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**HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM**

TEST PLAN

For The Phthalate Esters Category

Prepared by:

ExxonMobil Biomedical Sciences, Inc.

For The

**Phthalate Esters Panel HPV Testing Group
of the American Chemistry Council**

December 10, 2001

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LIST OF MEMBER COMPANIES
THE PHTHALATE ESTERS PANEL

The American Chemistry Council Phthalate Esters Panel includes the following member companies:

BASF Corporation
 CONDEA Vista Company
 Eastman Chemical Company
 ExxonMobil Chemical Company
 Ferro Corporation
 ICI Americas / Uniqema
 Sunoco Chemicals
 Teknor Apex Company

PHTHALATE ESTER CATEGORY

CAS Number	CAS Number Description
131-11-3	1,2-benzenedicarboxylic acid, dimethyl ester
84-66-2	1,2-benzenedicarboxylic acid, diethyl ester
68515-50-4	1,2,-benzenedicarboxylic acid, dihexyl ester, branched and linear
68515-44-6	1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear
71888-89-6	1,2-benzenedicarboxylic acid, di C6-8 branched alkyl ester, C7 rich
27554-26-3	1,2,-benzenedicarboxylic acid, diisooctyl ester
111381-89-6	1,2-benzenedicarboxylic acid (C7, C9) ester, branched and linear
111381-90-9	1,2-benzenedicarboxylic acid, (C7,C11) ester, branched and linear
68648-93-1	1,2-benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters
117-84-0	1,2,-benzenedicarboxylic acid, dioctyl ester
68515-40-2	1,2-benzenedicarboxylic acid, benzyl C7-9 branched and linear alkyl esters
68515-45-7	1,2,-benzenedicarboxylic acid, dinonyl ester, branched and linear
68515-43-5	1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters
84-77-5	1,2-benzenedicarboxylic acid, didecyl ester
3648-20-2	1,2-benzenedicarboxylic acid, diundecyl ester
85507-79-5	1,2-benzenedicarboxylic acid, di (C11) ester, branched and linear
111381-91-0	1,2-benzenedicarboxylic acid (C9, C11) ester, branched and linear
68515-47-9	1,2,-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich

PLAIN ENGLISH SUMMARY

The proposed Phthalate Esters category consists of eighteen phthalate esters. These substances are 1,2-benzenedicarboxylic acids, with side chain esters ranging in carbon chain length from C₁ to C₁₃. The phthalate esters were further subdivided into three subcategories based on their physicochemical and toxicological properties: Low molecular weight phthalates, Transitional phthalates, and High molecular weight phthalates.

Low molecular weight phthalates are produced from alcohols with straight-chain carbon backbones of $\leq C_3$. Two U.S. HPV chemicals, dimethyl (DMP) and diethyl (DEP) phthalate, are included in this subcategory. Low molecular weight phthalates are commonly used as solvents or in cellulose acetate polymers. They have greater aqueous solubility and aquatic toxicity potential than do the transitional and higher molecular weight phthalates. However, they have lower mammalian toxicity potential than do the transitional phthalates.

Transitional phthalates are produced from alcohols with straight-chain carbon backbones of C₄-6. Six of the U.S. HPV chemicals, dihexyl (DHP), diheptyl, diisooheptyl, diisooctyl, heptyl nonyl (C₇, C₉) and heptyl undecyl (C₇, C₁₁) phthalates are included in this subcategory. Transitional phthalates have varied uses from solvents to plasticizers for PVC. These phthalates have greater mammalian toxicity potential, particularly with regard to reproductive and developmental effects, compared to either the low or high molecular weight phthalate categories.

High molecular weight phthalates are produced from alcohols with straight-chain carbon backbones of $\geq C_7$ or a ring structure. Ten of the U.S. HPV chemicals fall into this subcategory, which include varying mixed isomers of linear and branched diheptyl, dioctyl, dinonyl, didecyl, diundecyl and ditridecyl phthalate. High molecular weight phthalates are used nearly exclusively as plasticizers of PVC. They are very insoluble in water, and have a very low vapor pressure. These substances have few biological effects.

The most common commercially available phthalate esters have been extensively studied for their potential toxicity. Existing toxicology data on the eighteen U.S. HPV phthalate esters were supplemented with published information on other phthalate esters currently being assessed under the OECD SIDS program.

The ACC Phthalate Esters Panel HPV Testing Group believes that there is a sufficient amount of available data on phthalate esters to adequately characterize the human health effects and environmental fate and effects endpoints for all members of this category under the U.S. HPV Challenge program. No additional toxicology tests are proposed for these materials.

EXECUTIVE SUMMARY

The American Chemistry Council (ACC) Phthalate Esters Panel HPV Testing Group and its member companies hereby submit for review and public comment the test plan for the Phthalate Ester category under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program (Program). It is the intent of the ACC Phthalate Esters Panel and its member companies to use existing data and scientific judgment/analyses to adequately characterize the SIDS (Screening Information Data Set) human health, environmental fate and effects, and physicochemical endpoints for this category.

This test plan addresses the 18 HPV phthalate esters listed in Table 1. Phthalate esters are produced by the reaction of phthalic anhydride with various linear and branched alcohols in the presence of an acid catalyst to form 1,2-benzenedicarboxylic acids. The phthalate esters were further subdivided into three subcategories based on their physicochemical and toxicological properties. The biological responses to phthalate esters vary based on the alcohol side chain length and the animal species tested. The proposed subcategories and test plan rationales are described below.

Subcategories:

Low molecular weight phthalates: produced from alcohols with straight-chain carbon backbones of $\leq C_3$. Two U.S. HPV chemicals, dimethyl (DMP) and diethyl (DEP) phthalate, are included in this subcategory. The low molecular weight phthalates are distinguished from phthalates in other subcategories by use, physicochemical properties, and identified effects in toxicology studies.

Low molecular weight phthalates are commonly used as solvents or in cellulose acetate polymers rather than as plasticizers for PVC. Their higher volatility and water solubility give them physicochemical and toxicological properties different than other phthalate esters. In particular, these phthalates have greater aqueous solubility and aquatic toxicity potential than do the transitional and higher molecular weight phthalates. However, they have lower mammalian toxicity potential than do the transitional phthalates.

Transitional phthalates: produced from alcohols with straight-chain carbon backbones of C4-6. Phthalate esters containing >10% C4-6 molecules were conservatively included in this subcategory. Six of the U.S. HPV chemicals, dihexyl (DHP), diheptyl, diisoheptyl, diisooctyl, heptyl nonyl (C7, C9) and heptyl undecyl (C7, C11) phthalates are included in this subcategory. Data for this subcategory were supplemented with published information on other phthalate esters currently being assessed under the OECD SIDS program, including dibutyl (DBP), butylbenzyl (BBP), and di(2-ethylhexyl) phthalate (DEHP). Data on a structurally similar material, di-n hexyl phthalate, were also included for read-across purposes.

Transitional phthalates have varied uses from solvents (e.g., dibutyl) to plasticizers for PVC (e.g., DEHP). Physicochemical properties also vary in that the lower transitional phthalates are more water-soluble than higher transitional phthalates, but none would be considered to fall into the “high water soluble” category. What distinguishes these phthalates from others is their greater mammalian toxicity potential, particularly with regard to reproductive and developmental effects, compared to either the low or high molecular weight phthalate categories.

High molecular weight phthalates: produced from alcohols with straight-chain carbon backbones of $\geq C7$ or ring structure. Ten of the U.S. HPV chemicals fall into this subcategory, which include varying mixed isomers of linear and branched diheptyl, dioctyl, dinonyl, didecyl, diundecyl and ditridecyl phthalate. Data for this subcategory were supplemented with published information on other phthalate esters currently being assessed under the OECD SIDS program, including di-isononyl (DINP) and di-isodecyl (DIDP) phthalate. Results of studies on other non-HPV phthalates were included to supplement the database, when appropriate.

High molecular weight phthalates are used nearly exclusively as plasticizers of PVC. They are very insoluble in water, and have a very low vapor pressure. The extant database demonstrates that these substances have few biological effects. A notable exception to this generalization is that hepatocarcinogenicity has been observed for DINP. The hepatocarcinogenicity effects of DINP are by a mechanism (peroxisomal proliferation) to which rodents are particularly sensitive. However, it does not appear to be relevant to humans.

Testing Rationale:

Low Molecular Weight Phthalates

There is a large amount of data for the physicochemical properties of dimethyl and diethyl phthalate. Computer models were also used to estimate these properties for comparison with measured values and additionally were used to predict environmental distribution. No additional physical / chemical studies are proposed for this subcategory.

A complete health effects SIDS data set is available for diethyl phthalate, and for dimethyl phthalate with the exception of adequate reproductive data. Both DMP and DEP show minimal acute toxicity, are not genotoxic, exhibit some liver and kidney effects at high doses, and are negative for developmental effects. Although the DMP database for reproductive effects is limited, the Panel believes that this endpoint can be adequately assessed by applying read-across to DEP. Data on DEP indicates that this material will not cause reproductive effects. This is further supported by data showing that neither DEP nor DMP had effects on male reproductive development (Gray et al., 2000). The lack of developmental effects observed with DMP, coupled with chronic toxicity studies showing no effects on reproductive organs (Lehman, 1955; NTP, 1995), negates the need to conduct a reproductive study for DMP. No additional toxicity studies are proposed for this subcategory.

There are numerous published acute aquatic toxicity studies in a variety of species of fish, daphnia and algae for DMP and DEP (Staples et al. 1997a). No additional environmental toxicity studies are necessary.

Transitional Phthalates:

There are measured physicochemical property data available for some of the transitional phthalates. Computer estimation models were also used to calculate physicochemical and fate data for phthalates in this category. The calculated data were developed from a computer model used by the EPA, as cited in an EPA guidance document prepared for the HPV Challenge Program. Depending upon the endpoint, the modeled data agree with measured data. The combination of measured values and calculated values is sufficient to provide the required information on the physiochemical and fate properties of the HPV phthalates in the transitional group. No additional physical/chemical studies are proposed for this subcategory.

A complete health effects SIDS data set is available for dibutyl, butyl benzyl and diethylhexyl phthalate. All of these substances are under review in Europe as part of the Existing Substances Risk Assessment, and have been included as reference compounds in the transitional phthalate subcategory. Data on di-n hexyl phthalate (non-HPV chemical) was also included to support read-across to dihexyl, diheptyl, and diisoheptyl phthalates. The available health effects data on other HPV chemicals in this subcategory are consistent with that reported for the above reference phthalates. Thus, studies from the reference compounds (DBP, BBP, DEHP and di-n hexyl) will be used as read-across to predict the toxicity of the remaining untested members. No additional testing is proposed for this subcategory.

There is a full data set for environmental toxicity data on DBP, BBP, DHP, DEHP, and DIOP. The lower transitional phthalates (DBP, BBP) are more water soluble than higher transitional phthalates and cause acute aquatic toxicity in the 1-10 mg/L range. There is an apparent cut-off in acute toxicity at dihexyl phthalate and higher; these results are further confirmed with QSAR modeling. Both calculated and measured values for environmental toxicity endpoints predict no effects at the limit of water solubility. The dihexyl phthalate data, together with read across from DIOP to diheptyl and diisoheptyl provide sufficient test data to indicate that these phthalates have no associated acute aquatic toxicity but may show chronic toxicity. Read across from DEHP, together with QSAR modeling also confirm that diisooctyl phthalate has neither acute nor chronic aquatic toxicity. No additional testing is proposed for this subcategory.

High Molecular Weight Phthalates

There are measured physicochemical property data available for some of the higher phthalates. Computer estimation models were also used to calculate physicochemical and fate data for phthalates in this subcategory. The calculated data were developed from a computer model used by the EPA, as cited in an EPA guidance document prepared for the HPV Challenge Program. Depending upon the endpoint, the modeled data agree with measured

data. The combination of measured values and calculated values is sufficient to provide the required information on the physiochemical and fate properties of the HPV phthalates in the high molecular weight subcategory. No additional physical/chemical studies are proposed for this subcategory.

A complete health effects SIDS data set is available for diisononyl (DINP) and diisodecyl (DIDP) phthalates. These substances are under review in Europe as part of the Existing Substances Risk Assessment, and have been included as reference compounds for the high molecular weight phthalate subcategory. Although not complete, health effects data are also available for many of the HPV substances in this subcategory. These phthalates all demonstrate minimal acute toxicity, are not genotoxic, exhibit some liver and kidney effects at high doses, and are negative for reproductive and developmental effects. Further, the available data indicate that the toxicological activity of these molecules diminishes with increasing molecular weight. The available data, supplemented with the data from the reference compounds (DINP, DIDP), are believed to be sufficient to use as read-across to the other category members, with side chains in the C7 - C13 range. No additional testing is proposed for this subcategory.

Ecotoxicity test data in fish, daphnia, and algae are available for 610P, 711P, DINP, DUP, DIDP and DTDP. These phthalates all contain alkyl chain lengths in the range of C7 to C13. The remaining members of this subgroup are all various mixtures of C7 through C11 alkyl chain isomers. All of the measured data for these higher phthalates show no effects on acute or chronic exposure to aquatic organisms. As with DIOP and DEHP, the higher phthalates are too insoluble to have acute or chronic toxicity. No additional testing is proposed for this subcategory.

TEST PLAN FOR THE PHTHALATE ESTERS CATEGORY

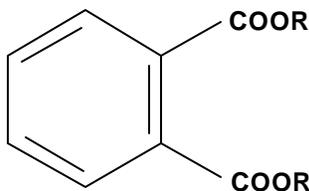
INTRODUCTION

The American Chemistry Council (ACC) Phthalate Esters Panel HPV Testing Group and its member companies have committed voluntarily to develop screening level human health effects, environmental effects and fate, and physicochemical data for the phthalate esters category under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Challenge Program.

This plan identifies CAS numbers used to characterize the SIDS endpoints for this category, identifies existing data of adequate quality for substances included in the category, and provides the Panel's rationale for applying the available SIDS data to characterize the hazards of all category members. The objective of this effort is to identify and adequately characterize the physicochemical properties, human health, and environmental fate and effects for the category in compliance with the EPA HPV Program.

DESCRIPTION OF THE PHTHALATE ESTERS CATEGORY

The phthalate esters comprise a family of chemicals synthesized by esterifying phthalic anhydride with various alcohols in the presence of an acid catalyst. The category includes the 18 HPV phthalate esters listed in Table 1. Phthalate esters in this category are all 1,2-benzenedicarboxylic acids with side chain ester groups ranging from C₁ to approximately C₁₃. The structural formula for phthalate esters varies depending on the isomeric composition of the alcohol used in their manufacture. Ester side chains may be linear isomers (e.g., di-methyl and di-n-heptyl phthalates), branched isomers (e.g., diisohexyl phthalate), and/or a combination of benzyl and linear or branched isomers (e.g., benzyl butyl phthalate and benzyl C7-C9 branched and linear phthalate).



Phthalate esters are generally clear to yellow, oily liquids with high boiling ranges (>250°C) and low vapor pressures; properties which contribute to their high physical stability. They are readily soluble in most organic solvents and miscible with alcohol, ether and most oils. The aqueous solubility of phthalate esters is inversely related to their

molecular weights. Lower molecular weight phthalates exhibit slight to moderate water solubility, whereas, higher molecular weight phthalates are insoluble.

The structural characteristics of the ester side chains affect both the physical/chemical and biological properties of phthalate esters. The phthalate esters were further subdivided into three subcategories based on their physicochemical and toxicological properties. The proposed subcategories are as follows:

Low molecular weight phthalates: produced from alcohols with straight-chain carbon backbones of $\leq C3$. Two U.S. HPV chemicals, dimethyl (DMP) and diethyl (DEP) phthalate, are included in this subcategory.

Low molecular weight phthalates are commonly used as solvents or in cellulose acetate polymers rather than as plasticizers for PVC. Their relatively higher volatility and water solubility give them properties different than other phthalate esters, some of which translate to different biological properties. In particular, these phthalates have greater aqueous solubility, resulting in a potential to cause acute toxic effects in aquatic organisms. The transitional phthalates, with the exception of C4, are too insoluble to cause acute effects but may show toxicity after chronic exposure, while the higher molecular weight phthalates cause neither acute nor chronic effects in aquatic organisms.

Transitional phthalates: produced from alcohols with straight-chain carbon backbones of C4-6. Phthalate esters containing $>10\%$ C4-6 molecules were conservatively included in this subcategory. Six of the U.S. HPV chemicals, dihexyl (DHP), diheptyl, diisooheptyl, diisooctyl, heptyl nonyl (C7, C9) and heptyl undecyl (C7, C11) phthalates are included in this subcategory. Data for this subcategory were supplemented with published information on other phthalate esters currently being assessed under the OECD SIDS program, including dibutyl (DBP), butylbenzyl (BBP), and di(2-ethylhexyl) phthalate (DEHP). Data on a structurally similar material, di-n hexyl phthalate, was also included for read-across purposes.

Transitional phthalates have varied uses from solvents (e.g., dibutyl) to plasticizers for PVC (e.g., DEHP). Physicochemical properties also vary in that the lower transitional phthalates are more water-soluble than higher transitional phthalates, but none would be considered to fall into the “high water soluble” category. What distinguishes these phthalates from others is their greater mammalian toxicity potential, particularly with regard to reproductive and developmental effects, compared to either the low or high molecular weight phthalate categories.

High molecular weight phthalates: produced from alcohols with straight-chain carbon backbones of $\geq C7$ or a ring structure. Ten of the U.S. HPV chemicals fall into this subcategory, which include varying mixed isomers of linear and branched diheptyl, dioctyl, dinonyl, didecyl, diundecyl and ditridecyl phthalate. Data for this subcategory were supplemented with published information on other phthalate esters currently being assessed under the OECD SIDS program, including di-isononyl (DINP) and di-isodecyl (DIDP) phthalate.

High molecular weight phthalates are used nearly exclusively as plasticizers of PVC. They are very insoluble in water, and have a very low vapor pressure. The extant database demonstrates that these substances have few biological effects. A notable exception to this generalization is that hepatocarcinogenicity has been observed for DINP. The hepatocarcinogenicity effects of DINP are by a mechanism (peroxisomal proliferation) to which rodents are particularly sensitive. However, it does not appear to be relevant to humans.

Substances were assigned to appropriate subcategories based on the composition of the ester side chain structures (Table 2). In some cases the substances have ester side chain constituents that span two subcategories (i.e., transitional and high molecular weight constituents). If the level of C4-C6 constituents in the substance exceeded 10%, the substance was conservatively placed in the transitional category.

DATA ADEQUACY REVIEW

Literature Search:

Literature searches were conducted by EMBSI Information Services on the environmental and mammalian toxicity endpoints for 18 chemicals, as supplied by the ACC Phthalate Ester Panel, using CAS numbers only. Several comprehensive review articles on these chemicals have been published recently (Staples et al., 1997a, 1997b, Cousins and Mackay, 2000, David et al., 2001). Therefore, the search was conducted using MEDLINE and TOXLINE databases and limited to studies published since 1995. In addition, the TSCATS database was searched for relevant unpublished studies on these chemicals. Standard handbooks and databases (Sax, CRC Handbook on Chemicals, IUCLID) were consulted for physical/chemical properties.

An initial search of MEDLINE/TOXLINE conducted in May 2000 found ~150 records since 1994 that contained the CAS number and a toxicology term. A second search found >600 records since 1994 that contained a generic name and a toxicology term. This set was further reduced to ~70 records by requiring a name fragment and a toxicology term to be in the title. An additional 283 records were found in the TSCATS database.

Approximately 125 reports were selected for review based on the following criteria: relevant SIDS endpoint, relevant CAS number, final report of company study (TSCATS), peer reviewed journal, or comprehensive review article (e.g., Staples et al 1997b, David et al., 2001, ATSDR review documents). With the exception of reports on dimethyl, diethyl, di C6-8 branched, dioctyl, and diundecyl phthalate, very few publications on other phthalate esters were discovered in the literature search.

Physical / Chemical Properties:

As noted above, a few of the chemicals on the HPV list are the more common phthalates and several of these (dimethyl, diethyl, dihexyl and dioctyl phthalates) are data rich. In

these cases, there are a variety of literature values for physical properties. For a number of reasons, these values vary greatly. Literature reviews by Staples et al., 1997b and Cousins and Mackay (2000) carefully evaluated the available values for these physical properties and selected representative values. The measured data presented in the robust summaries for these chemicals are these "best values" referencing the Staples et al. and Cousins and Mackay papers.

In addition, modeled data were entered into the robust summaries for all of the physical properties. There are a number of reasons for this approach:

- The EPA guidance (www.epa.gov/opptintr/chmrtk/robsumgd.htm) allows inclusion of calculated values in the robust summaries for physical/chemical elements
- The need for a complete set of physical property data in order to calculate environmental distribution
- The data gaps for physical properties for a few of these phthalates.

The physical properties were modeled using the SRI/EPA computer program EPIWIN, a modeling package that includes a number of algorithms developed at or for the EPA. EPIWIN is the program used and advocated by the EPA. Because the model is a structure-property model a specific discrete structure is required and EPIWIN contains a CAS number database which contains the structures for the chemicals. For mixtures, a single representative structure is contained in the database and in this work, these surrogate chemical structures were accepted for further modeling. It should be remembered that the resultant physical properties are for a single structure not a mixture so the values are discrete numbers rather than ranges.

Environmental Toxicity:

The environmental data selected for review were primarily obtained through a critique of the Environmental Toxicology and Chemistry review document Aquatic Toxicity of Eighteen Phthalate Esters, Staples, C.A. et al., 1997. This comprehensive review document summarized the data of multiple species for all eighteen phthalates. From this list of studies, the following criteria were applied to those phthalates matching the relevant CAS numbers.

- a) Standard test species
- b) Standard test endpoint or duration
- c) Measured versus nominal values
- d) Values representative of the data set presented

Once the study was identified, a review was performed of the original study document and a robust summary was prepared. A list of environmental studies that were identified from the literature search but not selected for robust summary, along with the reason why, is provided in **Appendix 1**.

Mammalian Toxicity:

The existing data for the mammalian toxicology endpoints were reviewed using the literature searches to identify the most relevant studies for each chemical in the group. A number of the individual chemicals on the list had no relevant studies identified in the searches. For the listed chemicals that contained relevant data, all available studies were reviewed using the criteria outlined in the EPA's methods for determining the adequacy of existing data for the HPV program and the ranking system proposed by Klimisch et al (1997). A list of the most relevant studies that were available for the mammalian health endpoints is presented in **Appendix 1**.

Studies that were chosen for robust summaries represented the best available data for a particular SIDS endpoint. Published studies from the general literature, as well as a number of unpublished company reports, were obtained and summarized. Some endpoints include multiple study summaries in order to present a more complete data set. Some of the reported studies (particularly older acute data) could not be summarized because of insufficient experimental detail to assess their quality or only were reported as LD₅₀ values in secondary sources. These studies are included in the data table (Table 3) as supplementary information.

Some phthalate esters can be described by more than one CAS number (e.g., DINP, DIDP) and/or are relevant to several different phthalates (e.g., 711P). In these cases, the robust summary was provided on the most relevant CAS number but cross referenced to other applicable CAS numbers in both the robust summary and the data table (Table 3).

One commercial test substance, 711P, is actually an equal composition mixture of six phthalate esters consisting of C7, C9, and C11 ester side chains. This test substance is considered by EPA under the following CAS nos.: 68515-44-6 (di C7), 68515-45-7 (di C9), 3648-20-2 (di C11), 111381-89-6 (C7, C9), 111381-90-9 (C7, C11), and 111381-91-0 (C9, C11). With the exception of 111381-90-9 (C7, C11), each of these substances is also commercially sold as a separate product. The overall content of C4-C6 isomers in 711P is approximately 10%, based on the contribution from branched C7 isomers e.g., di C7 (30% C4-C6); C7, C9 (15% C4-C6); and C7, C11 (15% C4-C6). Test data on 711P were used selectively as read-across to all substances in the mixture based on the C4-C6 content of each substance in the mixture. Phthalate esters with >10% C4-C6 isomers were conservatively placed in the transitional subcategory.

TESTING RATIONALE

Low Molecular Weight Phthalate Esters category (\leq C3)

Overview:

Low molecular weight phthalates are produced from alcohols with straight-chain carbon backbones of \leq C₃. The U.S. HPV chemicals, dimethyl (DMP) and diethyl (DEP) phthalate, are included in this subcategory. These phthalates are commonly used as solvents or in cellulose acetate polymers. The extant data base on DMP and DEP is

sufficient to adequately characterize their potential health and environmental effects. They have greater aqueous solubility and aquatic toxicity potential than do the transitional and higher molecular weight phthalates. However, they have lower mammalian toxicity potential than do the transitional phthalates.

A summary of the available toxicology data for this subcategory is shown in Table 3. Physical/chemical properties and environmental fate information is provided in Table 4. No additional testing is proposed for this subcategory.

	Acute	Repeat dose	Gentox (mut.)	Genetox (gene)	Repro	Develop	Acute fish	Acute daphnia	Algeal	Biodeg
DMP	A	A	A	A	R	A	A	A	A	A
DEP	A	A	A	A	A	A	A	A	A	A

A = adequate data; R = read-across

Physical / Chemical Properties:

There is a large amount of data for the physicochemical properties of dimethyl and diethyl phthalate (Table 4). Computer models were also used to estimate these properties for comparison with measured values and additionally were used to predict environmental distribution. The calculated data were developed from a computer model used by the EPA, as cited in an EPA guidance document prepared for the HPV Challenge Program (US EPA, 2000). Sufficient physical / chemical data exist for all members of this category and no further testing is necessary.

Mammalian Toxicity:

Acute Toxicity. DMP and DEP exhibit low acute toxicity by oral, dermal and inhalation routes of exposure. Although acute oral toxicity data on DEP are based on older, inadequate studies by current guidelines, the lack of lethality at doses >5 g/kg/day is consistent with that seen with other phthalate esters and subchronic studies on DEP.

Repeated Dose Toxicity. High dietary doses (5% or ~ 3,750 mg/kg/day) of DEP resulted in decreased body weights and tissue weights; no effects were seen in males at 1% (~ 750 mg/kg/day) or in females at 0.2 % (~ 150 mg/kg/day). These results are similar to that seen following dermal administration of DMP to rabbits for 90 days at 4g/kg/day. Neither DMP nor DEP exhibited chronic toxicity or carcinogenic effects in a one-year dermal initiation-promotion study in male mice (NTP, 1995). Further, no adverse effects were reported in rats fed diets containing up to 2% DMP for two years (Lehman, 1955).

Genetic Toxicity (Salmonella). Both DMP and DEP are negative for mutagenicity in the Ames assay (NTP, 1995). As all of these substances were inactive in these assays, no further testing of substances for point mutations is warranted.

Chromosomal Aberrations. Both DMP and DEP are negative for chromosomal damage in CHO cells *in vitro*. DMP was active in mouse lymphoma assay in the presence but not in

the absence of S9 (Barber et al., 2000); however, the overall weight of evidence from numerous genotoxicity assays indicates a lack of genotoxic effects (NTP, 1995).

Toxicity to Reproduction. No effects were seen in a two-generation reproductive study in mice fed DEP at doses of 3.2 g/kg/day. Although adequate reproductive studies are not available for DMP, data on DEP indicate that this material will not cause reproductive effects. This is supported by data showing that neither DEP or DMP had effects on male reproductive development (Gray et al., 2000). Although study details are lacking, no adverse effects on reproductive organs were reported in chronic studies conducted on DMP (Lehman, 1955; NTP, 1995). The lack of developmental effects observed with DMP, coupled with chronic toxicity studies showing no effects on reproductive organs, negates the need to conduct a reproductive study for DMP.

Developmental Toxicity/Teratogenicity. No developmental effects have been observed following dietary exposure to either DMP or DEP at doses up to 5% (~3.2 g/kg) in rats.

Environmental Toxicity:

There are numerous published acute aquatic toxicity studies in a variety of species of fish, daphnia and algae for DMP and DEP (Staples et al. 1997a). DMP and DEP are slightly soluble in aqueous systems. Acute effects on aquatic species are seen in the 10 to 100 ppm range. No additional environmental toxicity studies are necessary.

Transitional Phthalate Esters category (C4-C6)

Overview:

As described elsewhere, there are six phthalate esters in this category. The substances in this category have branched or linear side chains with carbon numbers ranging from C4 to C8. The chemical property that distinguishes this category of substances is that a predominant fraction of the alkyl side chains have linear portions with carbon numbers ranging from C4-C6. Contained within this category are substances with either linear or branched side chains, again with the stipulation that the branched molecules have a linear portion containing at least 4 but not more than 6 carbons. Some substances are predominantly linear; some predominantly branched; some with side chains of a single carbon number; and some with side chains covering a range of carbon numbers (e.g., di C6-C8 branched). Phthalate esters containing >10% C4-6 molecules were conservatively included in this subcategory. The grouping of these substances into a single category is also justified on toxicological grounds as described below.

The substances in this category which have been most extensively tested are dibutyl (DBP), butyl benzyl (BBP) and di-ethylhexyl phthalate (DEHP). All of these substances are under review in Europe as part of the Existing Substances Risk Assessment process, and, as a consequence, are already within the OECD SIDS process. They are included in this summary for reference purposes. The European risk assessments for DBP and DEHP, as well as the evaluation of the data at the OECD level, are expected to be substantially completed within 2001. There are several other phthalates including di-n-hexyl phthalate

(DnHP, 84-75-3) which are not high volume substances but nevertheless provide data useful for assessing this category of substances.

The data from the reference substances and other tested substances cover the majority of the carbon numbers and molecular types found in this category. Thus, it is reasonable to assume that the data from the extensively tested members of this category can be used to reasonably predict the toxicological properties of the less well studied members.

A summary of the available toxicology data for this subcategory is shown in Table 3. Physical/chemical properties and environmental fate information is provided in Table 4. No additional testing is proposed for this subcategory.

	Acute	Repeat dose	Gentox (mut.)	Genetox (gene)	Repro	Develop	Acute fish	Acute daphnia	Algal	Biodeg
DBP*	A	A	A	A	A	A	A	A	A	A
BBP*	A	A	A	A	A	A	A	A	A	A
DHP	R	A	R	A	R	R	A	A	A	A
DnHP*	A	A	A		A	A				
DEHP*	A	A	A	A	A	A	A	A	A	A
diheptyl	R	R	R	R	R	R	R	R	R	R
diisoheptyl	A	R	A	A	R	A	R	R	R	R
DIOP	R	R	A	A	R	R	A	A	A	A
C7, C9	R	R	A	A	R	A	R	R	R	R
C7, C11	R	R	A	A	R	A	R	R	R	R

*Not US HPV chemical; data included for read-across to other category members.

A= adequate data; R = read-across

Physical / Chemical Properties:

Melting point and boiling point data are available for all of the members of this group from Staples et al. or handbooks, except for diisoheptyl. All of the phthalates higher than DMP have melting points below 0°C. DEP has a boiling point of 295°C and all data for higher phthalates have boiling points >300°C. Thus, there is sufficient evidence that diisoheptyl phthalate would have a melting point <0°C and boiling point >300°C. The melting points calculated by the EPIWIN program agree poorly (too high) with measured values for the phthalates.

Cousins and Mackay have tabulated and analyzed all of the measured water solubility, vapor pressure, and partition coefficient (K_{ow}) for all of the transitional phthalate esters, except for the C7, C9 phthalate (CAS# 111381-89-6). They have used correlations with molar volume and fugacity considerations to select the best values for dihexyl, diisohexyl, diheptyl, disoheptyl and diisooctyl phthalates. These values are considered the best values for water solubility, vapor pressure and partitioning of these phthalates. These values also are in relatively good agreement with calculated values.

Hydrolysis half lives and atmospheric photodegradation rates are calculated by EPIWIN. Phthalate ester hydrolysis rates are quite low and not a significant fate route. Environmental distribution was modeled by the EQC model.

No measurements of the physicochemical or fate properties of this subgroup is necessary.

Mammalian Toxicity:

Acute Toxicity. The available data on phthalates spanning the carbon range from C4-C6 indicate that phthalate esters in the transitional group are minimally toxic by acute oral and dermal administration. Oral LD50 values for DBP and BBP exceed 2 g/kg, and for materials with higher molecular weights, the LD50 values exceed the maximum amounts which can be administered to the animals in a manner consistent with the principles of responsible animal use. Some of these data have already been published (e.g., Krauskopf, 1973; Lawrence et al., 1975), but there is also a substantial body of unpublished data. Only two members of this group (DBP and DEHP) have been tested for acute inhalation toxicity, but in both cases the inhalation LC50 exceeded the level tested. Further, considering the low volatility of these substances, inhalation exposure at toxicologically significant levels is not anticipated. Thus, further testing of substances in this category for acute toxicity is not proposed.

Repeated Dose Toxicity. Several substances in the C4-C6 range have been tested for repeated dose toxicity in studies ranging from 3 weeks to 2 years (e.g., Barber et al., 1987, David et al., 1999; 2000; 2001). The principal effects found in these studies were those associated with peroxisome proliferation including liver enlargement and induction of peroxisomal enzymes. As shown in a comparative study of liver effects (Barber et al., 1987), the strongest inducers of peroxisome proliferation are DEHP, DINP and DIDP with substances of shorter chain length (e.g., DBP, BBP) showing much less pronounced effects. Thus it is reasonable to conclude that other members of this category would show effects similar to but less pronounced than those associated with DEHP. It should also be noted that the relevance of these findings to human health is, at best, questionable. It has been shown that these effects are mediated through the peroxisome proliferation-activated receptor alpha (PPAR α ; Ward et al., 1998) and that levels of PPAR α are much higher in rodents than they are in humans (Tugwood et al., 1996; Palmer et al., 1998). Thus one would expect humans to be substantially less responsive than rodents to peroxisome proliferating agents. Empirical evidence that this is true is provided by studies in primates in which repeated administration of DEHP and DINP (Hall et al., 1999; Kurata et al., 1998; Pugh et al., 2000) had no effects on liver, kidney or testicular parameters.

Several of the substances in the transitional phthalate esters category, however, have been shown to produce testicular atrophy when given to juvenile rats at high levels. Testicular atrophy has been associated with DBP, BBP, DEHP (Lington et al., 1993) and other substances with C4-C6 linear carbon chains (Foster et al., 1980). However, molecules with fewer than 4 or more than 6 carbons did not produce testicular atrophy in these studies (Foster et al., 1980; Lington et al., 1993). Although the relevance of these data are uncertain as the testes is not a target organ for DEHP in primates (Kurata et al., 1998;

Pugh et al., 2000), these data do provide one of the distinguishing toxicological characteristics of this category and are one of the underlying reasons supporting the differentiation of phthalate esters on the basis of length of the linear region of the carbon chain.

In summary, there is no need for further repeated dose studies of transitional phthalate esters in rodents. The effects in rodents have been well described for a number of representatives of this category. The most sensitive indicators of effect are in the liver and associated with peroxisomal proliferation. The relevance of these effects to humans is questionable.

Genetic Toxicity (Salmonella). A number of the substances in this category including the reference substances DBP, BBP and DEHP have been assessed in the Salmonella (Zeiger et al., 1985) and mouse lymphoma (Barber et al. 2000) assays. As all of these substances were inactive in these assays, no further testing of substances in the transitional phthalate esters category for point mutations is warranted.

Chromosomal Aberrations. DBP, BBP and DHP were inactive in micronucleus assays in mice. DEHP was inactive in a cytogenetics assay in rat bone marrow. Diisooheptyl phthalate was inactive in CHO cells, in vitro. As substances spanning the range of materials in this category have been tested in the standard assays for chromosomal aberration and found to be inactive, no further testing of chromosome aberration is warranted for transitional phthalate esters.

Toxicity to Reproduction. A series of studies assessed the structure-activity relationship of the effects of phthalate esters on fertility using a continuous breeding protocol (Lamb et al., 1987; Heindel et al., 1989). The test substances included diethyl-, dipropyl-, dibutyl-, dipentyl-, d-n-hexyl-, di-2(ethylhexyl)-, and di-n-octyl phthalates. The most profound effects were on fertility (i.e., number of females delivering/number mated) and number of live births. The substance showing the greatest activity was DEHP which produced effects at dietary levels of 0.1% with a no effect level of 0.01%. The next most active compounds were di-n-hexyl- and di-n-pentyl phthalate which showed effects in the range of 0.3-0.5%; no effect levels were not experimentally defined. DBP had effects at 1.0% in the diet but 0.3% was a no effect level. Dipropyl phthalate had an effect on live birth index at 2.5% but produced no effects at 1.25%. Diethyl phthalate and di-n-octyl phthalate were inactive at the highest levels tested (2.5% and 5.0% respectively). These data demonstrated that molecules with linear alkyl chains of 4-6 carbons profoundly affect fertility in rodents, with DEHP being the most active. Molecules with longer or shorter side chains are essentially inactive in these assays. These data were also a basis for the separation of phthalates into three categories based on length of side chain.

In addition to these data there are reproductive toxicity studies on DBP (Wine et al., 1997, Patel et al., 2001), BBP (Nagao et al., 2000) and DEHP (Schilling et al., 1999). Additional work on DBP, BBP and DEHP is ongoing. These studies along with previous data provide a good basis to assess the reproductive effects of C4-C6 phthalate esters. Although several substances (diheptyl, heptyl nonyl, heptyl undecyl) have ester side chain

constituents that predominately fall in the high molecular weight subcategory, these substances are conservatively assumed to exhibit reproductive effects similar to other transitional phthalates. There will be no need for further reproductive toxicity studies of substances in this group once the ongoing studies are completed.

Developmental Toxicity/Teratogenicity. There have been extensive studies of the developmental toxicity of DBP, BBP, and DEHP (NTP, 2000). These substances produce structural malformations and also affect male reproductive development. No effect levels are in the range of 50 to 300 mg/kg bw/day. There is also an unpublished developmental toxicity study of di-isoheptyl phthalate (DIHP). The results of these studies are broadly consistent with the structure-activity relationships previously described, i.e., that phthalate esters with linear carbon chains of C4-C6 carbons produce much more profound effects than either shorter or longer molecules.

Phthalate esters with >10% C4-C6 isomers were conservatively placed in the transitional subcategory. This conclusion is supported by developmental test data on 711P, which showed structural malformations in rats at 1000 mg/kg day with a NOAEL of 200 mg/kg/day (Hellwig et al., 1997). As previously discussed, 711P is an equal composition mixture of six phthalate esters consisting of linear and methyl-branched C7, C9, and C11 ester side chains. This test substance is considered by EPA under the following CAS nos.: 68515-44-6 (di C7), 68515-45-7 (di C9), 3648-20-2 (di C11), 111381-89-6 (C7, C9), 111381-90-9 (C7, C11), and 111381-91-0 (C9, C11). The overall content of C4-C6 isomers in 711P is approximately 10%, based on the contribution from methyl-branched C7 isomers e.g., di C7 (30% C4-C6); C7, C9 (15% C4-C6); and C7, C11 (15% C4-C6). Test data on 711P were used selectively as read-across to the C7-containing substances in the mixture, based on the C4-C6 content of each substance in the mixture.

The available data permit an assessment of the developmental toxicity of this category of products, and no further testing of individual members is warranted.

Environmental Toxicity:

There is a full data set for aquatic toxicity data of dihexyl and diisooctyl phthalates in fish, invertebrates and algae. These data were supplemented with full environmental data sets on DBP, BBP and DEHP (currently being assessed under OECD SIDS program). Although DBP and BBP cause acute aquatic toxicity in fish, invertebrates and algae in the 1 to 10 mg/L range, dihexyl phthalate causes no acute effect in these classes of organisms at its maximum water solubility (Staples, 1997a). This cut-off in acute toxicity is due to the concentration causing acute toxicity being higher than the water solubility of the phthalate ester, as was elegantly shown by Parkerton and Konkel (2000). The same situation exists for those phthalates which are more non-polar (higher carbon number) than dihexyl. This is confirmed by a lack of measured acute toxicity to fish, invertebrates or algae for DEHP and DIOP (Staples, 1997a). These results are further confirmed with QSAR modeling. Thus, read across data for the other transitional phthalates, together with a phthalate specific aquatic toxicity QSAR (Parkerton and Konkel, 2000), leads to the conclusion that the other members of this subgroup, diheptyl and diisoheptyl phthalates,

will not cause acute aquatic toxicity. As a consequence, no further aquatic toxicity testing is necessary.

High Molecular Weight Phthalate Esters Category (\geq C7)

Overview:

As described elsewhere, there are ten phthalate esters in this category. The substances in this category have branched or linear side chains with carbon numbers ranging from C7 to C13. The distinguishing chemical property for this category of substances is that a predominant fraction of the alkyl side chains have linear portions containing at least 7 carbons. Contained within this category are substances with either linear or branched side chains, again with the stipulation that the branched molecules must have a linear portion of at least 7 carbons. Some substances are predominantly linear; some predominantly branched; some with side chains of a single carbon number; and some with side chains covering a range of carbon numbers (e.g., C7-C9 phthalate). In some cases the substances have a small fraction of smaller constituents (e.g., 610P), but if the level of such constituents exceeded 10%, the substance was placed in the lower (i.e., C4-C6) transitional category. The grouping of these substances in a single category is also justified on toxicologic grounds as described below.

The substances which have been most extensively tested are DINP (CAS # 28553-12-0, CAS # 68515-48-0) and DIDP (CAS # 26761-40-0 and CAS # 68515-49-1). Both of these substances are under review in Europe as part of the Existing Substances Risk Assessment Process, and, as a consequence are already within the SIDS review process. They are included in this review for reference purposes. The risk assessment of these substances as well as the evaluation of the data at the OECD level is expected to be substantially completed within 2001. There are several other substances including C7-C9 phthalate (CAS # 68515-41-3) and dtridecyl phthalate (CAS # 119-06-2) which are not high volume substances but nevertheless also provide data useful for assessing this category of substances.

Among those substances which are included on the HPV list and are not otherwise undergoing evaluation, there are several including DnOP, DUP, benzyl C7-9, C9-C11, and DTDP phthalates which have also been tested. The data from the HPV and reference substances cover the majority of carbon numbers and molecular types found within this category. Thus, it is reasonable to assume that the data from the extensively tested members of this category can be used to reasonably predict the toxicological properties of the less studied members.

A summary of the available toxicology data for this subcategory is shown in Table 3. Physical/chemical properties and environmental fate information is provided in Table 4. No additional testing is proposed for this subcategory.

	Acute	Repeat dose	Gentox (mut.)	Genetox (gene)	Repro	Develop	Acute fish	Acute daphnia	Algal	Biodeg
610P	R	R	R	R	R	R	A	A	A	A
DnOP	A	A	A	R	A	A	R	R	R	R
benzyl C7-9	A	R	A	R	R	R	A	A	A	R
C7-9*	A	A	A		A	A				A
DINP*	A	A	A	A	A	A	A	A	A	A
dinonyl	R	R	R	R	R	R	R	R	R	R
C9-11	R	R	R	R	A	A	R	R	R	R
didecyl	R	R	R	R	R	R	R	R	R	R
DIDP*	A	A	A	A	A	A	A	A	A	A
DUP	A	A	A	R	R	R	A	A	A	A
DIUP	R	R	R	R	R	R	R	R	R	R
C9, C11	R	R	R	R	R	R	R	R	R	R
DTDP	A	R	A	R	R	R	A	A	A	A
C13*	A	A	A	A	A	A				

*Not US HPV chemical; data included for read-across to other category members.

A = adequate data; R = read-across

Physical / Chemical Properties:

Melting points and boiling points are generally available for the phthalates in this subgroup, but the "melting points" are often pour points and the boiling points are measured at greatly reduced pressures. It can be safely extrapolated that the melting points of all of the phthalate esters in this group are <0°C and the boiling points are all >300°C (in most cases, >400°C).

Cousins and Mackay give best values for DnOP, DNP, DINP, DIDP, 610P, 711P, DUP and DTDP for water solubility, vapor pressure and partition coefficient. Data on 711P, which is a mixture of C7, C9 and C11 isomers, covers three CAS numbers in this subcategory (e.g., dinonyl, diundecyl, and nonyl undecyl). The physicochemical properties of these remaining phthalate esters may be adequately estimated by a combination of read-across and modeling.

Hydrolysis half lives and atmospheric photodegradation rates are calculated by EPIWIN. Phthalate ester hydrolysis rates are quite low and not a significant fate route. Environmental distribution was modeled by the EQC model. No measurements of the physicochemical or fate properties of this subgroup is necessary.

Mammalian Toxicity:

Acute Toxicity. The available data on phthalates spanning the carbon range from C8-C13 indicate that phthalate esters in the high molecular weight category are not toxic by acute

oral and dermal administration; LD50 values of all substances tested exceed the maximum amounts which can be administered to the animals. Some of these data have been published (e.g., Krauskopf, 1973; Lawrence et al., 1975), but there is also a substantial body of unpublished data. There are fewer data available on inhalation toxicity; only DINP and DIDP have been tested. However, the phthalates in the high molecular weight category have extremely low vapor pressures, and exposure by inhalation at potentially hazardous levels is not anticipated. Thus, further testing of the acute toxic properties of these materials is not warranted.

Repeated Dose Toxicity. Several substances ranging from C8-C11 have been tested for repeated dose toxicity in studies ranging from 21 days to two years (e.g., Barber et al., 1987; Butala et al., 1996; Lington et al., 1997; David et al., 2001). In addition, dinitridecyl phthalate (CAS no. 119-06-2) has been studied by the Japan Ministry of Health and Welfare (unpublished report) and is used as read-across for DTDP. The principal effects found are those associated with peroxisomal proliferation, including liver enlargement and induction of peroxisomal enzymes. As shown for example in a comparative study of liver effects (Barber et al., 1987), the strongest inducers of peroxisomal proliferation were DEHP, DINP and DIDP with substances of shorter and longer ester side chains (e.g., 610P, 711P, and DUP) showing less pronounced effects. Thus, it is reasonable to conclude that other members of this category would show effects similar to but not more pronounced than those associated with DINP and DIDP. It should also be noted that the relevance of these findings to human health is, at best, questionable. It has been shown that these effects are mediated through the peroxisome proliferation-activated receptor alpha (PPAR α ; Valles et al., 2000; Ward et al., 1998), and that levels of PPAR α are much higher in rodents than humans (Tugwood et al., 1996; Palmer et al., 1998). Thus, one would expect humans to be substantially less responsive than rodents to peroxisome proliferating agents. Empirical evidence supporting this postulation is provided by studies in primates in which repeated administration of DEHP and DINP (Hall et al., 1999; Kurata et al., 1998; Pugh et al., 2000) had no effects on liver, kidney or testicular parameters.

In this regard it should also be noted that kidney enlargement is also commonly observed but normally without any pathological changes. As shown by Ward (1998), there is a component of the kidney changes which is also PPAR α -related. It has also been shown that in male rats, DINP induces an alpha 2u-globulin nephropathy which is male rat-specific (Caldwell et al., 1999; Schoonhoven et al., 2001) but without relevance to humans (Baetcke et al., 1992). Thus, as was true for the liver changes, the relevance of the kidney changes to human health is also questionable (Woodard, 1990).

Finally, some of the lower molecular weight phthalates can induce testicular atrophy when administered to juvenile rats at high levels. However, the higher molecular weight phthalates including DnOP, DINP, DIDP, 610P and 711P do not induce testicular atrophy (Lington et al. 1993). Further, the testis was not a target organ for DINP in either marmosets (Hall et al., 1999) or cynomolgus monkeys (Pugh et al., 2000). Thus, testicular atrophy is not an effect associated with phthalates in the high molecular weight category.

In summary, there is no need for further repeated dose studies of high molecular weight phthalates in rodents. The effects in rodents for this category have been well described and are of questionable relevance to humans. Thus, further assessments of repeated dose toxicity of substances in this category are unwarranted.

Genetic Toxicity (Salmonella). The majority of the substances in the category of high molecular weight phthalates have been tested for genetic activity in the Salmonella assay, and all were inactive. One large program covering many of these substances was carried out by the National Institute of Environmental Health Sciences (Zeiger et al., 1985). Similarly, a range of substances covering the majority of the carbon numbers in this category were found to be inactive in mouse lymphoma tests (Barber et al., 2000). Thus, no further testing of phthalates in the high molecular weight category for the potential to induce point mutations is warranted.

Chromosomal Aberrations. Two representative members of the category of high molecular weight phthalates (DINP, DIDP) have been tested for chromosomal mutation in the mouse micronucleus test (McKee et al., 2000), and both were inactive. Ditridecyl phthalate (CAS # 119-06-2) induced neither structural chromosomal aberrations nor polyploidy in CHL cells up to the limit concentration of 4.75 mg/ml, in the absence or presence of an exogenous metabolic activation system (Japan Ministry of Health and Welfare, unpublished report). Further, all of the low molecular weight and transitional phthalates that have been tested were inactive. Thus, it is unlikely that the substances in this category are chromosomal mutagens. No further testing for chromosomal aberrations is proposed for this subcategory.

Toxicity to reproduction. Reproductive toxicity tests in rats have been carried out with DINP (Waterman et al., 1999), DIDP (Hushka et al., 2000), a linear C7-C9 phthalate (CAS # 68515-41-3), a linear C9-C11 phthalate (Willoughby et al., 2000), and ditridecyl phthalate (Japan Ministry of Health and Welfare, unpublished report). None of these affected fertility or profoundly affected male reproductive development. A slight decrease in offspring viability was reported for both DIDP and ditridecyl phthalate at levels associated with maternal effects. DnOP was tested for effects on fertility in a continuous breeding protocol in mice, and, like the other members of this category, did not reduce fertility. Thus, it can be concluded that the category of high molecular weight phthalates do not affect fertility and that no further reproductive testing of substances in this category is warranted.

Developmental toxicity. Developmental toxicity tests in rats have been carried out with DINP; DIDP; C7-9 phthalate (CAS # 68515-41-3); C9-11 phthalate (CAS # 68515-43-5); and ditridecyl phthalate (CAS # 119-06-2) (Fulcher et al., 2001; Waterman et al., 1999; Japan Ministry of Health and Welfare, unpublished report). None of the substances tested affected litter size, fetal survival or bodyweight, and none produced teratogenic effects. Increased frequencies of developmental variants including dilated renal pelvis, and supernumerary lumbar and cervical ribs were found at levels associated with maternal effects. The toxicological significance of these developmental variants is unclear. DnOP was not teratogenic in mice when tested at very high levels. Thus, it can be concluded that

this category of high molecular weight phthalates do not produce profound developmental effects in rodents and no further testing of substances in this category is warranted.

Environmental Toxicity:

Among the higher phthalates, acute aquatic test data in fish, invertebrates and algae are available for DINP, 610P, 711P, DUP, DIDP and DTDP. None of these shows any acute toxicity when tested at the maximum attainable water concentration (Staples et al., 1997a). These phthalates all contain alkyl chain lengths in the range of C7 to C13, as do the members of this subgroup. In fact, three of these (610P, DUP and DTDP) are contained within this group of CAS numbers. The remaining members of this subgroup are all various mixtures of C7 through C11 alkyl chain isomers. The fact that these phthalates do not show acute toxicity is due to their water solubility being well below their toxic concentration (Parkerton and Konkell, 2000). For similar reason, the higher phthalates also show no effects on chronic exposure, as is the case for DEHP (Parkerton and Konkell, 2000).

TEST PLAN SUMMARY

The American Chemistry Council Phthalate Esters Panel HPV Testing Group believes that there is a sufficient amount of information available on phthalate esters (as a chemical class) to substantially characterize the human health effects and environmental fate and effects endpoints for all members of this category under the U.S. HPV Challenge program. No additional toxicology tests are proposed for these materials.

Low Molecular Weight Phthalates

- Physicochemical properties and environmental fate for all category members were calculated using appropriate QSAR models, and supplemented with measured data from the literature.
- A complete mammalian and environmental SIDS data set is available for DMP and DEP, with the exception of adequate reproductive data on DMP. The lack of developmental effects observed with DMP, coupled with chronic toxicity studies showing no effects on reproductive organs (and read-across to DEP), fulfills the SIDS requirements for this endpoint.

Transitional Phthalates

- Physicochemical properties and environmental fate for all category members were calculated using appropriate QSAR models, and supplemented with measured data from the literature. The combination of measured and calculated values is sufficient to characterize the physicochemical and fate properties of all category members.
- Complete mammalian toxicity SIDS data sets are available under the OECD SIDS program for DBP, BBP and DEHP (reference compounds). Acute toxicity, mutagenicity and developmental toxicity data are available for many of the remaining

HPV chemicals in this subcategory. Studies from the reference compounds are used as read-across to predict the toxicity of the remaining untested members.

- There is a full data set for environmental toxicity data on DBP, BBP, DHP, DEHP, and DIOP (reference compounds). There is an apparent cut-off in acute toxicity at dihexyl phthalate and higher; these results are further confirmed with QSAR modeling. Both calculated and measured values for environmental toxicity endpoints predict no effects at the limit of water solubility. Studies from the reference compounds are used as read-across to predict the toxicity of the remaining untested members.

High Molecular Weight Phthalates

- Physicochemical properties and environmental fate for all category members were calculated using appropriate QSAR models, and supplemented with measured data from the literature. The combination of measured and calculated values is sufficient to characterize the physicochemical and fate properties of all category members.
- Complete mammalian toxicity SIDS data sets are available for DINP, DIDP, and ditridecyl phthalate (reference compounds). Acute toxicity, repeated dose toxicity, mutagenicity and reproductive/developmental toxicity data are available for several of the remaining HPV chemicals in this subcategory. Studies from the reference compounds are used as read-across to predict the toxicity of the remaining untested members.
- There is a full data set for environmental toxicity data on 610P, DINP, DIDP, DUP, and DTDP (reference compounds). As predicted based on their poor water solubility, all of the measured data for these chemicals show no effects on acute or chronic exposure to aquatic organisms. QSAR arguments and studies from the reference compounds are sufficient to predict no environmental effects at the limit of water solubility for the remaining category members.

Table 1. CAS Numbers And Descriptions.

CAS Number	CAS Number Description
Phthalates Group 1 - low MW phthalates (<C3 ester backbone)	
131-11-3	1,2-benzenedicarboxylic acid, dimethyl ester (dimethyl phthalate, DMP)
84-66-2	1,2-benzenedicarboxylic acid, diethyl ester (diethyl phthalate, DEP)
Phthalates Group 2 - transitional phthalates (C4-C6 ester backbone)	
68515-50-4	1,2,-benzenedicarboxylic acid, dihexyl ester, branched and linear (dihexyl phthalate, DHP)
68515-44-6	1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear (diheptyl phthalate)
71888-89-6	1,2-benzenedicarboxylic acid, di C6-8 branched alkyl ester, C7 rich (diisoheptyl phthalate, DIHP)
27554-26-3	1,2,-benzenedicarboxylic acid, diisooctyl ester (diisooctyl phthalate, DIOP)
111381-89-6	1,2-benzenedicarboxylic acid (C7, C9) ester, branched and linear (C7, C9 branched & linear)
111381-90-9	1,2-benzenedicarboxylic acid, (C7,C11) ester, branched and linear (C7,C11 branched & linear)
Phthalates Group 3 - high MW phthalates (>C7 ester backbone)	
68648-93-1	1,2-benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters (610P)
117-84-0	1,2,-benzenedicarboxylic acid, dioctyl ester (dioctyl phthalate, DnOP)
68515-40-2	1,2-benzenedicarboxylic acid, benzyl C7-9 branched and linear alkyl esters
68515-45-7	1,2,-benzenedicarboxylic acid, dinonyl ester, branched and linear (dinonyl phthalate, DNP)
68515-43-5	1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters
84-77-5	1,2-benzenedicarboxylic acid, didecyl ester (didecyl phthalate)
3648-20-2	1,2-benzenedicarboxylic acid, diundecyl ester (diundecyl phthalate, DUP)
85507-79-5	1,2-benzenedicarboxylic acid, di (C11) ester, branched and linear (diisoundecyl phthalate, DIUP)
111381-91-0	1,2-benzenedicarboxylic acid (C9, C11) ester, branched and linear (C9, C11 branched & linear)
68515-47-9	1,2,-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich (di-tridecyl phthalate, DTDP)

Table 2. Typical Composition Ranges (Percent) For Phthalate Esters

Substance		Ester Side Chain Composition Range (%)			
CAS #	Name	≤C3	C4 - C6	≥C7	benzyl ring
Phthalates Group 1 - low MW phthalates (≤C3 ester backbone)					
131-11-3	dimethyl	100			
84-66-2	diethyl	100			
Phthalates Group 2 - transitional phthalates (C4-C6 ester backbone)					
84-74-2*	dibutyl		100		
85-68-7*	butyl benzyl		50		50
68515-50-4	dihexyl		100		
71888-89-6	diisooheptyl		80	20	
27554-26-3	diisooctyl		70-75	<25	
117-81-7*	diethylhexyl		100		
68515-44-6	diheptyl		30	70	
111381-89-6	C7, C9		15	85	
111381-90-9	C7, C11		15	85	
Phthalates Group 3 - high MW phthalates (≥C7 ester backbone)					
68648-93-1	610P		<1	99	
117-84-0	dioctyl			100	
68515-40-2	benzyl C7-9		2	48	50
28553-12-0*	diisononyl		5-10	>90	
68515-48-0*					
68515-45-7	dinonyl			100	
68515-43-5	C9-11			100	
84-77-5	didecyl			100	
26761-40-0*	diisodecyl			100	
68515-49-1*					
111381-91-0	C9, C11			100	
3648-20-2	diundecyl			100	
85507-79-5	diisoundecyl			100	
68515-47-9	diisotridecyl			100	

*HPV chemicals currently in the OECD SIDS program. Data on these chemicals are being used for data read-across in appropriate subcategories.

Table 3

[Click to view/edit Excel Spreadsheet \(Table \) 3 - Toxicology Data Summary Phthalate Esters](#)

Table 4

[Click to view/edit Excel Spreadsheet \(Table\) 4 - Physical/Chemical Data Summary Phthalate Esters](#)

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Lamb, J. et al. (1987). Reproductive effects of four phthalic acid esters in the mouse. *Toxicology and Applied Pharmacology* 88:255-269.

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Wine, R. et al. (1997). Reproductive toxicity of di-n-butylphthalate in a continuous breeding protocol in sprague-dawley rats. *Environmental Health Perspectives* 105:102-107.

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*The list of references is not a comprehensive bibliography of all of the phthalate ester literature, merely a series of papers which illustrate key points made in the text. The information in these papers also supplements the robust summaries developed for toxicology studies of listed substances in tests addressing specific SIDS endpoints.

Appendix 1:
ACC Phthalate Esters Group HPV Literature Search

A. Review of Environmental Endpoints

The following documents were identified from the literature search as possible robust summary reviews for the ACC phthalates. Provided with each reference is the reason for its exclusion from the data review set.

- 1) Kleerebezem, R., et al, Anaerobic Biodegradability of Phthalic Acid Isomers and Related Compounds, *BIODEGRADATION* 10 (1) 1999, p. 63-67.

Anaerobic study not a conventional test design or SIDS endpoint. HPV focusing on aerobic biodegradation endpoints.

- 2) Gunatilleka, A.D., et al, Models for Estimating the Non-specific Aquatic Toxicity of Organic Compounds. *ANALYTICAL COMMUNICATIONS*;36 (6) 1999 p. 235-242.

New model for predicting aquatic toxicity endpoints. Laboratory data used in place of models. Phase III may identify models for use in filling data gaps versus testing.

- 3) Zou, E. et al, Effects of Exposure to Diethyl Phthalate, 4-(tert)-octylphenol, and 2,4,5-trichlorobiphenyl on Activity of Chitinase in the Epidermis and Hepatopancreas of the Fiddler Crab, *Uca pugilator*, *COMPARATIVE BIOCHEMISTRY and PHYSIOLOGY* 122 (1) 1999 p. 115-120.

Data generated not a SIDS endpoint.

- 4) Kurane, R., Microbial Degradation and Treatment of Polycyclic Aromatic Hydrocarbons and Plasticizers, *ANNALS of the NEW YORK ACADEMY of SCIENCE*, Vol 829.

Abstract from book chapter and conference on bioremediation of surface and subsurface contamination. Methodology review.

- 5) Mark, U., et al, Analysis of the ECETOC Aquatic Toxicity (EAT) Database. V- The Relevance of *Daphnia magna* as a Representative Species. *CHEMOSPHERE*; 36 (1) 1998.

A review of existing data through ECETOC, and a comparison of Daphnid sensitivity to other species. Not applicable to HPV robust summaries.

- 6) Russom C.L., et al, Predicting Modes of Toxic Action from Chemical Structure: Acute Toxicity in the Fathead Minnow (*Pimephales promelas*). *ENVIRONMENTAL TOXICOLOGY AND CHEMISTRY*; 16 (5) 1997.

Classification of chemicals in categories based upon their mode of toxicity. Not relevant to HPV robust summaries.

7) Ejlerstson, J. et al, Anaerobic Degradation of Phthalate Acid Esters During Digestion of Municipal Solid Waste Under Landfilling Conditions. *BIODEGRADATION*; 7 (4) 1996.

Anaerobic degradation not a SIDS endpoint. Not a routine test design.

8) Yan, H. et al, Kinetics of Phthalate Ester Biodegradation by *Chlorella pyrenoidosa*. *ENVIRONMENTAL TOXICOLOGY and CHEMISTRY*; 14 (6) 1995.

Biodegradation through plant bioaccumulation (modified algal study), not a SIDS endpoint.

9) Rhodes, J.E. et al, Chronic Toxicity of 14 Phthalate Ester to *Daphnia magna* and Rainbow Trout (*Oncorhynchus mykiss*). *ENVIRONMENTAL TOXICOLOGY and CHEMISTRY*; 14 (11) 1995.

Review article on chronic study endpoints for daphnids and fish. HPV robust summaries are focusing on acute endpoints only.

The following list contains literature search documents which are also referenced in comprehensive review paper (Staples et al., 1997).

* Represent portions of the document reviewed for robust summaries.

1) Acute Toxicity of Fourteen Phthalate Esters to Daphnia magna, CMA report, Study performed by Springborn Bionomics 1984 *

2) Acute Toxicity of Fourteen Phthalate Esters to Freshwater Algae, Selenastrum capricornutum, CMA report, Study performed by Springborn Bionomics 1984 *

3) Acute Flow-Through Toxicity of Thirteen Phthalate Esters to Fathead Minnow Pimephales promelas, CMA report, Study performed by Springborn Bionomics 1984

4) Acute Toxicity of Thirteen Phthalate Esters to Bluegill Sunfish L. macrochirus, CMA report, Study performed by Springborn Bionomics 1984

5) Chronic Toxicity of Fourteen Phthalate Esters to Daphnia magna, CMA report, Study performed by Springborn Bionomics 1984

6) Acute Toxicity of Thirteen Phthalate Esters to Sheepshead Minnow Cyprinodon variegatus, CMA report, Study performed by Springborn Bionomics 1984

7) Acute Toxicity of Fourteen Phthalate Esters to Rainbow Trout Oncorhynchus mykiss, CMA report, Study performed by Springborn Bionomics 1984 *

- 8) Acute Flow-through Toxicity of Fourteen Phthalate Esters to Rainbow Trout Oncorhynchus mykiss, CMA report, Study performed by Springborn Bionomics 1984 *
- 9) Acute Toxicity of Twelve Phthalate Esters to Mysid Shrimp Mysidopsis bahia, CMA report, Study performed by Springborn Bionomics 1984
- 10) Acute Toxicity of Twelve Phthalate Esters to Paratanytarsus parthenogenia, CMA report, Study performed by Springborn Bionomics 1984
- 11) Shake Flask Biodegradation of Fourteen Commercial Phthalate Esters. CMA report, Study performed by Syracuse Research Corp. 1983 *
- 12) Activated Sludge Biodegradation of Twelve Commercial Phthalate Esters. CMA report, Study performed by Syracuse Research Corp. 1983

B. Review of Mammalian Toxicity Endpoints

The following documents were identified from the literature search as possible robust summary reviews for the ACC phthalates. Those studies marked by an asterisk (*) were not used for robust summaries as they either contained insufficient information to assess data quality or were not relevant SIDS endpoints. Provided with each marked reference is the reason for its exclusion from the data review set.

1. 131-11-3 1,2-benzenedicarboxylic acid, dimethyl ester

Acute Toxicity

David, R. et al., (2001). Esters of aromatic mono-, di-, and tricarboxylic acids, aromatic diacids and di-, tri-, or polyalcohols. In: Patty's Toxicology, Fifth edition, Vol. 6, Bingham E., B. Cahrssen and C.H. Powell (eds.), John Wiley & Sons, Inc. pp. 635-932.

Draize, J. H. (1948). Toxicological investigations of compounds proposed for use as insect repellants, A. Local and system effects following topical skin application. Acute oral toxicity. C. Pathological Examination", Journal of Pharmacology and Experimental Therapeutics, 93, 26-39.

Genetic Toxicity - Mutagenicity

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. NTP TR 429, NIH Publication No. 95-3356. (May 1995).

*E. Zeiger, S. Haworth, K. Mortelmans and W. Speck. (1985). Mutagenicity testing of d-(2-ethylhexyl)phthalate and related chemicals in Salmonella. *Environmental Mutagenesis* **7**:213-232.

*D. K. Agarwal, W. H. Lawrence, L. J. Nunez, and J. Autian (1985). Mutagenicity evaluation of phthalic acid esters and metabolites. *Journal of Toxicology and Environmental Health* **16**:61-69.

*Chemical Manufacturers Association (1985). Evaluation of dimethyl phthalate in the in vitro transformation of Balb/3T3 cells assay (final report by Litton Bionetics, Inc.).

*Chemical Manufacturers Association (1986). Mutagenicity of dimethyl phthalate in a mouse lymphoma mutation assay (final report by Hazleton Biotech Co.).

*E. Barber, M. Cifone, J. Rundell, A. Lington, B. Astill, E. Moran, A. Mulholland, E. Robinson and B. Schneider. (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* **20**:69-80.

*Seed, J. (1982). Mutagenic activity of phthalate esters in bacterial liquid suspension assays. *Environmental health perspectives* **45**:111-114.

**Although data are mixed, weight of evidence from above screening studies provide supportive information that material is non-mutagenic.*

Genetic Toxicity - Chromosomal Aberration

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. *NTP TR 429, NIH Publication No. 95-3356*. (May 1995).

*K.Tsuchiya and K.Hattori (1976). Chromosomal study on human leucocyte cultures treated with phthalic acid esters. *Hokkaidoritsu Eisei Kenkyusho Ho* **26**:114.

*L. D. Katosova and G. I. Pavlenko (1985). Cytogenetic examination of the workers of chemical industry. *Mutation Research* **147**:301-302 .

*V. V. Yurchenko and S. E. Gleiberman, (1980). Study of long-term effects of repellent use. Part III. Study of mutagenic properties of dimethyl phthalate and phenoxyacetic acid N,N-dimethylamide by dominant lethal mutations. *Meditinskaya Parazitologiya i Parazitarnye Bolezni*. **49**:58-61.

**Weight of evidence from above screening studies provide supportive information that material is not genotoxic.*

Repeated Dose Toxicity

Draize, J. H. (1948). Toxicological investigations of compounds proposed for use as insect repellants, A. Local and system effects following topical skin application. Acute oral toxicity. C. Pathological Examination", *Journal of Pharmacology and Experimental Therapeutics*, 93, 26-39.

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. *NTP TR 429, NIH Publication No. 95-3356*. (May 1995).

*A. J. Lehman (1955). Insect repellents. *Food and Drug Officials of the United States, Quarterly Bulletin*, 19:87-99.

*L. A. Timofievskaya, et al. (1974). Experimental research on the effect of phthalate plasticizers on the body. *Gigiena i Sanitariya*, 12:26-28 (English translation of abstract.)

**Above studies provide insufficient information to support data quality.*

Developmental Toxicity/Teratogenicity

Field, et al. (1993). Developmental toxicity evaluation of diethyl and dimethyl phthalate in rats. *Teratology* 48:33-44.

A. R. Singh, W. H. Lawrence, and J. Autian. (1972). Teratogenicity of phthalate esters in rats. *Journal of Pharmaceutical Science* 61:51-55.

*M. R. Plasterer, W. S. Bradshaw, G. M. Booth, M. W. Carter, R. L. Schuler, and B. D. Hardin. (1985). Developmental toxicity of nine selected compounds following prenatal exposure in the mouse. *Journal of Toxicology and Environmental Health* 15:25-38.

*B. D. Hardin, R. Schuler, J. Burg, G. Booth, K. Hazelden, K. MacKenzie, V. Piccirillo and K. Smith (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratogenesis, Carcinogenesis and Mutagenesis* 7:29-48 .

**Above are screening study only; less relevant for HPV robust summaries.*

Toxicity to Reproduction

*P. M. D. Foster, L. Thomas, M. Cook and S. Gangolli (1980). Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. *Toxicology and Applied Pharmacology*. 54:392-398

*C. A. Harris, P. Henttu, M. G. Parker and J. P. Sumpter. (1997) The estrogenic activity of phthalate esters in vitro. *Environmental Health Perspectives* 105:802-811.

*S. Oishi and H. Hiraga (1980). Effect of phthalic acid esters on mouse testis. *Toxicology Letters* **5**:413-416.

*B. Fredricsson, L. Möller A. Pousette and R. Westerholm (1993). Human sperm motility is affected by plasticizers and diesel particle extracts. *Pharmacology and Toxicology*. **72**:128-133.

**Above studies examined specific testicular, androgenic, or estrogenic effects. Studies less relevant to HPV robust summaries.*

2. 84-66-2 1,2-benzenedicarboxylic acid, diethyl ester

Acute Toxicity

Eastman Kodak Company, Rochester NY (1968). Diethyl phthalate. Acute dermal toxicity. Unpublished report.

Eastman Kodak Company, Rochester NY (1968). Diethyl phthalate. Acute inhalation toxicity. Unpublished report.

*David, R. et al., (2001). Esters of aromatic mono-, di-, and tricarboxylic acids, aromatic diacids and di-, tri-, or polyalcohols. *In: Patty's Toxicology*, Fifth edition, Vol. 6, Bingham E., B. Cofrissen and C.H. Powell (eds.), John Wiley & Sons, Inc. pp. 635-932.
Kodak unpublished study not available for review.

*D. Brown, K. R. Butterworth, I. F. Gaunt, P. Grassom, and S. D. Gangolli. (1978). Short-term oral toxicity study of diethyl phthalate in the rat. *Food and Cosmetic Toxicology*, **16**: 415-422.
Screening study; insufficient information to support data quality.

Genetic Toxicity - Mutagenicity

E. Zeiger, S. Haworth, K. Mortelmans and W. Speck. (1985). Mutagenicity testing of d-(2-ethylhexyl)phthalate and related chemicals in Salmonella. *Environmental Mutagenesis* **7**:213-232.

*W. J. Kozumbo and R. J. Rubin. (1982). Assessment of the mutagenicity of phthalate esters. *Environmental Health Perspectives*, **45**:103-109

*D. K. Agarwal, W. H. Lawrence, L. J. Nunez, and J. Autian (1985). Mutagenicity evaluation of phthalic acid esters and metabolites. *Journal of Toxicology and Environmental Health* **16**:61-69.

*Seed, J. (1982). Mutagenic activity of phthalate esters in bacterial liquid suspension assays. *Environmental health perspectives* **45**:111-114.

**Although data are mixed, weight of evidence from above screening studies provide supportive information that material is non-mutagenic.*

Genetic Toxicity - Chromosomal Aberration

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. *NTP TR 429, NIH Publication No. 95-3356*. (May 1995).

*M. Ishidate and S. Odashima. (1977). Chromosome tests with 134 compounds on Chinese Hamster Cells in vitro - A screening for chemical carcinogens. *Mutation Research*, **48**:337-354.

*K.Tsuchiya and K.Hattori (1976). Chromosomal study on human leucocyte cultures treated with phthalic acid esters. *Hokkaidoritsu Eisei Kenkyusho Ho* **26**:114.

**Above screening studies provide supportive information that material is not genotoxic.*

Repeated Dose Toxicity

D. Brown, K. R. Butterworth, I. F. Gaunt, P. Grassom, and S. D. Gangolli. (1978). Short-term oral toxicity study of diethyl phthalate in the rat. *Food and Cosmetic Toxicology*, **16**: 415-422.

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. *NTP TR 429, NIH Publication No. 95-3356*. (May 1995).

Developmental Toxicity/Teratogenicity

A. R. Singh, W. H. Lawrence, and J. Autian. (1972). Teratogenicity of phthalate esters in rats. *Journal of Pharmaceutical Science* **61**:51-55.

Field, et al. (1993). Developmental toxicity evaluation of diethyl and dimethyl phthalate in rats. *Teratology* **48**:33-44.

*B. D. Hardin, R. Schuler, J. Burg, G. Booth, K. Hazelden, K. MacKenzie, V. Piccirillo and K. Smith (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratogenesis, Carcinogenesis and Mutagenesis* **7**:29-48 .

Screening study only; less relevant for HPV robust summaries.

Toxicity to Reproduction

J. C. Lamb, IV, R. E. Chapin, C. J. Teague, A. D. Lawton and J. R. Reel (1987). Reproductive effects of four phthalate acid esters in the mouse. *Toxicology and Applied Pharmacology* **88**:255-269 .

*P. M. D. Foster, L. Thomas, M. Cook and S. Gangolli (1980). Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. *Toxicology and Applied Pharmacology*. **54**:392-398.

*C. A. Harris, P. Henttu, M. G. Parker and J. P. Sumpter (1997). The estrogenic activity of phthalate esters in vitro. *Environmental Health Perspectives* **105**:802-811.

*B. Fredricsson, L. Möller A. Pousette and R. Westerholm, (1993). Human sperm motility is affected by plasticizers and diesel particle extracts. *Pharmacology and Toxicology*, **72**:128-133.

*H. B. Jones, D. A. Garside, R. Liu, and J. C. Roberts. (1993). The influences of phthalate esters on leydig cell structure and function in vitro and in vivo. *Environmental and Molecular Pathology* **58**:179-193.

**Above studies examined specific testicular, androgenic, or estrogenic effects. Studies less relevant to HPV robust summaries.*

*BASF AG, unpublished data (1974).
Unpublished study not available for review

3. 68515-50-4 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear

Genetic Toxicity - Chromosomal Aberration

ExxonMobil Biomedical Sciences, Inc. (1994). In Vivo Mammalian Bone Marrow Micronucleus Assay. Unpublished study. Company unpublished studies.

Repeated Dose Toxicity

Esso Research and Engineering Company (1962). Dihexyl Phthalate: 90-Day dietary administration study in rats and dogs. Unpublished study.

4. 68515-44-6 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear

No studies found on this CAS number, per se. The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson and B. Schneider. (1999). Results in the L5178Y mouse lymphoma and the in

vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* 20:69-80

Developmental Toxicity/Teratogenicity

J. Hellwig, H. Freudenberger and R. Jackh. (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* 35:501-512.

Developmental toxicity thought to be due to C4-C6 constituents in 711P mixture. Di-heptyl phthalate contains >10% C4-C6 molecules; thus 711P data are conservatively used to evaluate this substance.

5. 71888-89-6 1,2-benzenedicarboxylic acid, di C6-8 branched alkyl ester, C7 rich

Acute Toxicity

MB Research Laboratories (1979). Test for oral toxicity in rats. Project No. MB 79-3967. Conducted for Exxon Biomedical Sciences, Inc. Unpublished report.

MB Research Laboratories (1979). Test for dermal toxicity in rats. Project No. MB 79-3967. Conducted for Exxon Biomedical Sciences, Inc. Unpublished report.

Genetic Toxicity - Mutagenicity

Exxon Biomedical Sciences, Inc. (1995). Microbial Mutagenesis in Salmonella Mammalian Microsome Plate Incorporation Assay. Project No. 167634. Unpublished report.

Genetic Toxicity - Chromosomal Aberration

Hazleton Laboratories America, Inc. (1991). Mutagenicity Test in an In Vitro Cytogenetic Assay. Project No. 181232. Conducted for Exxon Biomedical Sciences, Inc., unpublished report.

Repeated Dose Toxicity

No studies found.

Developmental Toxicity/Teratogenicity

Exxon Biomedical Sciences, Inc. (1997). Developmental toxicity study in rats with diisooheptyl phthalate. Unpublished report.

Toxicity to Reproduction

No studies found.

6. 27554-26-3 1,2,-benzenedicarboxylic acid, diisooctyl ester

Acute Toxicity

*Krauskoph, L. (1973). Studies on the toxicity of phthalates via ingestion. *Environmental Health Perspectives*. **3**:61-72.
Secondary reference; insufficient to assess data quality.

Genetic Toxicity - Mutagenicity

Goodyear Fiber and Polymer Products Research Division (1981). Laboratory Report No. 81-4-7. Mutagenicity evaluation of di-isooctyl phthalate (USS Chemical). EPA document number 878210369, Fiche no. OTS0206046.

Litton Bionetics Inc. (1981). Evaluation of di-isooctyl phthalate in the in vitro transformation of BALB/c3T3 cells assay. Final Report. EPA Document No. 878101226 Fiche No. OTS 0206260.

Genetic Toxicity - Chromosomal Aberration

No studies found.

Repeated Dose Toxicity

*S. Shibko and H. Blumenthal (1973). Toxicology of phthalic acid esters used in food-packaging materials. *Environmental Health Perspectives* **3**:131-137.
Abbreviated non-GLP study; insufficient to support data quality.

Developmental Toxicity/Teratogenicity

No studies found.

Toxicity to Reproduction

No studies found.

7. 117-84-0 1,2,-benzenedicarboxylic acid, dioctyl ester

Acute Toxicity

R. K. Dogra, S. Khanna, L. J. Shukla, S. N. Srivastava, M. C. Bhatnagar, P. K. Gupta, and R. Shanker R. (1987). Modification of immune response in rats by di-octyl Phthalate. *Ind. Health* **25**:97-101.

R. K. S. Dogra, K. Chandra, S. Chandra, S. Khanna, S. N. Srivastava, L. Shukla, J. C. Katiyar, and R. Shanker. (1989). Di-octyl phthalate induced altered host resistance: viral and protozoal models in mice. *Ind. Health* **27**:83-87.

* David, R. et al., (2001). Esters of aromatic mono-, di-, and tricarboxylic acids, aromatic diacids and di-, tri-, or polyalcohols. *In: Patty's Toxicology*, Fifth edition, Vol. 6, Bingham E., B. Cofrissen and C.H. Powell (eds.), John Wiley & Sons, Inc. pp. 635-932.

Secondary reference citing older study.

Genetic Toxicity - Mutagenicity

E. Zeiger, S. Haworth, K. Mortelmans and W. Speck. (1985). Mutagenicity testing of d-(2-ethylhexyl)phthalate and related chemicals in Salmonella. *Environmental Mutagenesis* **7**:213-232.

*Seed, J. (1982). Mutagenic activity of phthalate esters in bacterial liquid suspension assays. *Environmental health perspectives* **45**:111-114.

Limited screening study in one tester strain.

Genetic Toxicity - Chromosomal Aberration

No studies found.

Repeated Dose Toxicity

R. Poon, P. Lecavalier, R. Mueller, V. E. Valli, B. G. Procter and I. Chu. (1997). Subchronic oral toxicity of di-n-octyl phthalate and di(2-ethylhexyl) phthalate in the rat. *Food and Chemical Toxicology* **35**:225-239.

*B. G. Lake, W. R. P. Rijcken, T. J. B. Gray, J. R. Foster and S. D. Gangolli (1984). Comparative studies of the hepatic effects of di- and mono-n-octyl phthalates, di-(2-ethylhexyl) phthalate and clofibrate in the rat. *Acta. Pharmacol. et Toxicol.* **54**:167-176.

*B. G. Lake, T. J. B. Gray and S. D. Gangolli. (1986). Hepatic effects of phthalate esters and related compounds- in vivo and in vitro correlations. *Environmental Health Perspectives.* **67**:283-290.

**Above studies examined specific effects on the liver. Studies less relevant to HPV robust summaries.*

Developmental Toxicity/Teratogenicity

B. D. Hardin, R. Schuler, J. Burg, G. Booth, K. Hazelden, K. MacKenzie, V. Piccirillo and K. Smith (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratogenesis, Carcinogenesis and Mutagenesis* **7**:29-48 .

*A. R. Singh, W. H. Lawrence, and J. Autian. (1972). Teratogenicity of phthalate esters in rats. *Journal of Pharmaceutical Science* **61**:51-55.

Abbreviated non-GLP study; insufficient to support data quality.

*T. R. Zacharewski, J. Clemons, M. Meek, Z. Wu, M. Fielden and J. Matthews. (1998). Examination of the in vitro and in vivo estrogenic activities of eight commercial phthalate esters. *Toxicological Sciences* **42**:282-293.

Study examined estrogenic effects; less relevant to HPV robust summaries.

Toxicity to Reproduction

J. J. Heindel, D. K. Gulati, R. C. Mounce, S. R. Russell, and J.C. Lamb. (1989). Reproductive toxicity of three phthalic acid esters in a continuous breeding protocol. *Fundamental and Applied Toxicology* **12**:508-518 .

*S. Oishi and K. Hiraga. (1980). Testicular atrophy induced by phthalate acid esters: Effect on testosterone and zinc concentration. *Toxicology and Applied Pharmacology*, **53**:35-41.

*P. M. D. Foster, L. Thomas, M. Cook and S. Gangolli (1980). Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. *Toxicology and Applied Pharmacology*. **54**:392-398.

*C. A. Harris, P. Henttu, M. G. Parker and J. P. Sumpter (1997). The estrogenic activity of phthalate esters in vitro. *Environmental Health Perspectives* **105**:802-811.

**Above studies examined specific testicular, androgenic, or estrogenic effects. Studies less relevant to HPV robust summaries.*

8. 68515-40-2 1,2-benzenedicarboxylic acid, benzyl C7-9 branched and linear alkyl esters

Data from Monsanto Company unpublished reports.

9. 111381-89-6 1,2-benzenedicarboxylic acid (C7, C9) ester, branched and linear

The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson and B. Schneider. (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* 20:69-80

Developmental Toxicity/Teratogenicity

J. Hellwig, H. Freudenberger and R. Jackh. (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* 35:501-512.

Developmental toxicity thought to be due to C4-C6 constituents in 711P mixture. Di-(C7, C9) phthalate contains >10% C4-C6 molecules; thus 711P data are conservatively used to evaluate this substance.

10. 68648-93-1 1,2-benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters

No relevant studies found.

11. 68515-45-7 1,2-benzenedicarboxylic acid, dinonyl ester, branched and linear

No studies found on this CAS number, per se. The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson and B. Schneider. (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* 20:69-80

Developmental Toxicity/Teratogenicity

*J. Hellwig, H. Freudenberger and R. Jackh. (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* 35:501-512.

Developmental toxicity thought to be due to C4-C6 constituents in 711P mixture. Di-nonyl phthalate contains <10% C4-C6 molecules; thus 711P data are not relevant to this substance.

12. 68515-43-5 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters

Toxicity to Reproduction

Willoughby, C.R., Fulcher, S.M., Creasy, D.M., Heath, J.A., Priston, R.A.J., and Moore, N.P. (2000). Two generation reproduction toxicity studies of di-(C7-C9 alkyl) phthalate and di-(C9-C11 alkyl) phthalate in the rat. *Reproductive Toxicology* 14:427-450.

Developmental Toxicity/Teratogenicity

Fulcher, S. et al. (2001). Developmental toxicity of di(C7-C9 alkyl) phthalate and di(C9-C11 alkyl)phthalate in the rat. *Reproductive Toxicology* 15:95-102.

13. 84-77-5 1,2-benzenedicarboxylic acid, didecyl ester

No relevant studies found.

14. 3648-20-2 1,2-benzenedicarboxylic acid, diundecyl ester

Acute Toxicity

W. Lawrence, M. Malik, J. Turner, A. Singh and J. Autian. (1975). A toxicological investigation of some acute, short-term, and chronic effects of administering di-2-ethylhexyl phthalate (DEHP) and other phthalate esters. *Environmental Research* 9:1-11.

*European Commission, European Chemicals Bureau, International Uniform Chemical Information Database (IUCLID).(1994). Diundecyl Phthalate Data Sheet. *Section 5.1, Version 3.0.4.*

Monsanto unpublished study not available for review

Genetic Toxicity - Mutagenicity

E. Zeiger, S. Haworth, K. Mortelmans and W. Speck. (1985). Mutagenicity testing of di-(2-ethylhexyl)phthalate and related chemicals in Salmonella. *Environmental Mutagenesis* 7:213-232.

E. Barber, M. Cifone, J. Rundell, A. Lington, B. Astill, E. Moran, A. Mulholland, E. Robinson and B. Schneider. (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* 20;69-80.

Genetic Toxicity - Chromosomal Aberration

No studies found.

Repeated Dose Toxicity

BIBRA, The British Industrial Biological Research Association. A 21-day feeding study of di-undecyl phthalate to rats: effects on the liver and liver lipids. *EPA Document No. 40/85262007, Fiche No. OTS0509538.*

Developmental Toxicity/Teratogenicity

*J. Hellwig, H. Freudenberger and R. Jackh. (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* **35**:501-512.
Developmental toxicity thought to be due to C4-C6 constituents in 711P mixture. Di(C11) phthalate contains <10% C4-C6 molecules; thus 711P data are not relevant to this substance.

Toxicity to Reproduction

*C. A. Harris, P. Henttu, M. G. Parker and J. P. Sumpter (1997). The estrogenic activity of phthalate esters in vitro. *Environmental Health Perspectives* **105**:802-811.
Study examined estrogenic effects; less relevant to HPV robust summaries.

15. 85507-79-5 1,2-benzenedicarboxylic acid, di (C11) ester, branched and linear

No relevant studies found.

16. 111381-90-9 1,2-benzenedicarboxylic acid, (C7, C11) ester, branched and linear

No studies found on this CAS number, per se. The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson and B. Schneider. (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* 20:69-80

Developmental Toxicity/Teratogenicity

J. Hellwig, H. Freudenberger and R. Jackh. (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* **35**:501-512.
Developmental toxicity thought to be due to C4-C6 constituents in 711P mixture. Di-(C7, C11) phthalate contains >10% C4-C6 molecules; thus 711P data are conservatively used to evaluate this substance.

17. 111381-91-0 1,2-benzenedicarboxylic acid (C9, C11) ester, branched and linear

No studies found on this CAS number, per se. The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson and B. Schneider. (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* 20:69-80

Developmental Toxicity/Teratogenicity

*J. Hellwig, H. Freudenberger and R. Jackh. (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* 35:501-512.
Developmental toxicity thought to be due to C4-C6 constituents in 711P mixture. Di(C9, C11) phthalate contains <10% C4-C6 molecules; thus 711P data are not relevant to this substance.

18. 68515-47-9 1,2,-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich

Acute Toxicity

Bio/dynamics, Inc. (1981). Acute Oral Toxicity in Rats. Conducted for Exxon Biomedical Sciences, Inc. Unpublished Report.

Bio/dynamics, Inc. (1981). Acute Dermal Toxicity in Rabbits. Conducted for Exxon Biomedical Sciences, Inc. Unpublished Report.

*Krauskoph, L. (1973). Studies on the toxicity of phthalates via ingestion. *Environmental Health Perspectives*. 3:61-72.

Secondary reference; insufficient to assess data quality.

Genetic Toxicity - Mutagenicity

E. Zeiger, S. Haworth, K. Mortelmans and W. Speck. (1985). Mutagenicity testing of d-(2-ethylhexyl)phthalate and related chemicals in Salmonella. *Environmental Mutagenesis* 7:213-232.

Table 3
Toxicology Data Summary
Phthalate Esters

Low Molecular Weight Phthalate Esters														
Ester Backbone Carbon Length	CAS Number	Chemical Name	Acute Oral LD50	Acute Dermal LD50	Acute Inhalation LC50	Repeated Dose Toxicity	GeneTox (Ames)	GeneTox (Chrom. Abs.)	Toxicity to Reproduction	Developmental Toxicity/Teratogenicity	Acute Fish (A) ppm	Daphnia (B) ppm	Algal (C) ppm	Biodegradation %
C1	131-11-3	dimethyl ester (DMP)	6.9 g/kg (rat)	> 10 ml/kg (rabbit)(4)		LOAEL = 4 ml/kg, kidney,liver effects (90 day dermal study, rabbits)	Negative	Negative (CHO)		NOAEL rat (maternal) 840mg/kg/day NOAEL (develop) >3570 mg/kg/day	56	>45.9	142	>99 primary & 85.9 ultimate(3)
C2	84-66-2	diethyl ester (DEP)	> 5.0 g/kg (rat)(4)	> 20 ml/kg (guinea pig)	> 4.64 mg/l (rat, nominal)	NOAEL (rat, dietary, 16 weeks) males ~750 mg/kg/day; females ~150 mg/kg/day	Negative	Negative (CHO)	NOAEL (mice) F0, F1, F2 = 3250 mg/kg/day	NOAEL rat (maternal) 1910 mg/kg/day NOAEL (develop) 3210 mg/kg/day	12	86	16	>99 primary & 94.6 ultimate(3)
Transitional Phthalate Esters														
C4	84-74-2*	dibutyl ester (DBP)	4840 mg/kg	>20,000 mg/kg (rabbit)	>15 mg/L (4 hr) (rat)	LOAEL (rat) = 357 mg/kg/day NOAEL (rat) = 177 mg/kg/day	Negative (Ames) Positive (mouse lymphoma)	negative (CHO in vitro, micronucleus in vivo)	LOAEL (rat)= 256 mg/kg (diet) NOAEL (rat) = 52 mg/kg (diet)	LOAEL (rat) = 100 mg/kg (gavage); 555 mg/kg (diet) NOAEL (rat) = 50 mg/kg (gavage); 331 mg/kg (diet)	3.3	3.8	1.6(8)	>99 primary & 99 ultimate(3)
C4, C6	85-68-7*	butylbenzyl ester (BBP)	2330 mg/kg	> 10,000 mg/kg (rabbit)		NOAEL (rat) = 151 mg/kg/day	Negative (Ames, mouse lymphoma)	Negative or equivocal (CHO in vitro, micronucleus in vivo)	One gen. NOAEL (rat) > 418 mg/kg/day	NOAEL (rat) = 418 mg/kg/day (mouse) = 182 mg/kg/day	2.1	2.8	0.27(8)	>99 primary & 96 ultimate(3)
C5-6	68515-50-4	dihexyl ester branched & linear (DHP)				NOAEL (rat)= 380 mg/kg/day NOAEL (dog)= 180 mg/kg/day		Negative (micronucleus, in vivo)			>0.2	>0.18	>0.33	79.66 (1)
C6	84-75-3*	di-n-hexyl ester	29.6 ml/kg (male) 38.9 ml/kg (female) (rat)			LOAEL (rat) = 1800 mg/kg/day liver effects (21 day, diet)	Negative (Ames)		Two gen. LOAEL (mice) = 430 mg/kg/day	LOAEL (mice) = 9900 mg/kg				
C5-7	68515-44-6	diheptyl ester branched & linear					Negative (mouse lymphoma)(5)			NOAEL (rat, oral) 200 mg/kg/day (maternal & develop) (5)				
C5-8	71888-89-6	di C6-8 branched	> 10g/kg (rat)	> 3.16 g/kg (rabbit)			Negative	Negative (CHO in vitro)		NOAEL rat (maternal) 750 mg/kg/day NOAEL (devel) 300 mg/kg/day				
C6	117-81-7*	diethylhexyl ester (DEHP)	>9860 mg/kg (rat)	>20,000 mg/kg (rabbit)	>4 mg/L (rat)	LOAEL (rat) = 37.6 mg/kg/day NOAEL (rat) = 3.7 mg/kg/day	Negative (Ames; mouse lymphoma)	Negative (CHO cells in vitro; rats in vivo, mouse dominant lethal)	LOAEL = 140 mg/kg/day (diet) NOAEL = 14 mg/kg/day (diet)	LOAEL = 91 mg/kg/day (diet, mice) NOAEL = 44 mg/kg/day (diet, mice)	>100(9)	>100(9)	>100(9)	>99 primary & 99 ultimate(3)
C6-8	27554-26-3	diisooctyl ester (DIOP)	> 22.6 g/kg (rat)(4)				Negative				>0.23	>0.22	>1.3	>99 primary & 57 ultimate(3)
C7, C9	111381-89-6	C7, C9, Branched & linear					Negative (mouse lymphoma)(5)			NOAEL (rat, oral) 200 mg/kg/day (maternal & develop) (5)				
C7, C11	111381-90-9	C7, C11, Branched & Linear					Negative (mouse lymphoma)(5)			NOAEL (rat, oral) 200 mg/kg/day (maternal & develop) (5)				

Table 3
Toxicology Data Summary
Phthalate Esters

High Molecular Weight Phthalate Esters														
Ester Backbone Carbon Length	CAS Number	Chemical Name	Acute Oral LD50	Acute Dermal LD50	Acute Inhalation LC50	Repeated Dose Toxicity	GeneTox (Ames)	GeneTox (Chrom. Abs.)	Toxicity to Reproduction	Developmental Toxicity/Teratogenicity	Acute Fish (A) ppm	Daphnia (B) ppm	Algal (C) ppm	Biodegradation %
C6, C8, C10	68648-93-1	mixed decyl & hexyl and octyl esters (610P)									>0.24	>0.33	>0.08	>99 primary & 90.3 ultimate(3)
C8	117-84-0	dioctyl ester	13 g/kg (mice); 54 g/kg (rat)			NOAEL (rat, dietary, 13 week) 38.8 mg/kg/day	Negative		NOAEL (mice, dietary) 7500 mg/kg/day (F1/F2)	NOAEL (mice, oral) 9780 mg/kg/day (maternal & devel)				
C6, C7-9	68515-40-2	benzyl C7-C9 branched & linear	>15.8 g/kg (rat)	>7.94 g/kg (rabbit)			Negative				>1000	4.5 (6)	674 (chloro) 521 (c #)	
C7-9	68515-41-3*	(C7-C9) branched & linear alkyl ester	>22 g/kg (rat)			NOAEL (rat) = 100 mg/kg	Negative		Two gen. NOAEL (rat) = 1% diet (repro effects); 0.5% (general toxicity)	NOAEL(rat, oral) = 500 mg/kg/day				>99
C9	28553-12-0* 68515-48-0*	diisononyl ester (DI NP)	> 10,000 mg/kg/day (rat)	> 3160 mg/kg/day (rabbit)	> 4.4 mg/l (rat)	NOAEL(rat) = 88 mg/kg/day	Negative (Ames, mouse lymphoma)	negative (CHO in vitro, micronucleus in vivo)	NOAEL(rat) = 633 mg/kg/day	NOAEL(rat, oral) = 500 mg/kg/day	>1000(9)	>0.3(9)	>0.1(9)	
C9	68515-45-7	dinonyl ester branched & linear					Negative (mouse lymphoma)(5)							
C9-11	68515-43-5	di-C9-C11 branched & Linear (911P)							Two gen. NOAEL (rat) = 1% diet (repro effects); 0.5% (general toxicity)	NOAEL(rat, oral) = 250 mg/kg/day				
C10	84-77-5	didecyl ester												
C7-11	26761-40-0* 68515-49-1*	diisodecyl ester (DI DP)	> 29,100 mg/kg/day (rat)	> 3160 mg/kg/day (rabbit)	> 12.5 mg/l (rat)	NOAEL (rat) ~ 60 mg/kg/day	Negative (Ames, mouse lymphoma)	Negative (micronucleus in vivo)	NOAEL(rat) = 50 mg/kg/day	NOAEL(rat, oral) = 500 mg/kg/day	>0.1(9)	>0.1(9)	>0.1(9)	
C11	3648-20-2	diundecyl ester (DU P)	> 15 g/kg (rat)(4)	> 7.9 g/kg (rabbit)(4)		NOAEL ~ 282 mg/kg (dietary, rats, 3 week)	Negative (Ames & mouse lymphoma)				>1.4	>0.02	>2.1	>99 primary & 76 ultimate(3)
C11	85507-79-5	di (C11) ester branched & linear (DI UP)												
C9, C11	111381-91-0	C9, C11, Branched & Linear					Negative (mouse lymphoma)(5)							
C11-14	68515-47-9	di-C11-C14, C13 rich ester (DT DP)	> 10 g/kg (rat)	> 3.16 g/kg (rabbit)			Negative				>1.5	>0.05	>0.6	>50 primary & 37 ultimate(3)
C13	119-06-2*	ditridecyl	>2 g/kg (rat)			NOAEL (rat)=10 mg/kg/day; LOAEL =50 mg/kg/day (F)	Negative	Negative (CHL cells)	NOAEL (rat)=250 mg/kg/day (male); =50 mg/kg/day (female)	NOAEL(rat, oral)=250 mg/kg/day				

Table 3
Toxicology Data Summary
Phthalate Esters

*Not a U.S. HPV chemical but included to facilitate category evaluation

Footnotes: A) Rainbow Trout data presented. Data on other fish species available - Fathead minnow, Sheepshead minnow and Bluegill Sunfish, ect.

B) *Daphnia magna* data presented. Data on other invertebrates available - Mysid shrimp, Midge, Brine shrimp, ect.

C) *Selenastrum capricornutum* data presented. Data on other species available - *S.subspicatus*, *S. Costatum*, etc.

References: Staples, C.A. et al, Aquatic Toxicity of Eighteen Phthalates Ester, 1997, Environmental Toxicology and Chemistry Vol. 16, No. 5.

(C #) Based upon algal cell number.

(1) Biodegradation by Manometric Respirometer Method

(2) Biodegradation by Modified Sturm Method

(3) Biodegradation by Shake Flask Method

(4) Values reported in secondary reference (Patty's); robust summary not prepared due to insufficient information.

(5) Test material (di heptyl, nonyl, undecyl phthalate) considered by EPA to be applicable to the following CAS nos: 111381-89-6, 111381-90-9, 111381-91-0, 68515-44-6, 68515-45-7, 3648-20-2

(6) Solvent used to enhance material solubility (acetone).

(7) Solvent used to enhance material solubility (DMF).

(8) 72 hr. *Scenedesmus subspicatus* data

(9) No mortality at water saturation

Table 4
Physical/Chemical Data Summary
Phthalate Esters

Chain Length	CAS Number	Chemical Name	MP** (°C)	BP*** (°C)	VP (hPa@25°C)	PC (log Pow)	Water Solubility (mg/L @25°C)	Photodeg Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
										Soil	Air	Water	Sediment
C1	131-11-3	dimethyl ester (DMP)	5.5 -23 c	285 249 c	2.63E-03 .0387c	1.61 1.66 c	5220 1778 c	18.6	2.75	3.6	7.6	88.8	0.8
C2	84-66-2	diethyl ester (DEP)	-40 -1.7 c	298 282 c	6.48E-04 6.7E-03 c	2.54 2.65 c	591 184 c	3.1	2.9	25.2	10.4	63.8	0.6
C4	84-74-2*	dibutyl ester (DBP)	-35 6 c	340 338 c	4.73E-05 3.40E-04 c	4.27 4.61c	9.9 1.89 c	0.2-2 1.15 c	22 3.4 c	94.0	0.068	3.77	2.09
C4, C6	85-68-7*	butylbenzyl ester (BBP)	-35 61 c	370 387 c	2.49E-05 1.03E-05	4.70 4.84 c	3.8 0.758 c	0.2-2 0.97 c	>0.3 1.39 c	96.4	0.037	1.37	2.14
C6	68515-50-4	dihexyl ester branched & linear (DHP)	-27 49 c	340 373 c	3.45E-06 3.01E-05 c	6.00 6.46 c	0.159 0.023 c			97.4	0.33	0.04	2.16
C6	84-75-3*	di-n-hexyl ester	<0 48 c	350 385 c	3.45E-06 1.61E-05 c	6.00 6.57 c	0.159 0.0115 c			97.5	0.28	0.03	2.17
C7	68515-44-6	diheptyl ester branched & linear	-45 43 c	>300 364 c	9.33E-07 1.08E-05 c	6.87 7.41 c	0.020 2.45E-03 c			97.6	0.14	0.004	2.17
C7	71888-89-6	di C6-8 branched	-45 43 c	>300 398 c	9.33E-07 1.08E-05 c	6.87 7.41 c	0.020 2.45E-03 c			97.6	0.14	0.004	2.17
C8	117-81-7*	diethylhexyl ester (DEHP)	-47 64 c	>400 417 c	2.52E-07 1.85E-06 c	7.73 8.39 c	2.49E-03 2.39E-04 c	0.2-2 0.49 c	2000 5.33 c	97.7	0.03	0.0035	2.17
C8	27554-26-3	diisooctyl ester (DIOP)	-46 64 c	>300 417 c	2.52E-07 1.85E-06 c	7.73 8.39 c	2.49E-03 2.4E-04 c	0.52 c	3.43 c	97.7	0.027	4.50E-04	2.17
C8	117-84-0	dioctyl ester	-25 90 c	390 431 c	1.33E-07 4.56E-07 c	7.73 8.54 c	2.49E-03 1.79E-04 c	0.52 c	7.69 c	97.7	0.06	3.18E-04	2.17
C8	68515-40-2	benzyl C7-C9 branched & linear	-37 90 c	427 c	5.79E-07 c	6.74 c	8.47E-03 c	0.64 c	1.39 c	97.7	0.01	0.02	2.17
C7, C9	111381-89-6	C7,C9, branched & linear	<-45 64c	417 c	1.85E-06 c	8.39 c	2.39E-04 c	0.49 c	4.17 c	97.7	0.03	4.50E-04	2.17
C6, C8, C10	68648-93-1	mixed decyl & hexyl and octyl esters (610P)	-45 64 c	417 c	1.31E-07 4.56E-07 c	8.17 8.54 c	8.76E-04 1.79E-04 c	0.52 c	7.69 c	97.7	0.006	3.18E-04	2.17
C9	28553-12-0* 68515-48-0*	diisononyl ester (DINP)	-48 115 c	>400 454 c	6.81E-08 6.6E-08 c	8.60 9.52 c	3.08E-04 1.74E-05 c	0.2-2 0.48 c	7.69 c	97.8	0.01	6.10E-04	2.17
C9	68515-45-7	dinonyl ester branched & linear	-48 115 c	>400 454 c	6.81E-08 6.6E-08 c	8.60 9.52 c	3.08E-04 1.74E-05 c	0.46	7.69 c	97.8	0.001	3.33E-05	2.17

Table 4
Physical/Chemical Data Summary
Phthalate Esters

Carbon Length	CAS Number	Chemical Name	MP* (°C)	BP (°C)	VP (hPa@25°C)	PC (log Pow)	Water Solubility (mg/L @25°C)	Photodeg Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%)			
										Soil	Air	Water	Sediment
C10	26761-40-0* 68515-49-1*	diisodecyl ester (DIDP)	-46 106 c	>400 463 c	1.84E-08 4.9E-08 c	9.46 10.36 c	3.81E-05 2.24E-06 c	0.41 c	3.43 c	97.8	9.90E-05	1.10E-04	2.17
C10	68515-43-5	di-C9-C11 branched & Linear (911P)	-50 138 c	466 c	2.04E-8 c	10.39 c	2.09E-06 c	0.47 c	4.74 c	97.8	3.95E-04	4.50E-06	2.17
C10	84-77-5	didecyl ester	<-48 136 c	477 c	1.84E-08 1.05E-08 c	9.46 10.5 c	3.81E-05 1.68E-06 c	0.41 c	7.69 c	97.8	1.97E-04	3.49E-06	2.17
C11	3648-20-2	diundecyl ester (DUP)	-9 156 c	270 501 c	4.97E-09 1.63E-09 c	10.33 11.49 c	4.41E-06 1.61E-07 c	0.37	7.69 c	97.8	3.46E-05	3.57E-07	2.17
C11	85507-79-5	di (C11) ester branched & linear	-9 142 c	270 499 c	4.97E-09 2.71E-09 c	10.33 11.83 c	4.41E-06 6.67E-8 c	0.34 c	6.3 c	97.8	6.54E-05	1.63E-07	2.17
C7, C11	111381-90-9	C7, C11, Branched & Linear	-50 85 c	440 c	6.81E-08 3.07E-07 c	8.6 9.37 c	3.08E-04 2.32E-05 c	0.43 c	6.24 c	97.7	0.00526	4.71E-05	2.17
C9, C11	111381-91-0	C9, C11, Branched & Linear	-50 93 c	456 c	1.01E-07 c	10.28 c	2.59E-06 c	0.38 c	6.24 c	97.8	0.00204	5.79E-06	2.17
C13	68515-47-9	di-C11-C14, C13 rich ester (DTDP)	-37 177 c	501 c	3.63E-10 9.3E-10 c	12.06 12.25 c	7.0E-08 2.4E-08 c	0.43 c	7.69 c	97.8	2.44E-05	6.21E-08	2.17

c = calculated data using EPWIN; all other values are derived from measurements

*Not a U.S. HPV chemical but included to facilitate category evaluation

** = all phthalate esters higher than DMP are liquids at zero degrees C. Mixtures are expected to have melting points below those of components. Modeled data do not accurately reflect melting points for these substances

*** = many of the higher phthalate boiling points are determined under reduced pressure but have been extrapolated to one atmosphere