Toxics Use Reduction Act

CERCLA Phthalate Ester Category

MA TURA Science Advisory Board Review

Toxics Use Reduction Institute

December 2016

TURI Report 2017-001

The Toxics Use Reduction Institute is a multi-disciplinary research, education, and policy center established by the Massachusetts Toxics Use Reduction Act of 1989. The Institute sponsors and conducts research, organizes education and training programs and provides technical support to help Massachusetts companies and communities to reduce the use of toxic chemicals. For more information, visit our website, www.turi.org, write to the Toxics Use Reduction Institute, University of Massachusetts Lowell, 600 Suffolk St., Suite 501, Wannalancit Mills, Lowell, Massachusetts 01854, or call 978-934-3275.

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This document defines the substances in the phthalate ester category and summarizes key scientific information on those substances. The report is a result of a review of phthalate esters by the TURA Science Advisory Board (SAB), in response to a request by MassDEP. The SAB review was completed in 2015.

This report has three main sections. The first section reviews the history and definition of the phthalate ester category. The second section summarizes the scientific information reviewed by the TURA Science Advisory Board, including scientific information on ortho, meta, and para phthalates and cumulative and low dose effects. The third part was prepared by TURI and discusses the policy context, such as information on substance identification, uses, substitution, and interchangeability.

Executive Summary

This report summarizes the TURA Science Advisory Board's (SAB) review of the CERCLA Phthalate Esters category, which is on the TURA list of Toxic and Hazardous Substances but has not been subject to reporting per MassDEP policy.The objective of the SAB review was to:

1) Better define the category for MassDEP;

2) Gather and review current information on health and environmental effects associated with the substances in the category.

Provide some general policy context, such as use informationThe following document is an overview of the process and data that the SAB used to evaluate substances in the phthalate ester category.

The Phthalate Esters Category

The phthalate esters category originated from the CERCLA list and has been on the TURA list since the program's inception. However, the category was not well defined and when the category was added in 1993 as part of the phasing in of the CERCLA chemical list, a DEP policy was put in place that exempted reporting of this category. (Note: 6 specific phthalate esters [DEHP, BBP, DBP, DEP, DMP, DnOP] are

specifically listed on CERCLA or TRI and are individually reportable). In spite of the DEP policy, 4 facilities erroneously reported the category between 1993 and 2005. The phthalate esters were listed on CERCLA because the Clean Water Act had identified them as toxic pollutants.

Phthalate esters (abbreviated here as "PEs") were considered in groups according to their structure, with position of the side chains at ortho-, meta- (or iso-) and para- (or tere-). The ortho-phthalates are the most commonly used, have the most scientific information on their hazard, and are of the most concern in terms of human hazard. Therefore, the SAB focused the majority of its review on the ortho-phthalates. Six ortho-PEs are currently TURA reportable; they have more information available and their health effects are better understood. The SAB selected 10 ortho-PEs of varying side chain lengths to review in detail.

The world of phthalate esters is a dynamic one of pure chemicals and mixtures of isomers, with a historically diverse and changing set of commercial products. In this summary the SAB assumed certain carbon side chain backbone lengths (abbreviated as Cx) for particular substances, but notes that different commercial products will sometimes have different structures, mixtures and carbon chain lengths, and sometimes different CAS numbers. Consequently, users should be cautioned about drawing bright lines and clear distinctions between substances. Ten specific PE's were reviewed - one that is currently TURA reportable (DnOP - C8) and nine that are not: two C3's (DAP and DMEP) and seven in the C6-C13 range (DPHP, DINP, Din911P, DIDP, DIUP, DUP, and DTDP).

The SAB focused mainly on reproductive and developmental effect studies; not all endpoints were reviewed thoroughly. That is, the literature available was reviewed; however, further work to verify results or establish validity was not undertaken. Also, the review focused on mammalian health effects, and not environmental, eco-toxicity or wildlife effects. In general, the higher molecular weight/longer carbon chain substances have been less used in industry, and their health effects are much less well studied.

Ortho-Phthalate Esters

Reproductive and developmental health effects (Also see Table ES-1):

Of most concern are so-called "transitional" PEs (C4-C7 branched or linear molecules), including several that are already TURA listed. Higher molecular weight/longer side chain backbone length substances also have health effects but are less potent. After C7, there is a general tendency as the carbon backbone chain length increases, for the effects to diminish and for there to be fewer scientific studies.

C1-C3 chain length substances have significant health effects, but not always the same effects as other PEs. These substances often are used as film-forming solvents; most of the known commercial plasticizer products are not in this range.

C4-C7 are the most well studied substances; there is a significant body of animal evidence of adverse health effects, as well as some human evidence from epidemiological studies.

Endocrine pathways: There is a general consensus from animal studies that some C4 and longer ortho-PEs are anti-androgens, interrupting the testosterone synthesis pathway. While the mechanisms for these effects are not well understood, there is general concern regarding the impact on hormone pathways.

Liver effects: Liver is a primary target organ for most ortho-PEs, showing effects in chronic and subchronic animal studies. There is concern, and no general agreement, about whether the liver effects involving peroxisome proliferation, including carcinogenicity, seen in animal studies are relevant to humans.

Thyroid: While not systematically evaluated by the SAB, thyroid effects were noted in a few of the reproductive studies reviewed, and may indicate an additional area of concern.

Cumulative Effects

Many phthalate esters have similar health effects and modes of action. As a result, they are expected, and have been shown, to have cumulative effects. The cumulative effects are of particular concern because of the ubiquity and "pseudo persistence" of phthalate esters in the environment and in biota.

There is evidence of additive effects from different phthalate esters, both those with similar effects (e.g. anti-androgenic effects), and those with the same or different modes of action. Nearly all of the evidence is from the more well-studied and more potent C4-C7 PEs. There is also some evidence of synergistic or antagonistic effects, typically between PEs and other endocrine active substances, such as some pesticides.

Low dose effects

There is some evidence that PEs can cause effects at low doses due to endocrine activity, although it is difficult to define "low dose." PE studies at environmentally relevant low doses were not identified. Research on other endocrine active substances has shown non-monotonic dose response curves, and different kinds of effects at very low, environmentally relevant, dose levels. This is an emerging field and an emerging area of concern.

Meta- (or iso-) phthalates and Para- (or tere-) phthalates

There is a general lack of information in the scientific literature for meta- and para-PEs, with the exception of DEHT (diethyl hexyl terephthalate). In general, the current literature supports a different and lower mammalian toxicity profile for meta- and para- than for the ortho-PEs.

DEHT has been the most studied of the terephthalates the Board has been able to review, and while there are data gaps, available information indicates low concern.

From the limited number of studies for meta-phthalates, evidence exists for migration and persistence in the environment as well as potential for adverse effects on the endocrine system, though the limited number of studies as well as the findings regarding relatively weak estrogenic activity in one species suggests a lower priority class of compounds as compared to the ortho-phthalates.

Toxics Use Reduction Act

CERCLA Phthalate Ester Category

Science Advisory Board Review

This document defines the substances in the phthalate ester category and summarizes key scientific information on those substances. The report is a result of a review of phthalate esters by the TURA Science Advisory Board (SAB), in response to a request by MassDEP. The SAB review was completed in 2015.

This report has three main sections. The first section reviews the history and definition of the phthalate ester category. The second section summarizes the scientific information reviewed by the TURA Science Advisory Board, including scientific information on ortho, meta, and para phthalates and cumulative and low dose effects. The third part was prepared by TURI and discusses the policy context, such as information on substance identification, uses, substitution, and interchangeability.

Introduction

This report summarizes the TURA Science Advisory Board's (SAB) review of the CERCLA Phthalate Esters category, which is on the TURA list of Toxic and Hazardous Substances but has not been subject to reporting per MassDEP policy.The objective of the SAB review was to:

1) Better define it

2) Gather and review current information on health and environmental effects associated with its substances

The following document is an overview of the process and information that the SAB used to evaluate substances in the phthalate ester category and the results of their review.

The Phthalate Esters Category

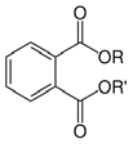
The phthalate esters category originated from the CERCLA list and has been on the TURA list since the program's inception. However, the category was not well defined and when the category was added in

1993 as part of the phasing in of the CERCLA chemical list, a DEP policy was put in place that exempted reporting of this category. (Note: 6 specific phthalate esters [DEHP, BBP, DBP, DEP, DMP, DnOP] are specifically listed on CERCLA or TRI and are individually reportable). In spite of the DEP policy, 4 facilities erroneously reported the category between 1993 and 2005. The phthalate esters were listed on CERCLA because the Clean Water Act had identified them as toxic pollutants. (see Appendix I)

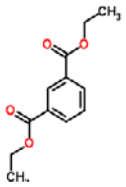
Definition of Phthalate Esters

Phthalate esters (abbreviated as "PEs") are esters of phthalic acid. They are widely used as plasticizers in plastics, and as stabilizers, emulsifying agents and lubricants in coatings, paints and other preparations. While six of the most commonly used phthalates (e.g., DEHP) are on the TURA list, there are many currently in use that are not. (See Appendix I)

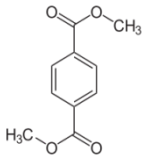
When side chains are positioned on adjacent carbons of the benzene ring, it is an ortho phthalate ester; when separated by one carbon, it is a meta- or iso- and on opposite sides of the ring it is a para- or tere-phthalate.



Ortho-phthalate



Isophthalate (meta-)



Terephthalate (para-)

Ability to Distinguish between Phthalate Esters

The Board identified the challenge of distinguishing between the different phthalate esters given that commercially available phthalates are often by nature mixtures and have a certain percentage of other phthalate esters present (e.g. 1,2-Benzenedicarboxylic acid, nonyl undecyl ester, branched and linear comprises 1/6th of the phthalate ester mixture 711P [US EPA 2001]).

During the process of organizing the group by carbon side chain length, it was noted that an individual would need to have a strong chemistry background to determine the correct carbon chain length, and even then, classifications of carbon chain length varied between experts and different information sources. Complications include the particular manufacturing process used and whether to count the total chain or the backbone length. The industry method is to count the longest linear backbone length.

Additionally, some of the phthalate esters may have secondary less common CAS numbers or ones that are no longer in commerce (e.g. EPA lists two new CAS numbers for DINP in their 2014 report), or may have additional CAS numbers that are slightly different structures or mixtures.

Science Advisory Board Review

The SAB reviewed approximately 100 documents over the course of three years including government reports and peer-reviewed journal articles on health and environmental effects. This review included:

- A deep review of reproductive and developmental toxicity of 10 selected specific ortho phthalate esters,
- A less intensive review of other effects from these 10 phthalate esters such as thyroid effects and liver effects,
- A limited review of other ortho phthalate esters,
- A review of the limited information on Meta and Para phthalates,
- A review of available studies on cumulative effects and low dose effects.

The initial list of phthalate esters reviewed by the SAB consisted of 32 phthalate esters compiled from publically available sources. Additional phthalate esters from various sources, including the primary literature were added as the project progressed. The SAB initially reviewed their standard set of information for the phthalate esters which includes data points on carcinogenicity, reproductive and developmental toxicity, acute toxicity, and PBT status among other factors (for a full set of endpoints see Appendix H1:Ortho EHS Data Spreadsheets). The SAB noted that listed phthalate esters tended to have reproductive, developmental, and liver toxicity primarily. The SAB requested information on the mechanism of action[1] and more detailed information regarding reproductive and developmental toxicity.

Additionally, the Board reviewed several overview studies (see Appendix B3: Overview Studies). Early in the process the list of phthalate esters was split into ortho-phthalate esters, meta-phthalate esters, and para-phthalate esters, in an effort to evaluate groups that were similar and more manageable. The Board decided it would evaluate one group at a time, beginning with the set of 58 ortho-phthalate esters.

Ortho-Phthalate Esters

The ortho-phthalate esters are the most widely used group of phthalate esters and also the group with the most toxicity and hazard information available. The chemical structure for each of the 58 ortho-phthalate ester substances was added to the EHS (Environmental, Health and Safety) data spreadsheet and the ortho-phthalate ester spreadsheet was organized by carbon side chain length in an effort to

[1] **NOTE: Mode of Action/Mechanism of action** Information on mode of action (MoA) is typically available, yet definitive information on the mechanism of action (MOA) is often not. For example, for DEHP the MOA is clear, but is not necessarily the same for other phthalate esters. Mode of action refers to "A description of key events or processes by which an agent causes a disease state or other adverse effect." (NAP 2007). Mechanism of action refers to "A detailed description, often at the molecular level, of the means by which an agent causes a disease state or other adverse effect." (NAP 2007). For example, many substances are antiandrogens, but may have different modes of action; some may be androgen receptor antagonists, while others (including ortho-PEs) interfere with testosterone synthesis. The mechanism by which they interfere with testosterone synthesis is a decrease in mRNA expression of key steroidogenic enzymes and also the peptide hormone insulin-like peptide 3 (insl3) from the foetal Leydig cells. (Wilson 2008)

look for health effects that were common for certain groups of carbon side chain lengths (see Appendix H1). *A Category Approach for Reproductive Effects of Phthalates* (Fabjan et al., 2006) was distributed and phthalate ester experts Dr. Earl Gray (US EPA) and Dr. Paul Foster (NIEHS) were invited to share their expertise with the Board. In addition, a phthalate ester expert representing the ACC Phthalate Ester Panel attended most of the SAB meetings as a visitor and contributed information and provided reference material.

At the September 2013 meeting, the Board decided to take a more in depth look at the reproductive and developmental studies for 10 specific phthalate esters. The Board chose 10 phthalate esters that covered a range of molecular weights and side chain lengths. Carbon chain lengths shown in the first column in the table below are from information available when the substances were selected in 2013. As the review progressed, additional information was gathered about how different government and industry entities characterized the carbon chain length of a particular substance. The ranges shown in the second column incorporates that research. As there was some consensus around the reproductive and developmental toxicity of the mid-range phthalates (C4 – C6, in particular), the substances chosen for in-depth review were in the lower and higher molecular weight/side chain length ranges.

10 Phthalate Esters Selected for In-Depth Review		**Carbon chain length**	
		As understood in 2013	After further research
DAP	Diallyl phthalate	C3	C3
DMEP	Bis(2-methoxyethyl) phthalate	C3	C3
DIDP	Diisodecyl phthalate	C7-C11	C8-C10
DnOP	Di-n-octyl phthalate	C8	C8
DINP	Diisononyl phthalate	C9, C8–C10	C8-C9
Din911P	1,2-Benzenedicarboxylic acid, 1-nonyl 2-undecyl ester, branched and linear	C9-C11	C8-C11
DPHP	Di-2-propyl heptyl phthalate	C10	C7, C10
DUP	Diundecyl phthalate	C11	C10-C11
DIUP	Diundecyl phthalate, branched and linear	C11	C9-C11
DTDP	Ditridecyl phthalate	C13-rich	C10-C13

A literature search was conducted for each phthalate ester and relevant articles along with the results of the literature search were distributed to SAB members. The members were split into teams, each covering specific substances, and were provided with a matrix to record the findings of each article so that they could easily be summarized and shared with the rest of the Board. The SAB reviewed the study results for general findings, statistical significance, relevance of outcomes, evidence of dose reponse, report of a NOAEL and/or LOAEL, and strengths and weaknesses as discussed by the authors. They did not conduct detailed evaluations of study methodology, validity, or potential bias. Specific chemical summaries can be found in Appendix A.

It should be noted that there have been many improvements in reproductive and developmental effect study design over the last decade. For example, older studies may not have looked for certain sensitive

effects (e.g., anogenital distance), observed multiple generations, or exposed animals during the most sensitive periods of fetal development.

Meta (*Iso*) and Para (*Tere*) Phthalates

Four studies were identified for meta-phthalates. These studies focused on dimethyl isophthalate (DMI or DMIP), diphenyl isophthalate, and diallyl isophthalate. See Appendix B4 for information on the Meta phthalate ester studies available on or after 1990.

Nineteen studies were identified for para-phthalates. The majority of studies focused on di(2-ethylhexyl) terephthalate (DEHT) or dimethyl terephthalate (DMP); there were also limited studies for diethyl terephthalate (DTP), and diallyl terephthalate. See Appendix B5 for information on the Para phthalate ester studies available on or after 1990.

Cumulative effects

Throughout the process the Board questioned the potential for cumulative effects from phthalate esters. Many phthalate esters have similar toxicity concerns. In addition, as commercial phthalate esters are mixtures, different phthalate esters may metabolize to some of the same monoester metabolites, which is often the primary source of toxicity.

The presentation by Dr. Gray and Dr. Foster showed examples of cumulative responses. In a cumulative effect study of DBP and DEHP, DBP alone caused no hypospadias in male rats and DEHP caused a low frequency of hypospadias (3%). However, the combination dose of DBP and DEHP significantly increased the incidence of hypospadias (25%).

A 2010 Consumer Product Safety Commission report cites three recent studies that show additive effects from exposure to multiple phthalate esters and/or other antiandrogens (Howdeshell et al. 2008; Christiansen et al. 2009; Rider et al. 2008). “Cumulative effects may occur even though the modes of action of antiandrogens may differ. Some are androgen receptor antagonists, while others (i.e., the *o*-DAP’s) interfere with testosterone synthesis.” [CPSC 2010g]. In addition, PubMed was searched and the articles in the cumulative effects table were added. See Appendix B1 for Cumulative Effects studies.

Low dose effects

Throughout their review of the phthalate esters category the question of potential effects of low doses recurred. PubMed was searched for “low-dose phthalate reproductive” and six studies were chosen for review. Two additional studies cited in the ECHA 2012 evaluation were added as well. Low-dose, for the purposes of this review ranged from .01mg/kg/day to 10mg/kg/day.

There is some evidence that PEs can cause effects at low doses due to endocrine activity, although it is difficult to define “low dose” (Hoshi and Ohtsuka, 2009). PE studies at environmentally relevant low doses were not identified. In other endocrine active substances, research has shown non-monotonic

dose response curves, and different kinds of effects at very low, environmentally relevant, dose levels. This is an emerging field and an emerging concern.

Summary Findings

Ortho phthalate esters

C1-C3 (includes TURA listed DMP and DEP, and non-listed DPP, DMEP, and DAP, among others):

C1-C3 chain length substances have significant health effects, but not always the same effects as other PEs. These substances often are used as film-forming solvents; most of the known commercial plasticizer products are not in this range. See Appendix A for effects noted for specific substances.

C4-C7 (includes TURA listed DBP, BBP, DEHP (C8 total: C6 backbone w/ C2 branch), and non-listed DIBP, DinHP, DnPP, DnHP, DCHP, DiHepP, among others):

C4-C7 are the most well studied substances; there is a significant body of animal evidence of adverse reproductive and developmental health effects, as well as some human evidence from epidemiological studies. (CPSC, 2010g)

Endocrine pathways: There is a general consensus from animal studies that some C4 and longer ortho-PEs are anti-androgens, interrupting the testosterone synthesis pathway. While the mechanisms for these effects are not well understood, there is general concern regarding the impact on hormone pathways.

Liver effects: Liver is a primary target organ for most ortho-PEs, showing effects in chronic and subchronic animal studies. There is concern, and no general agreement, about whether the liver effects involving peroxisome proliferation, including carcinogenicity, seen in animal studies are relevant to humans.

Thyroid: While not systematically evaluated by the SAB, thyroid effects were noted in a few of the reproductive studies reviewed; and may indicate an area of concern.

> C7- (includes TURA listed DnOP, and non-listed DINP, DIOP, DIDP, DNP, Din911P, DIUP, DUP, DPHP, DTDP, among others):

After C7, there is a general tendency as the carbon backbone chain length increases, for the adverse effects to diminish and for there to be fewer scientific studies. See Appendix A for study results for specific substances.

Meta- (or isophthalates) and Para- (or terephthalates)

There is a general lack of information in the scientific literature for meta- and para-PEs, with the exception of DEHT (diethyl hexyl terephthalate). In general, the current literature supports different and a lower mammalian toxicity profile for meta- and para- than for the ortho-PEs.

DEHT has been the most studied of the terephthalates the Board has been able to review, and while there are data gaps, available information indicates low concern.

From the limited number of studies for meta-phthalates, evidence exists for migration and persistence in the environment as well as potential for adverse effects on the endocrine system, though the limited number of studies as well as the findings regarding relatively weak estrogenic activity in one species suggests a lower priority class of compounds as compared to the ortho-phthalates.

Cumulative Effects

Concerns with anti-androgenic phthalate esters that interfere with enzymes and reduce testosterone synthesis include not only the anti-androgenic effects, but also other impacts from enzyme interference.

Many phthalate esters, with their similar health effects and modes of action, are expected, and have been shown to, have cumulative effects. The cumulative effects are of particular concern because of the ubiquity and "pseudo persistence" of phthalate esters in the environment and in biota.

There is evidence of additive effects from different phthalate esters, both those with similar effects (e.g. anti-androgenic effects), and those with the same or different modes of action. Nearly all of the evidence is from the more well-studied and more potent C4-C7 PEs. There is also some evidence of synergistic or antagonistic effects, typically between PEs and other endocrine active substances, such as some pesticides.

Policy and Other Considerations

During the course of the Science Advisory Board's review, the Board focused on the science related to phthalate esters. The following section on policy considerations has been added by TURI to provide context for the category.

Uses and Interchangeability

It is possible to substitute some phthalates for others in certain applications, although they do have different properties. For example, short side chain PEs, such as DEP, are used as solvents and emollients in cosmetics and personal care products, whereas longer side chain PEs, such as DINP, are used as plasticizers in solid resins.

Phthalate Ester Uses

Phthalate Esters are widely used as plasticizers to make plastics more flexible, for example, in PVC (polyvinyl chloride) resins. Transitional and higher molecular weight (≥ C4) PE's are typically used as plasticizers. PE's are also used to hold fragrances, as emollients, to provide a film or

gloss, and as solvents. Lower molecular weight PE's (C1- C4) are used as solvents, and in cosmetics, shampoos and fragrances.

Historic uses reported in Massachusetts under TURA include:

- compounded PVC and other resins used in a variety of end products
    - End products include wire and cable insulation and jacketing, PVC extrusions and profiles, PVC sheet, medical devices/tubing and bags, rubber gaskets, shoe soles, and marine moldings
- adhesives
- coatings
- personal care products
- coated fabric and paper
- membrane filters
- plastisol vinyl resins

See Appendix G for more information on uses nationally and in Massachusetts.

Brominated phthalate esters: In addition to the large universe of phthalate esters that is the focus of this report, there are commercially available brominated phthalate esters. The most commonly used is brominated DEHP, (2-ethylhexyl)tetrabromophthalate (TBPH) (CASRN 26040-51-7) which is one component of Chemtura's flame retardant Firemaster® 550. These substances are more often classified with flame retardants, as EPA has done with their Brominated Phthalates Cluster TSCA assessment, rather than with plasticizers. Nevertheless, they are phthalate esters, and are not individually listed on the TURA chemical list. TBPH is widely used in flexible furniture foam as a flame retardant, and reported under the TSCA inventory as used as a plasticizer in PVC for consumer and commercial electrical and electronic products. TBPH was not specifically reviewed by the SAB, but EPA estimates moderate concern for reproductive toxicity and liver effects based on data from structurally similar analogs.[2,3]

Substitutes and Interchangeability

Plasticizers: Plasticizer selection is based on a balance of cost, performance and availability. Performance criteria include: processing compatibility, efficiency, volatility, stability, low temperature flexibility, and electrical resistance. While every application and resin has its own specific requirements, there is usually a range of different phthalate ester plasticizers that are able to meet those requirements. In general, PE's with similar side chain lengths and

[2] USEPA.. *Flame Retardants Used in Flexible Polyurethane Foam: An Alternatives Assessment Update*. August 2015. Accessed 21NOV2016 at https://www.epa.gov/saferchoice/2015-update-report-flame-retardants-used-flexible-polyurethane-foam-publications.

[3] USEPA. *TSCA Work Plan Chemical Problem Formulation and Data Needs Assessment: Brominated Phthalates Cluster -Flame Retardants*. EPA Document# 740-Q1-4004 August 2015.

configurations are likely to have similar properties and be interchangeable. For example, in wire and cable and other extrusion applications, some higher molecular weight PE's such as DIDP and DINP are usually interchangeable. Many manufacturers have successfully substituted other higher molecular weight ortho- and tere-PE's for those that are currently under scrutiny or restricted.

As illustrated in a presentation to the Consumer Product Safety Commission by ExxonMobil[4], there are many different commercially available plasticizers, PE's and others, which can be used for any given type of application. For example, PE plasticizers used for vinyl resilient flooring include BBP, DEHP, DOTP, DINP, DIDP, and DPHP. Different applications have different critical attributes, for example, good film forming properties are important in paints, and low temperature flexibility is important in exterior cable jacketing. Within a given application, different base resins will also have different plasticizer requirements.

While several products might be feasible for any given application, substitution could require reformulation of the compounded resin, for example changes in loading rates, or other additives such as flame retardants or pigments. Substitution could also require changes in processing parameters.

Solvents: Similarly, there is some interchangeability among the different C1-C4 PE's for different applications. Important selection parameters for solvents in cosmetics, fragrances and personal care products include: solvency, cost, odor, and potential for irritation.

Regulatory/Policy Table by Carbon Chain Length

There is a significant amount of activity federally, in states, in other countries, and with supply chains and NGOs, to regulate, restrict and/or monitor phthalate esters. The attached table shows selected activity for ortho-phthalate esters of varying side chain length. The table is organized approximately by carbon side chain backbone length.

- The list of regulatory and policy actions is representative, not exhaustive, for example there are additional state and international programs that have targeted specific phthalate esters. In addition, only governmental activities are included. TURA currently reportable under TURA as individual phthalate ester
- SVHC Auth Subject to authorization under REACH as a Substance of Very High Concern

[4] ExxonMobil CPSC presentation July 26, 2010: Uses of Phthalates and Other Plasticizers. By Allen Godwin Accessed at https://www.cpsc.gov/PageFiles/126379/godwin.pdf

- SVHC Candidate for authorization under REACH as a Substance of Very High Concern
- CoRAP EU Community Rolling Action Plan -to be evaluated by the Member States in the next three years - initial reason for phthalate esters on CoRAP list is Human health/Suspected CMR
- EU Restrict EU Annex XVII to REACH; restricted for use in toys and childcare articles
- RoHS EU RoHS Directive: 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment
- CA Prop 65 Listed on California Prop 65 list of chemicals known to the state to cause cancer or reproductive toxicity
- CPSC Use restricted in children's products by US Consumer Products Safety Commission
- EPA CAP US EPA TSCA Chemical Action Plan
- EPA TSCA US EPA TSCA Work Plan for Chemical Assessments
- SNUR US EPA Significant New Use Rule
- ME CHC Maine Chemicals of High Concern (* indicates listing of mono ester metabolite, mono-n-butyl phthalate)
- WA CHCC Washington state Chemicals of High Concern to Children

Phthalate Esters by carbon side chain backbone length: Regulatory and Policy Activity (as of 10/13/16)

C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14
DMP	DEP		DBP	DnPP; DPP	DEHP		DINP		DTDP				
TURA	TURA CoRAP WA CHCC		TURA CA Prop 65 CPSC SVHC Auth EPA CAP EU Restrict RoHS ME CHC* WA CHCC	SVHC EPA CAP SNUR CPSC*	TURA SVHC Auth CA Prop 65 CPSC EPA CAP EU Restrict RoHS WA CHCC		CA Prop 65 CPSC EPA CAP EU Restrict WA CHCC		CoRAP				
		DIBP		DIPP	TBPH		DnOP	DIUP					
		SVHC Auth EPA CAP CPSC* RoHS		SVHC	EPA TSCA CoRAP		TURA CPSC** EPA CAP EU Restrict WA CHCC	CoRAP					
		DMEP	BBP (ring)	PIPP		DIOP	DIDP						
		SVHC	TURA SVHC Auth CA Prop 65 CPSC EPA CAP EU Restrict RoHS ME CHC* WA CHCC	SVHC		CPSC*	CA Prop 65 CPSC** EPA CAP EU Restrict WA CHCC						
		DAP	DCHP (ring)	DnHP; DHP		Benzyl C7-C9			DUP, DnUP				
		CoRAP	EPA TSCA CPSC* ME CHC	SVHC CA Prop 65 CPSC* WA CHCC		CoRAP			CoRAP				
			DHNUP 7-11 branched and linear 68515-42-4										
			SVHC										
					C6-8, C7 rich			C9-C11					
					SVHC			CoRAP					
						DPHP			DPHP				
						CoRAP			CoRAP				
					DiHepP								
					SVHC								
							Din911P						
					610P; Di C6-10PE								
					SVHC								

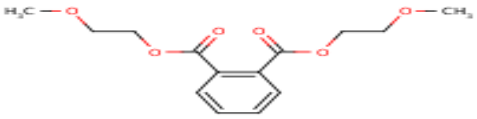
TURA	currently reportable under TURA as individual phthalate ester
SVHC Auth	Subject to authorization under REACH as a Substance of Very High Concern
SVHC	Candidate for authorization under REACH as a Substance of Very High Concern
CoRAP	EU Community Rolling Action Plan -to be evaluated by the Member States in the next three years - initial reason for phthalate esters on CoRAP list is Human health/Suspected CMR
EU Restrict	EU Annex XVII to REACH; restricted for use in toys and childcare articles
RoHS	EU RoHS Directive: 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment
CA Prop 65	Listed on California Prop 65 list of chemicals known to the state to cause cancer or reproductive toxicity
CPSC	Use restricted in children's products by US Consumer Products Safety Commission (may be permanent or interim) * indicates proposed ** indicates interim ban proposed to be removed
EPA CAP	US EPA TSCA Chemical Action Plan
EPA TSCA	US EPA TSCA Work Plan for Chemical Assessments
SNUR	US EPA Significant New Use Rule
ME CHC	Maine Chemicals of High Concern (* indicates listing of mono ester metabolite, mono-n-butyl phthalate)
WA CHCC	Washington state Chemicals of High Concern to Children
	SAB 10 Selected substances for in-depth review
	TURA Currently reportable as individual phthalate substances

Appendix A: 10 Specific Phthalates (ordered by carbon chain length)

Includes only articles reviewed at the time of the in-depth review

DMEP - Bis(2-methoxyethyl) phthalate [c3]

CAS #117-82-8



Three specific articles were reviewed regarding reproductive and developmental toxicity endpoints for DMEP. DMEP is an ortho-phthalate ester comprising two two-carbon backbones attached to methoxy groups. DMEP causes severe reproductive toxicity in adult animals: testicular atrophy; sperm damage; decreased testicular weight [CPSC 2011a: Kodak 1984, Cassidy, et al. 1983].

DMEP causes severe teratogenicity (severe skeletal malformations) in utero [CPSC 2011a: Parkhie, et al. 1982, Singh, at al. 1972].

DMEP is genotoxic [CPSC 2011a: NTP 1993]. No cancer studies have been performed [CPSC 2011a]. Liver and kidney effects were observed [Campbell, et al. 1984].

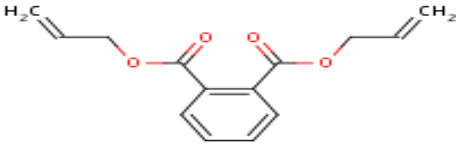
Metabolite information on DMEP is studied in [Campbell, et al. 1984]. DMEP and metabolites are rapidly transferred to the fetus through the placenta [Campbell, et al. 1984]. DMEP and one of its metabolites, ME, are embryotoxic and fetotoxic [Campbell, et al. 1984].

DMEP		
Author and Title	**Dose/Species/Strain**	**Findings**
Campbell 1984: Campbell J, et al. Dimethoxyethylphthalate metabolism: teratogenicity of the diester and its metabolites in the pregnant rat. *J Appl Toxicol.* 1984 Feb; **4(1):**35-41.	Female rat; Dosed on gestation days 8, 10, 12 & 14	ME, derived by the metabolism of DMEP, may be the teratogenic agent
CPSC 2011a: Consumer Product	Overview of published	Reproductive Toxicity- > Observed

Safety Commission Staff Toxicity Review of Two Phthalates and One Phthalate Alternative for Consideration by the Chronic Hazard Advisory Panel – 2011. Section on Bis(2-methoxyethyl) phthalate. 2011. Pages 19-31.	information on toxicity and exposure potential for DMEP.	Developmental Toxicity- > Observed Genotoxicity -> Observed, dose related trend
ECHA 2011: Support Document for Identification of Bis(2-Methoxyethyl)phthalate as a substance of very high concern because of its Carcinogenic, Mutagenic and Reproductive (CMR) properties. European Chemicals Agency, December 9, 2011.		DMEP meets the criteria for classification as toxic to reproduction and development

DAP - Diallyl phthalate [c3]

CAS #131-17-9



Five specific articles were reviewed regarding reproductive, developmental, and carcinogenic toxicity endpoints for DAP. DAP is an ortho-phthalate ester comprising two three-carbon backbones (CPSC 2011b).

Dystocia (difficult labor) was seen at 50 mg/kg (CPSC 2011b). Saillenfait 2008 observed reduced fetal weight at 250 mg/kg and bone growth delay. DAP was not found to be teratogenic until >250 mg/kg. Saillenfait 2008 concluded that carbon backbone length alone does not predict developmental effects.

The 2003 NTP CERHR noted uterine tumor effects (negative correlation – control highest). Saillenfait 2008 indicated hepatotoxic effects and maternal effects with a NOAEL of 50 mg/kg. Nakai 1999 noted that the ortho isomer of diallyl phthalate is most potent (3 times more potent vs. di-n-propyl) in binding to the estrogen receptor due to hydrophobic interaction.

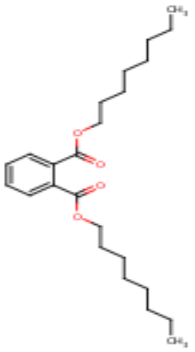
DAP		
Author and Title	**Dose/Species/Strain**	**Findings**
CPSC 2011b: Consumer Product Safety Commission Staff Toxicity Review of Two Phthalates and One Phthalate Alternative for Consideration by the Chronic Hazard Advisory Panel – 2011. Section on 1,2-Benzenedicarboxylic Acid, Di-2-propenyl ester. 2011. Pages 3-18.	Sprague-Dawley rats, M/F, gavaged with 16.7, 50, or 150 mg/kg bw/day DAP from 14 days prior to mating to four days post-partum; See NTP 1983 reference below	NOAEL for reproductive effects (DAP Consortium, 2004) was 50 mg/kg/day for dystocia. Two year assay in mice (NTP, 1983) do not provide evidence that DAP is carcinogenic to mice. Study notes “toxicity of DAP results from its metabolite, allyl alcohol, and the extent of DAP toxicity is related to the amount of glutathione conjugation with allyl alcohol or acrolein, an active metabolite of allyl alcohol” (Eigenberg, et al., 1986)
Kluwe 1986: Kluwe WM. Carcinogenic potential of phthalic acid esters and related compounds: structure-activity relationships. *Environ Health Perspect.* 1986 Mar; **65**:271-8.	Fischer 344 rats, M/F, 50 mg/kg and 100 mg/kg B6C3F_1 mice, M/F, 150 mg/kg and 200 mg/kg	Comparative evaluations of chronic toxic responses to several PAEs did not reveal common neoplastic lesions suggestive of structural correlates of toxic activity. “Compound-related deaths in these studies occurred only at the 400 mg/kg

DAP		
		dose of DAP in male rats. DAP also caused hepatocellular necrosis and hepatic fibrosis or cirrhosis in both sexes of rats at 200 and 400 mg/kg; no liver lesions were observed in the DAP-treated mice." "One each of the lower dose male and female mice and two each of the higher dose male and female mice in the DAP study exhibited papillomas of the forestomach. (DAP also caused gastric hyperplasia and chronic gastric inflammation in the mice.)" "DAP treatment was related to an increased occurrence of this same tumor [mononuclear cell leukemia] in female rats, as well as with an equivocal increase in the occurrence of lymphomas in male mice."
Nakai 1999: Nakai M, Tabira Y, Asai D, Yakabe Y, Shimyozu T, Noguchi M, Takatsuki M, Shimohigashi Y. Binding characteristics of dialkyl phthalates for the estrogen receptor. *Biochem Biophys Res Commun.* 1999 Jan 19; **254(2):**311-4.	Estrogen receptor binding assay	Ortho isomer of diallyl phthalate most potent (3 times more potent vs. di-n-propyl) in binding to estrogen receptor due to hydrophobic interaction. The lipophilic nature and long half life of alkyl phthalates may allow them to accumulate and persist in fatty tissues of the body thus increasing their concentration and bioavailability.
NTP 1983: National Toxicology Program. NTP Carcinogenesis Bioassay of Diallyl Phthalate (CAS No. 131-17-9) in B6C3F_1 Mice (Gavage Study). Natl Toxicol Program Tech Rep Ser. 1983 Apr; **242**:1-96.	0, 150, or 300 mg/kg DAP in corn oil by gavage, 5 days/week for 103 weeks, to groups of 50 male and 50 female B6C3F_1 mice.	Under the conditions of this bioassay, the development of chronic inflammation and hyperplasia of the forestomach in both male and female B6C3F_1 mice was considered to be related to the administration of diallyl phthalate. An increase in the incidence of male mice with lymphoma was observed, but this increase was considered only to be equivocally related to diallyl phthalate administration. "Chemically-induced clinical signs of morbidity were not observed at any time." Results do not indicate DAP is carcinogenic in B6C3F_1 mice, although a maximum tolerated dose may not have been achieved.
Saillenfait 2008: Saillenfait AM,	Pregnant Sprague-	Liver effects in rats NOAEL @ 50

DAP		
et al. Evaluation of the developmental toxicity of diallyl phthalate administered orally to rats. *Food Chem Toxicol.* 2008 June; **46 (6)** 2150-6.	Dawley rats were given DAP at doses of 0 (olive oil), 100, 150, 200, and 250 mg/kg/day, by gavage (5 ml/kg), on Gestational Days (GD) 6 through 20.	mg/kg/day based on histopathological findings. Prenatal toxic effects at 200 and 250 mg/kg/day – decreased fetal body weight. Developmental NOAEL at 150 mg/kg/day based on fetal weight changes and increased incidence of fetal skeletal variations. No evidence of teratogenicity up to 250 mg/kg/day, no adverse effect seen at 150 mg/kg/day. DAP showed a developmental toxicity that differed from DIBP. Impacts to fetus due to maternal toxicity @ 200 mg/kg/day or higher.

DnOP - Di-n-octyl phthalate [c8]

CAS #117-84-0



Four specific articles were reviewed regarding reproductive and developmental toxicity endpoints for DnOP. The DnOP structure is comprised of a pair of eight-carbon esters linked to a benzene-dicarboxylic acid ring and is the straight chain analog to DEHP (CPSC 2010a). This substance is already listed on the MA TURA list.

The 2003 NTP Center for the Evaluation for Risks to Human Reproduction (CERHR) report noted limited studies in animals show developmental effects at high doses. The report also indicated *some evidence of no adverse effect* with regard to reproductive toxicity. NTP also noted there were no estrogenic effects. NTP noted insufficient information for humans with regard to developmental toxicity and that it is not likely to affect the human reproductive system. It was noted that studies older than 2002 may not have looked for certain sensitive effects (e.g., anogenital distance), observed multiple generations, or exposed animals during the most sensitive periods of fetal development. Saillenfait 2011 noted that anogenital distance was not affected by DnOP.

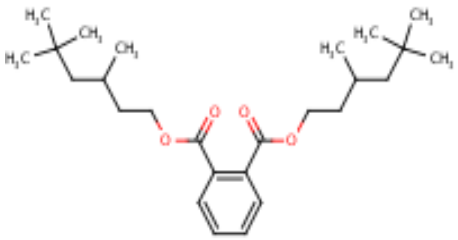
Several studies listed DnOP as a probable hepatotoxicant (CPSC 2010a). CPSC indicated "probable" (sufficient animal evidence) for thyroid toxicity, immunotoxicity, and nephrotoxicity.

DnOP		
Author and Title	**Dose/Species/Strain**	**Findings**
CPSC 2010a: Consumer Product Safety Commission Staff Toxicity Review of Di-n-Octyl Phthalate (DnOP). March 8, 2010.	Various	Hepatotoxicity -> Sufficient animal evidence, "Probable" Immunotoxicity -> Sufficient animal evidence, "Probable" Nephrotoxicity -> Sufficient animal evidence, "Probable" Carcinogenicity -> Limited or inadequate evidence Reproductive/Developmental Toxicity -> Limited or inadequate evidence
Kwack 2009: Kwack SJ, Kim KB,	DnOP administered orally to	DnOP ranks third in PE showing

DnOP		
Kim HS, Lee BM. Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. *J Toxicol Environ Health A*. 2009; **72(21-22):**1446-54.	Sprague-Dawley male rats at 500 mg/kg body weight (bw)/d for 4 weeks.	significantly lower sperm counts/decreased motility at a 500 mg/kg/day dose level.
NTP-CERHR 2003a: National Toxicology Program. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-n-Octyl Phthalate (DnOP). NTP CERHR MON. 2003 May;**(6)**:i-III90.	*Developmental:* Pregnant rats, treated with DnOP by IP injection on gestation days 5, 10, and 15, at doses 5,000 and 10,000 mg/kg bw/day; Pregnant mice were treated by gavage with ~ 10,000 mg/kg bw/day on gestation days 6-13. *Reproductive:* Mouse continuous breeding study, CD-1 mice exposed through dosed feed to ~ 1,800, 3,600, or 7,500 mg/kg bw/day; Sprague-Dawley male rats, oral, 2,800 mg/kg bw/day, 4 days; Sprague-Dawley male rats, oral, 350 mg/kg bw/day, 13 weeks	Developmental toxicity -> Limited evidence of adverse effects, insufficient data Reproductive toxicity -> Some evidence of no adverse effect, negligible concern Based on assumption that humans are exposed to levels of DnOP less than 30 ug/kg bw/day, NTP concurs with the CERHR Phthalates Expert Panel's conclusion that there is negligible concern for effects on adult reproductive systems. Reproductive Toxicity NOAEL in mice = 7,500 mg/kg bw/day and in rats is 350 mg/kg bw/day. They indicate that should be looking at DnOP (20%) as part of mixture with regard to human reproductive study.
Saillenfait 2011: Saillenfait AM, et al. Prenatal developmental toxicity studies on di-n-heptyl and di-n-octyl phthalates in Sprague-Dawley rats. *Reproductive Toxicology* 2011 Nov; **32(3):** 268-76.	Sprague-Dawley rats were administered 0, 0.25, 0.50 or 1 g/kg/day of DnOP, by gavage, on gestation days 6-20.	DnOP had no effect on AGD of male and female fetuses. The incidence of supernumerary lumbar ribs was significantly elevated in all DnOP treated groups. Results indicate that DnOP has a low toxic potential for pregnant rats and did not affect intrauterine growth or embryonic/fetal survival. The limited adverse developmental effect of DnOP in rats correlates with previous findings in mice. LOAEL for developmental toxicity was 250 mg/kg/day.

DINP – Diisononyl phthalate [c9,c8-c10]

CAS #28553-12-0; 68515-48-0



Twenty-one specific articles were reviewed regarding reproductive and developmental toxicity endpoints for DINP. DINP is a mixture of C9 Rich, C8-C10, branched chain dialkyl esters (CPSC 2010g). The 2003 NTP CERHR noted no concern for reproductive or developmental toxicity. Waterman 2000 shows no gross reproductive effects in a two generation study. CPSC 2010g finds that DINP is a probable developmental toxicant and causes liver and kidney tumors in rodents. Key studies showing effects on testosterone production and anogenital distance are Borch 2004, Boberg 2011, and Clewell 2013a. These effects are seen at higher doses than DEHP. Hannas 2011 notes that DINP is quantitatively different than other phthalates such as DEHP but not qualitatively different.

Kaufmann 2002 shows peroxisomal proliferation (activation of PPARα) as the mode of action for DINP induced liver tumors in mice. McKee 2000 finds that DINP is not genotoxic. California OEHHA recommended addition of DINP to the Proposition 65 list as a carcinogen on December 5, 2013, based on evidence of other carcinogenic mechanisms of action in addition to activation of PPARα, and study findings inconsistent with the PPARα hypothesis. A recent report by the European Chemicals Agency (ECHA, 2013) also commented on evidence of multiple pathways for liver carcinogenesis, which could change the relevance of rodent study results to humans. DINP enhances iodide uptake by the thyroid (Wenzel, 2005).

DINP		
Author and Title	**Dose/Species/Strain**	**Findings**
Adamsson 2009: Adamsson A, et al. Effects of maternal exposure to di-isononylphthalate (DINP)	250, 750 mg/kg Sprague-Dawley rats ED 13.5-17.5	No down-regulation of steroidogenesis on ED 19.5 No change in testicular and adrenal StAR,

DINP		
and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (*p,p'*-DDE) on steroidogenesis in the fetal rat testis and adrenal gland. *Reproductive Toxicology*, **28** (2009) 66-74.		P450scc, 3_HSD, or androgen receptor on ED 19.5
Boberg 2011: Boberg J, et al. Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats. *Reproductive Toxicology* **31** (2001) 200-209.	300, 600, 750 or 900 mg/kg bw/day Wistar rats GD7- PND17	Nipple retention, reduced anogenital distance, reduced sperm motility, and increased sperm count in male offspring. Improved spatial learning in female offspring.
Borch 2004: Borch J, et al. Steroidogenesis in fetal male rats is reduced by DEHP and DINP, but endocrine effects of DEHP are not modulated by DEHA in fetal, prepubertal and adult male rats. *Reprod Toxicol.* 2004 Jan-Feb;**18(1):**53-61.	DEHP 300 or 750 mg/kg/day; DINP 750 mg/kg/day; 300 mg/kg/day DEHP+750 mg/kg/day DINP Wistar rats	DEHP and DINP both reduced testicular testosterone ex vivo; reduced testosterone levels in testes and plasma of male fetuses GD21. Elevated plasma LH levels in male fetuses were observed. Tendency toward accumulating effects of DEHP and DINP on suppression of testosterone synthesis was observed.
Breous 2005: Breous E, et al. The promoter of the human sodium/iodide symporter responds to certain phthalate plasticisers. *Molecular and Cellular Endocrinology* **244** (2005) 75-78.	Studied effects on basal iodide uptake and responsible mode of action in rats.	No effect on the transcriptional activity of sodium/iodide symporter (NIS) was observed for DINP.
Clewell 2013: Clewell RA, et al. A dose response study to assess effects after dietary administration of diisononyl phthalate (DINP) in gestation and lactation on male rat sexual development. *Reproductive Toxicology* **35** (2013) 70-80.	0, 760, 3,800, 11,400 ppm DINP GD12-PND14	Reduced Maternal weight GD 20, PND 2 and 14 at 11,400 ppm. Reduced Pup weight PND 2 and 14 at 11,400 and 3,800 ppm. Induced MNGs (3,800 ppm) and LCAs (11,400 ppm) on PND 2, and reduced AGD (11,400 ppm) on PND 14. Did not cause alterations in AGD, nipple retention or reproductive tract malformations in offspring observed on PND 49.
Clewell 2013a: Clewell RA, et al. Disposition of diisononyl phthalate and its effects on sexual development of the male	50, 250, and 500 mg/kg/day GD 12 to 19 via corn oil gavage.	MiNP, MCiOP, MHiNP, MOiNP, MiNP-G found in all measured tissues. MCiOP was the major metabolite, followed in decreasing order by MiNP,

DINP		
fetus following repeated dosing in pregnant rats. *Reproductive Toxicology* **35** (2013) 56-69.	Sprague-Dawley rats	MHiNP, MOiNP, and MiNP-G. Percentage of dose absorbed decreased at 750 mg/kg/day. Testosterone concentration in the fetal testes was reduced at 250 and 750 mg/kg/day. Multinucleated germ cells were increased in the testes of rats at 250 and 750 mg/kg/day. The no observed effect level (NOEL) for this study was 50 mg/kg/day based on increased MNGs and reduced testes testosterone concentration in the fetal rat. Testes histopathology observed multinucleated germ cells (MNGs), but no structural abnormalities.
CPSC 2010g: Consumer Product Safety Commission Staff Toxicity Review of Diisononyl phthalate (DINP). April 7, 2010.	Overview of published information on toxicity and exposure potential for DINP.	Hepatotoxicity -> Sufficient evidence, "Probable" Immunotoxicity -> Limited or inadequate evidence Nephrotoxicity -> Sufficient evidence, "Probable" Carcinogenicity -> Limited animal evidence, "Possible" Reproductive Toxicity-> Limited or inadequate evidence Developmental Toxicity -> Sufficient evidence, "Probable"
Gray 2000: Gray EL, et al. Perinatal Exposure to the Phthalates DEHP, BBP, and DINP, but Not DEP, DMP, or DOTP, Alters Sexual Differentiation of the Male Rat. *Toxicological Sciences* **58**, 350-365 (2000).	750 mg/kg oral GD14 to PND 3 Sprague-Dawley Rats	Maternal toxicity or reduced litter size were not seen. Reduced pregnancy weight gain to GD21. Males displayed female-like areolas/nipples as infants. 7.7% of males with reproductive malformations. DINP about an order of magnitude less active than DEHP.
Hannas 2011: Hannas BR, et al. Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. *Toxicol Sci.* 2011 Sep; **123(1):**206-16.	Multiple rat types and dosing. Secondary mixture finding does not include DINP.	DINP 2.3-fold less potent than DEHP in reducing fetal testicular testosterone production. DINP less potent than DEHP at reducing StAR and Cyp11a gene expression levels. Administration of dilutions of a mixture of nine phthalates (DEHP, DIHP, DIBP, dibutyl-, benzyl butyl-, dicyclohexyl-, diheptyl-, dihexyl-, and dipentyl phthalate) reduced fetal testosterone production in a

DINP		
		dose dependent manner best predicted by dose addition.
Kaufmann 2002: Kaufmann W, et al. Tumor induction in mouse liver: di-isononyl phthalate acts via peroxisome proliferation. *Regul Toxicol Pharmacol.* 2002 Oct; **36(2):**175-83.	Mice (500, 1,500, 4,000, and 8,000 ppm, or approximately 100, 300, 800, and 1,600 mg/kg/day).	Liver weights, peroxisomal volume, and peroxisomal enzyme activity significantly elevated in both male and female mice at the tumorigenic levels. Cell proliferation elevated in male and female mice at 4,000 ppm and above. Apoptosis was elevated at the 4,000 and 8,000 ppm levels, paralleling the increases in liver weight. International Agency for Research on Cancer (IARC) criteria satisfied that peroxisomal proliferation was the mode of action for DINP-induced liver tumor induction in mice.
Kavlock 2002a: Kavlock R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di-isononyl phthalate. *Reprod Toxicol.* 2002 Sep-Oct; **16(5):**679-708. Review.	An overview of toxicity, toxicokinetics, consumer use, and exposure potential for DINP.	The Expert Panel believes that adult exposure to DINP will not exceed levels of 3–30 μg/kg bw/day, the estimates derived for DEHP.
Lee 2006: Lee HC, et al. Effects of perinatal exposure to phthalate/adipate esters on hypothalamic gene expression and sexual behavior in rats. *J Reprod Dev.* 2006 Jun; **52(3):**343-52.	Wistar Rats 40, 400, 4,000, 20,000 ppm from GD15 to PND21	Increase in hypothalamic grn and p130 in males and females on PND7 Decreased copulatory behavior in male rats. Lordosis quotient decreased in female rats. LH, FSH, estrous cycles not affected.
Lee and Koo 2007: Lee BM, Koo HJ. Hershberger assay for antiandrogenic effects of phthalates. *J Toxicol Environ Health A.* 2007 Aug; **70(15-16):**1365-70.	Castrated male Sprague-Dawley rats. Testosterone (0.4 mg/kg/d, sc), 20, 100, or 500 mg/kg body weight (bw)/d of 6 phthalates (DEHP, DBP, BBP, DINP, DIDP, or DnHP) or 10, 50, or 250 mg/kg bw/d of MEHP, orally in combination with	Seminal vesicles weights were significantly decreased by DEHP at > 100 mg/kg bw/d, DINP at > 20 mg/kg bw/d, DIDP at 500 mg/kg bw/d, or MEHP at 50 or 250 mg/kg bw/d, respectively. In addition, LABC weights were decreased by DEHP at 500 mg/kg bw/d, DINP at 500 mg/kg bw/d, and MEHP at 50 or 100 mg/kg bw/d.

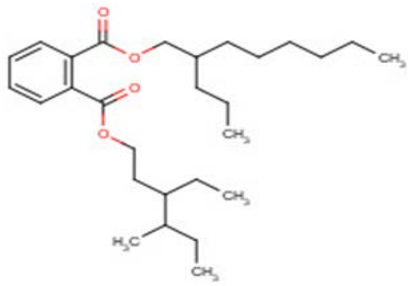
DINP		
	testosterone (0.4 mg/kg/d, sc) for 10 consecutive days.	
Masutomi 2003: Naoya Masutomi, et al. Impact of dietary exposure to methoxychlor, genistein, or diisononyl phthalate during the perinatal period on the development of the rat endocrine/reproductive systems in later life. *Toxicology* **192** (2003) 149-170.	Maternal Sprague–Dawley rats were fed three representative chemicals, methoxychlor (MXC; 24, 240, and 1,200 ppm), genistein (GEN; 20, 200, and 1,000 ppm), or diisononyl phthalate (DINP; 400, 4,000, and 20,000 ppm), from gestational day 15 to postnatal day 10.	All chemicals caused signs of maternal toxicity at high doses. Treatment with DINP at 20,000 ppm resulted in degeneration of meiotic spermatocytes and Sertoli cells in the testis and decrease of corpora lutea in the ovary at week 11, although changes remained minimal or slight. The SDN-POA (sexually dimorphic nucleus of preoptic area) volume remained unchanged with all three chemicals. The results demonstrated that perinatal dietary exposure to EDCs for a limited period causes endocrine disruption in offspring only at high doses.
McKee 2000: McKee RH, et al. Di(isononyl) phthalate (DINP) and di(isodecyl) phthalate (DIDP) are not mutagenic. *J Appl Toxicol.* 2000 Nov-Dec; **20(6):**491-7.	DINP was tested in *Salmonella*, *in vitro* cytogenetics and mouse micronucleus assays	Negative results
Mlynarcíková 2007: Mlynarcíková A, et al. The effects of selected phenol and phthalate derivatives on steroid hormone production by cultured porcine granulosa cells. *Altern Lab Anim.* 2007 Mar; **35(1):**71-7.	DINP tested on steroid hormone production by porcine ovarian granulosa cells after a 72-hour incubation. Note that DINP was tested, not the metabolites.	No changes were exhibited in basal progesterone production after treatment. An inhibitory action on oestradiol production by porcine granulosa cells was observed after the treatment.
NTP-CERHR 2003c: National Toxicology Program. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-isononyl Phthalate (DINP). NTP CERHR MON. 2003 Mar; **(2)**:i-III90.		See NTP-CERHR Brief Summary
Saravanabhavan and Murray 2012: Saravanabhavan G and Murray J. Human Biological Monitoring of Diisononyl	Summary of available metabolite and excretion kinetics data on DINP along with	Secondary metabolites of DINP and DIDP in urine were detected in almost all tested samples, while the primary metabolites were detected in only about 10% of the

DINP		
Phthalate and Diisodecyl Phthalate: A Review. *Journal of Environmental and Public Health*, **Volume 2012**, Article ID 810501, 11 pages.	human biomonitoring data.	samples. NHANES data indicate that the median concentrations of MCIOP and MCINP (secondary metabolites of DINP and DIDP, resp.) at a population level are about 5.1 μg/L and 2.7 μg/L, respectively. The available biological monitoring data suggest that infants/children are exposed to higher levels of phthalates than adults.
Takagi 2005: Takagi H, et al. Impact of maternal dietary exposure to endocrine-acting chemicals on progesterone receptor expression in microdissected hypothalamic medial preoptic areas of rat offspring. *Toxicol Appl Pharmacol.* 2005 Oct 15;**208(2):**127-36.	DINP at 4,000 and 20,000 ppm	DINP at 20,000 ppm down-regulated PR in females.
Waterman 2000: Waterman S, et al. Two-generation reproduction study in rats given di-isononyl phthalate in the diet. *Reproductive Toxicology* **14** (2000) 21-36.	CRL:CD(Sprague-Dawley)BR rats 0.0, 0.5, 1, or 1.5% (one-generation study) 0.0, 0.2, 0.4, or 0.8% (two-generation study).	No changes in classic reproductive parameters, i.e. mating, male or female fertility, fecundity, gestational index, or length of gestation in either study. NOAELs for these effects were the highest Dietary Level (%)'s tested, 500 mg/kg/day in the two-generation study and 1,000 mg/kg/day in the one-generation study. No testicular effects in parental animals exposed as juveniles and young adults at 960 mg/kg/day in the one-generation study. In the two-generation study, no testicular effects in either the P1 males, exposed as juveniles and young adults or the P2 (F1) offspring exposed in utero, through lactation, and continuously to terminal sacrifice. The NOAEL was 470 mg/kg/day. Offspring survival was reduced at the 1.5% level (~1,100 mg/kg/day) but unaffected at the 1% level (~760 mg/kg/day). Decreased offspring body weights both at postnatal day (PND) 0 and during lactation; however, the PND 0 effects were only clearly related to treatment at the 1.5% level.

DINP		
		Weights of offspring during lactation were significantly reduced but within the historical control range at Dietary Level (%)'s below 1%. Adult survival was unaffected at any level in either study, but weight gain was significantly reduced at the 1% level (~600 mg/kg/day). Liver and kidney weights were elevated at Dietary Level (%)'s above ~110 mg/kg/day, consistent with evidence from other studies of peroxisomal proliferation at these levels.
Wenzel 2005: Wenzel A, et al. Modulation of iodide uptake by dialkyl phthalate plasticisers in FRTL-5 rat thyroid follicular cells. *Mol Cell Endocrinol.* 2005 Dec 1; **244(1-2):**63-71.	Studied effects on basal iodide uptake and responsible mode of action in rats. Test used DINP, not metabolites.	DINP and DIDP enhanced iodide uptake in a rat thyroid cell line (FRTL-5) at concentrations of 0.1 - 1 mM but not at lower concentrations.

Din911P – 1,2-Benzenedicarboxylic acid, 1-nonyl 2-undecyl ester, branched and linear [c9-c11]

CAS #111381-91-0



Three specific articles were reviewed regarding reproductive and developmental toxicity endpoints for Din911P. Din911P is a C9-C11 branched and linear phthalate ester [CPSC 2010b].

Fulcher 2001 notes increased incidence of supernumerary lumbar ribs. Increased liver weights in young rats, histological changes, and decreased liver weights in mature rats were observed in Willoughby 2000.

The oral LD_{50} for mice/rats is greater than 20,000 mg/kg [CPSC 2010b; Brown et al. 1970]. In the systemic studies, some liver effects were noted, but considered not of toxicological significance [CPSC 2010b; Brown et al. 1970]. There was some minor skin irritation [CPSC 2010b: Brown et al. 1970].

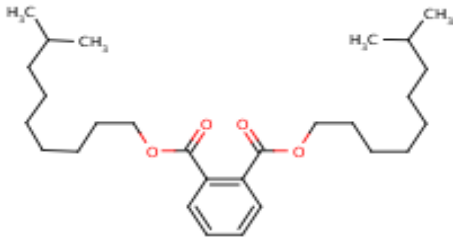
Din911P		
Author and Title	**Dose/Species/Strain**	**Findings**
CPSC 2010b: Consumer Product Safety Commission Staff Toxicity Review of 17 Phthalates for Consideration by the Chronic Hazard Advisory Panel – 2010. Section on 1,2-Benzenedicarboxylic acid, nonyl undecyl ester, branched and linear. 2010. Page 64.	Overview of published information on toxicity and exposure potential for Din911P.	Acute Toxicity -> greater than 20g/kg Irritation and Sensitization -> Not induced Systemic Toxicity -> Limited data
Fulcher 2001: Fulcher SM, et al. Developmental Toxicity of di-(C_7-C_9 alkyl) phthalate and di-(C_9-C_{11} alkyl) phthalate in the rat. *Reproductive Toxicology*, **15** (2001) 95-102.	Sprague-Dawley rats were administered 250, 500, or 1,000 mg/kg D79P or D911P daily by oral gavage (5 ml/kg) between gestation days (GD) 1 and 19.	No signs of maternal toxicity, as assessed by adjusted maternal bodyweight gain throughout gestation and clinical examinations, and no effects upon litter size, fetal survival or bodyweight. Pups of the high dose D79P and

Din911P		
		intermediate and high dose D911P groups showed increased incidences of supernumerary lumbar ribs. There was a significant increase in dilated renal pelves in pups of the low dose D79P and high dose D911P groups, but only for D911P was there a significant trend. The no observed adverse effect level (NOAEL) for maternal toxicity for both D79P and D911P is 1,000 mg/kg/day. The NOAEL values for developmental toxicity are 500 mg/kg/day D79P and 250 mg/kg/day D911P.
Willoughby 2000: Willoughby CR, et al. Two-generation reproduction toxicity studies of di-(C_7-C_9 alkyl) phthalate and di-(C_9-C_{11} alkyl) phthalate in the rat. *Reproductive Toxicology,* **14** (2000) 427-450.	Di-(C_7-C_9 alkyl) phthalate (D79P) and di-(C_9-C_{11} alkyl) phthalate (D911P), based on high-normality linear oxo-alcohols, have been assessed for their impact upon reproductive performance in Sprague–Dawley rats. Rats were continuously exposed to either D79P or D911P at dietary levels of 0%, 0.1%, 0.5%, or 1.0% over two generations. Selected F_0 offspring (F_1 generation) were exposed to the same dietary concentration of D79P or D911P as the respective F_0 animals, and were mated to produce F_1 offspring.	Both D79P and D911P markedly reduced body weight gain in F_0 and F_1 adult males at the highest dose, but females were affected to a lesser extent. There was no impairment of fertility, fecundity, or development in either generation, but body weights of offspring in the 1.0% D79P and 1.0% D911P groups were slightly and transiently reduced over the weaning period. Although decreases in the weight of several organs were accounted for by depressed body weight, ovary weights were reduced in both generations exposed to 1.0% D79P, and epididymidal weights were slightly reduced in adults of both generations exposed to 1.0% D911P. However, ovarian function—assessed by the oestrus cycle and mating behaviour—and epididymidal sperm concentration, motility, and morphology were unaffected

Din911P		
		by either substance. Treatment resulted in liver changes, particularly in males, characterised by increased liver weight in young animals, histopathologic changes and reduced organ weight in mature animals, and an increase in palmitoyl CoA oxidase activity. In conclusion, neither D79P nor D911P impaired reproductive function in rats when administered in the diet at levels that induce systemic toxicity, and the NOAEL for effects on reproduction in the rat is 0.5% for both D79P and D911P.

DIDP - Diisodecyl phthalate [c7-c11]

CAS #26761-40-0; 68515-49-1



Eleven specific articles were reviewed regarding reproductive, developmental, and carcinogenic toxicity endpoints for DIDP. In addition to these articles, relevant excerpts from a recent report by the European Chemicals Agency (ECHA 2013), "Evaluation of new scientific evidence concerning DINP and DIDP" were discussed by the small group at the SAB meeting. DIDP is a C10 phthalate ester. DIDP breaks down to carboxylic acid by oxidation, it does not metabolize to shorter side chain monoesters (Saravanabhavan 2012).

Some reproductive effects were observed. There was no significant change in sperm count, but there was an effect observed on sperm motility (Kwack et al. 2009). Anti-androgenic effects were observed (Lee and Koo 2007). Overall, DIDP was less potent than DEHP in producing reproductive effects. Developmental toxicant evidence: decreased pup survival, increase in skeletal variations [CPSC 2010f, NTP-CERHR 2003b]. There was no evidence of skin sensitization. DIDP seems to enhance iodide uptake in thyroid; the demonstrated stimulation is not very strong, but the accumulation of phthalates may contribute to thyroid hyperfunction [Wenzel 2005] (see also Low Dose section for Breous 2005, study from same research group, where DIDP increased the activity of the human NIS promoter construct 2.5-fold).
Studies show that, assuming the hypothesis of peroxisome proliferation as the sole mechanism of action is correct, it is unlikely to be carcinogenic to humans (however, ECHA 2013 and OEHHA 2013 cite concerns regarding multiple pathways). Liver and kidney effects (increased liver and kidney weights) were observed (Cho 2011). A small mammalian study of beagles (Hazelton 1968) shows a dose related increase in liver weights [NTP-CERHR 2003b].

DIDP		
Author and Title	**Dose/Species/Strain**	**Findings**
Cho 2011: Cho WS, et al. 26-Week carcinogenicity study of di-isodecyl phthalate by dietary	DIDP administered to 15 rasH2 mice/gender/group at dietary levels of 0, 0.1, 0.33, or 1% and	Non-neoplastic changes observed in the liver (parenchymal inflammation,

DIDP		
administration to CB6F1-rasH2 transgenic mice. *Arch Toxicol.* 2011 Jan;**85(1):**59-66.	15 wild-type mice/gender/group at dietary levels of 0 and 1% for 26 weeks.	fatty changes, diffuse hepatocyte hypertrophy with eosinophilic granules and focal necrosis) and kidneys (tubular basophilia and tubular hyperplasia) in rasH2 and wild-type mice. Neoplastic lesions had a higher number of hepatocellular adenomas in the male rasH2 mice receiving 1% DIDP, compared with the findings in the liver of control rasH2 mice or wild-type mice. Incidence of hepatocellular adenomas in the 0.1, 0.33, and 1% DIDP exposed rasH2 mice was 7% (1/15), 7% (1/15), and 33% (5/15), respectively.
Cho 2008: Cho WS, et al. Peroxisome proliferator di-isodecyl phthalate has no carcinogenic potential in Fischer 344 rats. *Toxicol Lett.* 2008 May 5;**178(2):**110-6. Erratum in: *Toxicol Lett.* 2010 Aug 16;**197(2):**156.	DIDP was fed to Fischer 344 rats in the diet at doses of 0, 400, 2,000 and 8,000 ppm for 2 years.	Significant decreases in overall survival and body weights, and increases in the relative weights of kidneys and liver were noted in both sexes of the highest dose groups. No treatment-related neoplastic lesions were observed in the internal organs. DIDP failed to maintain the catalase-inducing potential between early and late expressions of catalase protein from western blotting, immunohistochemistry and enzyme activity measurements. These results suggest that the non-carcinogenicity of DIDP in F344 rats was due to its limited potential for peroxisomal proliferating activity.
CPSC 2010f: Consumer Product Safety Commission Staff Toxicity Review of Di(isodecyl) phthalate (DIDP). April 7, 2010.	Overview of published information on toxicity and exposure potential for DIDP.	Carcinogenicity -> Not considered to be carcinogenic (based on assumption of liver peroxisome proliferation as MOA, and not relevant to humans)

DIDP		
		Reproductive/Developmental Toxicity -> "Probable" Probable toxicant in humans by oral route based on sufficient evidence of systemic (liver, kidney), reproductive and developmental effects in animals.
Hushka 2001: Hushka LJ, et al. Two-generation reproduction studies in Rats fed di-isodecyl phthalate. *Reprod Toxicol.* 2001 Mar-Apr;**15(2):**153-69.	Two generation reproductive toxicity study of Sprague-Dawley rats. Dietary levels ranged from 0.02 to 0.8% (or approximately 15 to 600 mg/kg/day).	No effects on fertility were observed. Decreases in adult body weight along with corresponding increases in liver and kidney weights and histopathologic changes indicative of peroxisomal proliferation were observed. No effects on live birth index were observed, but reduced offspring survival was observed at postnatal days 1 to 4. This reduced survival was more pronounced in the F2 generation in which statistical significance was achieved at levels of 0.2% DIDP and greater. Transient decreases in offspring body weights prior to weaning were observed, corresponding to rapid offspring growth, and high levels of food consumption. There were no notable alterations in developmental landmarks. Increase in age at vaginal opening of F1 generation females; relative testes, epidydimis and seminal vesicle weight increase vs. controls in F1 males without histological changes. Decrease in normal sperm in all treated groups. Overall, these studies provided experimentally defined No-Observed-Adverse-Effect Levels

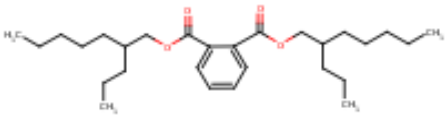
DIDP		
		(NOAELs) of 0.06% (approximately 50 mg/kg/day) for F2 offspring survival and 0.8% (approximately 600 mg/kg/day) for fertility, other measures of reproductive function, and developmental landmarks.
Kavlock 2002b: Kavlock R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di-isodecyl phthalate. *Reprod Toxicol.* 2002 Sep-Oct;**16(5):**655-78. Review.	An overview of toxicity, toxicokinetics, consumer use, and exposure potential for DIDP.	The expert panel believes that adult exposure to DIDP will not exceed levels of 3–30 µg/kg bw per day, the estimates derived for DEHP.
Kwack 2009: Kwack SJ, et al. Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. *J Toxicol Environ Health A*. 2009;**72(21-22):**1446-54.	Male Sprague-Dawley rats 500 mg/kg BW/day 4 weeks	Liver weights significantly increased Reduced sperm motility
Lee and Koo 2007: Lee BM, Koo HJ. Hershberger assay for antiandrogenic effects of phthalates. *J Toxicol Environ Health A.* 2007 Aug;**70(15-16):**1365-70.	Castrated male Sprague-Dawley rats. Testosterone (0.4 mg/kg/d, sc), 20, 100, or 500 mg/kg body weight (bw)/d of 6 phthalates (DEHP, DBP, BBP, DINP, DIDP, or DnHP) or 10, 50, or 250 mg/kg bw/d of MEHP, orally in combination with testosterone (0.4 mg/kg/d, sc) for 10 consecutive days.	Seminal vesicles weights were significantly decreased by DEHP at > 100 mg/kg bw/d, DINP at > 20 mg/kg bw/d, DIDP at 500 mg/kg bw/d, or MEHP at 50 or 250 mg/kg bw/d, respectively. Ventral prostate weights were significantly decreased in animals treated with DEHP or DBP at doses of 20 mg/kg bw/d or above, 500 mg/kg bw/d DIDP, and 250 mg/kg bw/d MEHP. These data suggest that some phthalates possess antiandrogenic activity, and that multiple cross-talk between androgen, estrogen, and steroid hormone receptors

DIDP		
		occurs.
McKee 2000: McKee RH, et al. Di(isononyl) phthalate (DINP) and di(isodecyl) phthalate (DIDP) are not mutagenic. *J Appl Toxicol.* 2000 Nov-Dec; **20(6):**491-7.	DIDP was tested in a mouse micronucleus assay	Negative results for mutagenicity
NTP-CERHR 2003b: National Toxicology Program. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-Isodecyl Phthalate (DIDP). NTP CERHR MON. 2003 Apr;**(3)**:i-III90.		See NTP-CERHR Brief Summary
Saravanabhavan and Murray 2012: Saravanabhavan G and Murray J. Human Biological Monitoring of Diisononyl Phthalate and Diisodecyl Phthalate: A Review. *Journal of Environmental and Public Health*, **Volume 2012**, Article ID 810501, 11 pages.	Summary of available metabolite and excretion kinetics data on DIDP along with human biomonitoring data.	Secondary metabolites of DINP and DIDP in urine were detected in almost all tested samples, while the primary metabolites were detected in only about 10% of the samples. NHANES data indicate that the median concentrations of MCIOP and MCINP (secondary metabolites of DINP and DIDP, resp.) at a population level are about 5.1 μg/L and 2.7 μg/L, respectively. The available biological monitoring data suggest that infants/children are exposed to higher levels of phthalates than adults.
Wenzel 2005: Wenzel A, et al. Modulation of iodide uptake by dialkyl phthalate plasticisers in FRTL-5 rat thyroid follicular cells. *Mol Cell Endocrinol.* 2005 Dec 1; **244(1-2):**63-71.	Effects of six different dialkyl phthalates were studied in vitro in the rat thyroid cell line FRTL-5 on their ability to modulate basal iodide uptake mediated by the sodium/iodide symporter (NIS).	The present study shows that diisodecyl phthalate (DIDP), dioctyl phthalate (DOP), diisononyl phthalate (DINP) and bis (2-ethylhexyl) phthalate (DEHP) significantly enhance iodide uptake when concentrations in the magnitude between 10^{-4}M and 10^{-3}M were applied. Specific inhibition of NIS demonstrated that enhancement of iodide uptake

DIDP		
		is due to NIS. DIDP seems to enhance iodide uptake in thyroid as a consequence of sodium/iodide symporter transcriptional activation. The demonstrated stimulation is not very strong, but the accumulation of phthalates may contribute to thyroid hyperfunction.

DPHP – Di-2-propyl heptyl phthalate [c10]

CAS #53306-54-0



Three specific articles and reports were reviewed regarding metabolites for DPHP. The only study reviewed at the group's first review focused on metabolites of several phthalates (Wittassek and Angerer 2007). The secondary oxidized metabolites are the main metabolites and have longer half-lives than simple monoesters; therefore they may reside longer in the body (also true for DIDP, DINP).

The group then added summaries from newer studies.

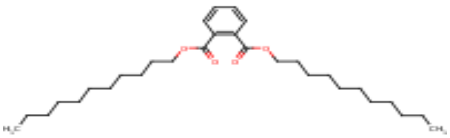
DPHP		
Author and Title	**Dose/Species/Strain**	**Findings**
Wittassek and Angerer 2007: Wittassek M, Angerer J. Phthalates: metabolism and exposure. *Int J Androl.* 2008 Apr;**31(2):**131-8. Epub 2007 Dec 7. Review.	Human metabolism study. Oral application of di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP) and di(2-propylheptyl) phthalate (DPHP).	74, 44 and 34%, respectively, are excreted via urine. Oxidized products, not the simple monoesters, were found to be the main metabolites. Based on urinary phthalate metabolite concentrations the authors estimated in 102 German subjects between 6 and 80 years of age median daily intakes (µg / kg / day) of 2.7 for DEHP, 2.1 for di-n-butyl phthalate, 1.5 for diisobutyl phthalate, 0.6 for DiNP, and 0.3 for butylbenzyl phthalate. In general, children have higher exposures compared to adults and seem to have a more effective oxidative metabolism of phthalates. The secondary oxidized

DPHP		
		metabolites are the main metabolites and have longer half-lives than simple monoesters; therefore they may reside longer in body (also true for DIDP, DINP).
CPSC 2010h: CPSC Toxicity Review of DPHP, 2010: Consumer Product Safety Commission Staff Toxicity Review of DPHP. For chronic toxicity, relied on 2 unpublished Union Carbide Corporation (UCC) TSCA submissions (1997, 1998), and a 2003 BASF study; and **CPSC 2014**: Report to the US CPSC by the Chronic Hazard Advisory Panel (CHAP) on Phthalates and Phthalate Alternatives, July 2014.	UCC 1997 high dose: male rats fed 1,000 mg/kg/day for 90 days. BASF 2003 Wistar rats presumed pregnant females dosed 0, 40, 200, and 1,000 mg/kg/day on gestation days (GD) 6-19. Not a multi-generational study. CPSC report describes studies as having poorly described methodologies.	UCC 1997 showed significant reduction in sperm velocity indices, reversible after 4 wk recovery. No other significant effect on sperm. BASF 2003: significant maternal toxicity at high dose (insuffic. care of fur; GD 6-10 reduced food consumption and reduced body wt gain; GD 6-8 loss of body wt; accum. of fluid in uterus, increased postimplantation loss, 2.2% dams with only resorptions in uterus. No teratogenicity observed; high dose fetuses had increased soft tissue variations. Note: UCC also found increased liver wt at all doses ≥ 40 mg/kg/day and dose-related adrenal effects (vacuolization of the zona glomerulosa) in both sexes and at all doses ≥40. Findings: insufficient amount of animal data and poorly described methodologies can only conclude "insufficient evidence." CPSC July 2014 CHAP summary report also notes that "currently, DPHP metabolites cannot be distinguished from the metabolites of DIDP."
GC3 2012: ToxServices LLC, **Draft** GreenScreen Assessment for DPHP	Note: Greenscreen™ assessment not yet validated	GreenScreen Benchmark Score of U (unspecified) based on

DPHP		
(Oct 2011).	Referenced studies: BASF 2009 - male and female Wistar rats 0, 40, 200 and 600 mg/kg over 2 gen (F0, F1). BASF 2003 (see CPSC 2010, although note that additional information may have been available for this evaluation via 2010 REACH robust summary for DPHP). BASF unpublished 90 day study reviewed by authors under NDA (see GreenScreen appendix C).	data gaps for carcinogenicity, neurotoxicity, respiratory sensitization. BASF 2009: no effects on fertility or repro performance (Repro. score Low) BASF 2003: developmental effects only in high dose group (Devel. score Low) Endocrine Activity score: Moderate based on unpublished BASF study: increased basophilic cells in anterior pituitary, inc. hypertrophy of follicular epithelium in thyroid, hepatocellular hypertrophy and induction of enzymes associated with peroxisome proliferation (PP). Noted that thyroid effects unlikely due to PP. All other endpoints rated low if data available.

DUP – Diundecyl phthalate [c11]

CAS #3648-20-2



Three specific articles were reviewed regarding reproductive and developmental toxicity endpoints for DUP. DUP (also known as DUDP) is C11 phthalate ester (CPSC 2010c).

Kwack 2009 reported significant effects on sperm counts and motility. Saillenfait 2013 noted small decreases in anogenital distances in male fetuses and also noted supernumerary lumbar ribs significantly higher than controls (this effect is considered reversible).

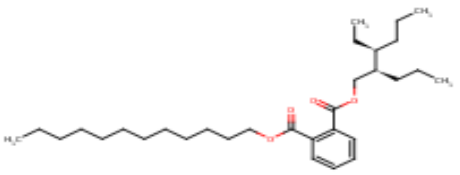
There is sufficient animal evidence of hepatotoxicity as noted in the CPSC report [CPSC 2010c; Kwack et al. 2009].

DUP		
Author and Title	**Dose/Species/Strain**	**Findings**
CPSC 2010c: Consumer Product Safety Commission Staff Toxicity Review of Diundecyl phthalate (DUP). October 25, 2010.	Overview of published information on toxicity and exposure potential for DUP.	Hepatotoxicity -> Sufficient animal evidence Reproductive/Developmental Toxicity -> Limited animal evidence
Kwack 2009: Kwack SJ, et al. Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. *J Toxicol Environ Health A.* 2009;**72(21-22):**1446-54.	Male Sprague-Dawley rats 500 mg/kg bw/day for 4 weeks	Significantly decreased sperm numbers and sperm motility
Saillenfait 2013: Saillenfait AM, et al. Prenatal developmental toxicity studies on diundecyl and ditridecyl phthalates in Sprague-Dawley rats. *Reprod Toxicol.* 2013 Jun;**37**:49-55.	Sprague-Dawley rats were administered 0, 0.25, 0.50, or 1 g/kg/day of DUDP or DTDP, by gavage, on gestation days 6–20.	No adverse effects on maternal body weight and food consumption. The number of live fetuses, percent of post-implantation loss and of resorptions, fetal sex, and fetal body weights were not affected. There was no evidence of teratogenicity.

DUP		
		Small decreases in the anogenital distance of male fetuses were noted at 0.5 and 1 g DUDP/kg/day though only significant at 0.5 after controlling for body weight. Observed decreases in DUDP group were greater than control values for animals randomly assigned to concurrent study of DTDP. The incidence of fetuses with supernumerary lumbar ribs was significantly higher than control at 0.5 and 1 g DUDP/kg/day.

DIUP – Diundecyl phthalate, branched and linear [c11]

CAS #85507-79-5



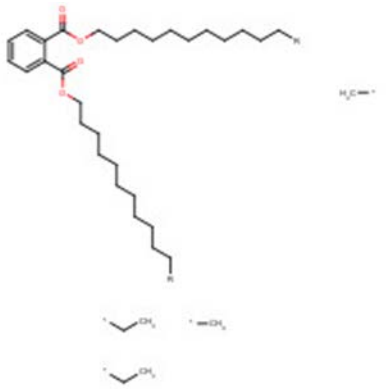
One specific article was reviewed regarding genotoxicity endpoints for DIUP. DIUP is a C11 branched and linear phthalate ester [CPSC 2010d]. There are no reproductive or developmental studies noted in the CPSC review [CPSC 2010d]. The CPSC review does note repeated dose toxicity evidence of peroxisomal proliferation [CPSC 2010d: ECB 2000].

The REACH dossier used read across to DIDP. For reproductive studies, 1 clearly used DIDP [Hushka et al. 2001], while 2 others did not specifically indicate read across to DIDP [Lington et al. 1993; Lake et al. 1991]. For developmental studies, 2 clearly used DIDP as the read across surrogate chemical [Nikiforov et al. 1995; Waterman et al. 1999]. Two other studies were not clear as to the specific surrogate chemical used for read across [Hellwig 1997; Hardin et al. 1987].

DIUP		
Author and Title	**Dose/Species/Strain**	**Findings**
CPSC 2010d: Consumer Product Safety Commission Staff Toxicity Review of 17 Phthalates for Consideration by the Chronic Hazard Advisory Panel – 2010. Section on 1,2-Benzenedicarboxylic acid, diundecyl ester, branched and linear. 2010. Pages 90-92.	Overview of published information on toxicity and exposure potential for DIUP.	Genotoxicity -> Negative

DTDP - Ditridecyl phthalate [c13-rich]

CAS#



Four specific articles were reviewed regarding reproductive and developmental toxicity and skin sensitization endpoints for DTDP. DTDP is a C13 rich phthalate ester comprising C11-C14 [CPSC 2010e]. Reproductive effects in a Japanese study were shown at higher doses [CPSC 2010e: CIPC 2010b,c]. Positive endocrine disruption effect is noted as likely due to BPA contamination [CPSC 2010e: Harris et al. 1997]. CPSC states the developmental evidence is not sufficient [CPSC 2010e: CIPC 2010b,c]. CPSC didn't calculate ADI [Acceptable daily intake is defined as the amount of a chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers] and included limited studies [CPSC 2010e].

DTDP has low acute toxicity [CPSC 2010e: NICNAS 2008]. The Japan Existing Chemical Data Base showed small thymus effects in all dose groups although not statistically significant or dose related.

DTDP		
Author and Title	**Dose/Species/Strain**	**Findings**
CPSC 2010e: Consumer Product Safety Commission Staff Toxicity Review of Ditridecyl phthalate (DTDP). October 25, 2010.	Overview of published information on toxicity and exposure potential for DTDP.	Hepatotoxicity and renal toxicity -> Limited animal evidence. Sufficient animal data in one study supported conclusion that DTDP had subchronic toxicity in a variety of organ systems (incl. liver and kidney). Low acute dermal and oral toxicity. No info on inhalation. Reproductive/Developmental Toxicity -> Inadequate evidence
Harris 1997: Harris CA, et al. The estrogenic activity of phthalate esters in vitro. *Environ Health Perspect*. 1997 Aug;**105(8):**802-11.	Phthalate esters were screened for estrogenic activity using a recombinant yeast screen	Inconsistent results for DTDP: one sample was weakly estrogenic, another from different source was inactive. Positive sample could have been from BPA contamination (0.5% ortho isomer of BPA).

DTDP		
Medeiros 1999: Medeiros AM, et al. Evaluation of skin sensitization response of dialkyl (C6-C13) phthalate esters. *Contact Dermatitis.* 1999 Nov;**41(5):**287-9.	7 PEs were tested in a 104-person panel human repeated insult patch test (HRIPT) using the modified Draize procedure.	Under the conditions of this HRIPT, no evidence of dermal irritation or sensitization.
Saillenfait 2013: Saillenfait AM, et al. Prenatal developmental toxicity studies on diundecyl and ditridecyl phthalates in Sprague-Dawley rats. *Reprod Toxicol.* 2013 Jun;**37**:49-55.	Sprague-Dawley rats were administered 0, 0.25, 0.50, or 1 g/kg/day of DUDP or DTDP, by gavage, on gestation days 6–20.	No adverse effects on maternal body weight and food consumption. The number of live fetuses, percent of post-implantation loss and of resorptions, fetal sex, and fetal body weights were not affected. There was no evidence of teratogenicity. DTDP was not developmentally toxic up to 1g/kg/day.

Appendix B: Cumulative Effects, Low Dose Effects, Overview, Meta and Para Studies

B1: Cumulative Effects Studies

Cumulative Effects		
Author and Title	**Dose/Species/Strain**	**Findings**
Howdeshell 2008a: Howdeshell KL, et al. Mechanisms of action of phthalate esters, individually and in combination, to induce abnormal reproductive development in male laboratory rats. *Environmental Research* **108** (2008) 168-176.	Multiple studies with multiple doses/species/strains including: DBP, BBP, DEHP, DINP, DIBP, DPP, DEP	Mixtures of phthalate esters with one another and with other anti-androgenic compounds exhibit cumulative, largely dose additive effects on male reproductive tract development when administered during sexual differentiation in utero. Since phthalate ester metabolites are detected in maternal and fetal body fluids, and androgen-signaling and insl3 are highly conserved among mammals, phthalates may potentially affect human reproductive development.
Howdeshell 2008b: Howdeshell KL, et al. A Mixture of Five Phthalate Esters Inhibits Fetal Testicular Testosterone Production in the Sprague-Dawley Rat in a Cumulative, Dose-Additive Manner. *Toxicological Sciences* **105(1),** 153-165 (2008).	The dose-response effects of six individual phthalates (BBP, DBP, DEHP, diethyl phthalate [DEP], diisobutyl phthalate [DiBP], and dipentyl phthalate [DPP]) were characterized on gestation day (GD) 18 testicular testosterone production following exposure of Sprague-Dawley rats on GD 8–18. In a second study, dams were dosed at 100, 80, 60, 40, 20, 10, 5, or 0% of the mixture. The top dose contained 1,300 mg of total phthalates/kg/day including BBP, DBP, DEHP, DiBP (300 mg/kg/day per chemical), and DPP (100 mg DPP/kg/day).	BBP, DBP, DEHP, and DiBP were equipotent (ED_{50} of 440 ± 16 mg/kg/day), DPP was about threefold more potent (ED_{50} 130 mg/kg/day) and DEP had no effect on fetal testosterone production. In the second study, testosterone production was reduced in a dose-additive manner. Several of the individual phthalates and the mixture also induced fetal mortality, due to pregnancy loss. These data demonstrate that individual phthalates with a similar mechanism of action can elicit cumulative, dose additive effects on fetal testosterone production and pregnancy when administered as a mixture. The ED_{50} value for the increase in fetal mortality observed with

		the phthalate mixture study was accurately predicted by the dose addition model (ED_{50}, observed = 735 mg/kg/day vs. ED_{50}, predicted = 720 mg/kg/day), whereas the predicted slope was steeper than that generated from the observed data.
Rider 2008: Rider CV, et al. A mixture of seven antiandrogens induces reproductive malformations in rats. *International Journal of Andrology*, **31**, 249-262, 2008.	Pregnant rats were exposed to four dilutions of a mixture containing vinclozolin, procymidone, linuron, prochloraz, benzyl butylphthalate, dibutyl phthalate and diethylhexyl phthalate during the period of sexual differentiation and male offspring were assessed for effects on hormone sensitive endpoints including: anogenital distance, infant areolae retention and reproductive tract tissue weights and malformations. The ratio of the chemicals in the mixture was based upon each chemical's ED_{50} for inducing reproductive tract malformations (hypospadias or epididymal agenesis). The observed responses from the mixture were compared with predicted responses generated with a toxic equivalency approach and models of dose addition, response addition or integrated addition.	The mixture of chemicals that alter the androgen signaling pathway via diverse mechanisms disrupted male rat reproductive tract differentiation and induced malformations in a cumulative, dose-additive manner. The toxic equivalency and dose addition models provided the best fit to observed responses even though the chemicals do not act via a common cellular mechanism of action.
Rider 2009: Rider CV, et al. Cumulative Effects of In Utero Administration of Mixtures of ''Antiandrogens'' on Male Rat Reproductive Development. *Toxicologic Pathology*, **37**: 100-113, 2009.	Rats were dosed during pregnancy with antiandrogens singly or in pairs at dosage levels equivalent to about one half of the ED_{50} for hypospadias or epididymal agenesis. The pairs include: AR antagonists (vinclozolin plus procymidone), phthalate esters (DBP plus BBP and DEHP plus	All binary combinations produced cumulative, dose additive effects on the androgen-dependent tissues. In the mixture study combining seven "antiandrogens" together, the complex mixture behaved in a dose-additive manner. The results indicate that compounds that act by disparate

	DBP), a phthalate ester plus an AR antagonist (DBP plus procymidone), and linuron plus BBP. A mixture study combining seven "antiandrogens" together was also conducted.	mechanisms of toxicity display cumulative, dose-additive effects when present in combination.
Rider 2010: Rider CV, et al. Cumulative Effects of In Utero Administration of Mixtures of Reproductive Toxicants that Disrupt Common Target Tissues via Diverse Mechanisms of Toxicity. *Int J Androl.* 2010 April; **33(2):** 443-462.	Previous mixture studies conducted with antiandrogenic chemicals are reviewed briefly and two new studies are described in detail. In all binary mixture studies, rats were dosed during pregnancy with chemicals, singly or in pairs at dosage levels equivalent to approximately one half of the ED_{50} for hypospadias or epididymal agenesis. The binary mixtures included: androgen receptor (AR) antagonists (vinclozolin plus procymidone), phthalate esters (DBP plus BBP and DEHP plus DBP), a phthalate ester plus an AR antagonist (DBP plus procymidone), a mixed mechanism androgen signaling disruptor (linuron) plus BBP, and two chemicals which disrupt epididymal differentiation through entirely different toxicity pathways: DBP (AR pathway) plus 2,3,7,8 TCDD (AhR pathway). Multi-component mixture studies were also conducted combining several "antiandrogens" together. In the first study, seven chemicals (four pesticides and three phthalates) that elicit antiandrogenic effects at two different sites in the androgen signaling pathway (i.e. AR antagonist or inhibition of androgen synthesis) were combined. In the second study, three additional phthalates	In both the binary mixture studies and the multi-component mixture studies, chemicals that targeted male reproductive tract development displayed cumulative effects that exceeded predictions based upon a response addition model and most often were in accordance with predictions based upon dose addition models. The results indicate that compounds that act by disparate mechanisms of toxicity to disrupt the dynamic interactions among the interconnected signaling pathways in differentiating tissues produce cumulative dose-additive effects, regardless of the mechanism or mode of action of the individual mixture component.

	were added to make a ten chemical mixture.	
NRC 2008: Phthalates and Cumulative Risk Assessment – The Tasks Ahead. Committee on the Health Risks of Phthalates, National Research Council, 2008.		In this report, the Committee on the Health Risks of Phthalates reviews risk-assessment practices and describes their strengths and weaknesses. The committee reviews the toxicity of and exposure to phthalates, considers the value of conducting a cumulative risk assessment of this chemical class, and provides recommendations for conducting the assessment. Data gaps and research needs are also identified, and the applicability of the committee's recommendations to other chemical classes is discussed.
Benson 2009: Benson R. Hazard to the developing male reproductive system from cumulative exposure to phthalate esters--dibutyl phthalate, diisobutyl phthalate, butylbenzyl phthalate, diethylhexyl phthalate, dipentyl phthalate, and diisononyl phthalate. *Regul Toxicol Pharmacol.* 2009 Mar;**53(2):** 90-101.	This paper derives a reference dose (RfD) for each of the phthalate esters (dibutyl phthalate, diisobutyl phthalate, butylbenzyl phthalate, diethylhexyl phthalate, dipentyl phthalate, and diisononyl phthalate) that cause male reproductive effects. As these phthalate esters cause similar adverse biological effects and have the same mechanism of action, it is appropriate in a risk assessment to consider the potential adverse effects from cumulative exposure to these chemicals using a dose addition model. This paper provides examples of a cumulative risk assessment using the hazard index and relative potency approaches from the RfDs derived from studies in laboratory animals and exposure information in people.	The results of the cumulative risk assessments for both a US and a German population show that the hazard index is below one. Thus it is unlikely that humans are suffering adverse developmental effects from current environmental exposure to these phthalate esters.
Kortenkamp and Faust 2010: Kortenkamp A, Faust M. Combined exposures to anti-	On the basis of exposure estimates for the individual chemicals and reference doses	Cumulative risks from anti-androgen exposures exceed acceptable levels for people on

androgenic chemicals: steps towards cumulative risk assessment. *International Journal of Andrology*, **33** (2010), 463-474.	for anti-androgenicity, the hazard index approach was used. Study included 15 substances, including 5 phthalates: BBP, DEHP, DnBP, DIBP, and DINP	the upper end of exposure levels. The value obtained for median exposures to the 15 substances can be judged tolerable. However, significant knowledge gaps exist that prevent the authors from arriving at definitive conclusions. Of greatest concern is an absence of appropriate in vivo toxicity data about large numbers of in vitro androgen receptor antagonists. Knowledge about the effect profiles of these chemicals will lead to higher risk estimates. The analysis suggests that risk reductions can be achieved by limiting exposures to the plasticizer diethyl hexyl phthalate, the cosmetic ingredients butyl- and propyl paraben, the pesticides vinclozolin, prochloraz and procymidone and bisphenol A.
Christiansen 2009: Christiansen S, et al. Synergistic Disruption of External Male Sex Organ Development by a Mixture of Four Antiandrogens. *Environmental Health Perspectives*, **117(12),** December 2009, 1839-1846.	Investigated the effects of mixtures of, di(2-ethylhexyl) phthalate (DEHP); two fungicides present in food, vinclozolin and prochloraz; and a pharmaceutical, finasteride, on landmarks of male sexual development in the rat, including changes in anogenital distance (AGD), retained nipples, sex organ weights, and malformations of genitalia. These chemicals were chosen because they disrupt androgen action with differing mecha-nisms of action.	The effect of combined exposure to the selected chemicals on malformations of external sex organs was synergistic, and the observed responses were greater than would be predicted from the toxicities of the individual chemicals. In relation to other hallmarks of disrupted male sexual development, including changes in AGD, retained nipples, and sex organ weights, the combined effects were dose additive. When the four chemicals were combined at doses equal to no observed adverse effect levels estimated for nipple retention, significant reductions in AGD were observed in male offspring.

B2: Low Dose Effects Studies

Throughout their review of the phthalate esters category the question of potential effects of low doses recurred. PubMed was searched for "*low-dose phthalate reproductive*" and six studies were returned for review. Two additional studies cited in the ECHA 2012 were added as well. Low-dose, for the purposes of this review ranged from .01mg/kg/day to 10mg/kg/day.

Low Dose Effects		
Author and Title	**Dose/Species/Strain**	**Findings**
Bao 2011: Bao AM, et al. Effects of di-n-butyl phthalate on male rat reproduction following pubertal exposure. *Asian Journal of Andrology* (2011) **13**, 702-709.	In the present study, pubertal male Sprague–Dawley rats were orally administered DBP at a wide range of doses (0.1, 1.0, 10, 100 and 500 mg/kg/day) for 30 days. The selected end points included reproductive organ weights, testicular histopathology and serum hormonal levels. Additionally, proteomic analysis was performed to identify proteins that are differentially expressed as a result of exposure to DBP at low doses (0.1, 1.0 and 10 mg/kg/day).	Toxic effects were observed in the high-dose groups, including anomalous development of testes and epididymides, severe atrophy of seminiferous tubules, loss of spermatogenesis and abnormal levels of serum hormones. Treatment with low doses of DBP seemed to exert a 'stimulative effect' on the serum hormones. Proteomics analysis of rat testes showed 20 differentially expressed proteins. Among these proteins, alterations in the expression of HnRNPA2/B1, vimentin and superoxide dismutase 1 (SOD1) were further confirmed by Western blot and immunohistochemistry. Taken together, the authors conclude that high doses of DBP led to testicular toxicity, and low doses of DBP led to changes in the expression of proteins involved in spermatogenesis as well as changes in the number and function of Sertoli and Leydig cells, although no obvious morphological changes appeared. The identification of these differentially expressed proteins provides important information about the mechanisms underlying the effects of DBP on male rat reproduction.
Breous 2005: Breous E, et al. The promoter of the human sodium/iodide	Investigates possible effects of six major phthalates (1mM) on the transcriptional activity of	Di-isodecyl phthalate (DIDP), benzyl butyl phthalate (BBP) and di-octyl phthalate (DOP)

symporter responds to certain phthalate plasticisers. *Molecular and Cellular Endocrinology* **244** (2005) 75-78.	sodium/iodide symporter (NIS). Test used diester, not monoester.	increased the activity of the human NIS promoter construct 2.5-, 2.6- and 2.4-fold, respectively. Likewise, these phthalates also enhanced the rat NIS endogenous mRNA expression ca. 2-fold. No effect was observed for bis-(2-ethylhexyl) phthalate (DEHP) and di-isononyl phthalate (DINP), whereas dibutyl phthalate (DBP) appeared to down-regulate hNIS promoter. Although the demonstrated stimulation of NIS gene transcription by DIDP, BBP and DOP is not very strong, this finding is of great importance as humans are routinely exposed for long periods to phthalate plasticisers, the accumulation of which may contribute to thyroid hyperfunction.
Christiansen 2010: Christiansen SC, et al. Low-dose perinatal exposure to di(2-ethylhexyl) phthalate induces anti-androgenic effects in male rats. *Reproductive Toxicology* **30** (2010) 313-321.	Perinatal di(2-ethylhexyl) phthalate (DEHP) exposure was examined in time-mated Wistar rats gavaged from gestation day 7 to postnatal day 16 with doses from 3 to 900 mg/kg-d. These doses covered the whole dose–response curve for the demasculinizing effects of DEHP including low-dose effects.	At a relatively low dose of 10 mg/kg-d, DEHP caused adverse anti-androgenic effects on male rat development as male anogenital distance was decreased, the incidence of nipple retention was increased, weight of levator ani/bulbocavernosus muscles and prostate was reduced and mild external genitalia dysgenesis was observed. Higher doses of DEHP induced histopathological effects on the testes, reduced testis weight, and expression of androgen-regulated genes in the prostate. The results provide new evidence of low-dose effects of DEHP and are consistent with the EU NOAEL of 5 mg/kg for DEHP. Our results also indicate a reason for concern about human exposure to DEHP.
Hoshi and Ohtsuka 2009:	Developmental neurotoxicity of	The body weight of all dams and

Hoshi H and Ohtsuka T. Adult Rats Exposed to Low-Doses of Di-n-Butyl Phthalate During Gestation Exhibit Decreased Grooming Behavior. *Bull Environ Contam Toxicol* (2009) **83**: 62-66.	low-dose di-n-butyl phthalate (DBP) to rats was studied. Pregnant rats were orally given DBP at doses less than 1.0 mg/kg/day during gestation period.	their offspring as well as the offspring's motor function showed no significant adverse effect. At 21 weeks, behaviors of male rats were examined by placing into a test cage. The rats born from dams exposed to 10 µg DBP/kg/day exhibited a significant decrease of grooming. This indicates low-dose DBP adversely affects emotional stability in a novel environment.
Hu 2013: Hu Y, et al. Low-dose monobutyl phthalate stimulates steroidogenesis through steroidogenic acute regulatory protein regulated by SF-1, GATA-4, and C/EBP-beta in mouse Leydig tumor cells. *Reproductive Biology and Endocrinology* 2013, **11**: 72.	MLTC-1 cells were cultured in RPMI 1640 medium supplemented with 2 g/L sodium bicarbonate. Progesterone level was examined by I^{125}-pregesterone Coat-A-Count radioimmunoassay (RIA) kits. mRNA and protein levels were assessed by reverse transcription-polymerase chain reaction (RT-PCR) and western blot, respectively. DNA-binding of several transcription factors was examined by electrophoretic mobility shift assay (EMSA). Various doses of MBP (0, $10^{(-9)}$), $10^{(-8)}$), $10^{(-7)}$), or $10^{(-6)}$) M) were added to the medium followed by stimulation of MLTC-1 cells with human chorionic gonadotrophin (hCG).	The results showed that MBP increased progesterone production and steroidogenic acute regulatory protein (StAR) mRNA and protein levels. However, the protein levels of cytochrome P450scc and 3 beta-hydroxy-steroid dehydrogenase (3 beta-HSD) were unchanged after MBP treatment. EMSA assay showed that DNA-binding of steroidogenic factors 1(SF-1), GATA-4 and CCAAT/enhancer binding protein-beta (C/EBP-beta) was increased in a dose-dependent manner after MBP exposure. Western blot tests were next employed and confirmed that the protein levels of SF-1, GATA-4 and C/EBP-beta were also increased. Additionally, western blot tests confirmed the expression of DAX-1, negative factor of SF-1, was dose-dependently down regulated after MBP exposure, which further confirmed the role of SF-1 in MBP-stimulated steroid biosynthesis.
Hu 2014: Hu Y, et al. Antagonistic Effects of a Mixture of Low-Dose Nonylphenol and Di-N-Butyl Phthalate (Monobutyl Phthalate) on the Sertoli Cells and Serum	In this study, the authors attempted to determine the mixture effects of NP and DBP on the testicular Sertoli cells and reproductive endocrine hormones in serum in male rats based on quantitative data analysis by a	In this study, the authors demonstrate the potential of Bliss Independence model for the prediction of interactions between estrogenic and antiandrogenic agents. Antagonism was identified as the

Reproductive Hormones in Prepubertal Male Rats *In Vitro* and *In Vivo*. *PLOS One*, March 2014, **9(3)** e93425.	mathematical model. In the *in vitro* experiment, monobutyl phthalate (MBP), the active metabolite of DBP, was used instead of DBP. Sertoli cells were isolated from 9-day-old Sprague-Dawley rats followed by treatment with NP and MBP, singly or combined. Cell viability, apoptosis, necrosis, membrane integrity and inhibin-B concentration were tested. In the *in vivo* experiment, rats were gavaged on postnatal days 23–35 with a single or combined NP and DBP treatment. Serum reproductive hormone levels were recorded. Next, Bliss Independence model was employed to analyze the quantitative data obtained from the *in vitro* and *in vivo* investigation.	mixture effects of NP and DBP (MBP).
Makris 2013: Makris SL, et al. Use of genomic data in risk assessment case study: I. Evaluation of the dibutyl phthalate male reproductive development toxicity data set. *Toxicology and Applied Pharmacology* **271** (2013) 336-348.	A case study was conducted, using dibutyl phthalate (DBP), to explore an approach to using toxicogenomic data in risk assessment. The toxicity and toxicogenomic data sets relative to DBP-related male reproductive developmental outcomes were considered conjointly to derive information about mode and mechanism of action. In this manuscript, we describe the case study evaluation of the toxicological database for DBP, focusing on identifying the full spectrum of male reproductive developmental effects.	The data were assessed to 1) evaluate low dose and low incidence findings and 2) identify male reproductive toxicity endpoints without well-established modes of action (MOAs). These efforts led to the characterization of data gaps and research needs for the toxicity and toxicogenomic studies in a risk assessment context. Further, the identification of endpoints with unexplained MOAs in the toxicity data set was useful in the subsequent evaluation of the mechanistic information that the toxicogenomic data set evaluation could provide. The extensive analysis of the toxicology data set within the MOA context provided a resource of information for DBP in attempts to hypothesize MOAs (for endpoints without a well-established MOA) and to phenotypically anchor toxicogenomic and other

		mechanistic data both to toxicity endpoints and to available toxicogenomic data. This case study serves as an example of the steps that can be taken to develop a toxicological data source for a risk assessment, both in general and especially for risk assessments that include toxicogenomic data.
Wenzel 2005: Wenzel A, et al. Modulation of iodide uptake by dialkyl phthalate plasticisers in FRTL-5 rat thyroid follicular cells. *Mol Cell Endocrinol.* 2005 Dec 1;**244(1-2):**63-71.	Effects of six different dialkyl phthalates were studied in vitro in the rat thyroid cell line FRTL-5 on their ability to modulate basal iodide uptake mediated by the sodium/iodide symporter (NIS).	The present study shows that diisodecyl phthalate (DIDP), dioctyl phthalate (DOP), diisononyl phthalate (DINP) and bis (2-ethylhexyl) phthalate (DEHP) significantly enhance iodide uptake when concentrations in the magnitude between 10^{-4}M and 10^{-3}M were applied. In this range, these phthalates do not assess toxicity on the cells. Specific inhibition of NIS demonstrated that enhancement of iodide uptake is due to NIS. In contrast, benzyl butyl phthalate (BBP) also augments iodide uptake at 1mM but this concentration has just exceeded the toxicity threshold and dibutyl phthalate (DBP), the most toxic compound did not modulate iodide uptake at any concentration applied. The authors deduce from their results, plasticisers are capable of significantly modulating NIS mediated iodide uptake activity.

B3: Overview Studies

Overview Phthalate Ester Articles Reviewed by the SAB		
Title	**Citation**	**Description**
A Category Approach for Reproductive Effects of Phthalates	**Fabjan 2006:** Fabjan E, et al. A Category Approach for Reproductive Effects of Phthalates, *Critical Reviews in Toxicology*, **36**:695-726, 2006.	Three ortho phthalates were used to test a category approach for 10 ortho phthalate esters in order to develop an approach that minimizes animal testing. C4 to C6 phthalates produced similar severe reproductive effects in experimental animals. It was concluded that detailed mechanistic information is needed on phthalates to apply the categories for regulatory toxicology.
Human Body Burdens of Chemicals Used in Plastics Manufacture	**Koch and Calafat 2009:** Koch HM, Calafat AM. Human body burdens of chemicals used in plastic manufacture. *Philosophical Transactions of The Royal Society Biological Sciences.* 2009 **364**, 2063-2078.	This article reviews relevant research on biomarkers of exposure for phthalates and includes biomonitoring data from Germany and the United States.
US EPA Phthalates Action Plan	**EPA 2012:** Phthalates Action Plan, Revised March 14, 2012.	EPA's Phthalates Action Plan includes the following phthalates: DBP, DIBP, BBP, DnPP, DEHP, DnOP, DINP, DIDP. A review of published information to date on toxicity, exposure and current regulations is included.
Overview of Phthalates Toxicity	**CPSC 2010:** Babich, MA. Overview of Phthalates Toxicity (Information provided to the Chronic Hazard Advisory Panel on Phthalates). United States Consumer Product Safety Commission, April 12, 2010.	Overview of the toxicity of ortho phthalate esters including consumer uses and human exposure.

B4: Meta Phthalate Ester Studies

Four studies were identified for meta phthalates. These studies focused on dimethyl isophthalate (DMI or DMIP), diphenyl isophthalate, and diallyl isophthalate.

Compared to ortho-phthalates, only a limited number of studies directly relevant to human, animal and ecotoxicity were available for meta-phthalates. Evidence exists for migration and persistence in the environment, as well as potential for adverse effects on the endocrine system, specifically modulation of glucocorticoids, though the limited number of studies as well as the findings regarding relatively weak estrogenic activity in one species suggests a lower priority class of compounds as compared to the ortho-phthalates.

In a study looking at both migration potential of several plasticizers from re-usable plastic water bottles and their effect on the reproductive effects on snails, one meta phthalate, dimethyl isophthalate (DMIP), was detected in all three tiers of the migration assay though all three concentrations were well-below the specific migration limits set by the European Union (0.902, 0.145, and 0.085 ug/kg as compared to the limit of 50 ug/kg)(Guart et al. 2013). Consistent with prior studies, where bisphenol A had a statistically significant effect on increased reproduction in snails, DMIP indicated only weak to no estrogenic activity in this model.

In a study that evaluated several chemicals as potential agonists or antagonists of glucocorticoid signaling, one meta phthalate, diphenyl isophthalate, was reported to significantly (p<0.001) induce activity of the glucocorticoids receptor (GR) in four independent experiments. The experiments used an vitro model of MDA-kb2 cells expressing luciferase activity in a GR-dependent manner (Kolsek et al. 2014). Glucocorticoids are an essential part of the endocrine system that is responsible for a variety of functions such as regulation of immune activity, appropriate brain function, and fetal development. Disturbance of glucocorticoid signaling can lead to various cardiovascular, inflammatory, and autoimmune diseases (Kolsek et al. 2014).

One study reported that in aquatic environments, the presence of oxygen and [a] type of bacteria impacted degradation of dimethyl phthalate esters (DMPE), including one meta phthalate, dimethyl isophthalate (DMI). DMPE and its metabolites were found to persist longer in sulfate-reducing environments (Cheung et al, 2007).

Author/Title	Substance	Findings
Cheung 2007: Cheung JK, et al. Environmental fate of endocrine-disrupting dimethyl phthalate esters (DMPE) under sulfate-reducing	Dimethyl isophthalate (DMI or DMIP)	Dimethyl phthalate (DMP), dimethyl isophthalate (DMI) and dimethyl terephthalate (DMT) could not be mineralized over an extended period of 6 months, but with the transformation to the respective monomethyl phthalate and/or phthalic acid. DMPE and their natural metabolites may accumulate in the sulfate-reducing environment. One study reported that in aquatic environments, the

condition. *Sci Total Environ.* 2007 Aug 1;**381(1-3):**126-33.		presence of oxygen and [a] type of bacteria impacted degradation of dimethyl phthalate esters (DMPE), including one metaphthalate, dimethyl isophthalate (DMI). DMPE and its metabolites werefound to persist longer in sulfate-reducing environments.
Guart 2013: Guart A, et al. Migration of plasticisers from Tritan™ and polycarbonate bottles and toxicological evaluation. *Food Chem.* 2013 Nov 1;**141(1):**373-80.	Dimethyl isophthalate (DMIP)	Compounds identified in Tritan™ were 2-phenoxyethanol (2-PE), 4-nonylphenol (4-NP), bisphenol A (BPA), benzyl butyl phthalate (BBP) and dimethyl isophthalate (DMIP) at levels from 0.027 ± 0.002 to 0.961 ± 0.092 µg/kg, although in the 3rd migration period, BBP and DMIP were the only compounds detected well below the specific migration limit. BPA and DMIP were estrogenic in high concentrations. In a study looking at both migration potential of several plasticizers from re-usable plastic water bottles and their effect on the reproductive effects on snails, one meta phthalate, dimethyl isophthalate (DMIP), was detected in all three tiers of the migration assay though all three concentrations were well-below the specific migration limits set by the European Union (0.902, 0.145, and 0.085 ug/kg as compared to the limit of 50 ug/kg); Consistent with prior studies, where bisphenol A had a statistically significant effect on increased reproduction in snails, DMIP indicated only weak to no estrogenic activity in this model.
Kolsek 2014: Kolsek K, et al. Molecular docking revealed potential disruptors of glucocorticoid receptor-dependent reporter gene expression. *Toxicology Letters* **226** (2014) 132-139.	Diphenyl isophthalate	Nine new potential modulators of the glucocorticoid receptor, belonging to six structurally diverse classes, were identified. Six of them, tetramethrin and cypermethrin, diethyl hexyl phthalate and diphenyl isophthalate, naphthol AS-OL and dicumyl peroxide, induced luciferase activity; while the other three, bisphenol P, bisphenol M, and Antioxidant 425, suppressed luciferase activity. In a study that evaluated several chemicals as potential agonists or antagonists of glucocorticoid signaling, one meta phthalate, diphenyl isophthalate, was reported to significantly (p<0.001) induce activity of the glucocorticoids receptor (GR) in four independent experiments. The experiments used an vitro model of MDA-kb2 cells expressing luciferase activity in a GR-dependent manner; Glucocorticoids are an essential part of the endocrine system that is responsible for a variety of functions such as regulation of immune activity, appropriate brain function, and fetal development. Disturbance of glucocorticoid signaling can lead to various cardiovascular, inflammatory, and autoimmune diseases.
Nakai 1999: Nakai M, et al. Binding	Diallyl isophthalate	Compounds with an alkyl chain of more than C3 (n = 3) exhibited a distinct full estrogen receptor binding in a dose-

characteristics of dialkyl phthalates for the estrogen receptor. *Biochem Biophys Res Commun.* 1999 Jan 19;**254(2):**311-4.		dependent manner. When the ring isomers of C3-diallyl (-CH2-CH=CH2) derivatives, namely diallyl phthalate, diallyl isophthalate, and diallyl terephthalate, were examined, the ortho isomer of diallyl phthalate was most potent to bind to the estrogen receptor.

B5: Para Phthalate Ester Studies

Fifteen studies were identified for para phthalates. The majority of studies focused on di(2-ethylhexyl) terephthalate (DEHT) or dimethyl terephthalate (DMP); there were also limited studies for diethyl terephthalate (DTP), and diallyl terephthalate. DEHT has been the most studied of the terephthalates the Board has been able to review, and while there are data gaps, available information indicates low concern.

Author/Title	Substance	Findings
Aoshima 2001: Aoshima H, et al. Effects of bisphenol A and its derivatives on the response of GABA(A) receptors expressed in Xenopus oocytes. *Biosci Biotechnol Biochem*. 2001 Sep;**65(9):**2070-7.	DTP	Diethyl terephthalate (DTP), which is also known to have estrogenic actions, had little effect on both the responses and the decay of both GABA receptors.
Ball 2012: Ball GL, et al. Toxicological review and oral risk assessment of terephthalic acid (TPA) and its esters: A category approach. *Crit Rev Toxicol.* 2012 Jan;**42(1):**28-67.	DMT and DEHT	Chronic dietary DMT exposure in rodents caused kidney inflammation, but not calculi. Chronic dietary DEHT exposure caused general toxicity unrelated to calculi, although urine pH was reduced suggesting the TPA metabolite was biologically-active, but of insufficient concentration to induce calculi. Respective oral reference doses of 0.5, 0.5, and 0.2 mg/kg-day and total allowable drinking water concentrations of 3, 3, and 1 mg/L were derived for TPA, DMT, and DEHT. An oral RfD of 0.2 mg/kg-day for the terephthalate category chemicals corresponded to a drinking water TAC of 1 mg/L.
Barber 1994: Barber ED. Genetic toxicology testing of di(2-ethylhexyl) terephthalate. *Environ Mol Mutagen*. 1994;**23(3):**228-33.	DEHT	All test results for both DEHT and MEHT were found to be negative, and it is therefore concluded that DEHT, like its isomeric relative DEHP, is not genotoxic.
Barber 1995: Barber ED, Topping DC. Subchronic 90-day oral toxicology of di(2-ethylhexyl) terephthalate in the rat. *Food Chem Toxicol.* 1995 Nov;**33(11):**971-8.	DEHT	No major organ or systemic toxicity resulted from consumption of the diets in any group of animals. Changes that were observed included slight effects on some haematology

		parameters including haemoglobin, haematocrit, mean corpuscular volume and mean corpuscular haemoglobin at the 1.0% dose; and slight increases in relative liver weights (11.2% in the males, 8.9% in the females), also at the 1.0% dose level. Thus, no significant adverse effects attributable to the test material were identified in animals consuming the two lower doses. In a morphometric study of liver sections, DEHT was found not to induce hepatic peroxisomes at the 1.0% dose level. The no-effect levels of DEHT in rats consuming the material for 90 days in the diet were 277 and 309 mg/kg/day in males and females, respectively. While DEHP at 1% in the diet is reported to produce significant effects on the liver, testes, kidney, brain, stomach and adrenal weights, DEHT has been shown in this study to have only a minor effect on liver weight in 90 days at 1.0% in the diet.
Cheung 2007: Cheung JK, et al. Environmental fate of endocrine-disrupting dimethyl phthalate esters (DMPE) under sulfate-reducing condition. *Sci Total Environ.* 2007 Aug 1;**381(1-3):**126-33.	DMT	Dimethyl phthalate (DMP), dimethyl isophthalate (DMI) and dimethyl terephthalate (DMT) could not be mineralized over an extended period of 6 months, but with the transformation to the respective monomethyl phthalate and/or phthalic acid. DMPE and their natural metabolites may accumulate in the sulfate-reducing environment.
David 2003: David RM, et al. Lack of sensitization for trimellitate, phthalate, terephthalate and isobutyrate plasticizers in a human repeated insult patch test. *Food Chem Toxicol.* 2003 Apr;**41(4):**589-93.	DEHT	Two subjects had slight erythema to DEHT, one that resolved by 96 h and one that occurred only after 96 h. Because of the low response, the overall conclusion is that none of the plasticizers

		demonstrated evidence of sensitization or irritation.
Deyo 2008: Deyo JA. Carcinogenicity and chronic toxicity of di-2-ethylhexyl terephthalate (DEHT) following a 2-year dietary exposure in Fischer 344 rats. *Food Chem Toxicol.* 2008 Mar;**46(3):**990-1005.	DEHT	No histological effects were noted in any organ at any dose and there was no increase in the incidence of any tumor types. Toxic responses were confined to lower weight gains and food conversion efficiency in males and females ingesting 6,000 or 12,000 ppm. The severity of a normal geriatric degenerative retinal change was exacerbated in females exposed to 6,000 or 12,000 ppm and in males exposed to 12,000 ppm. Therefore, the no-observed effect level (NOEL) for tumorigenicity was 12,000 ppm and the NOEL for chronic toxicity was 1,500 ppm.
Faber 2007: Faber WD, et al. Developmental toxicity and uterotrophic studies with di-2-ethylhexyl terephthalate. *Birth Defects Res B Dev Reprod Toxicol.* 2007 Oct;**80(5):**396-405.	DEHT	DEHT exposure did not affect clinical observations. A slight reduction in body weight gain was noted in the high-dose level rat group; the remaining groups were unaffected. At necropsy, increased liver weights were noted in the high-dose rat group and the mid- and high-dose mouse groups. Mean numbers of implantation sites and viable fetuses, mean fetal weights, and mean litter proportions of preimplantation loss, early resorptions, late resorptions, and fetal sex ratios were unaffected by DEHT exposures. No test article-related malformations or vari ations were observed at any concentration level in the rat and mouse developmental toxicity studies. In the uterotrophic assay for estrogenic activity, sexually immature female rats received oral gavage doses 20, 200, or 2,000 mg DEHT

		/kg bw/day from postnatal day (PND) 19-21. A slight reduction in rate of body weight gain was noted on the first day of dosing in the high dose group, but no other indications of toxicity were evident. DEHT exposure did not affect wet or blotted uterine weight parameters in any of these dose groups. The authors conclude that lack of adverse developmental effects with DEHT exposure are in contrast to the adverse developmental effects noted after di-2-ethylhexyl phthalate (DEHP) exposure. The difference between the effects noted with the ortho-constituent (DEHP) and the lack of effects reported with the para-constituent (DEHT) is due most likely to differences in metabolism and the formation of the stable monoester, mo no-2-ethylhexyl phthalate (MEHP) from the DEHP moiety.
Faber 2007a: Faber WD, et al. Two-generation reproduction study of di-2-ethylhexyl terephthalate in Crl:CD rats. *Birth Defects Res B Dev Reprod Toxicol.* 2007 Apr;**80(2):**69-81.	DEHT	DEHT exposure did not affect clinical observations. However, lethality was observed in F(0) and F(1) dams consuming the 1.0% diet during the post-weaning period. No treatment-related mortality occurred in any of the male groups exposed to DEHT or in the female groups exposed to 0.3% or 0.6% DEHT. Male rats consuming the 1.0% diet in both parental generations gained weight more slowly than the controls. There were no indications of adverse effects on reproductive performance in either the F(0) or F(1) generation. Male and female mating and fertility indices, pre-coital intervals, spermatogenic endpoints, reproductive organ

		weights, lengths of estrous cycle and gestation, live litter size, developmental landmarks, and postnatal survival were similar in all exposure groups. Additionally, ovarian follicle counts for the F(1) females in the high-exposure group were similar to the control values. No adverse exposure-related macroscopic pathology was noted at any exposure level in the F(0) and F(1) generations. Therefore, for parental and pup systemic toxicity, 0.3% DEHT in the diet (182 mg/kg/day) was considered no-observed-effect level (NOEL). The 1.0% DEHT (614 mg/kg/day) in the diet exposure concentration was considered a NOEL for F(0) and F(1) reproductive toxicity endpoints."
Geier 2001: Geier J, et al. Contact allergy to terephthalic acid diglycidylester in a powder coating. *Contact Dermatitis*. 2001 Jan;**44(1):**43-4.	Terephthalic acid diglycidylester	The authors diagnosed airborne allergic contact dermatitis due to terephthalic acid diglycidylester in the powder coating.
Monarca 1991: Monarca S, et al. In vitro genotoxicity of dimethyl terephthalate. *Mutat Res.* 1991 Feb;**262(2):**85-92.	Dimethyl terephthalate	The results of this battery of in vitro assays clearly show that DMTP is nongenotoxic. By contrast, other authors have found DMTP to be an in vivo clastogenic compound and suggested that the mechanisms involved in these in vivo effects seem to have nothing in common with genotoxicity and are still unknown.
Nakai 1999: Nakai M, et al. Binding characteristics of dialkyl phthalates for the estrogen receptor. *Biochem Biophys Res Commun.* 1999 Jan 19;**254(2):**311-4.	Diallyl terephthalate	Compounds with an alkyl chain of more than C3 (n = 3) exhibited a distinct full estrogen receptor binding in a dose-dependent manner. When the ring isomers of C3-diallyl (-CH2-CH=CH2) derivatives, namely diallyl phthalate, diallyl isophthalate,

		and diallyl terephthalate, were examined, the ortho isomer of diallyl phthalate was most potent to bind to the estrogen receptor.
Osimitz 2012: Osimitz TG, et al. Lack of androgenicity and estrogenicity of the three monomers used in Eastman's Tritan™ copolyesters. *Food Chem Toxicol.* 2012 Jun;**50(6):**2196-205.	DMT	Tritan's™ monomers were evaluated using QSAR for binding to the androgen receptor and estrogen receptors (alpha and beta) as well as a battery of in vitro and in vivo techniques to determine their potential androgenicity or estrogenicity. The findings were universally negative. Additional data presented also support such a conclusion for terephthalic acid (TPA). TPA is also a common polyester monomer and is the main mammalian metabolite formed from DMT.
ToxServices 2012: ToxServices, Di(2-ethylhexyl) terephthalate (DEHT) (CAS #6422-86-2) GreenScreen™ Assessment, October 11, 2012.	DEHT	Tox assessment using the GreenScreen tool. Assigned benchmark score of 3_{DG}. Data gaps exist for neurotoxicity and respiratory sensitization. Other endpoints meet benchmark 4, which is the lowest concern.
Wirnitzer 2011: Wirnitzer U, et al. Systemic toxicity of di-2-ethylhexyl terephthalate (DEHT) in rodents following four weeks of intravenous exposure. *Toxicol Lett.* 2011 Aug 10;**205(1):**8-14.	DEHT	DEHT had no effect on survival, body weight development, food and water consumption in the whole dose range investigated. There were no indications as to hematotoxicity or immunotoxicity. Clinical chemistry and histopathology indicated no exposure related effect on hepatic, thyroidal and reproductive functions or organs. (NOAEL=381.6 mg/kg/day).

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Appendix D: Ortho Phthalate Ester Table by Selected Health Effects and Carbon Chain Length

The following table, "*Ortho Phthalate Esters by Selected Health Effects and Carbon Chain Length",* **was requested by the Board *and* provides a visual overview of selected health effects and selected phthalate esters by carbon side chain length. The data in this table is current as of the April 1, 2015 meeting with regard to both carbon chain length and study results but does not reflect further refinements made later in the review process .**

Ortho Phthalate Ester Table by Selected Health Effects and Carbon Chain Length

10 Selected Phthalate Esters by Carbon Chain Length and Selected Endpoints for April 1, 2015 SAB Meeting (from 11/12/14 mtg)

# of carbons	C3	C4 C5 C6	C7	C8	C9	C10	C11	C12 C13 C14
Substances → Endpoint ↓	**DAP**	**E.g. DEHP, BBP, DBP**		**DINP**			**DTDP**	
	DMEP				**Din911P**		**Din911P**	
				DnOP		**DIDP**	**DUP/DUDP**	
							DiUP	
			DPHP			**DPHP**		
Reproductive/ Developmental		Consensus met re: reproductive toxicity hazards in this carbon chain length grouping.			**Din911P - See C11**		**Din911P - [Willoughby 2000, Fulcher 2001]**	
	DMEP - Severe reproductive toxicity in animals. [CPSC 2011] Embryotoxic and fetotoxic [Campbell 1984]			**DINP - Probable developmental toxicant [CPSC 2010]**			**DUP - Sperm counts & motility [Kwack 2009] small decreases in AGD in male fetuses, increase in supernumerary lumbar ribs over control [Saillenfait 2013]**	
	DAP (weak) - Teratogenic > 250 mg/kg [Saillenfait 2008]			**DnOP** - *Some evidence of no adverse effect (repro); Insufficient info for developmental [NTP 2003]*		**DIDP - Sperm motility [Kwack 2009] decreased pup survival, increased incidence in skeletal variations [CPSC 2010, NTP 2003]**	**DIUP** - *Data in most cases is read-across to DIDP [REACH various dates]*	
			DPHP - *Few R/D effects observed [CPSC 2010, TS 2012]*			**DPHP** - *Few R/D effects observed [CPSC 2010, TS 2012]*	**DUP - AGD/other developmental effects at 500 mg/kg to 1,000 mg/kg [Saillenfait 2013]**	
Liver	**DAP - Hepatotoxic effects [Saillenfait 2008]**	Consensus met re: liver toxicity hazards in this carbon chain length grouping.		**DINP - Causes liver and kidney tumors in rodents [CPSC 2010]**			**DTDP** - *Limited animal evidence for hepatotoxicity [CPSC 2010]*	
	DMEP - Liver and kidney effects observed [Campbell 1984]			**DnOP - Probable hepatotoxicant [CPSC 2010]**	**Din911P** - *See C11*		**Din911P** - *In systemic studies, liver effects noted, but not considered toxicologically significant [CPSC 2010; Brown 1970]*	
						DIDP - Liver weight increase [NTP 2003]	**DUP - Sufficient animal evidence of hepatotoxicity [CPSC 2010]**	
							DIUP - Peroxisomal proliferation in repeated dose tox study [CPSC 2010]	
			DPHP - Increased liver weight [CPSC 2010]			**DPHP - Increased liver weight [CPSC 2010]**		
Endocrine		Consensus met re: endocrine disruption potential in this carbon chain length grouping.		**DINP - Listed on TEDX Potential Endocrine Disruptors**			**DTDP** - *Positive endocrine disruption effect is noted as likely due to BPA contamination [CPSC 2010]*	
				DnOP - *No estrogenic effects [NTP 2003]*		**DIDP - Anti-androgenic effects [Lee and Koo 2007]**		
			DPHP - Thyroid effects [TS 2012]			**DPHP - Thyroid effects [TS 2012]**		

Key: **Bold Text = Effects observed;** *Italicized Text = Limited effects and/or evidence of no effect;* White Text = Indicates information pending review by individual groups and/or the Board

Appendix E: Comments from the American Chemistry Council Phthalate Ester Panel

The following comments from the American Chemistry Council were received during the process and shared with the Science Advisory Board during their review, but were not able to be resolved in the document. Therefore, they are documented here so DEP can see them as part of the process.

1) Gray 2000 (DINP)

Important to note this finding was not replicated in Boberg or Clewell. This percent is a compilation of multiple different findings that are most likely background incidence.

2) Lee 2006 (DINP)

If you look at the evidence tables generated for the DINP IRIS evaluation the Lee study is an outlier from all other studies. This could be due to inappropriate application of statistics or some other methodological consideration.

3) Lee and Koo 2007 (DINP)

If you look at the evidence tables generated for the DINP IRIS evaluation the Lee study is an outlier from all other studies. This could be due to inappropriate application of statistics or some other methodological consideration.

4) Wenzel 2005 (DINP)

This study was also conducted with the diester and is not applicable to the in-vivo situation. Additionally an independent review of the cell line points out there are several caveats that must be kept in mind "Although often left unsaid, it is widely acknowledged that cell lines may evolve and deviate from their parental counterparts. Perhaps due in part to their very broad dissemination, this is especially well documented in the case of FRTL-5 cells. This cell line was indeed reported to suffer from increasing instability (13, 14) and clonal variability (15, 16, 17), which explains the opposite results sometimes obtained in different laboratories." And "FRTL-5 have been "adapted" to the presence of 5% serum and survive in the absence of TSH (2). However, they derive from FRTL cells for which TSH and insulin not only support proliferation, but also are necessary for survival (11). Some vital functions might thus have come to depend on these hormones, which were present during the establishment of the cell strain. Recently, a survival function of TSH has been unmasked in FRTL-5 cells (12).", among other comments. Kimura, T., Van Keymeulen, A., Golstein, J., Fusco, A., Dumont, J.E., Roger, P.P., 2001. Regulation of thyroid cell proliferation by TSH and other factors: a critical evaluation of in vitro models. *Endocr. Rev.* **22**, 631– 656.

5) Christiansen 2009 (Cumulative effects)

Though the title and abstract state “synergistic” the description of the results on pg 1843 column 2 states “Our data suggest that the combined effects of DEHP, vinclozolin, prochloraz, and finasteride are **additive** when the evaluation is based on changes in AGD, retained nipples, prostate weights, and weights of LABC.” The endpoint for which “syngerism” was observed was also the endpoint for which the most assumptions were included in the mathematical model. It is no[t] clear whether the observed “synergism” was in fact synergism or an inappropriate model derived from the inputted assumptions.

6) GC3 2012: ToxServices LLC, **Draft** GreenScreen Assessment for DPHP (Oct. 2011) [comment by BASF] The *draft* GreenScreen™ assessment by ToxServices, LLC, should only be viewed as a “screen” and not as a rigorous hazard or risk assessment (also, draft documents *per se* should never be quoted when other sources in final form are available). This public document came out of a collaborative alternatives assessment that BASF participated in as part of a GC3 project. BASF considers their conclusion of possible “endocrine activity” to be inaccurate.3 The interpretation regarding possible endocrine disruption reflects a naivete of the ToxServices staff. Thyroid effects have long been associated with peroxisome proliferation (Hinton, et al, *Environ Health Perspect.* **70**, 195-210, 1986). Instead, the reviewers "hypothesized" on the potential endocrine effects.

Appendix F. Glossary of Acronyms and Definitions

(for additional information on common phthalate ester acronyms, see Appendix I)

ACC = American Chemistry Council
ADI = Acceptable daily intake value
AGD = Anogenital distance
BBP = Butyl benzyl phthalate, CAS# 85-68-7
BPA = Bisphenol A
CAS = Chemical Abstract Service
CERCLA = United States Comprehensive Environmental Response, Compensation, and Liability Act
CIPC = Chemical Investigation Promoting Council
CMR = Carcinogenic, mutagenic, and reprotoxic substances
CPSC = United States Consumer Product Safety Commission
CRL = Charles River Laboratories
DAP = Diallyl Phthalate, CAS# 131-17-9
DBP = Dibutyl Phthalate, CAS# 84-74-2
DDE = Dichlorodiphenyldichloroethylene
DEHA = Dioctyl adipate, CAS# 103-23-1
DEHP or DOP = Di(2-ethylhexyl) phthalate, CAS# 117-81-7
DEP = Diethyl phthalate, CAS# 84-66-2
DIBP = Diisobutyl phthalate, CAS# 84-69-5
DIDP = Diisodecyl phthalate, CAS# 26761-40-0, 68515-49-1
DIHP or DnHP = Diisohexyl phthalate, CAS# 68515-50-4
Din911P = 1,2-Benzenedicarboxylic acid, 1-nonyl 2-undecyl ester, branched and linear – CAS# 111381-91-0
DINP = Diisononyl phthalate, CAS# 28553-12-0; 68515-48-0
DMEP = Dimethoxyethyl phthalate, CAS# 117-82-8
DMP = Dimethyl phthalate, CAS# 131-11-3
DHP = Di-n-hexyl phthalate, CAS# 84-75-3
D911P = 1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, CAS# 68515-43-5
DnOP = Di-n-octyl phthalate, CAS# 117-84-0
DnPP = Di-n-pentyl phthalate, CAS# 131-18-0
DOTP or DEHT = Di-(2-ethylhexyl) terephthalate, CAS# 6422-86-2
DPHP = Di(2-propylheptyl) phthalate, CAS# 53306-54-0
DUP = Diundecyl phthalate, CAS# 3648-20-2
DIUP = Diundecyl phthalate, branched and linear, CAS# 85507-79-5
DTDP = Ditridecyl phthalate, CAS# 119-06-2
ECB = European Chemicals Bureau
ECHA = European Chemicals Agency
ED = Embryonic days or Endocrine disruptors
FSH = Follicle-stimulating hormone

GC3 = Green Chemistry and Commerce Council
GD = Gestational days
g/kg = grams/kilogram
HMW = High molecular weight
HRIPT = human repeated insult patch test
IARC = International Agency for Research on Cancer
IP = Intraperitoneal
LABC = levator ani/bulbocavernosus (muscles)
LCA = Leydig cell aggregates
LD_{50} = Median lethal dose
LH = Luteinizing hormone
LMW = Low molecular weight
LOAEL = Lowest observed adverse effect level
MA DEP = Massachusetts Department of Environmental Protection
MCiOP = Mono(carboxyisooctyl) phthalate
ME = 2-methoxyethanol
MEHP = Mono(2-ethylhexyl) phthalate
M/F = Male/Female
mg/kg = milligrams per kilogram
mg/kg/d, sc = milligrams per kilogram per day, administered by subcutaneous injection
MHiNP = Mono(hydroxyisononyl) phthalate
MiNP = Mono-3-methyl-5-dimethylhexyl phthalate
MiNP-G = Monoisononyl phthalate glucuronide
MNG = Multinucleated germ (cells)
MoA = Mode of Action
MOA = Mechanism of Action
MOiNP = Mono(oxo-isononyl) phthalate
NHANES = United States National Health and Nutrition Examination Survey
NICNAS = Australian Government, Department of Health, National Industrial Chemicals Notification and Assessment Scheme
NIEHS = United States National Institute of Environmental Health Sciences
NIS = sodium/iodide symporter
NOAEL = No observed adverse effect level
NOEL = No observed effect level
NTP = United States Department of Health and Human Services National Toxicology Program
NTP CERHR = National Toxicology Program Center for the Evaluation of Risks to Human Reproduction
OEHHA = California Office of Environmental Health Hazard Assessment
PAE = Phthalic Acid Esters
PE = Phthalate Ester
PMID = PubMed identifier
PND = post-natal day
PPM = Parts per million

PPARα = Peroxisome proliferator-activated receptor alpha
PR = progesterone receptor
REACH = European Union Regulation: Registration, Evaluation, Authorization and Restriction of Chemicals
SAB = Massachusetts Toxics Use Reduction Act Science Advisory Board
SD = Sprague-Dawley Rats or Standard Deviation
SDN-POA = sexually dimorphic nucleus of preoptic area
711P = 1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters, CAS# 68515-42-4
TRI = United States Environmental Protection Agency Toxics Release Inventory
TURA = Massachusetts Toxics Use Reduction Act
ug/kg/bw/day = microgram per kilogram by weight per day
ug/L = micrograms per liter
US EPA = United States Environmental Protection Agency

Appendix G – Phthalate Ester Uses and Substitutes

TURA Reported Uses

Below are listed common reportable uses for the six reportable phthalate esters, from 1990-2014. The list is representative, not exhaustive.

- Custom compounded resins, including PVC (BBP, DnOP, DEHP) TPE, TPO (DEHP)
- Adhesives (BBP, PE, DEHP), activators (DBP)
- Coatings (BBP, DBP, DnOP, PE, DEHP) , wood stains, urethanes, lacquer coatings (BBP)
- vinyl coated fabric (BBP, DnOP, DEHP), coated paper (DBP, DEHP)
- polishes (DBP)
- personal care products – shampoo (DBP), cosmetics (DEP)
- plastisol vinyl resins (DEP, DEHP)
- capacitor fluid (DEHP)
- wire and cable insulation and jacketing (although not commonly used by the many wire and cable companies, a few reported DEHP)
- PVC & rubber articles: shoe soles, rubber gaskets, belts, marine moldings, custom extrusions and profiles, sheet (roofing, windows, etc) (DEHP)
- medical devices – tubing, solution bags (DEHP)
- membrane filters (DEHP)
- color concentrates for compounded resins (although not commonly used, DEHP reported by one company)

Plasticizers

US Consumption of Plasticizers[5]

Plasticizer Type	***2014 (1000 metric tons)***	***Percent of total consumption***
Ortho-Phthalates	496.0	57.8
Terephthalates	95.0	11.1
Aliphatics	73.6	8.6
Epoxy	44.5	5.2
Benzoates	44.5	5.2
Trimellitates	35.2	4.1
Phosphates	23.5	2.7
Polymerics	21.6	2.5
Other	24.6	2.9
Total	**858.5**	**~100%**

[5] IHS Chemical estimates, from Malveda, et al, *Chemical Economics Handbook, Plasticizers 576.0000*, IHS Chemical, July 2015.

Plasticizer selection is based on a balance of cost and performance. Performance criteria include: processing compatibility, efficiency, volatility and electrical resistance. DEHP, DIDP, DINP, and DPHP have the broadest range of markets and the highest compatibility and ease of processing with PVC.[6]

US Consumption of Phthalate Plasticizers[6]

Ortho-Phthalate Esters with typical uses (not comprehensive)	***2014 (1000 metric tons)***	***Percent of Total***
DINP (wire and cable, film and sheet, resilient flooring, coated fabric, color concentrates)	164.0	33.1
DIDP (wire and cable, film and sheet, auto interiors & undercoating, coated fabric, color concentrates)	89.0	17.9
DPHP (wire and cable, auto interiors, roofing, food packaging, adhesives)	84.0	16.9
DEHP (medical devices, consumer goof, construction, weather stripping)	63.0	12.7
BBP (flooring, caulks and sealants, adhesives)	26.0	5.2
DUP (wire and cable, auto interiors, construction)	19.0	3.8
Linear C_9-C_{11} (outdoor applications, auto interiors)	16.0	3.2
DTDP (wire and cable, lubricants)	11.5	2.3
Linear C_8-C_{12} (outdoor applications, swimming pool liners, roofing membranes)	4.0	0.8
DMP (cellulose acetate applications)	3.5	0.7
DEP (cellulose acetate, film, tool handles, adhesives, typ. used with other plasticizers)	1.8	0.4
DBP (cellulose lacquers, PVAc emulsion adhesives, largely replaced by other plastizers)	1.2	0.2
Other	13.0	2.6
Total	**496.0**	**99.8%**

Tere-Phthalate Plasticizers[7]

Tere-Phthalate Esters with typical uses (not comprehensive)	***2014 (1000 metric tons)***	***Percent of total***
DOTP (flooring, toys, pool liners, wire and cable, consumer goods, auto interior)	90.0	94.7
DBT (water based adhesives, PVC plastisols, some food-contact uses)	5.0	5.3
Total	**95.0**	**100%**

[6] IHS Chemical estimates, from Malveda, et al, *Chemical Economics Handbook, Plasticizers 576.0000*, IHS Chemical, July 2015.

[7] IHS Chemical estimates, from Malveda, et al, *Chemical Economics Handbook, Plasticizers 576.0000*, IHS Chemical, July 2015.

Appendix H – EHS Data Spreadsheets

Appendix H1: Ortho Data Spreadsheet

Appendix H2: Meta/Para Data Spreadsheet

Appendix I - Background on Phthalate Ester Category

Background on

Phthalate Ester Category

on the TURA Toxic or Hazardous Substance List

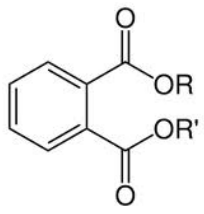
CERCLA categories, including Phthalate Esters, are listed under TURA, but by MassDEP policy, have never been reportable. Many of these categories are not unique - they include substances that are already specifically listed on the TURA chemical list.

Phthalate Esters

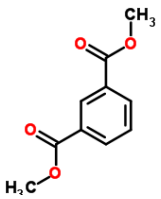
Phthalate esters are esters of phthalic acid. They are widely used as plasticizers in plastics, and as stabilizers, emulsifying agents and lubricants in coatings, paints and other preparations. While six of the most commonly used phthalates (e.g., DEHP) are specifically listed on the TURA list and are reportable, there are many now in use that are not.

When the side chains are located on adjacent carbons of the benzene ring, it is an ortho-phthalate ester; when separated by one carbon, it is a meta- or iso- and on opposite sides of the ring it is a para- or tere-phthalate. When there are 2 side chains, it is a diester. When there are three, it is a triester or trimellitate – see "Closely Related Substances" section below. The side chains may be either alkyl (straight chain) or alkyl aryl (straight and aromatic) chains, and either linear or branched. Examples of ortho-, meta- and para-phthalate esters are shown below.

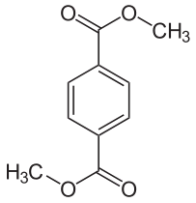
Historically, the most commonly used phthalate esters have been ortho- substituted diesters (2 side chains at adjacent positions on the ring). The following table represents the results of a literature search for phthalate esters, and gives the common abbreviation used in this report. Note that different sources and manufacturers may use different abbreviations for the same or similar commercial products.



Ortho- phthalate ester



Dimethyl isophthalate (or meta-phthalate)



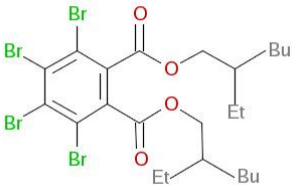
Dimethyl terephthalate (or para-phthalate)

Common Abbrev.	Common Name	CAS No.	TURA Listed (shaded rows)	Ortho- unless otherwise noted
DMP	Dimethyl phthalate	131-11-3	Yes	
DMT	Dimethyl terephthalate	120-61-6	No	Para-
	Dimethyl 4-aminophthalate	51832-31-6	No	
DEP	Diethyl phthalate	84-66-2	Yes	
DMIP	Dimethyl isophthalate	1459-93-4	No	Meta-
	Diethyl terephthalate	636-09-9	No	Para-
DPP	Di-n-propylphthalate	131-16-8	No	
DMEP	Bis(2-methoxyethyl) phthalate	117-82-8	No	
DAP	Diallyl phthalate	131-17-9	No	
	2-(2-hydroxyethoxy)ethyl 2-hydroxy propyl 3,4,5,6-tetra bromophthalate	20566-35-2	No	
DIBP	Diisobutyl phthalate	84-69-5	No	
DBP	Dibutyl phthalate	84-74-2	Yes	
DBTP	Dibutyl terephthalate	1962-75-0	No	Para-
	Bis(2-ethoxyethyl) phthalate	605-54-9	No	
	Di-tert-butyl phthalate	30448-43-2	No	
DinHP	1,2-Benzenedicarboxylic acid, diheptyl ester, branched and linear	68515-44-6	No	
	Diisohexyl phthalate	71850-09-4	No	
DnPP; DPP	Di-n-pentyl phthalate; 1,2-Benzenedicarboxylid acid, 1,2-dipentyl ester	131-18-0	No	
DIPP	Diisopentyl phthalate	605-50-5	No	
	n-pentyl-isopentylphthalate	84777-06-0	No	
PIPP	n-pentyl-isopentylphthalate	776297-69-9	No	
	Bis(2-ethoxyethyl) phthalate	605-54-9	No	
	Hexyl 2-ethylhexyl phthalate	75673-16-4	No	
DHP	Dihexyl phthalate	84-75-3	No	
DnHP	Diisohexyl phthalate	71850-09-4	No	
DnHP	Diisohexyl phthalate; 1,2-Benzenedicarboxylic acid, dihexylester, branched and linear	68515-50-4	No	
BBP	Butyl benzyl phthalate	85-68-7	Yes	
	Bis(2-n-butoxyethyl) phthalate	117-83-9	No	
DEHP	Di(2-ethylhexyl) phthalate	117-81-7	Yes	
DEHT	Bis(2-ethylhexyl) terephthalate	6422-86-2	No	Para-
DCHP	Dicyclohexyl phthalate	84-61-7	No	
DIHepP	Diisoheptyl phthalate	71888-89-6	No	
610P	1,2-Benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters	68648-93-1	No	
	Diheptyl phthalate	3648-21-3	No	
DnOP	Di-n-octyl phthalate	117-84-0	Yes	
DNP	Dinonyl phthalate	84-76-4	No	

Common Abbrev.	Common Name	CAS No.	TURA Listed (shaded rows)	Ortho- unless otherwise noted
	Diphenyl phthalate	84-62-8	No	
	Diphenyl isophthalate	744-45-6	No	Meta-
	Benzyl phthalate	523-31-9	No	
	Bis(4-methyl-2-pentyl) phthalate	146-50-9	No	
	Di-C6-10-phthalate	68515-51-5	No	
	Di-C7-9-phthalate	68515-41-3	No	
	1-methyl-2-[(2-methyl-1-oxoallyl) oxy]ethyl hydrogen phthalate	65859-45-2	No	
DNP	1,2-Benzenedicarboxylic acid, dinonyl ester, branched and linear	68515-45-7	No	
Din79P	1,2-Benzenedicarboxylic acid, heptyl nonyl ester, branched and linear	111381-89-6	No	
711P	1,2-Benzenedicarboxylic acid, 1-heptyl 2-undecyl ester, branched and linear	111381-90-9	No	
DHNUP	1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters	68515-42-4	No	
	Bis(methylcyclohexyl) phthalate	27987-25-3	No	
	Benzyl Hydrogen Phthalate	2528-16-7	No	
DOIP	Di-2-ethylhexyl isophthalate	137-89-3	No	Meta-
DINP	Diisononyl phthalate	28553-12-0	No	
DINP	Diisononyl phthalate	68515-48-0	No	
DIDP	Diisodecyl phthalate	26761-40-0	No	
DIDP	Diisodecyl phthalate	68515-49-1	No	
Din911P	1,2-Benzenedicarboxylic acid, 1-nonyl 2-undecyl ester, branched and linear	111381-91-0	No	
D911P	Di-C9-11-phthalate	68515-43-5	No	
B79P	1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters	68515-40-2	No	
DDP	Didecyl phthalate	84-77-5	No	
DUP	Diundecyl phthalate	3648-20-2	No	
DIUP	Diundecyl phthalate, branched and linear	85507-79-5	No	
	Di-n-dodecyl phthalate	2432-90-8	No	
DTDP	1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich	68515-47-9	No	
DTDP	Ditridecyl phthalate	119-06-2	No	
DITDP	Diisotridecyl phthalate	27253-26-5	No	
	bis[[1,4a-dimethyl-7-(1-methylethyl) tetra decahydrophenanthryl] methyl] phthalate	36388-36-0	No	
	tetramethyl ammonium hydrogen phthalate	79723-02-7	No	
	O'-methyl O-(1-methyl-2-	127244-43-3	No	

Common Abbrev.	Common Name	CAS No.	TURA Listed (shaded rows)	Ortho- unless otherwise noted
	methacryloyloxy-ethyl) -1,2,3,6 - tetrahydrophthalate			
	1,2-Benzenedicarboxylic acid, 1-(2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl) 2-(phenylmethyl) ester;	16883-83-3	No	
DIOP	Diisooctyl phthalate	27554-26-3	No	
DPHP	Di-2-propyl heptyl phthalate	53306-54-0	No	

Brominated Phthalate Esters[8]



Brominated DEHP

Brominated phthalate esters are used as both flame retardants and plasticizers. The following substances are part of the EPA "Brominated Phthalates Cluster (BPC)" TSCA assessment; TBPH and TBB are on EPA's TSCA Work Plan. Chemicals that are phthalate esters (all those in the cluster except TBB) could be considered as part of the phthalate ester category. There are also two confidential substances that are part of the BPC category; there is no information available about their chemical structure. TBPH and TBB are components of Chemtura's flame retardant product Firemaster® 550, and likely other commercial flame retardant products as well.

Common Abbrev.	Common Name	CAS No.	TURA Listed	structure
Brominated DEHP, or TBPH	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester, or (2-ethylhexyl)tetrabromophthalate	26040-51-7	No	Ortho-phthalate ester
TBB	Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester, or 2-ethylhexyl 2,3,4,5-tetrabromobenzoate	183658-27-7	No	Benzoic acid ester, or benzoate
TBPA Diol	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) ester	20566-35-2	No	Ortho-phthalate ester
TBPA Diol (mixed esters)	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, mixed esters with diethylene glycol and propylene glycol	77098-07-8	No	Ortho-phthalate ester
Bromo alkyl ester	1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester	7415-86-3	No	Ortho-phthalate ester

[8] USEPA Assessments for TSCA Work Plan Chemicals, Brominated Phthalate Cluster. Accessed at https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/assessments-tsca-work-plan-chemicals

Background Q&A on the Phthalate Ester Category

Where does this category come from?

The CERCLA Phthalate Ester category originates with the list of Toxic Pollutants in the Clean Water Act (CWA) section 307, Toxic and Pretreatment Effluent Standards.

Has EPA defined which substances are included in the CERCLA categories, either under CERCLA or the CWA?

No, EPA has not defined the categories either under CWA or CERCLA.

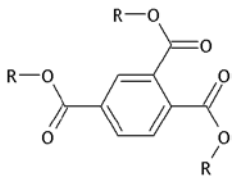
CERCLA: While the CWA toxic substance categories are on the CERCLA list and are considered CERCLA hazardous substances, no reportable quantity under CERCLA has been assigned to these broad classes of compounds, and therefore, no specific compounds have had to be identified as being part of the categories.

CWA: The CWA Toxic Pollutant List of 65 chemicals and classes of chemicals was established in 1976. In an effort to develop a practical regulatory system for this list, EPA developed a CWA Priority Pollutant List of 129 specific substances. This list includes some substances that are part of the categories, selected in the 1970's because analytical methods existed to measure them, because they were known to have health and environmental effects, and because they were known to be discharged by major industries. Over the years, EPA has focused on water quality criteria and standards, effluent limits and industrial pre-treatment, but not on updating either the Toxic Pollutant List or the Priority Pollutant List.

Closely Related Compounds used as plasticizers

Trimellitates

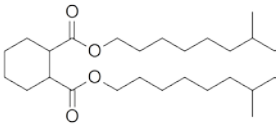
Trimellitates are also benzene rings with alkyl ester side chains, but there are 3 side chains, instead of 2. The building block is trimellitic acid, rather than phthalic acid, and so they are not considered phthalate esters.



Trimellitate (Benzene tricarboxylic acid ester)

Cyclohexane Aliphatic Esters

One popular plasticizer, 1,2-cyclohexane dicarboxylic acid diisononyl ester, sold under the tradename *Hexamoll DINCH*, is made by transforming the aromatic ring of a phthalate ester to a cyclohexane ring.



1,2-Cyclohexane dicarboxylic acid diisononyl ester

Other Plasticizers

Esters of other acids can also be used to produce plasticizers, e.g., adipates, benzoates, dibenzoates, and azelates.