SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

CHEMICAL CATEGORY NAME
Dibasic Esters (DBE)

Dimethyl Succinate (DMS, butanedioic acid, dimethyl ester)	**CAS No. 106-65-0**
Dimethyl Glutarate (DMG, pentanedioic acid, dimethyl ester)	**CAS No. 1119-40-0**
Dimethyl Adipate (DMA, hexanedioic acid, dimethyl ester)	**CAS No. 627-93-0**
DBE (Mixture of 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS)	**CAS No. 96481-62-2**

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SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program[1] 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 website[3].

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 EPA[2] and OECD[5] 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.

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[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
Dibasic Esters (DBE) Category

Introduction

The sponsor, Dibasic Esters Group of Synthetic Organic Chemical Manufactures Association, Inc. (SOCMA), submitted a Test Plan and Robust Summaries to EPA for the Dibasic Ethers Category on December 31, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 30, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/dbe/c13453tc.htm). EPA comments on the original submission were posted to the website on September 10, 2002. Public comments were also received and posted to the website. The sponsor provided EPA with revised documents on November 8, 2002 and May 30, 2003, which were posted to the ChemRTK website on November 29, 2002 and June 27, 2003, respectively. The Dibasic Esters Category consists of the following chemicals:

Dimethyl Succinate (DMS, butanedioic acid, dimethyl ester)	CAS No. 106-65-0
Dimethyl Glutarate (DMG, pentanedioic acid, dimethyl ester)	CAS No. 1119-40-0
Dimethyl Adipate (DMA, hexanedioic acid, dimethyl ester)	CAS No. 627-93-0
DBE (Mixture of 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS)	CAS No. 95481-62-2

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. Structure(s) of the sponsored chemical(s) is included in the appendix. 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 basis for the category is similarity in structure, physicochemical properties and toxicity responses among the category members. The three discrete compounds are short, straight-chain dicarboxylic acid dimethyl esters differing by one carbon atom, from four to six carbons, in the dicarboxylic acid moiety. The three category members and the mixture produce similar levels of acute and repeated-dose toxicity in experimental animals, such that information on one category member is expected to represent the toxicity of the category as a whole.

In response to EPA's comments, the sponsor conducted two environmental effects studies (daphnid and algae studies with DMA) for the purposes of the HPV Challenge Program. EPA agreed with the sponsor's approach to justify quantitative structure-activity relationships (QSAR) of the chemicals in this category.

Summary-Conclusion

The dibasic esters are liquids at room temperature with moderate vapor pressures and high water solubilities. They are moderately volatile and will be slowly photolyzed in the atmosphere. They are highly mobile in soil and water systems. They are not persistent and are not bioaccumulative. They are expected to hydrolyze slowly and biodegrade rapidly. Because the chemicals in this category are readily biodegradable and do not appreciably bioaccumulate they are classified as P1B1 and are not Persistent Organic Pollutants (POPs).

The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential hazard of the dibasic esters categories to aquatic organisms is low.

The acute oral and acute dermal toxicity for all category members is low. The category members are not skin irritants, but cause mild to moderate eye irritation.

Repeated exposures to these chemicals via inhalation show local effects (likely a result of irritation at the point of contact in the nasal region) as well as some changes in hormone levels that, although consistently observed, are not

considered to be toxicologically significant. In all 90-day inhalation studies (one each with DMS, DMA, and DMG and two with the mixture DBE), degeneration/atrophy and focal respiratory metaplasia of the olfactory mucosa with minimum to mild severity was observed in both males and females. Exposed animals also showed marked microscopic alterations in the DMS, DMA, and DMG studies as measured by increases in cell proliferation (CP) in the liver (males), nasal area (males and females) and lung (females).

The following effects on reproductive parameters were observed in the 90-day studies with DMS, DMA, and DMG: increase in epididymal sperm counts (2/3 studies), decrease in testosterone levels (1/3 studies), and decrease in leutenizing hormone levels (1/3 studies) - all in males, and decrease in estradiol levels in females (1/3 studies). The significance of these findings is unclear because the decrease in male hormone levels should result in a decrease in sperm counts, yet the opposite effect was observed. The single study showing changes in estradiol was not observed in the other two studies. Other reproductive parameters evaluated in these studies but which were not affected by treatment were: follicle stimulating hormone (FSH) and sperm motility/morphology in males and progesterone level and estrous cyclicity in females. In addition, a reproductive study was conducted with the fourth member of the category (DBE) and there were no effects on the following reproductive parameters: fertility, viability of pups at birth, and the ability of the mothers to lactate.

In a developmental toxicity study in rats, a marked reduction in maternal body weight gain and food consumption was seen during the exposure period at the highest concentration tested. No effects on fetal survival, fetal weight, litter size, implantations, or increased incidences of fetal malformations/variations were seen. In rabbits, reductions in body weights in dams and a marked increased in delayed ossification in fetuses were seen in the high dose group only. The dibasic esters category was not mutagenic in tested strains of *Salmonella typhimurium* and did not induce statistically significant increase in the mean number of micronucleated polychromatic erythrocytes in the bone marrow of CD-1 mice.

The potential health hazard of chemicals in the dibasic esters category is considered low because the effects observed were: (a) local effects to the nasal epithelium that are likely the result of irritation; (b) changes in hormone levels that do not appear to have toxicological significance; or (c) developmental toxicity at high doses.

No data gaps have been identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

This report was prepared using the best available data from a number of sources, including information within High Production Volume Test Plans for dibasic esters (SOCMA, 2002), the Hazardous Substance Data Bank (HSDB, 2007), and estimations using EPIWIN (EPA, 2007). Basic physical-chemical and environmental fate properties of these compounds are listed in Tables 1a and 1b, respectively. The structures of all category members are in the Appendix.

Physical-Chemical Properties Characterization

The category members are liquids at room temperature with moderate vapor pressures and high water solubilities.

Environmental Fate Characterization

The measured vapor pressures of these chemicals suggest that when released to the atmosphere they will exist primarily in the vapor phase. Vapor-phase DMS, DMG, and DMA are expected to degrade in the atmosphere by reaction with photochemically-produced hydroxyl radicals with estimated half-lives of 9.3, 4.2 and 2.7 days respectively. If released to soil, their estimated Log K_{oc} value suggests that these chemicals will be very mobile. They are not expected to volatilize from dry or wet soil surfaces based on this compound's vapor pressure and estimated Henry's Law constants . If released into water these chemicals are not expected to adsorb to suspended solids and sediment in the water column. The potential for bioconcentration of DMS in aquatic organisms is low based on its estimated Log BCF. Volatilization from water surfaces is moderate based on these compounds' Henry's Law constants. These compounds are expected to be easily biodegraded, with ultimate biodegradation occurring over a period of days to weeks. DMG has been shown to be easily biodegradable and the others members of the category are expected to be also. Hydrolysis is expected to be pH dependent. Estimated half-lives for the 3

individual bibasic esters range from 1.6 to 2.3 years at pH 7. This suggests that hydrolysis under environmental conditions will be slow to insignificant. Persistence and bioaccumulation are qualitatively characterized according to the criteria set forth in the PMN program (FR, 1999). Because the chemicals in this category are readily biodegradable and do not appreciably bioaccumulate they are classified as P1B1 and are not Persistent Organic Pollutants (POPs).

Table 1a. Physical-Chemical Properties of Dibasic Esters[1]

	Butanedioic acid, dimethyl ester (Dimethyl Succinate - DMS) CAS No. 106-65-0	**Pentanedioic acid, dimethyl ester (Dimethyl Glutarate – DMG) CAS No. 1119-40-0**	**Hexanedioic acid, dimethyl ester (Dimethyl Adipate – DMA) CAS No. 627-93-0**	**DBE - Mixture containing 10-25% DMA, 55-65% DMG, and 15-25% DMS CAS No. 95481-62-2**
Property	**Value/Descriptor**	**Value/Descriptor**	**Value/Descriptor**	**Value/Descriptor**
Melting Point (ºC)	19°C	-37°C	8.5°C	~ -20°C
Boiling Point Range (ºC)	196 °C at 1013 hPa	213.5-214°C at 752 mm Hg	230.9°C at 1013 hPa	196-225°C at 760 mm Hg
Vapor Pressure (mm Hg at 25 ºC)	0.41	0.18	0.0604	0.41 (RA)
Log K_{ow}	0.19	0.62	1.03	0.19
Water Solubility (mg/L)	131 g/L at 25°C	43.0 g/L at 20°C	29.9 g/L at 20°C	53.3 g/L at 20°C

(1) = HSDB, 2007 or US EPA 2007
(RA) = Read Across

Table 1b. Environmental Fate Characteristics of Dibasic Esters				
	Butanedioic acid, dimethyl ester (Dimethyl Succinate - DMS) CAS No. 106-65-0	**Pentanedioic acid, dimethyl ester (Dimethyl Glutarate – DMG) CAS No. 1119-40-0**	**Hexanedioic acid, dimethyl ester (Dimethyl Adipate – DMA) CAS No. 627-93-0**	**DBE - Mixture containing 10-25% DMA, 55-65% DMG, and 15-25% DMS CAS No. 95481-62-2**
Property	**Value/Descriptor**	**Value/Descriptor**	**Value/Descriptor**	**Value/Descriptor**
Direct Photodegra-dation	Not expected to undergo direct photolysis because chemicals do not contain functional groups that absorb light at greater than 290 nm.			
Indirect (OH^-) Photodegradation $t_{1/2}$ (hr)	$t_{1/2}$ = 9.3 days (1)	$t_{1/2}$ = 4.17 days (1)	$t_{1/2}$ = 2.69 days (1)	$t_{1/2}$ = 9.3 days (RA)
Hydrolysis	No data $t_{1/2}$ =2 years (1) (RA)	No data $t_{1/2}$ =2 years (1) (RA)	$t_{1/2}$ =2 years (1)	No data $t_{1/2}$ =2 years (1) (RA)
Henry's Law (atm m^3/ mol)	2.1 x 10^{-6} (1)	1.9 x 10^{-6} (1)	2.0 x 10^{-5} (1)	--
Log K_{oc}	1 (1)	1 (1)	1 (1)	1 (1)
Distribution (Level III fugacity model)	About 1 % air, 40 %water, 60 % soil			
Biodegradation	Readily biodegradable (RA)	Readily biodegradable; 98% degraded after 28 days (2)	No Data Readily biodegradable (RA)	Readily biodegradable (RA)
Bioconcentration Factor	3.162 (1)	3.162 (1)	1.2 (1)	No data 3.16 (1) (RA)
Persistance [3]	P1 (low)	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation [3]	B1 (low)	B1 (low)	B1 (low)	B1 (low)

(1) Estimated data, (USEPA, 2007)
(2) Measured data - OECD Guideline 301 C -Ready Biodegradability: Modified MITI Test (I) (SOCMA, 2002).
(3) FR 1999
RA = Read Across

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. All data presented below are from the submission by the sponsor (SOCMA, 2002) unless otherwise noted.

Acute Toxicity to Fish

Dimethyl succinate (DMS, butanedioic acid, dimethyl ester; CAS No. 106-65-0)
Brachydanio rerio were exposed to DMS. Limited study information was available.
96-h LC_{50} = 50 – 100 mg/L

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)
Bluegill sunfish (*Lepomis macrochirus;* 10/per concentration were exposed to DMG at nominal concentrations of 20 – 50 mg/L for 96 hours under static conditions.
96-h LC_{50} = 30.9 mg/L

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)
Fathead minnows (*Pimephales promelas*) were exposed to DBE at nominal concentrations ranging from 18 – 24 mg/L for 96 hours under static conditions.
96-h LC_{50} = 18 – 24 mg/L

Acute Toxicity to Aquatic Invertebrates

Dimethyl succinate (DMS, butanedioic acid, dimethyl ester; CAS No. 106-65-0)
A 48-hour EC_{50} for *Daphnia*, estimated by ECOSAR, was provided to support evaluation of the acute toxicity of DMS.
48-h EC_{50} = 3317.3 mg/L (estimated)

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)
A 48-hour EC_{50} for *Daphnia*, estimated by ECOSAR, was provided to support evaluation of the acute toxicity of DMG.
48-h EC_{50} = 1275 mg/L (estimated)

Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester; CAS No. 627-93-0)
D. magna (20/concentration) were exposed to DMA at mean measured concentrations of 6.9, 14, 29, 58 or 120 mg/L for 48 hours under static conditions.
48-h EC_{50} = 72 mg/L

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)
(1) *D. magna* were exposed to DBE at nominal concentrations ranging from 100 to 300 mg/L for 48 hours under static conditions.
48-h EC_{50} = 136 mg/L

(2) *D. magna* were exposed to DBE at nominal concentrations of 112 and 150 mg/L for 48 hours under static conditions.
48-h EC_{50} > 112 and < 150 mg/L

Toxicity to Aquatic Plants

Dimethyl succinate (DMS, butanedioic acid, dimethyl ester; CAS No. 106-65-0)
A 96-hour EC_{50} for green algae, estimated by ECOSAR, was provided to evaluate the acute toxicity of DMS.
96-h EC_{50} = 11.9 mg/L (estimated)

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)
A 96-hour EC_{50} for green algae, estimated by ECOSAR, was provided to evaluate the acute toxicity of DMG.
96-h EC_{50} = 7.2 mg/L (estimated)

Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester; CAS No. 627-93-0)
Green algae (*Pseudokirchneriella subcapitata*) were exposed to DMA for 72 hours at measured concentrations of 6.25, 12.5, 25, 50, and 100 mg/L, under static conditions.
EC_{50} (biomass) = >100 mg/L
EC_{50} (growth) = >100 mg/L

Conclusion: The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential hazard of the dibasic esters categories to aquatic organisms is low.

Table 2. Summary of Environmental Effects – Aquatic Toxicity Data				
Endpoints	**Dimethyl succinate (DMS, butanedioic acid, dimethyl ester) (CAS No. 106-65-0)**	**Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester) (CAS No. 1119-40-0)**	**Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester) (CAS No. 627-93-0)**	**DBE - Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)**
Fish **96-h LC_{50} (mg/L)**	**50 – 100 (m)**	**30.9 (m)**	No Data 30.9 (RA)	**18 - 24 (m)**
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	3317 (e)	1275 (e)	**72 (m)**	**136 (m)** **112 – 150 (m)**
Aquatic Plants **72-h EC_{50} (mg/L)**	11.9 (e)	7.2 (e)	**> 100 (m)**	No Data 7.2 (RA)

(**m) = measured data (i.e. derived from testing);** (e) = estimated data (i.e. derived from modeling); (RA) = read across;

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. All data presented below are from the submission by the sponsor (SOCMA, 2002) unless otherwise noted.

Acute Oral Toxicity

Dimethyl succinate (DMS, butanedioic acid, dimethyl ester; CAS No. 106-65-0)
Sprague-Dawley rats (5/sex/dose) were administered DMS via gavage at a 500 and 5000 mg/kg-bw and observed for 14 days. No mortalities occurred at 500 mg/kg-bw and all animals died at 5000 mg/kg-bw.
LD_{50} > 500 and < 5000 mg/kg-bw

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)
Sprague-Dawley rats (5/sex/dose) were administered DMG via gavage at 5000 mg/kg-bw and observed for 14 days. All animals survived to 14 days.
LD_{50} > 5000 mg/kg-bw

Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester; CAS No. 627-93-0)
Sprague-Dawley rats (5/sex/dose) were administered DMA via gavage at a 500 and 5000 mg/kg-bw and observed for 14 days. No mortalities occurred at 500 mg/kg-bw and two animals died at 5000 mg/kg-bw.
LD_{50} > 5000 mg/kg-bw

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)
Sprague-Dawley rats (5/sex/dose) were administered DBE via gavage at a 500 and 5000 mg/kg-bw and observed for 14 days. At 500 and 5,000 mg/kg-bw mortality rates were 0/10 and 8/10, respectively. The mortalities occurred in the first two days.
LD_{50} > 500 and < 5000 mg/kg-bw

Acute Dermal Toxicity

Dimethyl succinate (DMS, butanedioic acid, dimethyl ester; CAS No. 106-65-0)
New Zealand White rabbits (5/sex) were administered a single dose (5000 mg/kg-bw) of DMS applied directly to the skin for 24 hours and were observed for 14 days after removal of excess test substance. No mortalities occurred.
LD_{50} > 5000 mg/kg-bw

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)
New Zealand White rabbits (5/sex) were administered a single dose of DMG applied directly to the skin for 24 hours and were observed for 14 days after removal of excess test substance. No mortalities occurred.
LD_{50} > 5000 mg/kg-bw

Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester; CAS No. 627-93-0)
New Zealand White rabbits (5/sex) were administered a single dose (5000 mg/kg-bw) of DMA applied directly to the skin for 24 hours and were observed for 14 days after removal of excess test substance. No mortalities occurred.
LD_{50} > 5000 mg/kg-bw

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)
New Zealand White rabbits (5/sex) were administered a single dose (5000 mg/kg-bw of DBE applied directly to the skin for 24 hours and were observed for 14 days after removal of excess test substance. No mortalities occurred.
LD_{50} > 5000 mg/kg-bw

Acute Inhalation Toxicity

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)
Crl:CD rats (5/sex) were exposed nose-only for a single 4-hour period to aerosol/vapor mixtures of DBE in air at 5.6 and 11 mg/L and observed for 14 days. Transient clinical signs observed at concentrations of 5.6 mg/L or greater include red ocular or nasal discharge, lethargy, labored breathing or hunched posture, and slight to sever weight loss. Ophthalmologic examination revealed mild chemosis (swelling) in the bulbar conjunctiva. No mortalities occurred.
LD_{50} > 11 mg/L

Repeated-Dose Toxicity

Dimethyl succinate (DMS, butanedioic acid, dimethyl ester; CAS No. 106-65-0)
Sprague-Dawley rats were exposed to DMS via inhalation at 0 or 400 mg/m^3 (0.4 mg/L), 6 hours/day, 5 days/week for 90 days. A 1-month recovery group was included in the study. Neurobehavioral test battery; evaluation of male reproductive organs including sperm count, motility and morphology; cell proliferation (CP—hepatic, lung, and nasal tissues); female estrous cycle determination; and hormonal analysis (serum leutenizing hormone (LH), follicle stimulating hormone (FSH) and testosterone in males and serum estradiol and progesterone concentrations in females) were included in the test. Test-substance-related effects seen in the noses of male and female rats at 400 mg/m^3 DMS included degeneration/atrophy and focal respiratory metaplasia of the olfactory mucosa with minimum to mild severity. Degeneration/atrophy of the olfactory mucosa was evident in recovery animals in the same locations as observed in the animals examined after 90 days of exposure. Male rats exposed to 400 mg/m^3 showed marked increase in CP in the liver and the females had greater CP in the nose level III relative to controls. Females showed a statistically significant decrease (43% of control) in serum estradiol concentrations. In male rats, epididymal sperm counts were significantly increased (141 – 153% of control).
LOAEL = 400 mg/m^3 (0.4 mg/L; based on effects on nasal tissues, decrease in estradiol concentration in females and increased epididymal sperm counts in males**)**
NOAEL = Not established

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)
Sprague-Dawley rats were exposed to DMG via inhalation at 0, 10, 50 or 400 mg/m^3 (0, 0.01, 0.05 or 0.4 mg/L), 6 hours/day, 5 days/week for 90 days. A 1-month recovery group was included in the study. Neurobehavioral test battery; evaluation of male reproductive organs including sperm count, motility and morphology; cell proliferation (CP—hepatic, lung, and nasal tissues); female estrous cycle determination; and hormonal analysis (serum LH, FSH

and testosterone in males and serum estradiol and progesterone concentrations in females) were included in the test. Male rats exposed to 400 mg/m^3 showed lower mean body weight and body weight gains during the study and male and female rats had lower food consumption. Test substance-related effects seen in the noses of male and female rats at 400 mg/m^3 DMG included degeneration/atrophy and focal respiratory metaplasia of the olfactory mucosa with minimum to mild severity. Degeneration/atrophy of the olfactory mucosa was evident in recovery animals in the same locations as observed in the animals examined after 90 days of exposure. Male and female rats exposed to 400 mg/m^3 DMG showed marked increase in CP in the nose level III. Male rats showed a statistically significant decrease in serum testosterone levels at 50 and 400 mg/m^3 (59 and 50% of control, respectively). Serum LH concentration was decreased in a dose-dependent manner and was statistically significant at 400 mg/m^3 (71% of control). In addition, a significant increase in epididymal sperm count was seen in the animals exposed to 50 and 400 mg/m^3 (124 and 131% of control, respectively).
LOAEL = 50 mg/m^3 (0.05 mg/L, based on decrease in serum LH concentration in a dose-dependent manner, decrease in testosterone concentration, effects on nasal tissues, increased epididymal sperm counts at 50 mg/m^3 and above in males**)**
NOAEL = 10 mg/m^3 (0.01 mg/L)

Dimethyl adipate (DMA, Hexanedioic acid, dimethyl ester; CAS No. 627-93-0)
Sprague-Dawley rats were exposed to DMA via inhalation at 0 or 400 mg/m^3 (measured as 390 mg/m^3; 0.39 mg/L), 6 hours/day, 5 days/week for 90 days. A 1-month recovery group was included in the study. Neurobehavioral test battery; evaluation of male reproductive organs including sperm count, motility, and morphology; cell proliferation (CP—hepatic, lung, and nasal tissues); female estrous cycle determination; and hormonal analysis (serum LH, FSH and testosterone in males and serum estradiol and progesterone concentrations in females) were included in the test. Test-substance-related effects seen in the noses of male and female rats at 400 mg/m^3 DMA included degeneration/ atrophy and focal respiratory metaplasia of the olfactory mucosa with minimum to mild severity. Degeneration/ atrophy of the olfactory mucosa was evident in recovery animals in the same locations as observed in the animals examined after 90 days of exposure. Male rats exposed to 400 mg/m^3 showed marked increase in CP in the liver and had greater CP in the nose level II relative to controls. Female rats exposed to 400 mg/m^3 had greater CP in the lungs relative to controls. In male rats, although not statistically significant, an increase in epididymal sperm counts was noted.
LOAEL = 400 mg/m^3 (~ 0.4 mg/L; based on effects on nasal tissues, increase in CP in liver, lungs and nose**)**
NOAEL = Not established

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)
(1) In a 90-day inhalation toxicity study, rats were exposed to DBE aerosol-vapor mixture at 160, 400 or 1000 mg/m^3 (~0.160, 0.400 or 1.0 mg/L) 6 hours/day, 5 days/week for approximately 14 weeks. Histopathological examination of nasal tissues showed degeneration of the olfactory epithelium in all DBE-exposed groups. Effects were of minimal severity in the 160 mg/m^3 group and mild to moderate at the mid- and high-concentrations. A dose-dependent decrease in liver to body weight ratio was seen in male and female rats from the 400 and 1000 mg/m^3 groups and a slight increase in lung/body weight ratio and decreased body weights in animals from the 1000 mg/m^3 group.
LOAEL = 160 mg/m^3 (~ 0.16 mg/L; based on degeneration of olfactory epithelium**)**
NOAEL = Not established

(2) In another 90-day inhalation toxicity study, male and female rats were exposed to DBE at 20, 76 or 390 mg/m^3 (0.02, 0.076 or 0.39 mg/L) for 13 weeks. A 6-week recovery group was also included in the study. The results indicated degeneration of olfactory epithelium in male rats exposed to 76 or 390 mg/m^3 and in female rats exposed to all test concentrations. At the end of the 6-week recovery period, these effects were still visible in affected animals. In female rats exposed to 390 mg/m^3, depressed body weight gain and liver weights were evident compared to controls. A slight decrease in sodium levels was evident at 76 and 390 mg/m^3 in male and female rats. After 6 weeks of recovery, the sodium level was still low in animals exposed to 390 mg/m^3. A NOAEC was not demonstrated in female rats.
NOAEL = 20 mg/m^3 (0.02 mg/L; based on degeneration of olfactory epithelium in males**)**
LOAEL = 20 mg/m^3 (~0.020 mg/L; based on degeneration of olfactory epithelium at all concentrations in females**)**

(3) In an oral toxicity study, male and female rats were dosed with DBE daily via oral gavage at 0, 100, 300 or 1000 mg/kg-bw/day for 1 month. Except for a small decrease in urine pH in male and female rats at 1000 mg/kg-bw/day, no other systemic toxicity was evident.
NOAEL = 1000 mg/kg-bw/day

Reproductive Toxicity

No data were submitted to address the reproductive toxicity endpoint for DMS, DMG or DMA. Evaluations of reproductive parameters reported in the repeated-dose toxicity studies along with the submitted developmental toxicity study (next section) were used to address the reproductive endpoints for the purposes of the HPV Challenge Program. Therefore, NOAEL/LOAELs for fertility and/or reproductive toxicity cannot be determined for these studies.

Dimethyl succinate (DMS, Butanedioic acid, dimethyl ester; CAS No. 106-65-0)
In the repeated-dose study described previously, Sprague-Dawley rats were exposed to DMS via inhalation at 0 or 400 mg/m^3, 6 hours/day, 5 days/week for 90 days. A 1-month recovery group was included. Evaluation of male reproductive organs included sperm count, motility, and morphology. Female estrous cycle determination and hormone analyses, serum LH, FSH and testosterone in males and serum estradiol and progesterone concentrations in females were included in the test. No test substance related effects were observed on sperm motility or morphology or female estrous cycle. In females, DMS caused a statistically significant decrease in serum estradiol concentrations (43% of control); progesterone was not affected. In male rats, epididymal sperm counts were significantly increased (141 – 153%).

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)
In the repeated-dose study described previously, Sprague-Dawley rats were exposed to DMG via inhalation at 0, 10, 50 or 400 mg/m^3 (0, 0.01, 0.05 or 0.4 mg/L), 6 hours/day, 5 days/week for 90 days. A 1-month recovery group was included in the study. Evaluation of male reproductive organs including sperm count, motility, and morphology; female estrous cycle determination; and hormone analyses serum LH, FSH and testosterone in males and serum estradiol and progesterone concentrations in females, were included in the test. No test substance related effects were observed on sperm motility or morphology or female estrous cycle. In females, DMG exposure did not affect estradiol or progesterone concentrations. Male rats showed a statistically significant decrease in serum testosterone levels at 50 and 400 mg/m^3 (59 and 50% of control, respectively). Serum LH concentrations were statistically significantly decreased at 400 mg/m^3 (71% of control). Significant, treatment-related increases in epididymal sperm count were seen in the 50 and 400 mg/m^3 (124 and 131% of control, respectively) animals.

Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester; CAS No. 627-93-0)
In the repeated-dose study described previously, Sprague-Dawley rats were exposed to DMA via inhalation at 0 or 400 mg/m^3 (measured as 390 mg/m^3; 0.39 mg/L), 6 hours/day, 5 days/week for 90 days. A 1-month recovery group was included in the study. Evaluation of male reproductive organs including sperm count, motility, and morphology; female estrous cycle determination; and hormone analyses, serum LH, FSH and testosterone in males and serum estradiol and progesterone concentrations in females, were included in the test. No test-substance related effects were observed on sperm motility or morphology, estrous cycle or serum hormone levels. In male rats, although not statistically significant, increase in epididymal sperm counts were noted.

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)
Groups of male and female rats were mated after 14 weeks of inhalation exposure to DBE vapor for 6 hours/day, 5 days/week at concentrations of 160, 400 or 1000 mg/m^3 (0.16, 0.4 or 1.0 mg/L). DBE exposure continued during the mating, gestation and lactation periods, discontinued for the dams after the 19th gestation day and begun again on postpartum day 4. Offspring were not exposed to DBE. The only observed DBE exposure-related effect was decreased pup weights in the 1000 mg/m^3 exposure group from postpartum days 1 – 21. DBE exposure did not affect male or female fertility indices, live birth index, viability index, or gestational and lactation indices. Gross pathological examination of 21-day-old rats whose parents had been exposed to DBE did not show any exposure-related effects.
LOAEL = 1000 mg/m^3 (1.0 mg/L; based on decreased pup weights in the high-dose group)
NOAEL = 400 mg/m^3 (0.4 mg/L)

Developmental Toxicity

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)
The developmental toxicity data summary for DMG provided here was not part of the data submission provided by the sponsor; rather, it was provided to EPA as part of a TSCA Section 4 Enforceable Consent Agreement (available at www.regulations.gov, docket number EPA-HQ-OPPT-2002-0009-0011).
New Zealand White rabbits were exposed via inhalation to DMG concentrations of 0, 30, 100, 300 or 1000 mg/m^3 (0.03, 0.1, 0.3 or 1.0 mg/L) during gestation. Treatment-related signs of toxicity (ocular discharge – likely due to eye irritation) and significant reductions in body weight gain were seen in does at 300 mg/m^3 and above. Two mortalities (one doe found dead and one sacrificed *in extremis*) were observed in the highest dose group. Fetal effects included a marked increase in delayed ossification at 1000 mg/m^3.
LOAEL (maternal toxicity) = 300 mg/m^3 (0.3 mg/L; based on body weight effects**)**
NOAEL (maternal toxicity) = 100 mg/m^3 (0.1 mg/L)
LOAEL (developmental toxicity) = 1000 mg/m^3 (1.0 mg/L; based on delayed ossification**)**
NOAEL (developmental toxicity) = 300 mg/m^3 (0.3 mg/L)

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)
Pregnant rats were exposed to DBE via inhalation 6 hours/day during days 7 – 16 of gestation at 160, 400 or 1000 mg/m^3 DBE. Maternal body weight gains and food consumption were significantly reduced during the exposure period at 400 and 1000 mg/m^3. No effects on fetal survival, fetal weight, litter size or implantations were seen. The incidence of fetal malformations and variations showed no exposure-related changes.
LOAEL (maternal toxicity) = 400 mg/m^3 (based on decreased body weight gain and food consumption)
NOAEL (maternal toxicity) = 160 mg/m^3
NOAEL (developmental toxicity) = 1000 mg/m^3 (highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro
Dimethyl succinate (DMS, butanedioic acid, dimethyl ester; CAS No. 106-65-0)
In an Ames assay, DMS was tested using *Salmonella typhimurium* strains in the presence and absence of metabolic activation and up to 20,000 µg/plate of test substance. At high doses, cytotoxicity was seen, but the chemical did not induce increases in revertant colonies.
Dimethyl succinate was not mutagenic in this assay.

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)
In an Ames assay, DMG was tested using *Salmonella typhimurium* strains in the presence and absence of metabolic activation and up to 20,000 µg/plate of test substance. At high doses, cytotoxicity was seen, but the chemical did not induce increases in revertant colonies.
Dimethyl glutarate was not mutagenic in this assay.

Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester; CAS No. 627-93-0)
In an Ames assay, DMA was tested using *Salmonella typhimurium* strains in the presence and absence of metabolic activation and up to 20,000 µg/plate of test substance. At high doses, cytotoxicity was seen, but the chemical did not induce increases in revertant colonies.
Dimethyl adipate was not mutagenic in this assay.

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)
In an Ames assay, DBE was tested using *Salmonella typhimurium* strains in the presence and absence of metabolic activation and up to 20,000 µg/plate of test substance. At high doses, cytotoxicity was seen, but the chemical did not induce increases in revertant colonies.
DBE was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo

Dimethyl succinate (DMS, butanedioic acid, dimethyl ester; CAS No. 106-65-0)

An *in vivo* mammalian bone marrow micronucleus assay was conducted in mice. The chemical did not induce statistically significant increases in the mean number of micronucleated polychromatic erythrocytes in the bone marrow of CD-1 mice.

Dimethyl succinate was not mutagenic in this assay.

Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester; CAS No. 1119-40-0)

An *in vivo* mammalian bone marrow micronucleus assay was conducted in mice. The chemical did not induce statistically significant increases in the mean number of micronucleated polychromatic erythrocytes in the bone marrow of CD-1 mice.

Dimethyl glutarate was not mutagenic in this assay.

Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester; CAS No. 627-93-0)

An *in vivo* mammalian bone marrow micronucleus assay was conducted in mice. The chemical did not induce statistically significant increases in the mean number of micronucleated polychromatic erythrocytes in the bone marrow of CD-1 mice.

Dimethyl adipate was not mutagenic in this assay.

DBE—Mixture containing 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS (CAS No. 95481-62-2)

An *in vivo* mammalian bone marrow micronucleus assay was conducted in mice. The chemical did not induce statistically significant increases in the mean number of micronucleated polychromatic erythrocytes in the bone marrow of CD-1 mice.

DBE was not mutagenic in this assay.

Additional Information

Irritation

The members of the dibasic esters category are not irritating to skin but cause mild to moderate eye irritation.

Conclusion: The acute oral and acute dermal toxicity for all category members is low. The category members are not skin irritants, but cause mild to moderate eye irritation. Repeated exposures to these chemicals via inhalation show degeneration/atrophy and focal respiratory metaplasia of the olfactory mucosa with minimum to mild severity. Male rats showed marked increase in cell proliferation (CP) in the liver and had greater CP in the nose level II relative to controls. Female rats exposed to 400 mg/m^3 has greater CP in the lungs. Effects on reproductive parameters, increase in epididymal sperm counts, were noted following repeated exposures to all category members. In developmental toxicity studies in rats, a marked reduction in maternal body weight and food consumption was seen during the exposure period. No effects on fetal survival, fetal weight, litter size or implantations were seen. The incidence of fetal malformations and variations showed no exposure-related changes. In rabbits, reductions in body weights in dams and a marked increased in delayed ossification in fetuses were seen in the high dose group. The dibasic esters category was not mutagenic in tested strains of *Salmonella typhimurium* and did not induce statistically significant increase in the mean number of micronucleated polychromatic erythrocytes in the bone marrow of CD-1 mice.

Table 3. Summary of Human Health Data				
Endpoints	**Dimethyl succinate (DMS, butanedioic acid, dimethyl ester) (CAS No. 106-65-0)**	**Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester) (CAS No. 1119-40-0)**	**Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester) (CAS No. 627-93-0)**	**DBE - Mixture containing 10 – 25% DMA, 55 – 65% DMG, and 15 – 25% DMS (CAS No. 95481-62-2)**
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**> 500 and < 5000**	**> 5000**	**> 5000**	**> 500 and < 5000**
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	**> 5000**	**> 5000**	**> 5000**	**> 5000**
Acute Inhalation Toxicity LC_{50} (mg/L)	No Data	No Data	No Data	**> 11**
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	No Data	No Data	No Data	**NOAEL = 1000**
Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L/day)	**NOAEC = Not established LOAEC = 0.4**	**NOAEC = 0.01 LOAEC = 0.05**	**NOAEC = Not established LOAEC = 0.4**	**NOAEC = Not established LOAEC = 0.16** **NOAEC = 0.02 LOAEC = 0.02**
Reproductive Toxicity Inhalation (mg/L/day)	Evaluation of reproductive parameters from 90-day study—Increased epididymal sperm counts and increased estradiol in females	Evaluation of reproductive parameters from 90-day study—Increased epididymal sperm counts, and decreased testosterone and LH levels in males	Evaluation of reproductive parameters from 90-day study—non-significant increase in epididymal sperm counts	**NOAEL = 0.4 LOAEL = 1.0**
Developmental Toxicity **Maternal Toxicity** **Developmental Toxicity All Inhalation (mg/L/day)**	 NOAEC = 0.1 LOAEC = 0.3 NOAEC = 0.3 LOAEC = 1.0 (RA[1])	 **NOAEC = 0.1** **LOAEC = 0.3** **NOAEC = 0.3** **LOAEC = 1.0**	 NOAEC = 0.1 LOAEC = 0.3 NOAEC = 0.3 LOAEC = 1.0 (RA[1])	 **NOAEC = 0.16** **LOAEC = 0.4** **NOAEC = 1.0** **LOAEC = Not established**
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**	**Negative**	**Negative**	**Negative**
Genetic Toxicity – Chromosomal Aberrations *In vivo*	**Negative**	**Negative**	**Negative**	**Negative**
Skin Irritation	**Not a skin irritant**	**Not a skin irritant**	**Not a skin irritant**	**Not a skin irritant**
Eye Irritation	**Mild to moderate**	**Mild to moderate**	**Mild to moderate**	**Mild to moderate**

Measured data in bold text; (RA) = read across

[1] Data from DMA is used in the read-across because it represents a pure substance as opposed to the DBE data which are from a mixture of DMA, DMS, and DMG.

4. Hazard Characterization

The dibasic esters are liquids at room temperature with moderate vapor pressures and high water solubilities. They are moderately volatile and will be slowly photolyzed in the atmosphere. They are highly mobile in soil and water systems. They are not persistent and are not bioaccumulative. They are expected to hydrolyze slowly and biodegrade rapidly. Because the chemicals in this category are readily biodegradable and do not appreciably bioaccumulate they are classified as P1B1 and are not Persistent Organic Pollutants (POPs).

The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential hazard of the dibasic esters categories to aquatic organisms is low.

The acute oral and acute dermal toxicity for all category members is low. The category members are not skin irritants, but cause mild to moderate eye irritation.

Repeated exposures to these chemicals via inhalation show local effects (likely a result of irritation at the point of contact in the nasal region) as well as some changes in hormone levels that, although consistently observed, are not considered to be toxicologically significant. In all 90-day inhalation studies (one each with DMS, DMA, and DMG and two with the mixture DBE), degeneration/atrophy and focal respiratory metaplasia of the olfactory mucosa with minimum to mild severity was observed in both males and females. Exposed animals also showed marked microscopic alterations in the DMS, DMA, and DMG studies as measured by increases in cell proliferation (CP) in the liver (males), nasal area (males and females) and lung (females).

The following effects on reproductive parameters were observed in the 90-day studies with DMS, DMA, and DMG: increase in epididymal sperm counts (2/3 studies), decrease in testosterone levels (1/3 studies), and decrease in leutenizing hormone levels (1/3 studies) - all in males, and decrease in estradiol levels in females (1/3 studies). The significance of these findings is unclear because the decrease in male hormone levels should result in a decrease in sperm counts, yet the opposite effect was observed. The single study showing changes in estradiol was not observed in the other two studies. Other reproductive parameters evaluated in these studies but which were not affected by treatment were: follicle stimulating hormone (FSH) and sperm motility/morphology in males and progesterone level and estrous cyclicity in females. In addition, a reproductive study was conducted with the fourth member of the category (DBE) and there were no effects on the following reproductive parameters: fertility, viability of pups at birth, and the ability of the mothers to lactate.

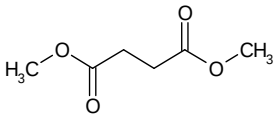
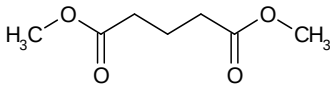
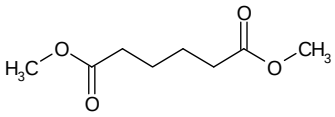
In a developmental toxicity study in rats, a marked reduction in maternal body weight gain and food consumption was seen during the exposure period at the highest concentration tested. No effects on fetal survival, fetal weight, litter size, implantations, or increased incidences of fetal malformations/variations were seen. In rabbits, reductions in body weights in dams and a marked increased in delayed ossification in fetuses were seen in the high dose group only. The dibasic esters category was not mutagenic in tested strains of *Salmonella typhimurium* and did not induce statistically significant increase in the mean number of micronucleated polychromatic erythrocytes in the bone marrow of CD-1 mice.

The potential health hazard of chemicals in the dibasic esters category is considered low because the effects observed were: (a) local effects to the nasal epithelium that are likely the result of irritation; (b) changes in hormone levels that do not appear to have toxicological significance; or (c) developmental toxicity at high doses).

5. Data Gaps

No data gaps were identified under the HPV Challenge Program.

Appendix

Dibasic Esters		
CAS No.	**Chemical Name**	**Structure**
SPONSORED CHEMICALS		
106-65-0	**Dimethyl succinate (DMS, butanedioic acid, dimethyl ester)**	 $C_6H_{10}O_4$
1119-40-0	**Dimethyl glutarate (DMG, pentanedioic acid, dimethyl ester)**	 $C_7H_{12}O_4$
627-93-0	**Dimethyl adipate (DMA, hexanedioic acid, dimethyl ester)**	 $C_8H_{14}O_4$
95481-62-2	**DBE (Mixture of 10 – 25% DMA, 55 – 65% DMG and 15 – 25% DMS)**	Mixture of structures provided above

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