No. 68515-75-3; 9th CI name: hexanedioic acid, di-C7 – C9 branched and linear alkyl ester) on November 19, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on December 16, 2002, http://www.epa.gov/chemrtk/pubs/summaries/hexanedi/c14079tc.htm. EPA comments on the original submission were posted to the website on April 21, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on June 11, 2003, which were posted to the ChemRTK website on June 30, 2003.

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. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from 2002 to June 2008: the NLM databases (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, ATSDR, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical(s) is included in the appendix. The screening-level hazard characterization for environmental and human health effects is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Justification for Supporting Chemicals

The sponsor submitted information for two supporting chemicals: di(n-hexyl) adipate (9th CI name: hexanedioic acid, dihexyl ester, CAS No. 110-33-8) and adipic acid, bis(2-ethylhexyl) ester (9th CI Name: hexanedioic acid, bis(2-ethylhexyl) ester, CAS No. 103-23-1). EPA agrees with the sponsor that based on structural similarities and physical-chemical and toxicological properties, these supporting chemicals are acceptable for evaluation of hexanoic acid, diC7-C9 branched and linear alkly ester for the purposes of the HPV Challenge Program. In this hazard assessment, EPA has used data for adipic acid, bis(2-ethylhexyl) ester to address data gaps for human health effects endpoints (reproductive toxicity and chromosomal aberrations) and in support of aquatic toxicity endpoints (chronic toxicity to aquatic invertebrates). Adipic acid, bis(2-ethylhexyl) ester has been assessed in the Organization for Economic Cooperation and Development (OECD) High Production Volume (HPV) program (http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html) and is also a supporting chemical for the Diesters Category submitted under the HPV Challenge Program.

Hazard Characterization

Hexanedioic acid, di-C7–9 branched and linear alkyl ester (C20-24) is a viscous liquid or solid. Supporting chemicals, hexanedioic acid, dihexyl ester (C18) and hexanedioic acid, bis(2-ethylhexyl) ester (C22) are liquids with low water solubility and low vapor pressures. They are expected to have low to moderate mobility in soil. The rate of volatilization of these chemicals is considered low to moderate based on their Henry's Law constants. The rate of hydrolysis is considered negligible for these chemicals. The rate of atmospheric photooxidation is considered rapid. These chemicals are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Adequate acute toxicity data for fish, aquatic invertebrates, and aquatic plants were not submitted. EPA used ECOSAR estimates and the hazard information available in the Diesters Category to conclude that acute toxicity of hexanedioic Acid, diC7 – C9 branched and linear alkyl ester (C20-24) to aquatic organisms is low. The evaluation

[12] Test substance is also known as '97 Adipate', 'Di(C7-9-Alkyl)Adipate', 'Santicizer 97A'.

of chronic toxicity data for aquatic invertebrates for the supporting chemical, adipic acid, bis(2-ethylhexyl) ester (C22), indicates that the potential chronic hazard of hexanedioic Acid, diC7 – C9 branched and linear alkyl ester to aquatic organisms is low.

The acute oral toxicity in rats and the acute dermal toxicity in rabbits for adipic acid, di-C7-9 branched and linear alkyl ester is low. Adipic acid, di-C7-9 branched and linear alkyl ester is slightly irritating to rabbit skin and eye. A repeated-dose oral toxicity study on adipic acid, di-C7-9 branched and linear alkyl ester showed no systemic toxicity. Two separate one-generation reproductive toxicity studies with the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, showed no reproductive toxicity. Likewise, numerous repeated-dose toxicity studies in rats on adipic acid, di-C7-9 branched and linear alkyl ester, as well as the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, with examination of various reproductive organs and endpoints showed either no reproductive toxicity or low reproductive toxicity. A prenatal developmental toxicity study on adipic acid, di-C7-9 branched and linear alkyl ester showed low maternal and developmental toxicity. A prenatal developmental toxicity study on the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, that included an assessment of postnatal growth and development, also showed low maternal and developmental toxicity. Adipic acid, di-C7-9 branched and linear alkyl ester did not induce gene mutation, and the supporting chemicals, di(n-hexyl) adipate and adipic acid, bis(2-ethylhexyl) ester, did not induce chromosomal aberrations *in vitro or in vivo*. IARC has classified the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, into Group 3 (substances not classifiable as to its carcinogenicity to humans).

No data gaps were identified under the HPV Challenge Program

1. Physical-chemical Properties and Environmental Fate

The physical-chemical properties of hexanedioic acid, di-C7–9 branched and linear alkyl ester and supporting chemicals hexanedioic acid, dihexyl ester (C18) and hexanedioic acid, bis(2-ethylhexyl) ester (C22) are summarized in Table 1a, while their environmental fate properties are given in Table 1b. The structures of the compounds are provided in the Appendix.

Physical-Chemical Properties Characterization

Hexanedioic acid, di-C7–9 branched and linear alkyl ester (C20-24), is a viscous liquid or solid. Hexanedioic acid, dihexyl ester (C18) and hexanedioic acid, bis(2-ethylhexyl) ester (C22) are liquids with low water solubility and low vapor pressures.

Table 1a. Physical-Chemical Properties of Hexanedioic acid, di-C7–9 branched and linear alkyl ester[1]			
Property	**Hexanedioic acid, di-C7–9 branched and linear alkyl ester (C20-24)**	**Hexandioic acid, dihexyl ester (C18) (Supporting Chemical)**	**Hexandioic acid, bis(2-ethylhexyl) ester (C22) (Supporting Chemical)[2]**
CAS No.	68515-75-3	110-33-8	103-23-1
Molecular Weight	356-413	314.47	371
Physical State	Viscous liquid or solid	Liquid	Colorless or pale amber liquid[3]
Melting Point	No Data[4]	**-13.8; -9 to -7 (measured)[5]**	**-67.8°C (measured)[5]**
Boiling Point	**224°C at 9.75 mmHg (measured)[4]** 355°C (estimated)	**348 (measured)[5]**	**417°C (measured)[6]**
Vapor Pressure	**9.75 at 224°C (measured)[2]** 8.2×10^{-6} mmHg at 25°C (estimated)	**2.88×10^{-6} mm Hg at 25°C (measured)[6]**	**1.58×10^{-2} mm Hg At 100°C** **8.5×10^{-7} mmHg at 20°C (measured)**
Water Solubility	**< 0.048 mg/L at 25°C (measured)**	0.042 mg/L at 20°C (estimated)[5]	**0.0032 mg/L at 22°C (measured)**
Henry's Law Constant[5]	1.8×10^{-5} atm m^3/mol (estimated)	4.85×10^{-8} atm-m^3/mol (estimated)	1.3×10^{-5} atm m^3/mol (estimated)
Log K_{ow}	**> 6.48 (measured)**	6.30 (estimated)[6]	8.12 (estimated)[6]

[1]Solutia Inc. 2003. Revised Robust Summary for Hexanedioic acid, di-C7-9-branched and linear alkyl esters. http://www.epa.gov/chemrtk/pubs/summaries/hexanedi/c14079tc.htm
[2]Data obtained from Robust Summaries submitted for Diesters Category. http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm.
[3]HSDB. 2008. Hazardous Substances Data Bank. As cited in record for bis(2-ethylhexyl) adipate. http://toxnet.nlm.nih.gov/. Accessed June 3, 2008.
[4]The substance is a complex mixture. The melting point value will change depending upon composition.
[5]Beilstein E (IV), Vol. 2/3, p. 1963; E(III), Vol. 2/2, p. 1714.
[6]US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.

Environmental Fate Characterization

Hexanedioic acid, diC7–C9 branched and linear alkyl ester (C20-C24)and supporting chemicals, hexanedioic acid, dihexyl ester (C18), and hexanedioic acid, bis(2-ethylhexyl) ester (C22), are expected to have low to moderate mobility in soil. Based data indicating ready biodegradability for supporting chemical, hexanedioic acid, bis(2-ethylhexyl) ester, the chemicals are expected to have low persistence. The rate of volatilization of these chemicals is considered low to moderate based on their Henry's Law constants. The rate of hydrolysis is considered negligible for these chemicals. The rate of atmospheric photooxidation is considered rapid. Although measured and estimated Log K_{ow} values indicate these are highly hydrophobic chemicals, their BCFs are low due to metabolism by biota. These chemicals are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 1b. Environmental Fate Properties Hexanedioic acid, di-C7–9 branched and linear alkyl ester[1]			
Property	**Hexanedioic acid, di-C7–9 branched and linear alkyl ester (C20-C24)**	**Hexandioic acid, dihexyl ester (C18) (Supporting Chemical)**	**Hexandioic acid, bis(2-ethylhexyl) ester (C22) (Supporting Chemical)**
Photodegradation Half-life	0.45 days (estimated)[2]	0.584 days (estimated)[3]	0.4 days (estimated)[3]
Direct Photolysis	0% in 14 days[2]		
Hydrolysis Half-life	2 years at pH 7 120 days at pH 8 (estimated)[2]	2 years at pH 7 75 days at pH 8 (estimated)[3]	3.2 years at pH 7 117 days at pH 8 (estimated)[3]
Biodegradation	No Data 83% at 28 days Readily biodegradable (RA) **67-88% at 24 hours (measured)** **Inherently biodegradable**	No Data Data not required for supporting chemical	**83% at 28 days[3] (measured)** **Readily biodegradable**
Bioconcentration (BCF)[2,5]	359 (estimated)	446 (estimated)	61 (estimated)
Log K_{oc}	4.4[2] (estimated)	3.7[2] (estimated)	4.7[2] (estimated)
Fugacity (Level III Model)[2]	Air = 0.3% Water = 3.6% Soil = 27.3% Sediment = 68.6%	Air = 0.4%[3] Water = 7.6% Soil = 42.6% Sediment = 49.3%	Air = 0.5%[3] Water = 5.6% Soil = 31.8% Sediment = 62.1%
Persistence[4]	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation[4]	B1 (low)	B1 (low)	B1 (low)

[1]Solutia Inc. 2003. Revised Robust Summary for Hexanedioic acid, di-C7-9-branched and linear alkyl esters. http://www.epa.gov/chemrtk/pubs/summaries/hexanedi/c14079tc.htm
[2]US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.
[3]Value obtained from Robust Summaries submitted for Diesters Category. http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm.
[4]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.
[5]Although measured and estimated Log K_{ow} values indicate these are highly hydrophobic chemicals, their BCFs are low due to metabolism by biota.

Conclusion: Hexanedioic acid, di-C7–9 branched and linear alkyl ester (C20-24)is a viscous liquid or solid. Supporting chemicals, hexanedioic acid, dihexyl ester (C18) and hexanedioic acid, bis(2-ethylhexyl) ester (C22), are liquids with low water solubility and low vapor pressures. They are expected to have low to moderate mobility in soil. The rate of volatilization of these chemicals is considered low to moderate based on their Henry's Law constants. The rate of hydrolysis is considered negligible for these chemicals. The rate of atmospheric photooxidation is considered rapid. These chemicals are expected to have low persistence (P1) and low bioaccumulation potential (B1).

2. Environmental Effects- Aquatic Toxicity

Acute Toxicity to Fish

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

EPA considered the submitted acute toxicity data for fish, aquatic invertebrates and aquatic plants inadequate because this chemical was tested above its water solubility and without measured concentrations. Therefore, EPA

used ECOSAR estimates and information available for the Diesters Category to evaluate acute toxicity. EPA's evaluation of data for a number of other diesters indicates low acute toxicity is expected for diesters having 20 or more carbons. In comments on the test plan, EPA recommended a 21-day chronic toxicity study in daphnia based on the greater than 4.2 log K_{ow} value and low water solubility (0.048 mg/L) for this chemical. Although the sponsor did not provide this chronic data, EPA identified that data for chronic toxicity to aquatic invertebrates for the supporting chemical adipic acid, bis(2-ethylhexyl) ester, which has water solubility (0.0032 mg/L) and log K_{ow} (> 6.11 to 8.39) similar to adipic acid, di-C7-9 branched and linear alkyl ester, was available in the HPV Challenge submission for the Diesters Category.

Chronic Toxicity to Aquatic Invertebrates

Adipic acid, bis(2-ethylhexyl) ester (CAS No. 103-23-1, Supporting Chemical)

Chronic toxicity to daphnia as reported in the SIDS dossier indicates toxicity was seen, but the study was conducted above the water solubility limit of the chemical (http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html). Another chronic daphnia study (described below), conducted subsequent to publication of the SIDS dossier, indicates chronic toxicity was not observed at the water solubility limit (measured concentrations).

Water flea (*Daphnia magna*) were exposed to the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, at measured concentration of 0.00436 mg/L. No effects were observed on survival, growth or reproduction. (http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm).
No effects at saturation

Conclusion: Adequate acute toxicity data for fish, aquatic invertebrates, and aquatic plants were not submitted. EPA used ECOSAR estimates and the hazard information available in the Diesters Category to conclude that acute toxicity of hexanedioic acid, diC7 – C9 branched and linear alkyl ester (C20) to aquatic organisms is low. The evaluation of chronic toxicity data for aquatic invertebrates for the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, indicates that the potential chronic hazard of hexanedioic acid, diC7 – C9 branched and linear alkyl ester to aquatic organisms is low.

3. Human Health Effects

Acute Oral Toxicity

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3)
Sprague-Dawley rats (10, single rats were used for the lower doses and five rats (three males, two females) were used at 15,800 mg/kg-bw) were administered adipic acid, di-C7-9 branched and linear alkyl ester (commercial-grade) via gavage at doses of at 2000, 3160, 5010, 7940, 12,600, or 15,800 mg/kg-bw and were observed for 7 days. A complete necropsy was performed after 7 days. No animals died at any dose level. Signs of toxicity included reduced appetite and activity for 1 – 4 days and slight weakness. All rats were normal after 7 days. At necropsy, two of five rats at 15,800 mg/kg-bw showed congestion of the lungs.
LD_{50} > 15,800 mg/kg-bw

Acute Dermal Toxicity

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3)
New Zealand white rabbits were administered (5, single animals were used for the lower doses and two (one male and one female) rabbits were used at 7940 mg/kg-bw) adipic acid, di-C7-9 branched and linear alkyl ester (commercial-grade) dermally on to closely clipped, intact skin at 2000, 3160, 5010 or 7940 mg/kg-bw under occlusive conditions for 24 hours and were observed for 14 days. No deaths were observed in the study. Signs of toxicity included reduced appetite and activity, slight lethargy (2 – 5 days duration) and slight tremors (1 – 2 days) at 5010 and 7940 mg/kg-bw. At necropsy, rabbits at 5010 and 7940 mg/kg-bw showed slight congestion of the lungs and areas of slight discoloration of the liver.
LD_{50} > 7940 mg/kg-bw

Repeated-Dose Toxicity Study

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3)
In a repeated-dose toxicity study, Sprague-Dawley rats (number unspecified) were administered adipic acid, di-C7-9 branched and linear alkyl ester at 2.5% in the diet (approximately 1,500 mg/kg-bw/day in male rats; 1,950 mg/kg-bw/day in female rats) for 13 weeks (90 days). No other details were provided. No systemic toxicity was reported and no adverse effects to male or female reproductive organs were observed. No other effects were indicated.
NOAEL (systemic toxicity) = 2.5% in the diet (approximately 1,500 mg/kg-bw/day for males; 1950 mg/kg-bw/day in females)

Adipic acid, bis (2-ethylhexyl) ester (CAS No. 103-23-1, Supporting Chemical)
(1) In a repeated-dose toxicity study in which male reproductive toxicity was assessed under conditions of renal disease, Fisher 344 rats (males only) were administered adipic acid, bis (2-ethylhexyl) ester in the diet at doses of 0, 6,000, or 25,000 ppm (approximately 0, 600, 2500 mg/kg-bw/day) for 4 weeks following five consecutive weekly subcutaneous injections of folic acid (for induction of chronic renal dysfunction) (Nabae et al., 2006). Control animals received adipic acid, bis (2-ethylhexyl) ester in the diet but without folic acid pretreatment. Endpoints included body weight, and organ and histopathological examination of the kidneys, testes, epididymides, prostate and seminal vesicles. Spermatogenesis was also evaluated. No effects were observed on any parameters measured in any dose groups.
NOAEL (systemic toxicity) = 25,000 ppm (or 2500 mg/kg-bw/day)

(2) In a repeated-dose toxicity study, Sprague-Dawley rats were administered by gavage 0, 40, 200, and 1000 mg/kg-bw/day adipic acid, bis (2-ethylhexyl) ester for 28 days from 8 weeks of age (Miyata et al., 2006). General signs and clinical observations were recorded daily. Body weight and food consumption were also recorded. Clinical chemistry, hematology, hormone analysis, spermatology, estrous cycling, and necroscopic and histopathological examination of organs were conducted. Increased liver weight, without histopathology, was also observed in male and female rats at 1000 mg/kg-bw/day. In male rats only, increased kidney weight and histopathological changes (increased eosinophilic bodies and hyaline droplets) were observed at 1000 mg/kg-bw/day. Male rat kidney weight was also increased at 200 mg/kg-bw/day, but in the absence of any histopathology. Therefore, this is not considered to be treatment-related. Additionally, since it cannot be determined from the study whether the observed kidney effects are male rat specific, it is not clear whether or not these effects are relevant to humans, therefore, they are not being considered here. Also, it was not specified in the study if the liver/kidney weight changes were relative or absolute. No other effects were reported.
NOAEL (systemic toxicity) = 1,000 mg/kg-bw/day

(3) In a one-generation reproductive toxicity study, Wistar rats (number not specified) were exposed to adipic acid, bis (2-ethylhexyl) ester in the diet 10 weeks prior to mating only, and then again for 36 days post partum at 0, 0.03, 0.18, and 1.20% (corresponding to approximately, 0, 33, 200 and 1111 mg/kg-bw/day, respectively). No clinical signs of toxicity were noted in males or females. No changes in body weight or food consumption occurred during the premating exposure period, but the high-dose dams had reduced body weight gain during gestation compared with the control group. At necropsy, liver weights (absolute and relative to body weight) were increased in high-dose males and females. No other effects were reported in adult animals.
LOAEL (adult systemic toxicity) = 1111 mg/kg-bw/day (based on decreases in body weight gains in dams; increases in liver weights for males/females)
NOAEL (adult systemic toxicity) = 200 mg/kg-bw/day

Reproductive Toxicity

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3)
In the 13 week (90 days) toxicity study in Sprague-Dawley rats previously described, 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 at doses up to 1950 mg/kg-bw/day.

Adipic acid, bis (2-ethylhexyl) ester (CAS No. 103-23-1, Supporting Chemical)

(1) In the repeated-dose toxicity study in Fisher 344 rats previously described (Nabae et al., 2006), no effects were reported on any reproductive parameters measured in any dose group.
NOAEL (male reproductive toxicity) = 25,000 ppm (or 2500 mg/kg-bw/day)

(2) In the repeated-dose toxicity study in Sprague-Dawley rats previously described (Miyata et al., 2006), disturbance of the estrous cycle and increased ovarian follicle atresia were observed at 1000 mg/kg-bw/day. No other reproductive effects were reported.
LOAEL (female reproductive toxicity) = 1,000 mg/kg-bw/day (based on disturbance of the estrous cycle and increased ovarian follicle atresia)
NOAEL (female reproductive toxicity) = 200 mg/kg-bw/day
NOAEL (male reproductive toxicity) = 1000 mg/kg-bw/day

(3) In the one-generation reproductive toxicity study in Wistar rats previously described, no clinical signs of toxicity were noted in males or females. No changes in body weight or feed consumption occurred during the premating exposure period, but the high-dose dams had reduced body weight gain during gestation compared with the control group. No treatment-related effects on male or female fertility were noted. Mean pup weight gain, total litter weight, and litter size at the high-dose were reduced throughout the post-partum period. The percentage of live-birth litters and their survival to post-partum day 22 in treated groups were comparable to controls. At necropsy, liver weights (absolute and relative to body weight) were increased in high-dose males and females. No treatment-related microscopic changes occurred in the reproductive tissues of the parental generation. No treatment-related gross pathologic changes occurred in the F1 generation. No other effects were reported.
NOAEL (reproductive toxicity) = 1111 mg/kg-bw/day
LOAEL (maternal/developmental toxicity) = 1111 mg/kg-bw/day (based on reductions in body weights in the dams; increases in liver weight in the dams/decreases in mean pup weight gain, total litter weight, and litter size)
NOAEL (maternal/developmental toxicity) = 200 mg/kg-bw/day

(4) In a one-generation reproductive toxicity study, male and female Sprague-Dawley rats were administered 0, 300, 1,800, and 12,000 ppm (approximately 0, 23, 1,200, and 2,400 mg/kg-bw/day) adipic acid, bis (2-ethylhexyl) ester in the diet for 10 weeks prior to mating and continuing in the females for an additional 8-9 weeks until the production of one generation of offspring. No other details were provided. No effects were seen on male or female fertility parameters. Signs of maternal toxicity consisted of decreases in body weight at 2,400 mg/kg-bw/day. Signs of developmental toxicity consisted of decreases in offspring body weight, total litter weight, and litter size at 2,400 mg/kg-bw/day. No other effects were observed.
NOAEL (adult/reproductive toxicity) = 2,400 mg/kg-bw/day
LOAEL (maternal/developmental toxicity) = 2,400 mg/kg-bw/day (based on decreases in body weight in dams; and decreases in body weight, total litter weight and litter size in offspring)
NOAEL (maternal/developmental toxicity) = 1,200 mg/kg-bw/day

Developmental Toxicity

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3)
In a prenatal developmental toxicity study, pregnant 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, bis (2-ethylhexyl) ester (CAS No. 103-23-1, Supporting Chemical)
(1) In a Chernoff-Kavlock screening test, pregnant Wistar rats (number not specified) were administered adipic acid, bis (2-ethylhexyl) ester in the diet at 0, 0.03, 0.18, and 1.2% (corresponding to approximately 0, 33, 200 and 1111 mg/kg-bw/day, respectively) during days 1 through 22 of gestation. No other details were provided. Reductions in maternal body weight and food consumption were reported at 1111 mg/kg-bw/day. A slight decrease in litter size was also reported at 1111 mg/kg-bw/day, but it was not statistically significant. A slight incidence of minor skeletal abnormalities was seen at 200 and 1111 mg/kg-bw/day, but no other details were reported. Given that this study was available in summary form only and limited details on study parameters and results were provided, the adequacy of this study is questionable and therefore was not considered in evaluating the developmental toxicity in the hazard characterization.

(2) In a prenatal developmental toxicity study, pregnant Sprague-Dawley rats were administered 0, 300, 1,800, and 12,000 ppm (approximately 0, 28, 170, and 1,080 mg/kg-bw/day) adipic acid, bis (2-ethylhexyl) ester in the diet on gestation days 1-22. No other details were provided. Signs of maternal toxicity consisted of decreases in body weight and food consumption and increases in implantation losses at the highest dose group of 1,080 mg/kg-bw/day. Signs of developmental toxicity consisted of ureteral malformations and skeletal abnormalities at doses of 170 mg/kg-bw/day and higher. No other details were provided and no other effects were reported. This study was available in summary form only and limited details on study parameters and results were provided. The results of this study were not observed in the previously described developmental toxicity on adipic acid, bis (2-ethylhexyl) ester, which appeared to be a more robust study and which also used a dose range close to the 170 mg/kg-bw/day. Therefore, the adequacy of this study is questionable and was not considered in evaluating the developmental toxicity in the hazard characterization.

(3) In a study similar in design to an OECD Test Guideline 426 Developmental Neurotoxcity Study, pregnant Wistar rats were administered 0, 200, 400, or 800 mg/kg-bw/day adipic acid, bis (2-ethylhexyl) ester from gestation day 7 to pup age day 17 (Dalgaard et al., 2003). Pregnancy data, prenatal and postnatal growth and development, and endpoints of relevance for antiandrogenic effects were also included. From gestation day 21, the animals were inspected twice daily until delivery. Following delivery, body weights of dams and individual pup weights were recorded. Pups were counted, sexed, and checked for anomalies; any found dead were examined macroscopically. The day of delivery was designated postnatal day (PND) 0 (or gestation day 21). One male and one female from each litter were kept after weaning for investigation of sexual maturation, hormone and sperm analysis, and histopathology at adulthood. The pups were randomly selected and housed in pairs of the same sex and same exposure status. Assessment of postnatal development of the pups was conducted by examining the following parameters: body weights (PND 3 and 13), anogenital distance (PND 3), presence of nipples (PND13 and 14), and evidence of sexual maturation (vaginal opening in females, balano-preputial cleavage in males). At PND 21, the remaining pups and dams were euthanized and examined macroscopically, organs were weighed and examined microscopically (in males only), and the numbers of uterine implantations sites were counted in the dams. Effects observed included a prolonged gestation period at 800 mg/kg-bw/day, a dose-related increase in postnatal deaths at

400 and 800 mg/kg-bw/day (with statistical significance at 800 mg/kg-bw/day), and a permanent decrease in offspring body weight at 800 mg/kg-bw/day (in both sexes during the lactation period as well as in adult males). No antiandrogenic endpoints were affected, that is, no effects on endocrine related endpoints such as anogenital distance, nipple retention, sexual maturation, hormone levels, sperm parameters, organ weights/histopathology of the reproductive system were observed. No other effects were reported.
LOAEL (maternal toxicity) = 800 mg/kg-bw/day (based on prolonged gestation)
NOAEL (maternal toxicity) = 400 mg/kg-bw/day
LOAEL (developmental toxicity) = 400 mg/kg-bw/day (based on increased postnatal deaths)
NOAEL (developmental toxicity) = 200 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
Adipic acid, di-C7-9 branched and linear alkyl ester (CAS No. 68515-75-3)
(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/plate 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.

Di(n-hexyl) adipate (CAS No. 110-33-8, Supporting Chemical)
Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to di(n-hexyl)adipate at 0, 167, 500, 1670, 5000, 7500 or 10,000 µg/plate in the presence and absence of metabolic activation. Positive controls tested concurrently, but their response was not provided.
Di(n-hexyl) adipate was not mutagenic in this assay.

Adipic acid, bis (2-ethylhexyl) ester (CAS No. 103-23-1, Supporting Chemical)
(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to 0.15, 0.47, 1.5, 4.74, 15.8, 47.4 or 150 µL/plate of dioctyl adipate in the presence and absence of metabolic activation. Positive controls tested but their response was not provided. Negative and solvent controls were also used. No cytotoxicity was observed up to the highest level tested.
Adipic acid, bis (2-ethylhexyl) ester was not mutagenic in this assay.

(2) Adipic acid, bis (2-ethylhexyl) ester is reported to be negative for mutagenic potential with or without metabolic activation for the following: a reverse mutation tests with *Salmonella typhimurium* or *Escherichia coli* strains; an Ames test using urine from Sprague-Dawley rats given adipic acid, bis (2-ethylhexyl) ester by oral gavage at 2,000 mg/kg-bw/day for 15 days; a DNA repair test with primary rat hepatocyte cultures; a reverse mutation test using mouse lymphoma cells; and in the BALB 3T3 cell transformation assay.
Adipic acid, bis (2-ethylhexyl) ester was not mutagenic in these assays.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Di(n-hexyl) adipate (CAS No. 110-33-8, Supporting Chemical)
Chinese hamster ovary cells were exposed to 0, 50, 250, 1250 or 2500 µg/mL of di(n-hexyl)adipate in the presence and absence of metabolic activation. Test concentrations were based on findings of a preliminary cytotoxicity study. Positive controls used were tested concurrently, but their responses were not provided. No increases in proportion of aberrant metaphases or in the frequency of aberrations per metaphase were observed at any level tested.
Di(n-hexyl) adipate did not induce chromosomal aberrations in this assay.

In vivo

Di(n-hexyl) adipate (CAS No. 110-33-8, Supporting Chemical)

(1) Sprague-Dawley rats (24/sex/dose) were administered a single dose of di(n-hexyl)adipate via gavage at 0, 1000, 3000 or 10,000 mg/kg-bw. Each animal was injected 2 hours prior to scheduled sacrifice with colchicine to inhibit mitosis. Groups of six male and six female rats from each dose were sacrificed 6, 12, 24 and 48 hours after treatment. Cyclophosphamide was used as the positive control. Bone marrow cells were processed and scored for chromosomal. Response to the positive control was not provided. No differences were observed in mean mitotic indices between treated and control groups.

Di(n-hexyl) adipate did not increase the frequency of chromosomal aberrations in bone marrow cells in this assay.

(2) CD-1 mice (5/sex) were administered di(n-hexyl)adipate via a single intraperitoneal dose of 0, 500, 1600 or 5000 mg/kg-bw. Positive and negative controls were tested concurrently. Animals were sacrificed 12, 24 and 48 hours after treatments and slides were prepared from cells obtained from femoral marrow. Response to the positive controls was not indicated.

Di(n-hexyl) adipate did not induce chromosomal aberrations in this assay.

Adipic acid, bis (2-ethylhexyl) ester (CAS No. 103-23-1, Supporting Chemical)

CD-1 mice (6/sex/dose) were administered intraperitoneal doses of dioctyl adipate: Group 1 was administered a single dose of 5000 mg/kg-bw; Group 2 was administered two doses of 5000 mg/kg-bw, 24 hours apart. Positive and negative controls were tested concurrently. Bone marrow was excised from the tibia of each animal and processed and 1000 polychromatic erythrocytes (PCEs) were scored for micronucleated PCEs. Response to the positive control was not indicated. No statistically significant differences were observed between treated and control animals in the percent micronucleated PCEs identified; no mitotic depression was observed in the treated groups.

Adipic acid, bis (2-ethylhexyl) ester did not induce micronuclei in this assay.

Adipic acid, bis (2-ethylhexyl) ester (CAS No. 103-23-1, Supporting Chemical)

Adipic acid, bis (2-ethylhexyl) ester is reported to be negative in either sex in a micronucleus test in bone marrow cells from B6C3F1 mice given singly or by two repeated administrations and in a sex-linked recessive lethal assay in Drosophilia melanogaster. In a dominant lethal test in male ICR mice treated intraperitoneally, adipic acid, bis (2-ethylhexyl) ester affected spermatogenesis, decreased pregnancy rate, and increased early embryonic death at 9,200 mg/kg-bw/day.

Additional Information

Skin Irritation

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

New Zealand white rabbits (2 females, 1 male) were administered 0.5 mL of undiluted test substance onto the clipped, intact skin under occluded conditions for 24 hours. Observations for irritation were made over a period of seven days according to Draize method. Very slight erythema was noted at 24 and 48 hours observation period which was cleared by 72 hours. (http://www.syrres.com/esc/tscats.htm)

Adipic acid, di-C7-9 branched and linear alkyl ester was slightly irritating to rabbit skin.

Eye irritation

New Zealand white rabbits (2 females, 1 male) were instilled 0.1 mL of undiluted test substance onto the conjunctival sac of the right eye of each rabbit. The eyes were rinsed with warm isotonic saline solution after 24 hours. Observations were made over a period of seven days. Signs of mild discomfort were seen immediately after the test substance instillation. Mild to moderate erythema, moderate discharge, barely perceptible to slight edema and mild to moderate discharge were seen for up to 24 hours after test substance instillation. The eyes were normal at 48 hours interval. (http://www.syrres.com/esc/tscats.htm)

Adipic acid, di-C7-9 branched and linear alkyl ester was slightly irritating to rabbit eyes.

Carcinogenicity

Adipic Acid, bis (2-ethylhexyl) ester (CAS No. 103-23-1, Supporting Chemical)
In a 103-week carcinogenicity study, adipic acid, bis (2-ethylhexyl) ester was administered in the diet to male and female B6C3F1 mice (6 weeks of age) and Fisher 344 rats (5 weeks of age) at dietary concentrations of 0, 12,000, and 25,000 ppm (approximately 0, 1,080, and 3,750 mg/kg-bw/day in mice; 0, 600, and 1,250 mg/kg-bw/day in rats). An increased incidence of hepatocellular carcinoma and adenoma was observed in female mice in the 1,080 mg/kg-bw/day groups and higher; and in male mice in the 3,750 mg/kg-bw/day. Hepatocellular tumor incidence did not increase in the rats. IARC has classified adipic acid, bis (2-ethylhexyl) ester into Group 3 (substances not classifiable as to its carcinogenicity to humans), since proliferation of peroxisome seen in rodents has not been observed in primates and no relevant human epidemiological data are available.

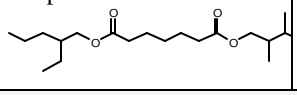
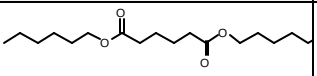
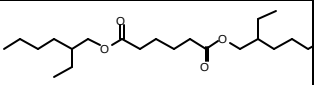
Conclusion: The acute oral toxicity in rats and the acute dermal toxicity in rabbits for adipic acid, di-C7-9 branched and linear alkyl ester is low. Adipic acid, di-C7-9 branched and linear alkyl ester is slightly irritating to rabbit skin and eye. A repeated-dose oral toxicity study on adipic acid, di-C7-9 branched and linear alkyl ester showed no systemic toxicity. Two separate one-generation reproductive toxicity studies with the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, showed no reproductive toxicity. Likewise, numerous repeated-dose toxicity studies in rats on adipic acid, di-C7-9 branched and linear alkyl ester, as well as the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, with examination of various reproductive organs and endpoints showed either no reproductive toxicity or low reproductive toxicity. A prenatal developmental toxicity study on adipic acid, di-C7-9 branched and linear alkyl ester showed low maternal and developmental toxicity. A prenatal developmental toxicity study on the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, that included an assessment of postnatal growth and development, also showed low maternal and developmental toxicity. Adipic acid, di-C7-9 branched and linear alkyl ester did not induce gene mutation, and the supporting chemicals, di(n-hexyl) adipate and adipic acid, bis(2-ethylhexyl) ester, did not induce chromosomal aberrations *in vitro or in vivo*. IARC has classified the supporting chemical, adipic acid, bis(2-ethylhexyl) ester, into Group 3 (substances not classifiable as to its carcinogenicity to humans).

References:

Miyata, K., Shiraishi, K., Houshuyama, S., Imatanaka, N., Umano, T., Minobe, Y., and Yamasaki, K. 2006. Subacute oral toxicity of di(2-ethylhexyl)adipate based on the draft protocol for the "Enhanced OECD Test Guideline no. 407". Arch. Toxicol. 80:181-186.

Nabae, K., Doi, Y., Takahashi, S., Ichihara, T., Toda, C., Ueda, K., Okamato, Y., Kojima, N., Tamano, S., and Shirai, T. 2006. Toxicity of di(2-ethylhexyl) phthalate (DEHP) and di(2-ethylhexyl)adipate (DEHA) under conditions of renal dysfunction induced with folic acid in rats: Enhancement of male reproductive toxicity of DEHP is associated with an increase of the mono-derivative. Reprod. Toxicol. 22:411-417.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program			
Endpoints	**SPONSORED CHEMICAL Adipic acid, di-C7 – C9 branched and linear alkyl ester (68515-75-3)**	**SUPPORTING CHEMICAL Di(n-hexyl) adipate (110-33-8)**	**SUPPORTING CHEMICAL Adipic acid bis(2-ethylhexyl)ester (103-23-1)**
Structure	Representative structure 		
Summary of Environmental Effects – Aquatic Toxicity Data			
Fish 96-h LC_{50} (mg/L)	–*	–**	–**
Aquatic Invertebrates 48-h EC_{50} (mg/L)	–*	–**	–**
Aquatic Plants 72-h EC_{50} (mg/L)	–*	–**	–**
Aquatic Invertebrates 21-d Reproduction (mg/L)	No data No Effects at Saturation (RA)	–**	**No Effects at Saturation**
Summary of Human Health Data			
Acute Oral Toxicity LD_{50} (mg/kg-bw)	> 15,800	–**	-**
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	> 7940	–**	-**
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 1500 (male) (hdt) 1900 (female) (hdt)	–**	-**
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 1500 (male) (hdt) 1900 (female) (hdt)	–**	NOAEL = 1000 (male)(hdt) LOAEL = 1000(female)(hdt) NOAEL= 200 (fetus)
Developmental Toxicity NOAEL/LOAL Oral (mg/kg-bw/day) **Maternal Toxicity** **Developmental Toxicity**	NOAEL = 4000 LOAEL = 7000 NOAEL = 4000 LOAEL = 7000	–**	NOAEL = 400 LOAEL = 800 NOAEL = 200 LOAEL = 400
Genetic Toxicity – Gene Mutation ***In vitro***	Negative	Negative	Negative

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program			
Endpoints	**SPONSORED CHEMICAL Adipic acid, di-C7 – C9 branched and linear alkyl ester (68515-75-3)**	**SUPPORTING CHEMICAL Di(n-hexyl) adipate (110-33-8)**	**SUPPORTING CHEMICAL Adipic acid bis(2-ethylhexyl)ester (103-23-1)**
Genetic Toxicity – Chromosomal Aberrations *In vitro*	No Data Negative (RA)	Negative	–**
Genetic Toxicity – Chromosomal Aberrations *In vivo*	No Data Negative (RA)	Negative	Negative
Other Information – **Skin irritation** **Eye irritation** **Carcinogenicity**	 Slightly irritating Slightly irritating -	 –** –** –**	 –** –** No evidence

(RA) = read-across; (hdt) = highest dose tested; - Indicates that endpoint was not addressed for this chemical;
*Chronic data are preferred and fulfill the endpoint; -** Data not required for supporting chemical;

Screening Level Exposure Characterization for HPV Challenge Chemical

Adipic acid, di-C7-9 branched and linear alkyl ester

CAS # 68515-75-3

September 2008

Prepared by

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Screening Level Exposure Characterization

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS# 68515-75-3)

Non-CBI Executive Summary

Adipic acid, di-C7-9 branched and linear alkyl ester (CAS# 68515-75-3) has an aggregated production and/or import volume in the range of 500,000 to 1 million pounds[13]. Non-confidential information in the Inventory Update Reporting (IUR) indicates that this chemical was manufactured and/or imported at the following company:

- BASF Corporation

There may be other companies that are claimed confidential. Non-confidential IUR information reported processing activities in various industrial sectors but didn't specify the function. IUR information also indicated its use in commercial settings or consumer products as a component of transportation products.

Information submitted as part of the High Production Volume (HPV) Challenge Program indicates that this chemical is used as a plasticizer to give PVC film, sheet and coatings low-temperature flexibility[14]. It is also used as a plasticizer in rubber formulations.

Potential Exposures to the General Population and the Environment: There is potential for environmental release to water during industrial processing and use, as well as during commercial/consumer use, based on the IUR use information and other data sources. Diester chemicals are not on the Toxics Release Inventory[15]. Based on the information considered, including information found from non-confidential public sources, EPA identifies, for purposes of risk-based prioritization, a high potential that the general population and the environment might be exposed.

Persistence and bioaccumulation ratings for this chemical are P1 and B1. These ratings indicate that this chemical is not persistent in the environment; and is not bioaccumulative.

Potential Exposures to Workers: Based on the information considered including IUR data, and from the HPV Challenge Program, and in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a medium relative ranking for potential worker exposure. The medium relative ranking is based on the potential dermal exposure during industrial processing and use activities and commercial uses, as well as potential inhalation exposure to particulates, and the number of workers potentially exposed.

Potential Exposures to Consumers: EPA identifies, for the purposes of risk-based prioritization, a high potential that consumers might be exposed based on the use of products containing this chemical. IUR submissions indicate uses in commercial settings or consumer uses. The non-

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[13] USEPA, 2006. Partial Updating of TSCA Chemical Inventory.
[14] Solutia, 2003. Revised Test Plan for CAS 68515-75-3. http://www.epa.gov/HPV/pubs/summaries/hexanedi/c14079rt.pdf. Accessed, 6/12/2008.
[15] USEPA, 2006. Toxic Release Inventory. http://www.epa.gov/tri/. Accessed, 6/12/08.

confidential commercial/consumer uses for this chemical are as transportation products. The specifics as to whether this is a commercial use as well as a consumer use are not defined. Other IUR submissions reported consumer uses as Not Readily Obtainable (NRO). There is also potential for exposure to consumers based on information from public data sources. This chemical is contained in fabrics used in raingear and luggage, as well as in food-contact packaging, a non-TSCA use[16].

Potential Exposures to Children: The IUR reported that information on products intended for use by children is NRO. No uses in products intended to be used by children are found in any other data sources. Based on this uncertainty (NRO), and that there may be potential exposure of children through the use of some consumer products, EPA identifies, for the purposes of risk-based prioritization, a high potential that children might be exposed.

Below is a summary of non-confidential information in the IUR for this chemical.

This exposure characterization was completed using both public, non-confidential sources, and one or more IUR submissions that were available as of this writing.

[16] OECD 2007. Organization for Economic Cooperation and Development. http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html.

Non Confidential IUR Data Summary: Adipic acid, di-C7-9 branched and linear alkyl ester (68515-75-3)

Manufacturing/Import Information

Production and import volume:	> 500,000 to 1 million pounds
List of non-CBI companies*:	BASF Corporation
Maximum number of potentially exposed workers**:	1,000 or greater (including those of manufacturing, industrial processing and use)
Highest non-CBI maximum concentration:	up to 100% by weight
Non-CBI physical forms*:	liquid

* There may be other companies and physical forms that are claimed confidential.
** There may be additional potentially exposed industrial workers that are not included in this estimate since not all submitters were required to report on industrial processing and use and/or there may be at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions.

Table 1
Industrial Processing and Use Information
Reported in 2006 IUR

Processing Activity	Industrial Sector	Function in Industrial Sector
Processing-incorporation into article	Other Plastics Product Manufacturing	Other
Processing-incorporation into article	Other Rubber Product Manufacturing	Other
Processing-incorporation into article	Plastics Packaging Materials and Unlaminated Film and Sheet Manufacturing	Other
Processing-incorporation into formulation, mixture, or reaction product	Other Plastics Product Manufacturing	Other
Use—non-incorporative activities	Other Chemical and Allied Products Merchant Wholesalers	Other
Not Readily Obtainable	Not Readily Obtainable	Not Readily Obtainable
Additional line item(s) may be claimed as CBI		

Table 2
Commercial/Consumer Uses
Reported in 2006 IUR

Commercial/ Consumer Product Category Description	Highest Maximum Concentration Range	Use in Children's Products
Transportation products	1% - 30%	No
Not readily obtainable	NRO	NRO
Additional line item(s) may be claimed as CBI		