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

Chemical/Category: **Dibasic Esters Category**

CAS 106-65-0, dimethyl succinate (DMS)
CAS 1119-40-0, dimethyl glutarate (DMG)
CAS 627-93-0, dimethyl adipate (DMA)
CAS 95481-62-2, dibasic ester mixture

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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR
Dibasic Esters Category

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**
Dibasic ester (Mixture of 10-25% DMA, 55-65% DMG and 15-25% DMS)	**CAS No. 95481-62-2**

1. Background

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 (U.S.) 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 and environmental fate.

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. Data submitted to the Organisation for Economic Co-operation and Development (OECD) HPV Programme are also being evaluated. OPPT developed a screening-level hazard characterization that consists of an objective evaluation, conducted according to established EPA guidance[2,3], of the quality and completeness of the data set provided and is based primarily on hazard data provided by sponsors. The characterization does not draw conclusions regarding the completeness of all data generated with respect to a specific chemical substance or mixture. The OECD SIDS documents (SIDS Initial Assessment Profile; SIAP and SIDS Initial Assessment Report; SIAR) provide similar information. Under both the HPV Challenge and OECD HPV Programs, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. Evaluation of chemical category formation and data extrapolation(s) among category members is performed in accord with established U.S. EPA[1] and OECD[4] guidance.

In 2006 and 2007, EPA received data on uses and exposure-related data for chemicals on the Toxic Substances Control Act (TSCA) Inventory of existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule[5]. Information is collected every five years under IUR, promulgated under the authority of section 8(a) of TSCA. The most recent reports pertain to chemicals manufactured in (including imported into) the U.S. during calendar year 2005 in quantities of 25,000 pounds or more at a single site. Information is reported on the identity of the chemical manufactured or imported and the quantity, physical form, and number of persons 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 during calendar year 2005, additional information was reported on the industrial processing and uses of the chemical, the number of industrial processing sites and of employees reasonably likely to be exposed to the chemical at these sites, the consumer and commercial uses of the chemical and an indication whether the chemical is used in products intended for use by children under 14 years of age.

For these qualitative screening-level risk characterization documents, EPA has reviewed the IUR data to evaluate exposure potential. In addition, exposure information that may have become available through prior Agency actions

[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. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[4] OECD. Guidance Document on the Development and Use of Chemical Categories; http://www.oecd.org/document/7/0,2340,en_2649_34379_1947463_1_1_1_1,00.html.
[5] U.S. EPA – Basic IUR Information: http://www.epa.gov/opptintr/iur/pubs/guidance/basic-information.htm

has been considered, as appropriate. The resulting exposure information has been combined with the screening-level hazard characterizations to develop this qualitative screening-level risk characterization[6,7]. These screening-level risk characterizations are technical documents intended to support subsequent decisions and actions by OPPT. Accordingly, the document is not written with the goal of informing the general public. The purpose of the qualitative screening level risk characterizations is two-fold: to support initial risk-based decisions to prioritize chemicals and inform risk management options and to identify data needs for individual chemicals or chemical categories.

2. Category Justification

The dibasic esters are discrete short, straight-chain dicarboxylic acid dimethyl esters that differ by one carbon atom (from four to six carbons) in chain length. As presented in the sponsor's submission and as further discussed both in the EPA comments to the submitter and the Hazard Characterization, the basis for considering butanedioic acid, dimethyl ester (dimethyl succinate, or DMS), pentanedioic acid, dimethyl ester (dimethyl glutarate or DMG), hexanedioic acid, dimethyl ester (dimethyl adipate or DMA) and the dibasic ester mixture (containing DMS, DMG, and DMA) as a category ("dibasic esters category") is similarities in structure, physicochemical properties, and toxicity. The category is both acceptable and reasonable for the purposes of the HPV Challenge Program. In addition, this category is related to another, similar category called the dicarboxylic acids (which consist of succinic acid, glutaric acid, and adipic acid).

3. Physical-Chemical Properties and Environmental Fate

This report was prepared using the best available data from a number of sources, but draws no conclusions regarding whether additional relevant data exist. The dibasic esters are all 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 expected to hydrolyze slowly and biodegrade rapidly. They are not persistent (B1) and are not bioaccumulative (P1).

4. Hazard Characterization

Aquatic Organism Toxicity. The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of all dibasic esters category members to aquatic organisms is low.

Human Health Toxicity. In available animal studies, 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 in animals.

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. These studies showed changes in the cells of the nasal region (degeneration/atrophy with minimum to mild severity) in both male and female animals exposed daily for 90 days via the inhalation route of exposure. Exposed animals also showed microscopic alterations in the liver (males) and lung (females).

The hormonal changes observed in these studies with DMS, DMA, and DMG were: an increase in sperm counts (2/3 studies), a decrease in testosterone levels (1/3 studies), and a decrease in leutenizing hormone levels (1/3 studies) - all in males and a 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. In addition, a

[6] U.S. EPA Guidelines for Exposure Assessment; http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=15263
[7] U.S. EPA. Risk Characterization Program; http://www.epa.gov/osa/spc/2riskchr.htm.

reproductive study was conducted with the fourth member of the category (the mixture of DMS, DMG and DMA) and there were no effects on fertility, viability of pups at birth, and the ability of the mothers to lactate.

There is low concern for potential developmental toxicity associated with this category of chemicals. A prenatal developmental toxicity study in rats showed maternal toxicity (reduced body weight), but there was no evidence of developmental toxicity. A prenatal study in rabbits showed a reduction in maternal body weight and an increase in delayed ossification in fetuses at high doses. Members of dibasic esters category are not mutagenic *in vitro* and did not show chromosomal aberrations *in vivo*.

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. Exposure Characterization

This exposure characterization was completed using available 2006 Inventory Update Rule (IUR) submissions. Data and information that are claimed Confidential Business Information (CBI) by the submitter were reviewed and considered by EPA in preparing this assessment but are not disclosed in this summary.

In addition, the following sources were reviewed to identify exposure and use information: the HPV Challenge Submission, OECD SIDS data, the Toxics Release Inventory (TRI), OSHA PEL documentation, various databases and public sources.

Production Volume Information for Each Member

DMA was manufactured (including imported) in the United States in the range of >1 million to 10 million lbs. in 2005.

DMG and DMS were manufactured (including imported) in the United States in the range of >10 million to 50 million lbs. in 2005.

Information Applicable to All Category Members

IUR information for 2005 was submitted for three of the four category members; the exception being the dibasic ester mixture (CAS No. 95481-62-2). Therefore, Exposure Characterizations are available for only three category members (DMA, DMG, and DMS).

All category members have public information on toxicity, fate and transport under the HPV Challenge Program and have some use and exposure information. The information indicates that the dibasic esters category chemicals are used as solvents, plasticizers, polymer intermediates and specialty chemical intermediates[8]. In addition, publicly available data sources (referenced in the Exposure Characterizations) indicate that a major use of DMS is as a food additive and DMS, DMA, and DMG are all identified as being a component of consumer paint strippers, polishes and lacquer thinners.

Exposures to Workers
Data suggest the potential for a high number of exposed workers and use sites (including industrial and commercial sites). The National Occupational Exposure Survey (NOES), conducted between 1981 and 1983, estimated a total of 15,417; 24,748; and 24,766 workers potentially exposed to DMS, DMG, and DMA, respectively. The more recently submitted IUR data indicate that the maximum total number of workers likely to be exposed to the category members during manufacturing, industrial processing, and use are: 1,000 or greater (DMS); less than 1,000 (DMA); and less than 5,000 (DMG). There may be additional potentially exposed workers not included in these estimates, since not all of the production volume is accounted for in the IUR submissions and there is at least one use that

[8] http://www.epa.gov/chemrtk/pubs/summaries/dbe/c13453tc.htm

contains a "Not Readily Obtainable" (NRO) response for each of the category members. The vapor pressure value for each member of the category (see attached Hazard Characterization supporting document) are above 0.001 torr. OPPT has established 0.001 torr as a value above which worker exposures to vapors should be estimated for chemical assessments. Therefore, the vapor pressures of all category members could result in significant worker exposures to vapors if workers are proximal to the liquid. Based on the reported uses, exposures to workers may be by the inhalation and dermal routes. None of the category members have an OSHA Permissible Exposure Limit.

Because of the number of potentially exposed workers and the use codes, the IUR-based ranking for worker exposure is high for all three category members.

Exposures to the General Population and the Environment
None of the dibasic esters are on the Toxics Release Inventory. Based on the known uses, it is likely that there would be some releases to water during manufacturing, processing, and use. EPA assumes for the purpose of this risk prioritization that there is potential for exposures to the general population and the environment.

The IUR-based ranking for the general population and the environment is high due to the assumption that there will be exposure to all members of the dibasic esters category.

Exposures to Commercial Workers and Consumers
There are potential exposures to commercial workers and/or consumers based on the use of products containing DMS, DMA and DMG, including paint strippers, polishes, and lacquer thinners. The IUR data do not distinguish between commercial and consumer products so, it is uncertain to what extent either or bother populations may be exposed. The vapor pressure value for each member of the category (as described above) could result in significant exposures if people are near products containing the chemical.

A study of a paint stripping activity in 1994 has shown the potential for high exposures to dibasic esters for persons working in poorly ventilated areas. Under these exposure conditions, there is a potential exposure to the general population and through consumer activities. This activity prompted rulemaking under the Toxic Substances Control Act[9]. There is also potential for dermal and inhalation DMS, DMA and DMG exposures to commercial workers and/or consumers based on information that is claimed to be CBI in the IUR.

The IUR-based ranking for commercial workers and consumers is high due to the assumption that DMS, DMA and DMG are used in commercial worker/consumer products.

Exposures to Children
Based on IUR data, the likelihood that DMS, DMA and DMG will be used in products intended for use by children is low. Therefore, the IUR-based ranking for exposure to children is low.

6. Risk Characterization

The statements and rationale provided below are intended solely for the purpose of this screening-level and qualitative risk characterization and will be used for prioritizing substances for future work in the U.S. HPV Challenge Program.

[9] http://www.epa.gov/fedrgstr/EPA-TOX/1995/March/Day-22/pr-55.html

6.1. Risk Statement and Rationale

Potential Risk to Aquatic Organisms from Environmental Releases (LOW CONCERN): EPA assumes there is potential for exposure to aquatic organisms from environmental releases. The low acute aquatic hazard and the overall environmental fate characteristics (e.g., not persistent or bioaccumulative) of all members of the dibasic esters category suggest a low concern for potential risk to aquatic organisms from environmental releases.

Potential Risk to the General Population from Environmental Releases (LOW CONCERN). EPA assumes there is potential for exposure to the general population from environmental releases. The low overall hazard profile of the dibasic esters to human health and the environmental fate characteristics of the category members (as described above) suggest a low concern for potential risk to the general population from environmental releases.

Potential Risk to Workers (LOW CONCERN). Worker exposures to all four category members are likely; although hazard communication and standard industrial hygiene practices, if properly followed, may be sufficient to address this concern. There is no OSHA PEL for any category member. The available hazard data suggest a low overall hazard profile to human health. Thus, the information suggests a low concern for potential risk to workers.

Potential Risk to Commercial Workers and Consumers from Known Uses (MEDIUM CONCERN): A study of paint stripping activity in 1994 has shown the potential for high exposures to consumers working with members of the dibasic esters category in poorly ventilated areas[10]. These conditions may also apply to the commercial workers, although hazard communication and standard industrial hygiene practices, if properly followed, may be sufficient to address this occupational concern. Under these exposure conditions, coupled with the available hazard data showing irritation effects in respiratory passages in animals, changes in some hormone levels, and developmental toxicity at high exposures there may be a potential concern for risk to commercial workers and consumers. It is not known whether concern for this exposure scenario still exists. Thus, the information suggests a medium concern for potential risk to commercial workers and consumers.

Potential Risk to Children (LOW CONCERN). Although no children-specific exposure scenarios were identified, it is likely that children would be exposed to dibasic esters as part of the general consumer population. The paint stripping consumer use described above is not likely to involve children. The available hazard data suggest a low overall hazard profile to human health, although some developmental effects (delayed hardening of bones) were observed in animals following exposure to high doses. Thus, the information suggests a low concern for potential risk to children.

6.2. Uncertainties

There is some uncertainty associated with the extent of commercial worker/consumer exposure to dibasic esters.

6.3. Data Needs

A data need has been identified to better understand the magnitude of environmental releases and consumer and commercial worker exposures to members of the dibasic esters category.

[10] US EPA (1994) Consumer exposure to paint stripper solvents (Final Report). Conducted by Midwest Research Institute (EPA Contract #68-00-137) for the Technical Program Branch, Chemical Management Division, Office of Pollution Prevention and Toxics, Washington, D.C.

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[11] 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[1,12]) 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[13].

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[2,14] 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[15] 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[4,16]. 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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[11] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[12] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[13] U.S. EPA. HPV Chemicals Hazard Characterization website (http://www.epa.gov/hpvis/abouthc.html).
[14] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[15] OECD. Guidance on the Development and Use of Chemical Categories; http://www.oecd.org/dataoecd/60/47/1947509.pdf.
[16] 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)	2.1×10^{-6} (1)	1.9×10^{-6} (1)	2.0×10^{-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.

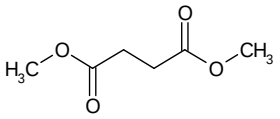
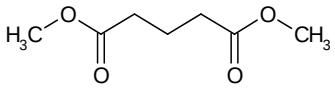
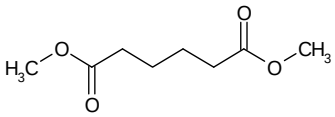
In a developmental toxicity study in rats, a marked reduction in maternal body weight gain and food consumption was seen during the exposure period at the highest concentration tested. No effects on fetal survival, fetal weight, litter size, implantations, or increased incidences of fetal malformations/variations 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

References

FR 1999, Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) Page 60194-60204

HSDB,2007. Hazard Substances Data Base. Accessed August 2, 2007
As cited in HSDB records for:
DIMETHYL SUCCINATE. http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~FkUaQ1:1

DIMETHYL GLUTARATE
http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~A5fogi:1

DIMETHYL ADIPATE
http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~i6Atep:2

OECD, 2001. OECD Series on Testing and Assessment, Number 33. Harmonized Integrated Classification System For Human Health and Environmental Hazards of Chemical Substances and Mixtures. Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, August 14, 2001.

SOCMA, 2002. Dibasic Esters (DBE) GroupTest Plan for Dibasic Esters, 2007. Robust Summaries & Test Plans: Dibasic Esters Category HPV Test Plan, submitted by Synthetic Organic Chemical Manufacturers Association, http://www.epa.gov/chemrtk/pubs/summaries/dbe/c13453tc.htm

USEPA, 2007. EPI Suite™ (version 3.2) PC-Computer software developed by EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm

Screening Level Exposure Characterization for HPV Challenge Chemical

Butanedioic Acid, Dimethyl Ester

CAS #106-65-0

March 14, 2008

Prepared by

Exposure Assessment Branch
Chemical Engineering Branch
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Screening Level Exposure Characterization of IUR Data

Butanedioic Acid, Dimethyl Ester (106-65-0)

Non-CBI Executive Summary

The dibasic esters category chemicals are used as solvents, plasticizers, polymer intermediates and specialty chemical intermediates (USEPA, 2007a). Butanedioic acid, dimethyl ester was manufactured (including imported) in the United States in the range of >10 million to 50 million lbs. in 2005 (USEPA, 2006). Persons submitting Inventory Update Reporting information in 2005 asserted that some or all of the information was confidential and therefore cannot be disclosed. Data and information that are CBI have been excluded from this summary.

This draft exposure characterization was completed using both public, non-confidential sources, and one or more IUR submissions that were available as of this writing. If additional information warrants an update of the exposure characterization, it will be posted on the EPA website.

A SIDS dossier has not been prepared for this chemical (OECD, 2007).

Publicly available data sources indicate that a major use of butanedioic acid, dimethyl ester is as a food additive (HSDB, 2007), as well as being a component of consumer paint strippers (NIH, 2007) and of polishes and lacquer thinners (USEPA, 2004).

Exposures to Workers

This chemical has a vapor pressure of 0.42 torr at 25°C (USEPA, 2007b). OPPT has established 0.001 torr as a value above which worker exposures to vapors should be estimated for chemical assessments. Therefore, this chemical's vapor pressure could result in worker exposures to vapors if workers are proximal to the liquid. This chemical does not have an OSHA Permissible Exposure Limit (NIOSH, 2007a). The National Occupational Exposure Survey (NOES), conducted from 1981 to 1983, estimated a total of 15,417 workers potentially exposed to this chemical (NIOSH, 2007b). The more recently submitted IUR data indicate that the maximum total number of workers likely to be exposed to this chemical during manufacturing, industrial processing, and use is 1,000 or greater. There may be additional potentially exposed workers that are not included in this estimate, since not all the production volume has been accounted for and there is at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions. This estimate does not include potentially exposed commercial workers either.

Differences between numbers of workers estimated by IUR submitters and by the NOES are attributable to many factors, including time, scope, and method of the estimates. For example, NOES estimates are for all workplaces while IUR are for industrial workplaces only, and NOES used a survey and extrapolation method while IUR submitters simply provide their best estimates based on available information for the specific reporting year.

Based on the reported uses, exposures to workers may be by the inhalation and dermal routes. Based on IUR data, specifically the number of potentially exposed workers and the use codes, the potential worker exposure is considered high.

Exposures to the General Population and the Environment

This chemical is not on the Toxics Release Inventory (USEPA, 2007a). Based on the known uses, the totality of the information considered, and expert judgment, it is likely that there would be some releases to water during manufacturing, processing, and use. EPA assumes for the purposes of risk based prioritization, that the potential for environmental release and subsequent exposure to the general population and the environment is high.

Persistence and bioaccumulation ratings for this chemical are P_1 (low) and B_1 (low). These ratings indicate that this chemical will not persist long in the environment and that it will be slow to bioaccumulate in environmental media.

Exposures to Commercial Workers and Consumers

There are potential exposures to commercial workers and/or consumers based on the use of products containing this chemical, including paint strippers, polishes, and lacquer thinners (USEPA, 1994). The IUR data do not distinguish between commercial and consumer products so, it is uncertain to what extent either or bother populations may be exposed. This chemical has a vapor pressure of 0.42 torr at 25° C. Therefore, any commercial workers and/or consumers proximal to the liquid could be exposed. A study of a paint stripping activity in 1994 has shown the potential for high exposures to dibasic esters for persons working in poorly ventilated areas (USEPA, 1994). There is also potential for dermal and inhalation exposures to commercial workers and/or consumers based on information that is claimed to be CBI in the IUR. The likelihood that this chemical is used in commercial/consumer products is high based on IUR data.

Exposures to Children

The dibasic ester chemicals are not in the Voluntary Children's Chemical Evaluation Program (USEPA, 2007c). The likelihood that this chemical is used in products intended to be used by children is low based on IUR data.

REFERENCES

HSDB, 2007 Hazard Substances Data Base. Accessed August and December 2007, DIMETHYL SUCCINATE. http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?.temp/~FkUaQ1:1

NIH, 2007. Household Products Database. Accessed December 2007. http://hpd.nlm.nih.gov/products.htm

NIOSH, 2007a. OSHA PEL Project Documentation. Accessed August, 2007. http://www.cdc.gov/niosh/pel88/npelcas.html

NIOSH, 2007b. National Occupational Exposure Survey (NOES, 1981-1983). Accessed December 2007. http://www.cdc.gov/noes/noes2/x6235occ.html

USEPA (1994) Consumer exposure to paint stripper solvents (Final Report). Conducted by Midwest Research Institute (EPA Contract #68-00-137) for the Technical Program Branch, Chemical Management Division, Office of Pollution Prevention and Toxics, Washington, D.C.

USEPA, 2004. Source Ranking Database. Accessed December, 2007. http://www.epa.gov/opptintr/exposure/pubs/srd.htm

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USEPA, 2007a. http://www.epa.gov/chemrtk/pubs/summaries/dbe/c13453tc.htm

USEPA, 2007b. Toxic Release Inventory. Accessed August, 2007. http://www.epa.gov/tri/

USEPA, 2007c. Voluntary Children's Chemical Evaluation Program. Accessed December 2007. http://www.epa.gov/oppt/vccep/pubs/vcceprsp.pdf

Screening Level Exposure Characterization for HPV Challenge Chemical

Pentanedioic Acid, Dimethyl Ester

CAS #1119-40-0

March 14, 2008

Prepared by

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Washington, DC 20460-0001

Screening Level Exposure Characterization for HPV Challenge Chemical

Pentanedioic Acid, Dimethyl Ester (1119-40-0)

Non-CBI Executive Summary

The dibasic esters category chemicals are used as solvents, plasticizers, polymer intermediates and specialty chemical intermediates (USEPA, 2007a). Pentanedioic acid, dimethyl ester was manufactured (including imported) in the United States in the range of >10 million to 50 million lbs. in 2005 (USEPA, 2006). Persons submitting Inventory Update Reporting information in 2005 asserted that some or all of the information was confidential and therefore cannot be disclosed. Data and information that are CBI have been excluded from this summary.

This draft exposure characterization was completed using both public, non-confidential sources, and one or more IUR submissions that were available as of this writing. If additional information warrants an update of the exposure characterization, it will be posted on the EPA website.

A SIDS dossier has not been prepared for this chemical (OECD, 2007).

Publicly available data sources indicate that pentanedioic acid, dimethyl ester is used as a component of consumer paint strippers (HSDB, 2007; NIH, 2007), as well as of polishes and lacquer thinners (USEPA, 2004).

Exposures to Workers

This chemical has a vapor pressure of 0.17 torr at 25°C (USEPA, 2007b). OPPT has established 0.001 torr as a value above which worker exposures to vapors should be estimated for chemical assessments. Therefore, this chemical's vapor pressure could result in worker exposures to vapors if workers are proximal to the liquid. This chemical does not have an OSHA Permissible Exposure Limit (NIOSH, 2007a). The National Occupational Exposure Survey (NOES), conducted from 1981 to 1983, estimated a total of 24,748 workers potentially exposed to this chemical (NIOSH, 2007b). The more recently submitted IUR data indicate that the maximum total number of workers likely to be exposed to this chemical during manufacturing, industrial processing, and use is less than 5,000. There may be additional potentially exposed workers that are not included in this estimate, since not all the production volume has been accounted for and there is at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions. This estimate does not include potentially exposed commercial workers either.

Differences between numbers of workers estimated by IUR submitters and by the NOES are attributable to many factors, including time, scope, and method of the estimates. For example, NOES estimates are for all workplaces while IUR are for industrial workplaces only, and NOES used a survey and extrapolation method while IUR submitters simply provide their best estimates based on available information for the specific reporting year.

Based on the reported uses, exposures to workers may be by the inhalation and dermal routes. Based on IUR data, specifically the number of potentially exposed workers and the use codes, the potential worker exposure is considered high.

Exposures to the General Population and the Environment

This chemical is not on the Toxics Release Inventory (USEPA, 2007a). Based on the known uses, the totality of the information considered, and expert judgment, it is likely that there would be some releases to water during manufacturing, processing, and use. EPA assumes for the purposes of risk based prioritization, that the potential for environmental release and subsequent exposure to the general population and the environment is high.

Persistence and bioaccumulation ratings for this chemical are P_1 (low) and B_1 (low). These ratings indicate that this chemical will not persist long in the environment and that it will be slow to bioaccumulate in environmental media.

Exposures to Commercial Workers and Consumers

There are potential exposures to commercial workers and/or consumers based on the use of products containing this chemical, including paint strippers, polishes, and lacquer thinners (USEPA, 1994). The IUR data do not distinguish between commercial and consumer products so, it is uncertain to what extent either or bother populations may be exposed. This chemical has a vapor pressure of 0.17 torr at 25° C. Therefore, any commercial workers and/or consumers proximal to the liquid could be exposed. A study of a paint stripping activity in 1994 has shown the potential for high exposures to dibasic esters for persons working in poorly ventilated areas (USEPA, 1994). There is also potential for dermal and inhalation exposures to commercial workers and/or consumers based on information that is claimed to be CBI in the IUR. The likelihood that this chemical is used in commercial/consumer products is high based on IUR data.

Exposures to Children

The dibasic ester chemicals are not in the Voluntary Children's Chemical Evaluation Program (USEPA, 2007c). The likelihood that this chemical is used in products intended to be used by children is low based on IUR data.

REFERENCES

HSDB, 2007 Hazard Substances Data Base. Accessed August and December 2007, DIMETHYL GLUTARATE. http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?.temp/~FkUaQ1:1

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NIOSH, 2007a. OSHA PEL Project Documentation. Accessed August, 2007. http://www.cdc.gov/niosh/pel88/npelcas.html

NIOSH, 2007b. National Occupational Exposure Survey (NOES, 1981-1983). Accessed December 2007. http://www.cdc.gov/noes/noes2/t1492occ.html

USEPA (1994) Consumer exposure to paint stripper solvents (Final Report). Conducted by Midwest Research Institute (EPA Contract #68-00-137) for the Technical Program Branch, Chemical Management Division, Office of Pollution Prevention and Toxics, Washington, D.C.

USEPA, 2004. Source Ranking Database. Accessed December, 2007. http://www.epa.gov/opptintr/exposure/pubs/srd.htm

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USEPA, 2007c. Voluntary Children's Chemical Evaluation Program. Accessed December 2007. http://www.epa.gov/oppt/vccep/pubs/vcceprsp.pdf

Screening Level Exposure Characterization for HPV Challenge Chemical

Hexanedioic Acid, Dimethyl Ester

CAS #627-93-0

March 14, 2008

Prepared by

Exposure Assessment Branch
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Screening Level Exposure Characterization for HPV Challenge Chemical

Hexanedioic Acid, Dimethyl Ester (627-93-0)

Non-CBI Executive Summary

The dibasic esters category chemicals are used as solvents, plasticizers, polymer intermediates and specialty chemical intermediates (USEPA, 2007a). Hexanedioic acid, dimethyl ester was manufactured (including imported) in the United States in the range of >1 million to 10 million lbs. in 2005 (USEPA, 2006). Persons submitting Inventory Update Reporting information in 2005 asserted that some or all of the information was confidential and therefore cannot be disclosed. Data and information that are CBI have been excluded from this summary.

This draft exposure characterization was completed using both public, non-confidential sources, and one or more IUR submissions that were available as of this writing. If additional information warrants an update of the exposure characterization, it will be posted on the EPA website.

A SIDS dossier has not been prepared for this chemical (OECD, 2007).

Publicly available data sources indicate that hexanedioic acid, dimethyl ester is used as a component of consumer paint strippers (HSDB, 2007; NIH, 2007), as well as of polishes and lacquer thinners (USEPA, 2004).

Exposures to Workers

This chemical has a vapor pressure of 0.067 torr at 25°C (USEPA, 2007b). OPPT has established 0.001 torr as a value above which worker exposures to vapors should be estimated for chemical assessments. Therefore, this chemical's vapor pressure could result in worker exposures to vapors if workers are proximal to the liquid. This chemical does not have an OSHA Permissible Exposure Limit (NIOSH, 2007a). The National Occupational Exposure Survey (NOES), conducted from 1981 to 1983, estimated a total of 24,766 workers potentially exposed to this chemical (NIOSH, 2007b). The more recently submitted IUR data indicate that the maximum total number of workers likely to be exposed to this chemical during manufacturing, industrial processing, and use is less than 1,000. There may be additional potentially exposed workers that are not included in this estimate, since not all the production volume has been accounted for and there is at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions. This estimate does not include potentially exposed commercial workers either.

Differences between numbers of workers estimated by IUR submitters and by the NOES are attributable to many factors, including time, scope, and method of the estimates. For example, NOES estimates are for all workplaces while IUR are for industrial workplaces only, and NOES used a survey and extrapolation method while IUR submitters simply provide their best estimates based on available information for the specific reporting year.

Based on the reported uses, exposures to workers may be by the inhalation and dermal routes. Based on IUR data, specifically the number of potentially exposed workers and the use codes, the potential worker exposure is considered high.

Exposures to the General Population and the Environment

This chemical is not on the Toxics Release Inventory (USEPA, 2007a). Based on the known uses, the totality of the information considered, and expert judgment, it is likely that there would be some releases to water during manufacturing, processing, and use. EPA assumes for the purposes of risk based prioritization, that the potential for environmental release and subsequent exposure to the general population and the environment is high.

Persistence and bioaccumulation ratings for this chemical are P_1 (low) and B_1 (low). These ratings indicate that this chemical will not persist long in the environment and that it will be slow to bioaccumulate in environmental media.

Exposures to Commercial Workers and Consumers

There are potential exposures to commercial workers and/or consumers based on the use of products containing this chemical, including paint strippers, polishes, and lacquer thinners (USEPA, 1994). The IUR data do not distinguish between commercial and consumer products so, it is uncertain to what extent either or bother populations may be exposed. This chemical has a vapor pressure of 0.67 torr at 25° C. Therefore, any commercial workers and/or consumers proximal to the liquid could be exposed. A study of a paint stripping activity in 1994 has shown the potential for high exposures to dibasic esters for persons working in poorly ventilated areas (USEPA, 1994). There is also potential for dermal and inhalation exposures to commercial workers and/or consumers based on information that is claimed to be CBI in the IUR. The likelihood that this chemical is used in commercial/consumer products is high based on IUR data.

Exposures to Children

The dibasic ester chemicals are not in the Voluntary Children's Chemical Evaluation Program (USEPA, 2007c). The likelihood that this chemical is used in products intended to be used by children is low based on IUR data.

REFERENCES

HSDB, 2007 Hazard Substances Data Base. Accessed August and December 2007, DIMETHYL ADIPATE. http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?.temp/~FkUaQ1:1

NIH, 2007. Household Products Database. Accessed December 2007. http://hpd.nlm.nih.gov/products.htm

NIOSH, 2007a. OSHA PEL Project Documentation. Accessed August, 2007. http://www.cdc.gov/niosh/pel88/npelcas.html

NIOSH, 2007b. National Occupational Exposure Survey (NOES, 1981-1983). Accessed December 2007. http://www.cdc.gov/noes/noes2/t1493occ.html

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USEPA, 2004. Source Ranking Database. Accessed December, 2007. http://www.epa.gov/opptintr/exposure/pubs/srd.htm

USEPA, 2006 Partial Updating of TSCA Chemical Inventory (confidential business information)

USEPA, 2007a. http://www.epa.gov/chemrtk/pubs/summaries/dbe/c13453tc.htm

USEPA, 2007b. Toxic Release Inventory. Accessed August, 2007. http://www.epa.gov/tri/

USEPA, 2007c. Voluntary Children's Chemical Evaluation Program. Accessed December 2007. http://www.epa.gov/oppt/vccep/pubs/vcceprsp.pdf

CPSC
United States
Consumer Product
Safety Commission

EPA
United States
Environmental Protection
Agency

What You Should Know About Using PAINT STRIPPERS

What You Should Know About Using Paint Strippers

If not properly used, paint strippers are hazardous to your health and safety.

Paint strippers contain chemicals that loosen paint from surfaces. These chemicals can harm you if not used properly. Some paint stripping chemicals can irritate the skin and eyes, or cause headaches, drowsiness, nausea, dizziness, or loss of coordination. Some may cause cancer, reproductive problems, or damage of the liver, kidney, or brain. Others catch fire easily. Proper handling and use of paint strippers will reduce your exposure to these chemicals and lessen your health risk.

General Safety Precautions

Paint strippers contain different chemicals, and the potential hazards are different for various products. Each product has specific safety precautions (see the section on paint stripper types, page 4). However, there are some general safety steps to keep in mind when using any paint stripper. If you use paint strippers frequently, it is particularly important that you follow these steps:

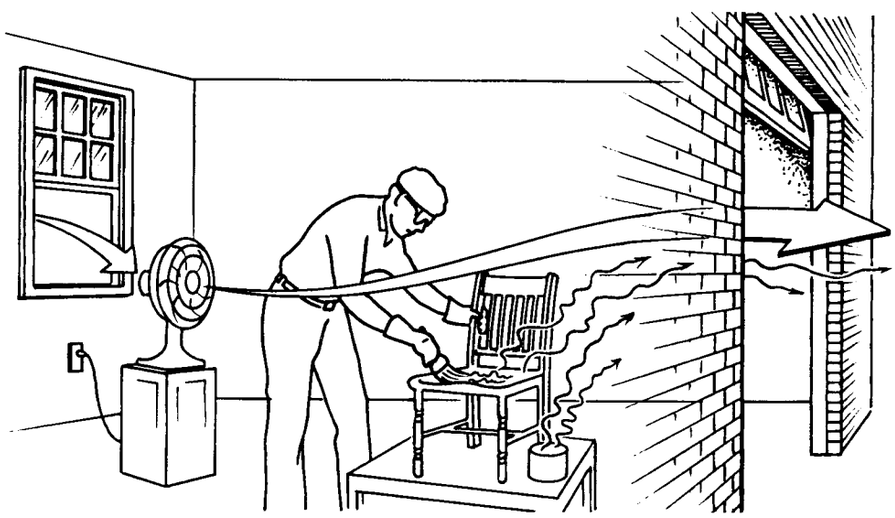
1. **Always read and follow all the instructions and safety precautions on the label.** Do not assume you already know how to use the product. The hazards may be different from one product to another, and the ingredients in individual products often change over time. The label tells you what actions you should take to reduce hazards and the first aid measures to use.

2. **Wear chemical-resistant gloves** appropriate to the type of stripper being used (see manufacturer's instructions). Common kitchen latex gloves do not provide enough protection.

3. **Avoid getting the paint stripper on your skin or in your eyes.** Wear protective clothing and goggles appropriate for the project and type of stripper.

4. Use paint strippers outdoors if possible. If you must use them indoors, cross-ventilate by opening all doors and windows. Make sure there is fresh air movement throughout the room. Ventilate the area before, during, and after applying and stripping. Never use any paint stripper in a poorly ventilated area. If work must be done indoors under low ventilation conditions, consider having the work done professionally instead of attempting it yourself.

5. If you must work indoors, always work so the stripper fumes are blowing away from you and to the outside (see illustration below). A fan can be used to improve cross-ventilation and to ensure fresh air movement. A fan is particularly important for *nonflammable* products that evaporate quickly, such as methylene chloride. Electrical sparks from fans may increase the chance of *flammable* paint strippers fumes to catch fire.



6. **Do not use flammable paint strippers near any source of sparks, flame, or high heat.** Do not work near gas stoves, kerosene heaters, gas or electric water heaters, gas or electric clothes dryers, gas or electric furnaces, gas or electric space heaters, sanders, buffers, or other electric hand tools. Open flames, cigarettes, matches, lighters, pilot lights, or electric sparks can cause the chemicals in the paint strippers to suddenly catch fire.

7. **Only strip paint with chemicals that are marketed as paint strippers.** Never use gasoline, lighter fluid, or kerosene to strip paint.

8. **Dispose of paint strippers according to the instructions on the label.** If you have any questions, ask your local environmental sanitation department about proper disposal.

Types of Paint Strippers

Solvent-Based Strippers

Most paint strippers are solvent-based. Solvents dissolve the bond between wood and paint. Solvents also can dissolve other materials, including the latex or rubber of common household or dish washing gloves. Some solvents will irritate or burn the skin. Some solvents may cause serious health effects even if contact does not immediately cause pain. In addition, many solvents evaporate quickly and you can easily inhale them. Inhalation of these solvents can produce health effects immediately or years after exposure.

It is especially important to use paint strippers containing solvents that evaporate quickly either outdoors or in an indoor area with strong fresh air movement. Some paint strippers contain solvents that do not evaporate quickly. When using these strippers indoors, be sure to open windows and doors to provide fresh air movement in and out of the work site. You should always follow the manufacturer's instructions and safety precautions.

Use the amount of stripper recommended by the manufacturer to avoid buildup of harmful fumes.

The different types of solvent-based paint strippers and their potential hazards and safety precautions are:

Methylene chloride (also called dichloromethane, or DCM) —

Methylene chloride is the most commonly used chemical in paint strippers. Methylene chloride products come in two varieties. One type is nonflammable, while the other type is flammable. The flammable paint strippers have less methylene chloride but have other flammable chemicals, including acetone, toluene, or methanol.

Methylene chloride causes cancer in laboratory animals. The U.S. Environmental Protection Agency (EPA) and the U.S. Consumer Product Safety Commission (CPSC) consider the chemical to be a potential cause of cancer in humans. Methylene chloride evaporates quickly, and you can inhale it easily. Breathing high levels of methylene chloride over short periods can irritate the eyes, skin, nose, and lungs. It can also cause dizziness, headache, and lack of coordination. Your body changes some inhaled methylene chloride to carbon monoxide. Carbon monoxide lowers the blood's ability to carry oxygen. This can cause problems for people with heart, lung, or blood diseases who use methylene chloride paint strippers indoors without fresh air cross-ventilation. High exposures to methylene chloride for long periods can also cause liver and kidney damage.

- It is very important to reduce your exposure to methylene chloride vapors.

- It is very important to have a lot of fresh air when using methylene chloride products.

- Use methylene chloride paint strippers outdoors if possible. If you must use them indoors, open all doors and windows to ensure that the fresh air is moving in and out of the room.

- For indoor use of *nonflammable* methylene chloride strippers, also use a fan to keep fresh air moving

throughout the work area. Electrical sparks from fans may increase the chance of *flammable* paint strippers fumes to catch fire.

- The safest place to use *flammable* methylene chloride strippers is outdoors away from any source of sparks, flame, or high heat.

Acetone, toluene, and methanol —
These chemicals are commonly used together. All three chemicals evaporate quickly and are very flammable. Breathing high levels of these chemicals can cause a variety of effects, including drowsiness, dizziness, and headache. Breathing high levels of toluene may harm unborn children. Breathing very high levels for a long period may cause brain damage. Toluene and methanol are poisonous if swallowed.

- To avoid fire and health problems, it is very important to use products containing these chemicals only in areas with plenty of fresh air.

- Do not work near an open flame, pilot lights, or electrical sparks when using flammable paint strippers. Do not use strippers near gas stoves, kerosene heaters, gas or electric water heaters, gas or electric clothes dryers, gas or electric furnaces, gas or electric space heaters, sanders, buffers, or other electric hand tools.

N-methylpyrrolidone (NMP) —
Excessive contact with NMP may cause skin swelling, blistering, and burns. These skin reactions may not appear until some time after exposure. N-methylpyrrolidone can readily get into the body through the skin and may cause health problems. NMP may cause reproductive problems and harm to unborn children.

- It is very important to wear chemical-resistant gloves and avoid skin contact when using this solvent.

- Wash hands immediately after use, even when wearing gloves.

- Gloves should fit properly and be chemical-resistant. Common kitchen latex gloves do not provide enough protection.

- Avoid using this product for extended periods in an enclosed area without open doors or windows to the outside for cross-ventilation.

Dibasic esters (DBE), including dimethyl adipate ester, dimethyl succinate ester, and dimethyl glutarate ester—
Much less is known about the possible health effects of these chemicals than about most of the other paint stripping chemicals. Some people using DBE products without fresh air have reported temporary blurred vision. Repeatedly breathing DBE damages the cells lining the nose of laboratory animals. Some strippers include a mixture of DBE products and NMP.

- Avoid using this product for extended periods in an enclosed area without open doors or windows to the outside for cross-ventilation.

- Use appropriate protective clothing and provide fresh air to the work site when using these products.

Caustic-Based Strippers (not flammable)

Caustic alkalis react with the paint coating and loosen it from the surface. One of the chemicals in this type of stripper is sodium hydroxide (lye). Some people do not use caustic alkalis because caustic products can darken wood and raise the grain. Caustics can cause severe burns to skin and eyes even on short contact. Therefore, be very careful to keep caustic chemicals away from skin and eyes and wear protective clothing. If contact occurs, wash off immediately with cold water. Caustics are also highly toxic if swallowed.

- It is very important to avoid skin and eye contact when using caustic alkalis.

- Use gloves that fit properly and are appropriate for caustic alkalis.

- Wear appropriate protective clothing and goggles when using caustic alkalis.

Other Types of Paint Strippers

Some paint strippers have a citrus smell or make "environmentally friendly" claims. However, these paint strippers may be hazardous despite the smell and environmental claims.

- It is important to use appropriate protective clothing and fresh air for cross-ventilation when using these products.

For more information on indoor air quality, contact:

U.S. Environmental Protection Agency
Washington, DC 20460
800-438-4318

or

U.S. Consumer Product Safety Commission
Washington, DC 20207
800-638-2772

TTY for individuals who are deaf or hard of hearing or people with speech impairments: 800-638-8270.

Consumers can get recall information via Internet gopher services at cpsc.gov or report product hazards to info@cpsc.gov.

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