UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Mr. Stephen P. Risotto
Senior Director, Phthalate Esters
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

MAR 14 2012

Dear Mr. Risotto:

This letter is the response to the Phthalate Esters Panel (Panel) of the American Chemistry Council Request for Correction (RFC) #10001, which was received on May 10, 2010. In the RFC, the Panel challenges the "objectivity" of eight statements found in the Environmental Protection Agency's (EPA) Phthalates Action Plan[1]. The Panel alleges these statements are not consistent with the *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency*[2]. The Panel also recommends eight specific corrective actions to address its information quality concerns.

The EPA, after reviewing the Panel's RFC, has concluded that the underlying information and conclusions presented in the Plan are objective and of high quality, consistent with the EPA's Information Quality Guidelines (IQGs). However, to clarify several points noted by the Panel, the EPA has made appropriate revisions to the Action Plan. The EPA's specific response to each of the Panel's information quality concerns can be found in the enclosed document. A copy of the revised Action Plan is also enclosed. In addition, the revised Action Plan, your letter and this RFC response will be placed in the docket for the Phthalates Action Plan (Docket ID No. EPA-HQ-OPPT-2010-0342). As necessary, the EPA's website will also be updated to reflect these revisions.

The Action Plan is intended to describe the courses of action the EPA plans to pursue in the near term to address its concerns. The EPA also includes contextual scientific information to accompany the Action Plan. In preparing the Action Plan, the EPA followed the EPA IQGs to ensure the utility, objectivity, and integrity of the information disseminated in the Action Plan. The information provided in the Action Plan is accurate and reliable, providing specific references to the best available science and supporting studies, and is presented in an unbiased manner with applicable uncertainties and limitations discussed. The Action Plan is also formatted and designed with the intended audience in mind, and posted on the website in a secure manner as to protect the Action Plan from deliberate or accidental alteration. In addition, like other planning tools used by the EPA, Action Plans are not risk assessments or major work products undergoing peer review. Rather, Action Plans are brief public summaries and explanations of the EPA's interest in a chemical and the actions the EPA intends to take concerning that chemical based on its preliminary review of available information. Moreover, Action Plans do not constitute the support

[1] Phthalates Action Plan, U.S. EPA (December 2009).
http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/phthalates_ap_2009_1230_final.pdf
[2] 67 FR 63657 (October 15, 2002).
http://www.epa.gov/quailty/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf.

documents for the actions they describe. The EPA provides the underlying scientific and technical support for an action described in an Action Plan at the time we initiate the action. Action Plans are simply intended to make the EPA planning process more accessible and transparent to the public at an early stage. Any regulatory or other substantive actions undertaken by the EPA subsequent to the publication of an Action Plan would include the EPA specific identification and assessment of the data on which the EPA relied, which may differ from the information presented in the Action Plan.

If you are dissatisfied with this response, you may submit a Request for Reconsideration (RFR). The EPA requests that any such RFR be submitted within 90 days of the date of the EPA's response. If you choose to submit a RFR, please send a written request to the EPA Information Quality Guidelines Processing Staff via mail (Information Quality Guidelines Processing Staff, Mail Code 2811R, U.S. EPA, 1200 Pennsylvania Avenue, NW, Washington, DC 20460); electronic mail (quality@epa.gov); or fax ([202] 565-2441). If you submit a RFR, please reference the request number assigned to the original Request for Correction (RFC #10001). Additional information about how to submit an RFR is listed on the EPA Information Quality Guidelines website at http://epa.gov/quality/informationguidelines/index.html.

Sincerely,

James J. Jones
Acting Assistant Administrator

Enclosures

cc: Malcolm D. Jackson, Assistant Administrator and Chief Information Officer, Office of Environmental Information

Enclosure #1:
EPA Response to Specific Statements
from the Phthalate Esters Panel (Panel) of the American Chemistry Council
(Request for Correction (RFC) #10001)

Below are the EPA's responses to the eight statements for which the Phthalate Esters Panel (Panel) of the American Chemistry Council requested correction (see Panel's RFC for full description of the requested changes).

1. "The most sensitive health outcomes following exposure to some phthalates in animal studies are the phthalate syndrome effects, which consist of changes in the fetal development of the reproductive system."

EPA Response: The spectrum of effects observed in male animals after exposure to various phthalates was referred to as the phthalate syndrome in the 2008 NAS report, "Phthalates and Cumulative Risk Assessment; The Tasks Ahead", (http://dels.nas.edu/Report/Phthalates-Cumulative-Risk-Assessment/12528). On page 38 of this report, NAS states: "Furthermore, although the committee clearly recognized that cumulative risk assessment must encompass the assessment of multiple agents and other stressors to which people are exposed by multiple pathways and routes and for varied durations and that cause varied health effects, it restricted its examination to the most sensitive outcomes (that is, effects on the development of the male reproductive system) exhibited in laboratory animals as a result of phthalate exposure." On page 6 of this report, phthalate syndrome is described as "That group of effects observed in male animals is known as the phthalate syndrome and includes infertility, decreased sperm count, cryptorchidism (undescended testes), hypospadias (malformation of the penis in which the urethra does not open at the tip of the organ), and other reproductive tract malformations." Hence, because phthalate syndrome includes effects on the male reproductive system, this term was used. The EPA used this secondary source for the Action Plan and considers the NAS a credible source.

2. "Several human studies have reported associations of exposure of some phthalates with adverse reproductive outcomes and developmental effects similar to those in the rat, although no causal link has been established (Swan et al., 2005, Huang et al., 2009)."

EPA Response: The statement is a factual summary of the content of the paragraph (i.e. topic sentence), which describes in more detail the variety of adverse reproductive and developmental effects that have been observed in humans. Both the Swan et al. and Huang et al. papers report an association between prenatal exposure to phthalates and certain adverse outcomes in newborns. In Huang et al. (2009), an association between phthalate metabolite concentration in amniotic fluid (MBP-AF) and anogenital indices (AGI-W) and AGI-L is reported on page 18, stating "The significantly negative correlations (Spearman and Pearson) between MBP-AF and AGI-W and AGI-L suggest that *in utero* exposure to phthalates may alter the sexual development of females in early pregnancy." In Swan et al. (2005), the final paragraph states "We report that AGD, the most sensitive marker of anti-androgen action in toxicologic studies, is shortened and testicular descent impaired in boys whose mothers had elevated prenatal phthalate exposure. These changes in male infants, associated with prenatal exposure to some of the same phthalate metabolites that cause similar alterations in male rodents, suggest that commonly used phthalates may undervirilize humans as well as rodents."

ED_012964_00017288-00003

3. "The reproductive developmental effects observed in humans include shortened anogenital distance observed in newborn boys; and shortened pregnancy, lower sex and thyroid hormones, and reduced sperm quality in adults."

EPA Response: This sentence is the EPA's synopsis of a effects reported in a large body of research presented in the in the NAS 2008 report (Chapter 3), which has already been cited in the *Human Health Effects* section of the Action Plan. The EPA used this secondary source for the Action Plan and considers the NAS a credible source. Full discussion of these studies can be found in the 2008 NAS report. The studies report the observations described in the Action Plan. For clarification, the EPA has revised the Action Plan to add a cite to the NAS 2008 report at the end of this sentence.

4. "In addition, recent studies in animals evaluating the cumulative effects of mixtures of several active phthalates on testosterone production, fetal mortality, and male and female reproductive development later in life showed all mixtures were cumulative for all endpoints (Rider et al., 2008, 2009; Howdeshell, et al., 2007, 2008a, 2008b; Gray et al., 2006; Hotchkiss et al., 2004)."

EPA Response: The references cited all conclude that the mixtures of chemicals tested, including phthalates, caused effects in a cumulative, dose-additive manner, hence, the sentence as supported by the references provided is factual.

The Panel has suggested the addition of text to the EPA's Action Plan. However, the EPA's review of the references provided by the Panel indicates lack the objectivity needed to support the Panel's suggested change. The references provided by the Panel in support of its suggested text "similar effects have not been observed at environmentally-relevant exposure concentrations" consist of the following: Foster et al., 2002; Christiansen et al., 2009; Chapin et al., 1989; Heindel et al., 1995 and Benson, 2009. The Foster et al., reference is an abstract from a poster presentation at a Society of Toxicology meeting. Abstracts are very short summaries, often based on preliminary or non-peer reviewed data/information and therefore potentially lack the level of quality and objectivity appropriate as a reference supporting an Action Plan. The reference by Benson describes an analysis of human exposures, whereas the EPA's statement is clearly summarizing animal data. The references by Chapin and Heindel are generally more than a decade older, not "more recent" as the Panel states, than the references the EPA provided. Neither of these studies examines the effect of mixtures of phthalates on the endpoints that are listed in the sentence provided by the EPA. Therefore, they are of limited utility incomparing or contrasting to the EPA's text, which is limited to a discussion of phthalates only. The 2009 Christiansen reference is as follows: Christiansen S, Scholze M, Dalgaard M, Vinggaard AM, Axelstad M, et al. 2009 Synergistic Disruption of External Male Sex Organ Development by a Mixture of Four Antiandrogens. Environ Health Perspect 117(12): 1839-1846 found at http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info%3Adoi%2F10.1289%2Fehp.0900689. (The reference information appears to contain a typographical error), the EPA's review of Christiansen et al. indicates the study examined effects of mixtures of a variety of different types of chemicals in addition to phthalates. For example, the Christiansen paper reports "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 weight, and weights of LABC." It further states "The experimentally observed responses

ED_012964_00017288-00004

clearly exceeded the predictions, suggesting that the combined effect of DEHP, vinclozolin, prochloraz, and finasteride is synergistic with respect to genital malformations." Both of these conclusions indicate interactive effects among the different chemicals rather than a lack of cumulative effects and therefore are of limited utility in comparing or contrasting to the EPA's text, which is limited to a discussion of phthalates only. Finally, in the Christiansen study, none of the chemicals were actually tested at environmentally relevant exposure levels.

5. "For example, inhalation exposure for adults and children could be of concern in vehicle interiors, particularly in summer due to elevated temperatures in vehicles given the vapor pressure range of these chemicals."

EPA Response: This statement is an example based on the physical-chemical properties provided in the previous section of the Action Plan. However, for clarification, the EPA has revised the Action Plan by adding citations to the EU RAR for DEHP, EU RAR for DIDP and the NTP-CERHR for DIDP.

As to the accuracy of the statement, the Panel refers to a secondary reference (Research Institute for Chromatography, 2000) from the EU Risk Assessment Report (RAR) for DIDP, but omits the conclusion in that EU report: (1) "DIDP can be released during fogging (when sheets of PVC as dashboard, doors trim, seats are heated by the sun);" and (2) "Use of plasticisers, and particularly DIDP, in the material use in interior cars (dashboard, coverings…) can lead levels of plasticiser vapour being present in car air under normal indoor conditions." See section 4.1.1.3.5.

The Panel also cites a 2001 Australian Government press release about its research on VOC levels in 3 new automobiles (reference 21: CSIRO, 2001); the absence of phthalates from the non-exclusive list of air toxics in this press-release does not contradict the EPA's statement. Finally, the Panel references a study (reference 22: Buters, et al., 2007) that has a sample size of 2, one new and one old car. This study suggests that the concentration of phthalates are "low" in old cars compared to new cars, but not that phthalates are not present in old cars. Nothing in these studies constitutes contrary scientific evidence that would warrant the retraction of the EPA's statement in the Action Plan.

6. 'Due to their pervasive use and release, as well as its propensity for global transport, phthalates are found in most environmental media, for example ambient air, surface water, soil, sediment, etc (EC, 2003a-b; 2008a-b; NTP-CERHR, 2003 a-e; 2006)."

EPA Response: The Panel's basis for correction includes various characterizations that are used to define persistence and bioaccumulation; however, these are not relevant to the EPA's statement regarding the global transport of phthalates (above). As previously stated in the section on *Human Exposure*, the EPA provides the hypothesis "…due the total volume of plasticized PVC produced, it is possible that PVC or other polymer/polymeric-like materials containing phthalates may be long-term and dispersive sources of human and environmental exposures to phthalates." Evidence of global plastic contamination and global transport of plastic contamination abounds. For example, there is evidence micro plastics are in the ocean (http://marinedebris.noaa.gov/projects/pdfs/Microplastics.pdf) in great quantity. It is well established that some plastics contain and may release phthalates. Therefore, it is a reasonable conclusion that phthalates have a propensity to be transported globally via plastics. To clarify this point, the EPA has amended this sentence in the Action Plan to read: "Due to their pervasive

ED_012964_00017288-00005

use and release, as well as the propensity for global transport of plastics, many of which contain phthalates, phthalates are found in most environmental media....

7. "Among other provisions, the Consumer Product Safety Improvement Act of 2008 (CPSIA) banned the use of six phthalates in toys and child care articles at concentrations greater than 0.1 percent: DEHP, DBP, BBP, DINP, DIDP and DnOP."

EPA Response: The Panel expresses a concern that the Action Plan does not adequately distinguish the CPSIA's permanent phthalate ban from its interim phthalate ban. Yet the Action Plan makes clear, immediately following the cited quote, that use of DINP, DIDP, and DnOP "may be reinstituted by CPSC." The EPA recognizes that the interim ban applies to (among other products) "any children's toy that can be placed in a child's mouth." Yet this is not inconsistent with the statement in the Action Plan that the ban applies to "toys." In point of fact, it is the Panel's suggested correction text that misstates the requirements of the CPSIA ("[T]he act also imposes an interim prohibition on DINP, DIDP, and DnOP in toys and child care articles that can be placed in a child's mouth.") The interim ban also covers child care articles that cannot be placed in a child's mouth: "(1) INTERIM PROHIBITION.—Beginning on the date that is 180 days after the date of enactment of this Act and until a final rule is promulgated under paragraph (3), it shall be unlawful for any person to manufacture for sale, offer for sale, distribute in commerce, or import into the United States any children's toy that can be placed in a child's mouth <u>or child care article</u> that contains concentrations of more than 0.1 percent of diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), or di-n-octyl phthalate (DnOP)." CPSIA, § 108(b)(1) (emphasis added).

8. "As part of a statute concerning chemicals in children's products generally, Washington prohibits a manufacturer, wholesaler, or retailer from manufacturing, knowingly selling, offering for sale, or distributing for sale or for use in the state a children's product or product component containing phthalates (DEHP, DBP, BBP, DINP, DIDP, DnOP) individually or in combination, at a concentration exceeding 0.1% by weight (CRS, 2008)."

EPA Response: The Panel's observations about the regulatory activities of Washington's Department of Ecology (DOE) do not detract from the accuracy of the EPA's description of the 2008 Act of the Washington State legislature to address particular phthalates. The EPA's description of the Act matches what was enacted. However, we are aware that the Washington State DOE issued a notice on November 5, 2008 [WSR 08-23-040, 11/12/08], that it was withdrawing a May 20, 2008, proposed regulations intended to clarify how lead, cadmium and phthalate standards apply to certain products. The Washington DOE concluded this implementing regulation was not necessary because the federal law (CPSIA) "substantially preempted" the state standards and the pursuit of an exemption "would likely result in a protracted legal argument with marginal improvement in the safety of children's products." The Washington DOE's decision not to pursue further regulatory action did not revoke CPSA, which remains in the Revised Code of Washington, and is being implemented in other aspects not subject to federal preemption concerns.

ED_012964_00017288-00006

Phthalates Action Plan[1]

I. Overview

U.S. Environmental Protection Agency's (EPA's) current management plan includes the following eight phthalates: dibutyl phthalate (DBP), diisobutyl phthalate (DIBP), butyl benzyl phthalate (BBP), di-*n*-pentyl phthalate (DnPP), di(2-ethylhexyl) phthalate (DEHP), di-*n*-octyl phthalate (DnOP), diisononyl phthalate (DINP), and diisodecyl phthalate (DIDP). In developing this plan, EPA considered the toxicity of phthalates, their prevalence in the environment and their widespread use and human exposure.

Phthalates are produced in high volume, over 470 million pounds per year (EPA 2006). Manufacturers use them in numerous industrial and consumer products, primarily as plasticizers in poly(vinyl chloride) (PVC) products. Many phthalates can potentially lead to high exposure, both individually and together with other phthalates. They can often substitute for each other in products. They are used in medical applications and have been detected in food. A number of phthalates appear in biomonitoring surveys of human tissues, evidencing widespread human exposure (CDC 2009). Although exposure to phthalates can produce a variety of effects in laboratory animals, for certain phthalates the adverse health effects on the development of the male reproductive system are the most serious. Several studies have shown associations between phthalate exposures and human health (although no causal link has been established). Recent scientific attention is focusing on evaluating the cumulative effects of mixtures of phthalates in an exposed organism.

EPA is concerned about phthalates because of their toxicity and the evidence of pervasive human and environmental exposure to them. Thus, EPA intends to initiate action to address the manufacturing, processing, distribution in commerce, and/or use of these eight phthalates. EPA intends to take action as part of a coordinated approach with the Consumer Product Safety Commission (CPSC) and the Food and Drug Administration (FDA).

II. Introduction

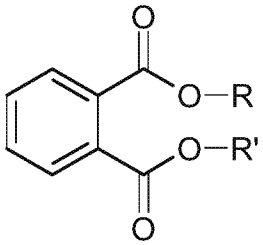
As part of EPA's efforts to enhance the existing chemicals program under the Toxic Substances Control Act (TSCA)[2], the Agency identified an initial list of widely recognized chemicals, including phthalates (e.g., see Section VIII of this document), for action plan development based on one or more of the following factors their presence in humans; persistent, bioaccumulative, and toxic (PBT)[3] characteristics; use in consumer products; production volume. This Action Plan is based on EPA's initial review of readily available use, exposure, and hazard information on eight phthalate esters. EPA considered which of the various authorities provided under TSCA and other statutes might be appropriate to address potential concerns with phthalates in developing the Action Plan. The Action Plan is intended to describe the courses of action the Agency plans to pursue in the near term to address its concerns. The Action Plan does

1 The Action Plan was originally issued on 12/30/2009.
2 15 U.S.C. §2601 *et seq.*
3 Information on PBT chemicals can be found on the EPA website at http://www.epa.gov/pbt/.

not constitute a final Agency determination or other final Agency action. Regulatory proceedings indicated by the Action Plan will include appropriate opportunities for public and stakeholder input, including through notice and comment rulemaking processes.

III. Scope of Review

Dialkyl *ortho*-phthalates (or phthalate esters) have the general chemical structure shown below:



(R, R' groups can be linear, branched, or linear/branched or cyclic ring)

For purposes of this Action Plan, EPA identified eight individual phthalate esters as appropriate subjects for developing an assessment and management strategy. This group of eight phthalates includes the phthalates identified by CPSIA and those being evaluated by EPA for the Integrated Risk Information System (IRIS), based on advice from the National Academy of Sciences (NAS, 2008). Four phthalates are common to CPSIA and the IRIS assessment. This Action Plan includes the following eight chemical substances, identified by 10 separate Chemical Abstracts Service Registry Numbers (CASRNs):

No	CASRN	CA Index Name	Acronym	Common Name
1	84-74-2	1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester	DBP	Dibutyl phthalate
2	84-69-5	1,2-Benzenedicarboxylic acid, 1,2-bis-(2-methylpropyl) ester	DIBP	Diisobutyl phthalate
3	85-68-7	1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester	BBP	Butyl benzyl phthalate
4	131-18-0	1,2-Benzenedicarboxylid acid, 1,2-dipentyl ester	DnPP	Di-*n*-pentyl phthalate
5	117-81-7	1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester	DEHP	Di(2-ethylhexyl) phthalate
6	117-84-0	1,2-Benzenedicarboxylic acid, 1,2-dioctyl ester	DnOP	Di-*n*-octyl phthalate
7	28553-12-0	1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester	DINP*	Diisononyl phthalate
	68515-48-0	1,2-benzenedicarboxylic acid, di-C_8-C_{10}-branched alkyl esters, C_9-rich	(Part of DINP)*	Di-(C_9-rich branched C_8-C_{10}-alkyl) phthalate
8	26761-40-0	1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester	DIDP*	Diisodecyl phthalate
	68515-49-1	1,2-Benzenedicarboxylic acid, di-C_9-C_{11}-branched alkyl esters, C_{10}-rich	(Part of DIDP)*	Di-(C_{10}-rich branched C_9-C_{11}-alkyl) phthalate

* Note that each of the commercial products DINP and DIDP is a mixture of two phthalates.

IV. Uses and Substitutes Summary

According to the 2006 TSCA Inventory Update Reporting (IUR) database (EPA, 2006), reported volume of production (including imports) for the 10 individual phthalates ranged from none up to 500 million pounds. DINP had the highest production volume, followed by DIDP and

DEHP, then BBP, DBP, DnOP and DIBP. There was no production volume data reported for DnPP in the 2006 IUR database.

The major use of phthalates is as plasticizers (Australian Government, 2008a-h; HSDB, 2009). A major application of plasticizers is in PVC, [poly(vinyl chloride)], where they are added to impart flexibility and other desirable properties. Phthalate-containing PVC products included a variety of industrial and commercial products, as well as specialized medical and dental applications. The particular phthalate or combination of phthalates used in a particular product's formulation depends on the properties the phthalates impart, as well as their cost. BBP is the most widely used stain-resistant plasticizer in PVC (Wickson, 1993); vinyl tile represents its largest use (NTP, 2003e). A number of uses of DBP have been identified including the manufacture of plastics, paints, wood varnishes and lacquers, use in cosmetics, medical supplies, textiles, propellants, food packaging, dental materials, and paper (OSHA, 2009). More specifically, it is used as a plasticizer in uses such as nail polishes, explosives, and solid rocket propellants. Nearly half of DEHP consumption in the United States occurs in medical devices, such as intravenous (IV) tubing and blood bags. The rest is split between consumer products and construction-related products (TURI, 2006). DIBP is considered a specialty plasticizer, too volatile to be used in PVC, and is often combined with other phthalates. As such, it is used in nitrocellulose, cellulose ether, and polyacrylate and polyacetate dispersions (ECPI, 2009). The major use of DIDP is in PVC as a plasticizer (95%) (EC2003b). DIDP is extensively used in wire and cable applications, and is, the main plasticizer used in this application (TURI, 2006). Non-PVC uses of DIDP include polymer-related uses and nonpolymer uses such as anti-corrosion and anti-fouling paints, sealing compounds, and textile inks (EC2003b). DINP is a mixture of phthalates and is a commonly used plasticizer (TURI, 2006). PVC applications account for 95 percent of the volume. There are no known commercial uses for pure DnOP. However, DnOP constitutes approximately 20 percent of the C_{6-10} phthalate mixtures used in PVC products (NTP, 2003a).

There are various possible alternatives for phthalates in plasticized PVC (Biron, 2009; SCENIHR, 2007). Four chemicals have been cited as already being used in various children's products; they are acetyl tri-*n*-butyl citrate (ATBC); di(2-ethylhexyl) adipate (DEHA); 1,2-cyclohexanedicarboxylic acid, diisononyl ester (DINCH), and di(2-ethylhexyl) terephthalate (DEHT or DOTP). Citrate-based plasticizers, like ATBC, are drop-in substitutes for DEHP made from citric acid and have been available for years as plasticizers in medical devices (Tickner, 2001). DINCH is an alternative for applications such as medical devices (SCENIHR, 2007). Another chemical, trioctyltrimellitate (TOTM) performs as a plasticizer in PVC and it has potential to be used commercially. Promising non-phthalate substitutes for DEHP in vinyl flooring material include DGD (dipropylene glycol dibenzoate) and DEHA (di(2-ethylhexyl) adipate). Other possible phthalate substitutes include: phosphate esters (e.g., tris(2-ethylhexyl)phosphate); sebacate and azelate esters (e.g., diisodecyl sebacate (DIDS), di-butyl sebacate, and di(2-ethylhexyl) azelate (DOZ)); isosorbide esters (made from renewable resources), and other organic esters such as isobutyrate trimethylpentanediol, and diethyl succinate. In addition, low-molecular-weight polymeric ester plasticizers that are derived from polymeric multifunctional alcohols and adipic, sebacic or glutaric acid; polymeric rubbers and plastics; and reactive plasticizers may also be potential substitutes for phthalates (Biron, 2009;

SCENIHR, 2007). As part of its inquiry, EPA will explore the potential risks as well as costs presented by phthalate substitutes.

In response to a European ban on the use of some phthalates in toys and personal care products for children, plasticizers based on isosorbide esters were developed (Roquett, 2009). These plasticizers can cover a broad range of phthalate applications, such as adhesive, sealants, inks, floor coverings, wall paper, and medical disposables. It is worth noting that isosorbide esters could be prepared under solvent-free conditions (Chalecki, 1997), providing an environmentally friendly approach to manufacturing.

V. Hazard Identification Summary

Human Health Effects

A comparison of toxicity information from laboratory animal studies for phthalates as a chemical group allows generalizations to be drawn with respect to certain health endpoints. For example, acute toxicity, skin and eye irritation and sensitization potential are low for all phthalates tested, and the majority of the phthalates were not genotoxic. The most sensitive health outcomes following exposures of some phthalates in animal studies are the phthalate syndrome effects, which consist of changes in the fetal development of the reproductive system (NAS, 2008; NTP-CERHR, 2003a-e, 2006; EC, 2003a-b, 2003-4, 2008a-b; Australian Government, 2008a-h). The phthalates that are the most potent at causing the phthalate syndrome effects are generally those with linear ester side chains having 4-6 carbons. Phthalates with shorter or longer chain lengths typically exhibit less severe or no effects; however, branching of the ester side chain is important. It appears that the age of the animal at the time of exposure is critical with respect to the severity of the effects; pubertal animals show effects at doses lower than those in the corresponding studies in adult animals. The fetus is the most sensitive life stage (NAS 2008).

Several human studies have reported associations of exposure of some phthalates with adverse reproductive outcomes and developmental effects similar to those in the rat, although no causal link has been established (Swan et al, 2005; Huang et al., 2009). The reproductive developmental effects observed in humans include shortened anogenital distance observed in newborn boys; and shortened pregnancy, lower sex and thyroid hormones, and reduced sperm quality observed in adults (NAS, 2008). Since the pathway for sexual differentiation in the fetus is highly conserved in all mammals, the reproductive developmental effects observed in the rat studies are potentially relevant to humans. Data from the National Health and Nutrition Examination survey (NHANES) indicates widespread exposure of the general population to phthalates (CDC, 2009). Biomonitoring data from amniotic fluid and urine have demonstrated that humans are exposed to phthalates *in utero*, as infants, during puberty, and in adult life, and that people are exposed to several phthalates at once. In addition, recent studies in animals evaluating the cumulative effects of mixtures of several active phthalates on testosterone production, fetal mortality, and male and female reproductive development later in life showed all mixtures were cumulative for all endpoints (Rider et al., 2008, 2009; Howdeshell, et al., 2007, 2008a, 2008b; Gray et al., 2006; Hotchkiss et al., 2004). In conclusion, taken together, the reproductive effects observed in animal studies and in humans, the human biomonitoring data,

and the data on cumulative effects of mixtures support EPA's concern for potential human health hazard following exposure to phthalates.

A major cumulative hazard assessment of phthalates is scheduled to be conducted by the CPSC's Chronic Hazard Advisory Panel (CHAP) as directed by the Consumer Product Safety Improvement Act of 2008 (CPSIA). The anticipated date of completion for the CPSC/CHAP activity is 2012[4]. EPA is conducting its own cumulative hazard assessment of six of the phthalates in this Action Plan as part of the updating of the IRIS database. In a separate effort EPA is screening certain phthalates to assess their endocrine disrupting properties.

Environmental Effects

Of the 8 phthlates, BBP, DEHP, and DBP elicit the most toxicity to terrestrial organisms, fish, and aquatic invertebrates (EC, 2008a,; Staples et al. 1997). Ecotoxicity studies with these phthalates showed adverse effects to aquatic organisms with a broad range of endpoints and at concentrations that coincide with measured environmental concentrations. Toxic effects were observed at environmentally relevant exposures in the low ng/L to µg/L range (Oehlmann et al. 2008). The other three phthalates which had data: DIBP, DINP, and DIDP, exhibited much lower toxicity to aquatic organisms (Staples et al. 1997). There are no available ecotoxicity data for DnPP or DnOP.

Some phthalates studied have been shown to affect reproduction and impair development in all studied animal groups. Most phthalates appear to act by interfering with the functioning of various hormone systems, but some phthalates have wider pathways of effects (Jobling et al. 1995). Effect concentrations of phthalates in laboratory experiments are consistent with measured environmental concentrations (Oehlmann, et al., 2008).

VI. Physical/Chemical Properties andFate Characterization Summary

The chemicals in this category are oily liquids at room temperature. They have low to moderate vapor pressures and negligible to moderate water solubility. The water solubility and vapor pressure decrease and the octanol-water partition coefficient (log K_{ow}) increases with increasing molecular weight (i.e., as the side chain length increases). The vapor pressure ranges from 8 H 10^{-5} to 1.38 H10^{-8} mm Hg at 20°C; the water solubility range from 10 mg/L to 3.81 H10^{-5} mg/L at 20°C; and the log K_{ow} ranges from 4.11 (for DIBP) to 9.46 (for DIDP) (Australian Government, 2008a-h; HSDB, 2009; Crossfire Beilstein, 2009; ExxonMobil Biomedical Sciences, Inc., 2001).

The chemicals in this category have moderate volatility from moist soil surfaces and water. They have low to moderate mobility in soil and water systems. They are expected to be readily biodegradable and the rate of abiotic hydrolysis is considered negligible to slow under environmental conditions. Based on available data, the phthalates are ranked low for persistence

[4] CPSIA gives the CHAP 18 months to complete its evaluation, and 6 months to complete its final report, for a total of 24 months. Previous CHAPs have requested additional time. The CPSC staff estimates that the CHAP will begin work in early calendar year 2010. Thus, for planning purposes, the staff estimates that the report will be completed in 2012

ED_012964_00017288-00011

and low for bioaccumulation although bioconcentration factors for DEHP in freshwater shrimp were moderate (HSDB, 2009; NITE, 2002).

VII. Exposure Characterization Summary

Releases

Phthalates are released to the environment from multiple sources including industrial releases, the disposal of manufacturing, processing and industrial wastes, municipal solid waste, land application of sewage sludge, and release from products containing phthalates. Only two (DBP and DEHP) of the 8 phthalates are listed on EPA's Toxics Release Inventory (TRI).list of toxic chemicals. The available release data for these two phthalates indicate that releases of phthalates can be expected to all primary environmental media. 2007 TRI data (EPA, 2009) for DBP and DEHP show total on-site and off-site releases of more than 336,000 pounds from 134 sites and 1,229,000 pounds from 251 sites, respectively; however, under TRI, some volume of releases are not reported by some facilities. These data also indicate that the volume of releases to particular media generally ranks in the following order (from highest to lowest release volume): land, air, water. Some facilities report relatively high releases and may create potentially high localized environmental concentrations of phthalates. Based on a comparison of TRI releases to IUR data, production and import volumes indicate that the vast majority (likely between 95% and 99.9%) of phthalates can be expected to be incorporated into plastics and other products.

Human Exposure

People may be exposed to phthalates from multiple sources, (including air, water, food, soil, sediments, and biota) and in multiple environments (including home, work, and when undergoing medical procedures) (Babich, 2004; Clausen 2004; EC, 2003 a-b; 2003-04; 2008 a-b; CPSC, 2001; 2002). The most studied population and route of exposure for this class of chemicals has been direct exposure via ingestion by small children and infants from the mouthing of toys, teethers, or other children's products made of flexible PVC (Babich, 2004; EU 2003 a,b; 2003-04; 2008 a,b; CPSC 2001, 2002). Exposures have also been shown to occur via prenatal exposures. (Adibi et al., 2004)

Medical device assessments for DEHP have been developed by FDA, Health Canada Medical Devices Bureau and the European Union Scientific Committee on Medicinal Products and Medical Devices (FDA, 2002a; Health Canada, 2002; EC 2002). The overarching conclusion is that premature infants are the population most highly exposed to phthalates via these uses. In 2002, the FDA recommended the use of alternatives to DEHP-containing medical devices for a specific list of procedures that were to be performed on high-risk individuals. Depending on the procedure, these individuals include male neonates, pregnant women who are carrying male fetuses, and peripubertal males (FDA, 2002b).

Exposure routes of concern will depend on the product and its use patterns. For example, inhalation exposure for adults and children could be of concern in vehicle interiors, particularly in summer due to elevated temperatures in vehicles given the vapor pressure range of these

chemicals (EC, 2003b; EC, 2008a; NTP-CERHR, 2003c). Exposure to phthalates can occur from releases that result from the manufacturing, processing or industrial use of phthalates as well as contamination of air, water, food, and dust from the use or disposal of products containing phthalates. The published literature indicates that the exposure sources listed from highest to lowest are: food, cosmetics, consumer products (other than toys), and toys (NTP-CERHR, 2003 a-e, 2006; HSDB, 2009). There are limited data on the migration of phthalate from plasticized PVC into environmental media. However, due the total volume of plasticized PVC produced, it is possible that PVC or other polymer/polymeric-like materials containing phthalates may be long-term and dispersive sources of human and environmental exposures to phthalates.

Data from the NHANES (CDC, 2009) indicates widespread exposure of the general population to phthalates. Biomonitoring data from amniotic fluid and urine have demonstrated that humans are exposed to phthalates *in utero*, as infants, during puberty, and in adult life, and that people are exposed to several phthalates at once. For example, NHANES detected a DEHP urinary metabolite in 78% of the 2541 samples tested with women having a higher exposure than men (CDC, 2009). Children have been reported as having the highest exposures; specifically to DEHP, DBP, BBP and DnOP.

Available information indicates that workers may be exposed to phthalates by inhalation and dermal routes, with the dermal route seeming to be more prevalent. The Occupational Safety and Health Administration (OSHA) has established Permissible Exposure Limits (PELs) of 5 mg/m^3 time-weighted average (TWA) for both DBP and DEHP (OSHA, 2006). According to the IUR data, industrial workers exposed to these phthalates number in the thousands.

Environmental Exposure

Due to their pervasive use and release, as well as the propensity for global transport of plastics, many of which contain phthalates, phthalates are found in most environmental media, for example ambient air, surface water, soil, sediment, etc (EC, 2003a-b; 2008a-b; NTP-CERHR, 2003 a-e; 2006). Aquatic organisms, fish and terrestrial animals have evident exposure to DEHP (EC 2008a; Staples et al. 1997).

VIII. Risk Management Considerations

Phthalate exposures can produce a variety of adverse effects in laboratory animals; especially on the development of the male reproductive system, and therefore there are implications for human health. Animal data on the cumulative effect of mixtures of several phthalates showed an increase in the reproductive effects in the organism exposed. Phthalates are produced in high volume and they are used in numerous industrial and consumer products. Phthalates appear in biomonitoring surveys, such as NHANES, that provide evidence of widespread human exposure. Phthalates are also found in the environment and wildlife species. EPA is concerned with phthalates based on toxicity, particularly to the development of the male reproductive system, prevalence in the environment, widespread use and human exposure and recent work focusing on the potential cumulative effect of mixtures of phthalates.

Potential Impacts on Children

Phthalate exposures are a potential concern for children's health. In animal studies, exposure to phthalates during fetal development results in adverse effects on the male reproductive system. The timing of exposure is critical to the severity of effects. The fetus is the most sensitive life stage for male reproductive effects, and pubertal animals show effects at lower doses than those showing effects in adult animals. Children are exposed to phthalates through environmental sources (e.g., air, water, food) as well as consumer products (e.g., toys).. Children's estimated exposures are often greater than those in adults which may be due to increased intakes of food, water, and air on a bodyweight basis, as well children's unique exposure pathways such as mouthing of objects and ingestion of non-food items. The 1999-2000 and 2001-2002 biomonitoring data in the *Third National Report on Human Exposure to Environmental Chemicals* demonstrate that children have the highest exposures to phthalates of all groups monitored, and other biomonitoring data indicate *in utero* exposures to phthalates (CDC, 2005). Given the well-characterized health effects of phthalate exposure in animals in conjunction with the demonstrated widespread phthalate exposure in children, EPA believes that the cumulative health risks of phthalates should be assessed to determine what actions are warranted to insure protection of children's health from this group of chemicals.

Existing Risk Management Activities

Federal Government

The federal government both regulates and continues to study phthalates. Federal entities involved in phthalate management and research include:

Consumer Products Safety Commission (CPSC) – Among other provisions, the Consumer Product Safety Improvement Act of 2008 (CPSIA) banned the use of six phthalates in toys and child care articles at concentrations greater than 0.1 percent: DEHP, DBP, BBP, DINP, DIDP and DnOP. The use of three of these banned phthalates, DINP, DIDP, and DnOP may be reinstituted by CPSC pending review by the Chronic Hazard Advisory Panel. The CPSIA tasks the CPSC with appointing a Chronic Hazard Advisory Panel and examining the cumulative health risks of phthalates and phthalate substitutes. The CHAP will recommend to the Commission whether to continue the ban of DINP, DIDP, and DnOP and whether any other phthalates or phthalate substitutes should be banned.

Food and Drug Administration (FDA) – The FDA regulates phthalates in food contact substances (such as plastic wrap), cosmetics, pharmaceuticals and medical devices. FDA announced in June 2008 that it is conducting a comprehensive inventory of regulated products that contain phthalate and is reviewing available use and toxicology information associated with phthalate exposure from FDA regulated products to better characterize any potential risk from these uses.

Environmental Protection Agency (EPA) – Existing EPA Actions affecting phthalates include:

- DEHP is regulated under the Safe Drinking Water Act. The highest concentration allowed, the maximum contaminant level (MCL), is 0.006 mg/L.

- DEHP and DBP are listed as hazardous air pollutants under the Clean Air Act.

- Under the Resource Conservation and Recovery Act (RCRA), phthalates are regulated as a hazardous waste if discarded as a commercial chemical product.

- DBP and DEHP are reportable to the Toxic Release Inventory (TRI) under section 313 of the Emergency Planning and Community Right-to-know Act (EPCRA).

- BBP, DBP and DEHP are included in the first group of 67 chemicals to be screened as part of the Endocrine Disruptor Screening Program (EDSP).

- Phthalates that are listed on the TSCA Inventory are subject to TSCA section 8(e) Inventory Update Reporting (IUR) requirements, including production and use information for sites having production volumes of at least 25,000lbs/yr. All eight Phthalates (10 CASRNs) included in this Action Plan are listed on the TSCA Chemical Substance Inventory.

- In 1989, EPA entered an Enforceable Consent Agreement under TSCA section 4 with six companies to perform certain chemical fate and environmental effects on certain Alkyl Phthalates (54 FR 618).

- In 2001, under the voluntary HPV Challenge Program, the Phthalate Esters Panel Testing Group of the American Chemical Council sponsored a phthalates ester category. The panel has submitted to EPA robust study summaries or other information for 26 phthalates, including several of those being considered in this Action Plan (BBP, DEHP, DINP, DIDP and DnOP)

State Governments

California, Vermont and Washington have established standards for the content of certain phthalates in children's articles. California prohibits the manufacture, sale, or distribution in commerce of any toy or child-care article that contains DEHP, DBP, or BBP at greater than 0.1% and of any toy or child-care article, intended for use by children under three years of age that can be mouthed, that contains DINP, DIDP or DnOP at greater than 0.1%. Vermont prohibits the manufacture, sale, or distribution in commerce of any toy or child-care article intended for use by a child younger than three years old that contains DEHP, DBP, or BBP in concentrations greater than 0.1% and of any toy or child-care article intended for use by a child under three years of age that can be placed in the mouth and that contains DINP, DIDP, or DnOP in concentrations greater than 0.1% (CRS, 2008).

As part of a statute concerning chemicals in children's products generally, Washington prohibits a manufacturer, wholesaler, or retailer from manufacturing, knowingly selling, offering for sale, or distributing for sale or for use in the state a children's product or product component containing phthalates (DEHP, DBP, BBP, DINP, DIDP, DnOP) individually or in combination, at a concentration exceeding 0.1% by weight (CRS, 2008). Other States such as Hawaii have introduced legislation to prohibit the manufacture, sale, or distribution of certain toys and child care articles containing certain types of phthalates (Hawaii House of Representatives, 2009; CRS, 2008)

Foreign Governments

A number of nations have taken steps to manage risk associated with phthalates or further assess those risks. For example, in 2005, the European Commission banned DEHP, DBP and BBP in all toys and childcare articles (Directive 2005/84/EC). DINP, DIDP and DnOP were banned from use in toys and childcare articles, if they can be put in the mouth by children. Canada proposed in June, 2009 to harmonize their phthalate requirements with those already in effect in the EU and U.S., ensuring the same level of protection as children in the U.S. and the EU (Canada Consumer Product Safety Act). In 2006, the Australian Government declared the phthalates DEHP, DIDP, DMP, DINP, DBP, BBP, DnOP, DEP and bis(2-methylethyl) phthalate as Priority Existing Chemicals and initiated public risk assessments for these phthalates. Phase 1 the development of the public health hazard assessments was concluded in 2008 (Australian Government, 2008a-h). Phase 2 the development of the risk assessments is currently in progress (Australian Government, 2009).

Risk Management Approach

Phthalates are used in products that are subject to EPA, FDA, and the CPSC. People may be exposed to phthalates from a variety of product uses, as well as from industrial releases and environmental exposures; these exposure pathways should be assessed together to appropriately characterize exposures and avoid underestimating risk. The assessment of combined exposure is important to determine the potential impacts of these chemicals. Focusing individually on these phthalates would likely underestimate their impact since they appear to produce similar adverse effects. Also, many phthalates are interchangeable in their uses as plasticizers for flexible PVC products, so restrictions on one could simply shift use to another of similar toxicity. Given this cumulative impact, the management of the risk from combined exposure requires a coordinated approach by all three agencies, and, as appropriate, additional federal agencies. Therefore, EPA intends to work closely with CPSC and FDA to address the range of exposures.

In assessing potential restrictions on certain phthalates, EPA plans to weigh the relative toxicity and feasibility of other phthalate substitutes. Identification of safer and affordable non-phthalate substitutes will be an important consideration in any action that would restrict the use of these chemicals.

IX. Next Steps

On the basis of existing information, the Agency believes that the following regulatory actions would be warranted to manage the risk that may be presented by the eight phthalates identified in the plan.

EPA intends to initiate rulemaking to add the 8 phthalates to the list under TSCA section 5(b)(4). Section 5(b)(4) authorizes the EPA to compile and keep current a list of chemicals it finds present or may present an unreasonable risk of injury to health or the environment. EPA intends to publish a notice of proposed rulemaking in autumn, 2010.

EPA intends to initiate rulemaking in late 2010 to add the six phthalates not listed on the Toxics Release Inventory to that list. Only two of the eight phthalates in this Action Plan are currently on this Emergency Planning and Community Right-to-Know Act (EPCRA) section 313 list of toxic chemicals.

EPA intends to lay the groundwork to consider initiating in 2012 rulemaking under TSCA section 6(a) to regulate the eight phthalates In preparation for rulemaking, EPA intends, in cooperation with CPSC and FDA, to continue its work to more fully assess the use, exposure and substitutes for these chemicals. In its further review, EPA plans to consider the future results of the cumulative assessment that will be developed by the CPSC. The cumulative assessment approach under development by CPSC, which may be completed in 2012, as well as the ongoing review of phthalates at the FDA and the assessment for EPA's IRIS program, due to be completed in 2011, will inform EPA's determination of the extent of any future TSCA section 6 action addressing these chemicals. Depending on the nature of its final determination about the eight phthalates, EPA's potential control measures may include a ban of all or several of these chemicals. EPA expects to exercise its risk management authorities in coordination with CPSC, FDA and, as appropriate, other agencies. EPA will develop more detailed assessments to support the TSCA section 6(a) "presents or will present an unreasonable risk" findings. If these more detailed assessments indicate that a different approach to risk management is appropriate, EPA will consider additional approaches.

Before taking TSCA section 6(a) action on DnPP, EPA may consider pursuing additional rulemaking under TSCA section 5(a)(2) in late 2010 or early 2011 to require manufacturers and processors of DnPP to notify EPA before manufacturing or processing DnPP for a significant new use. The most recent Inventory Update Reporting data contains no reports of this phthalate being produced or imported into the United States, and thus it is possible that any use of DnPP may be a significant new use.

EPA intends to conduct a Design for the Environment and Green Chemistry alternatives assessment by 2012. The information developed could be used to encourage industry to move away from phthalates in a non-regulatory setting to expand risk management effects beyond whatever regulatory action might be taken under TSCA or could be used as input to a regulatory action. The alternatives assessment would build upon existing knowledge and would consider exposures for all human subpopulations, as well as environmental exposure.

As part of the Agency's efforts to address phthalates, EPA also intends to evaluate the potential for disproportionate impact on children and other sub-populations.

ED_012964_00017288-00017

X. References

Adibi, J.; Perera, F.; Jedrychowski, W.; Camann, D.; Jacek, R.; Whyatt, R. 2003. Prenatal Exposures to Phthalates among Women in New York City and Krakow, Poland. *Environ. Health Perspect.* **2003,** *111 (14)*, 1719–1722.

Australian Government. 2008a. *Existing Chemical Hazard Assessment Report for Butylbenzyl Phthalate.* Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme (NICNAS): Sydney, Australia, 2008.
http://www.nicnas.gov.au/Publications/CAR/Other/Phthalates.asp (accessed Aug 13, 2009).

Australian Government. 2008b. *Existing Chemical Hazard Assessment Report for Dibutyl Phthalate.* Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme (NICNAS): Sydney, Australia, 2008.
http://www.nicnas.gov.au/Publications/CAR/Other/Phthalates.asp (accessed Aug 13, 2009).

Australian Government. 2008c. *Existing Chemical Hazard Assessment Report for Diethylhexyl Phthalate.* Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme (NICNAS): Sydney, Australia, 2008
http://www.nicnas.gov.au/Publications/CAR/Other/Phthalates.asp (accessed Aug 13, 2009).

Australian Government. 2008d. *Existing Chemical Hazard Assessment Report for Diisobutyl Phthalate.* Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme (NICNAS): Sydney, Australia, 2008.
http://www.nicnas.gov.au/Publications/CAR/Other/Phthalates.asp (accessed Aug 13, 2009).

Australian Government. 2008e. *Existing Chemical Hazard Assessment Report for Diisodecyl Phthalate.* Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme (NICNAS): Sydney, Australia, 2008.
http://www.nicnas.gov.au/Publications/CAR/Other/Phthalates.asp (accessed Aug 13, 2009).

Australian Government. 2008f. *Existing Chemical Hazard Assessment Report for Diisonoyl Phthalate.* Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme (NICNAS):Sydney, Australia, 2008.
http://www.nicnas.gov.au/Publications/CAR/Other/Phthalates.asp (accessed Aug 13, 2009).

Australian Government. 2008g. *Existing Chemical Hazard Assessment Report for Di-n-octyl Phthalate.* Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme (NICNAS): Sydney, Australia, 2008.
http://www.nicnas.gov.au/Publications/CAR/Other/Phthalates.asp (accessed Aug 13, 2009).

Australian Government. 2008h. *Phthalates Hazard Compendium. A Summary of Physicochemical and Human Health Hazard Data for 24 Ortho-Phthalate Chemicals.* Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme (NICNAS): Sydney, Australia, 2008.
www.nicnas.gov.au/Publications/CAR/Other/Phthalates.asp (accessed Aug 13, 2009).

Australian Government. 2009. NICNAS *Existing Chemicals Information Sheet: Phthalates December 2009.* Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme (NICNAS): Sydney, Australia, 2009.
http://www.nicnas.gov.au/Publications/Information_Sheets/Existing_Chemical_Information_Sheets/ECIS_Phthalate_PDF.pdf (accessed Dec 28, 2009).

Babich, M.; Chen, S.; Greene, M.; Kiss, C.; et al. 2004. Risk Assessment of Oral Exposure to Diisononyl Phthalate from Children's Products. *Regul. Toxicol. Pharmacol.* **2004,** *40 (2)*, 151–167.

ED_012964_00017288-00018

Biron, M. Phthalate Ousting: Not So Easy But Some Alternatives are Viable. SpecialChem. http://www.specialchem4polymers.com/resources/print.aspx?id=3980 (accessed Oct 14, 2009).

CDC. 2005. Centers for Disease Control and Prevention. *Third National Report on Human Exposure to Environmental Chemicals*. http://www.cdc.gov/exposurereport/. July 2005.

Chalecki, Z.; Guibe-Jampel, E. 1997. Lipozyme-Mediated Regioselective Esterification of Isosorbide under Solvent-Free Conditions. *Synth. Commun.* **1997,** *27(22)*, 3847–3852.

Clausen, P. A.; Hansen, V.; Gunnarsen, L.; Afshari, A. 2004. Emission of Di-2-ethylhexyl Phthalate from PVC Flooring into Air and Uptake in Dust: Emission and Sorption Experiments in FLEC and CLIMPQA. *Environ. Sci. Technol.* **2004,** *38*, 2531–2537.

CPSC. 2001. U.S. Consumer Product Safety Commission. Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP). Directorate of Health Sciences: Bethesda, MD 20814.

CPSC. 2002. U.S. Consumer Product Safety Commission. Memorandum to Marilyn L. Wind from S.B. Chen. Screening of Toys for PVC and Phthalates Migration.

Crossfire Beistein Database. 2009. Elsevier Information Systems GmbH. Frankfurt, Germany. http://www.info.crossfirebeilstein.com/

CRS. 2008 Congressional Research Service. *CRS Report to Congress Phthalates in Plastics and Possible Human Health Effects*, Updated July 29, 2008. http://www. policyarchive.org/bitstream/handle/10207/19121/RL34572_20080729.pdf?sequence=2 (accessed Dec 28, 2009).

EC. 2002. European Commission. Opinion on Medical Devices Containing DEHP Plasticised PVC; Neonates and Other Groups Possibly at Risk from DEHP Toxicity. 26 September 2002. Scientific Committee on Medicinal Products and Medical Devices. http://ec.europa.eu/health/ph_risk/committees/scmp/documents/out43_en.pdf.

EC. 2003a. European Commission. *European Union Risk Assessment Report: 1,2-Benzenedicarboxylic Acid, Di-C8-10-Branched Alkyl Esters, C9-Rich And Di-"Isononyl" Phthalate (DINP), CAS-Nos. 68515-48-0, 28553-12-0.* Vol. 35; EUR 20784EN; Office for Official Publications of the European Communities: Luxembourg, 2003.

EC. 2003b. European Commission. *European Union Risk Assessment Report: 1,2-Benzenedicarboxylic Acid, Di-C9-11-Branched Alkyl Esters, C10-Rich And Di-"Isodecyl" Phthalate (DIDP), CAS-Nos 68515-49-1 and 26761-40-0.* Vol. 36; EUR 20785EN; Office for Official Publications of the European Communities: Luxembourg, 2003.

EC. 2003-04. European Commission. *European Union Risk Assessment Report: Dibutyl Phthalate, CAS-No. 84-74-2.* Vol. 29; EUR 19840EN; Office for Official Publications of the European Communities: Luxembourg, 2003-04.

EC. 2008a. European Commission. *European Union Risk Assessment Report Bis(2-Ethylhexyl) Phthalate (DEHP), CAS-No. 117-81-7.* Vol. 80; EUR 23384EN; Office for Official Publications of the European Communities: Luxembourg, 2008.

EC. 2008b. European Commission. *European Union Risk Assessment Report Benzyl Butyl Phthalate (BBP), CAS-No. 85-68-7.* Vol. 76; EUR 22773EN; Luxembourg: Office for Official Publications of the European Communities, 2008.

ECPI. 2009. European Council for Plasticisers and Intermediates. DIBP—A Specialty Plasticiser. http://www.dibp-facts.com/ (accessed Dec 9, 2009).

EPA. 2006. U.S. Environmental Protection Agency. Inventory Update Reporting (IUR): Non-Confidential 2006 TSCA Inventory Update Rule (IUR) Records. http://cfpub.epa.gov/iursearch/index.cfm?s=chem. (accessed Dec 9, 2009).

ED_012964_00017288-00019

EPA. 2009. U.S. Environmental Protection Agency. Toxics Release Inventory (TRI) Program: Get TRI Data and Tools. 2007 Public Data Release, Released March 14, 2009. http://www.epa.gov/tri/tridata/index.htm#pdr. (accessed Dec 9, 2009).

ExxonMobil Biomedical Sciences, Inc. 2001. *Robust Summary and Test Plan for the Phthalate Esters Category.* Dec 10, 2001. http://www.epa.gov/chemrtk/pubs/summaries/benzene/c13467tc.htm (accessed Aug 13, 2009).

FDA. 2002a. U.S. Food and Drug Administration. Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices. 2002. Center for Devices and Radiological Health. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080457.pdf (accessed Dec 9, 2009).

FDA 2002b. U.S. Food and Drug Administration. FDA Public Health Notification: PVC Devices Containing the Plasicizer DEHP. July 12, 2002. Med Watch, HF-2 Fishers Lane, Rockville, MD 20857. 2002. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062182.htm

Gray L.E. Jr, Wilson V.S., Stoker T., Lambright C., Furr J., Noriega N., Howdeshell K., Ankley GT, Guillette L. 2006. Adverse effects of environmental antiandrogens and androgens on reproductive development in mammals. Int J Androl. Feb;29(1):96-104; discussion 105-8. Review.

Hawaii House of Representatives. 2009. Twenty-fifth Legislature, House Bill No. 796. http://www.capitol.hawaii.gov/session2009/bills/HB796_.pdf (accessed Dec 28, 2009).

Health Canada. 2002. DEHP in Medical Devices: An Exposure and Toxicity Assessment. Medical Devices Bureau Therapeutic Products Directorate, Health Products & Foods Branch, Health Canada, July 2001; Revised: February 2002. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/sapdehp_rep_gcsdehp_rap_2001-04-26-eng.pdf (accessed Dec 22, 2009).

Hotchkiss A..K, Parks-Saldutti L..G, Ostby .J.S, Lambright C., Furr .J, Vandenbergh J.G., Gray L.E. Jr. 2004. A mixture of the "antiandrogens" linuron and butyl benzyl phthalate alters sexual differentiation of the male rat in a cumulative fashion. Biol Reprod. 71(6):1852-61.

Howdeshell KL, Furr J, Lambright CR, Rider CV, Wilson VS, Gray LE Jr. 2007. Cumulative effects of dibutyl phthalate and diethylhexyl phthalate on male rat reproductive tract development: altered fetal steroid hormones and genes. Toxicol Sci. Sep;99(1):190-202.

Howdeshell K.L., Rider C.V., Wilson V.S., Gray L.E. Jr. 2008a. Mechanisms of action of phthalate esters, individually and in combination, to induce abnormal reproductive development in male laboratory rats. Environ Res. Oct;108(2):168-76. Review.

Howdeshell K.L., Wilson V.S., Furr J., Lambright C.R., Rider C.V., Blystone C.R., Hotchkiss A.K., Gray L.E. Jr. 2008b. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the sprague-dawley rat in a cumulative, dose-additive manner. Toxicol Sci. Sep;105(1):153-65.

HSDB. 2009. Hazardous Substance Data Bank. U.S. National Library of Medicine TOXNET System. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (accessed Aug 13, 2009).

Huang, P. C.; Kuo, P. L.; Chou, Y. Y.; Lin, S. J.; Lee, C. C. 2009. Association between prenatal exposure to phthalates and the health outcome of newborns. *Environ. Int.* **2009,** *35(1)*, 14–20.

Jobling, S.; Reynolds, T.; White, R.; Parker, M. G.; Sumpter, J. P. 1995. A Variety of Environmentally Persistent Chemicals, including Some Phthalate Plasticizers, Are Weakly Estrogenic. *Environ. Health Perspect.* **1995,** *103*, 582–587.

NAS. 2008. National Academy of Sciences. Phthalates and Cumulative Risk Assessment; The Tasks Ahead. Dec 2008. http://dels.nas.edu/dels/rpt_briefs/phthalates_final.pdf (accessed Dec 9, 2009).

ED_012964_00017288-00020

NITE. 2002. National Institute of Technology and Evaluation (Japan). Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html (accessed Aug 13, 2009).

NTP-CERHR. 2003a. National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction. *Monograph on the Potential Human Reproductive and Developmental Effects of Di-n-Octyl Phthalate (DnOP);* NIH Pub. No. 03-4488; U.S. Department of Health and Human Services, May 2003.

NTP-CERHR. 2003b. National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction. *Monograph on the Potential Human Reproductive and Developmental Effects of Di-n-Hexyl Phthalate (DnHP);* NIH Pub. No. 03-4489; U.S. Department of Health and Human Services, May 2003.

NTP-CERHR. 2003c. National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction. *Monograph on the Potential Human Reproductive and Developmental Effects of Di-Isodecyl Phthalate (DIDP);* NIH Pub. No. 03-4485; U.S. Department of Health and Human Services, April 2003.

NTP-CERHR. 2003d. National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction. *Monograph on the Potential Human Reproductive and Developmental Effects of Di-Isodecyl Phthalate (DIDP);* NIH Pub. No. 03-4485; U.S. Department of Health and Human Services, April 2003.

NTP-CERHR. 2003e. National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction. *Monograph on the Potential Human Reproductive and Developmental Effects of Butyl Benzyl Phthalate (BBP);* NIH Pub. No. 03-4487; U.S. Department of Health and Human Services, March 2003.

NTP-CERHR. 2006. National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction. *Monograph on the Potential Human Reproductive and Developmental Effects of Di-(2-ethylhexyl) Phthalate (DEHP);* NIH Pub. No. 06-4476; U.S. Department of Health and Human Services, March 2006.

Oehlmann, J.; Schulte-Oehlmann, U.; Werner, K.; Jagnytsch, O.; Lutz, I.; Kresten, K.; Wollenberger, L.; Santos, E. M.; Paull, G. C.; Van Look, K. J. W.; Tyler, C. R. 2008. A Critical Analysis of the Biological Impacts of Plasticizers on Wildlife. *Philos. Trans. R. Soc., B: Biol. Sci.* **2008,** *364(1526)*, 2047–2062.

OSHA. 2006. Occupational Safety and Health Administration. Permissible Exposure Limits (PELs) Establishing PELs. Regulations (Standards - 29 CFR) Table Z-1 Limits for Air Contaminants. - 1910.1000 Table Z-1. http://www.osha.gov/SLTC/pel/recognition.html (accessed Dec 9, 2009).

OSHA 2009. Occupational Safety and Health Guideline for Dibutyl Phthalate. http://www.osha.gov/SLTC/healthguidelines/dibutylphthalate/recognition.html (accessed Dec 22, 2009).

Rider C.V., Furr J., Wilson V.S., Gray L.E. Jr. 2008. A mixture of seven antiandrogens induces reproductive malformations in rats. *Int J Androl.* Apr;31(2):249-62.

Rider CV, Wilson VS, Howdeshell KL, Hotchkiss AK, Furr JR, Lambright CR, Gray LE Jr. 2009. Cumulative effects of in utero administration of mixtures of "antiandrogens" on male rat reproductive development. *Toxicol Pathol.* 37(1):100-13.

Roquette. 2009. Roquette receives the 2009 Pierre Potier prize for its POLYSORB® ID 37. http://www.roquette.com/delia-CMS/t1/article_id-5614/topic_id-1691/roquette-receives-the-2009-pierre-potier-prize-for-its-polysorb-r-id-37.html (accessed Oct 14, 2009).

SCENIHR. 2007. Scientific Committee on Emerging and Newly-Identified Health Risks. European Commission. *Preliminary Report on The Safety of Medical Devices Containing DEHP-Plasticized PVC or Other Plasticizers on Neonates and Other Groups Possibly at Risk.* Approved for public consultation during the 19th Plenary of June 21-22, 2007. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_008.pdf (accessed Oct 27, 2009).

Staples, C. A.; Adams, W. J.; Parkerton, T. F.; Gorsuch, J. W.; Biggingers, G. R.; Reiner, K. H. 1997. Aquatic Toxicity of Eighteen Phthalate Esters. *Environ. Toxicol. Chem.* 1997, *16 (5)*, 875–891.

Swan, S. H.; Main, K. M.; Stewart, S. L.; Kruse, R. L.; Calafat, A. M.; Mao, C. S.; Redmon, J. B.; Ternand, C. L.; Sullivan, S.; Teague. J. L. 2005. Study for Future Families Research Team. Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure. *Environ. Health Perspect.* **Aug 2005,** *113(8)*, 1056–61.

Tickner, J. A.; Schettle, T. R.; Guidotti, T.; McCally, M.; Rossi, M. 2001. Health Risks Posed by Use of Di-2-Ethylhexyl Phthalate (DEHP) in PVC Medical Devices: A Critical Review. *Am. J. Ind. Med.* **2001,** *39(1)*, 100–111. http://www3.interscience.wiley.com/cgi-bin/fulltext/76505754/PDFSTART (accessed Dec 9, 2009).

TURI. 2006. Massachusetts Toxics Use Reduction Institute. *Five Chemicals Alternatives Assessment Study.* University of Massachusetts Lowell: Lowell, Massachusetts, June 2006. http://www.turi.org/library/turi_publications/five_chemicals_study (accessed Dec 9, 2009).

Wickson, E. J. 1993. *Handbook of Polyvinyl Chloride Formulating;* John Wiley & Sons: Baton Rouge, Louisiana, 1993.

ED_012964_00017288-00022