Review of Exposure and Toxicity Data for Phthalate Substitutes*

Prepared for:

Michael A. Babich, Ph.D.
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

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Prepared by:

Versar, Inc.
Exposure and Risk Assessment Division
6850 Versar Center
Springfield, VA 22151

and

Syracuse Research Corporation (SRC)
7502 Round Pond Road
North Syracuse, NY 13212

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EXECUTIVE SUMMARY

In August 2008, the U.S. Congress passed the Consumer Product Safety Improvement Act of 2008 (CPSIA) placing restrictions on the use of six dialkyl *ortho*-phthalates (*o*-DAPs) in children's toys or child care articles. The CPSIA also directs the Consumer Product Safety Commission (CPSC) to convene a Chronic Hazard Advisory Panel to investigate the potential health effects of phthalates and phthalate substitutes. The purpose of this report is to identify *o*-DAP substitutes that are currently being used in children's articles, or are probable future candidates, and to summarize the potential human health risks associated with using these chemicals in this manner. Chemicals were identified as the most likely alternatives to *o*-DAPs in children's articles based on a variety of factors which included their compatibility with polyvinyl chloride (PVC).

The five chemicals identified by this report as the most likely *o*-DAP alternatives are acetyl tri-n-butyl citrate (ATBC), di(2-ethylhexyl) adipate (DEHA), 1,2-cyclohexanedicarboxylic acid, dinonyl ester (DINCH), trioctyltrimellitate (TOTM),and di(2-ethylhexyl) terephthalate (DEHT or DOTP). All, except TOTM, have been cited as already being used in children's articles. However, TOTM is compatible with PVC – the most popular resin for children's soft plastic toys and other articles – and thus a likely *o*-DAP alternative. The review of the potential risks of using these chemicals in children's articles focused on the amount and quality of data available for the chemical. Key parameters included physical-chemical properties, migration rates, and all available exposure, hazard, and dose-response information. Current data limitations were identified, and comparisons were made among the five *o*-DAP substitutes with regards to both the strength and the implications of available exposure and toxicity data.

The physical-chemical properties of DEHP, DINP, and the five potential *o*-DAP alternatives chosen for review, are presented in the report. Parameters that are predictors of exposure include water solubility and bioconcentration factor (BCF). Water solubility is low for all of these chemicals, with the exception of TOTM. BCF is particularly high for DEHT, but for the other alternatives is lower than values observed for DEHP and DINP, indicating the potential for these chemicals to be metabolized by organisms.

Measured migration rate data are available for select chemicals. When available, these were the most informative measures used to assess potential exposure. The chemicals ATBC and DEHA have been shown to migrate from food wraps and films in various studies. Recently developed, DINCH lacks extensive toxicology data, but its low migration into aqueous substances and poor solubility in water has earned it approval from several governments to be used as a food contact substance. TOTM, of relatively high molecular weight and with a bulky structure, appears to have the lowest migration potential; no mobility data were available for DEHT.

In order to evaluate chemical toxicity, criteria such as the number, type, and quality of studies performed on each chemical were considered. Hazard information, as well as dose-response information (e.g., no-observed-adverse-effect levels (NOAELs) and

lowest-observed-adverse-effect level (LOAELs)), for a variety of non-cancer endpoints, as well as carcinogenicity data, were evaluated.

Overall, a significant amount of toxicity information is currently available on these five chemicals, although the quality of some studies is questionable. No published studies of DINCH were available. Acute oral toxicity for ATBC appears to be the lowest of the five chemicals, and it has been approved by the U.S. Food and Drug Administration (FDA) for use as a food additive and food contact substance. In chronic exposure studies performed in rats, NOAELs were highest for DEHA and ATBC and significantly lower for DINCH and DEHT. No such study was available for TOTM.

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1.0 INTRODUCTION

1.1 Purpose

Dialkyl *ortho*-phthalates (*o*-DAPs) comprise a class of commercially important compounds used primarily as plasticizers in polyvinyl chloride (PVC). They can be found in floor and wall-coverings, and common household products such as children's soft plastic toys. Lower molecular weight *o*-DAP's are used as solvents in inks, waxes, polishes, and coatings. *o*-DAPs are also a vital component of many types of medical devices, laboratory tubing, and cosmetics. Due to extensive use over the past fifty years, *o*-DAPs are now ubiquitous environmental contaminants. They are present in food, air, and water, and their metabolites have been detected in the urine of all humans tested (Fromme et al., 2007; Sathyanarayana et al., 2008; Wittassek et al., 2007), with children often showing urinary metabolite levels significantly higher than those of adults (Koch et al., 2006). Recently, *o*-DAPs have come under increasing scrutiny due to concerns about potential health effects in animal studies, which include reproductive and developmental toxicity, chronic organ toxicity, and cancer (IHCP, 2008; NTP-CERHR, 2006). Consequently, their use in children's articles, such as soft plastic teethers, rattles, and toys, is of concern to consumers, with many believing that safer alternatives should be actively sought.

The purpose of this report is to identify *o*-DAP substitutes that are currently being used in children's articles, or are probable future candidates, and to summarize the potential risks associated with using these chemicals in this manner. First, this review identifies a broad list of chemical classes that have the potential to serves as alternatives to *o*-DAP plasticizers in children's PVC articles. Then, five substitutes are chosen from this list for detailed chemical profiles including use, physico-chemical properties, exposure, and toxicology data.

1.2 Plasticizers, Phthalates and Children's Toys

1.2.1 Plasticizer Use

Plasticizers are substances – usually low-melting solids or high-boiling organic liquids – which, when added to hard plastics, improve their flexibility and durability. Plasticizers work by embedding themselves between the chains of polymers, spacing them apart and thus making the plastic softer (ECPI, 2009a). Worldwide, approximately six million tons of plasticizers are produced and consumed every year. Of this, over 90% are phthalate plasticizers (Arbeitsgemeinschaft, 2006).

o-DAPs comprise a family of phthalate esters that have been used to soften polyvinyl chloride (PVC) products for over 50 years. As a class of chemicals, *o*-DAPs are oily, colorless, odorless liquids that do not evaporate readily (ACC, 2009). They are manufactured from phthalic anhydride (Figure 1-1) and a wide array of alcohols. The latter range from short chains

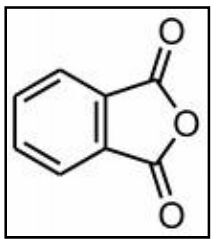

Figure 1-1. Phthalic Anhydride

such as methanol and ethanol (C1/C2), up to the much larger iso-decanol (C13), with either straight or branching chains. The resulting large variety of *o*-DAPs equates to a wide range of physiochemical properties, allowing these phthalate esters to find use in PVC products that include U.S. Food and Drug Administration (FDA) approved medical devices (such as medical tubing and blood bags), footwear, electrical cables, packaging, stationery, toys, PVC cladding (facing for buildings) and roofing (such as in PVC coated steel girders) (ECPI, 2009b). Non-PVC applications include paints, rubber products and some adhesives (Craver and Carraher, 2000). Phthalic anhydride derivatives have also been approved by the FDA for use as food contact substances (FDA, 2009).

1.2.2 Hazard Identification and Regulation of Phthalates

Consumer concern arises because *o*-DAPs are not chemically bound to PVC, and therefore may be released from the plastic when consumers, specifically children, place these products in their mouths (Shea, 2003). Until about 1985, di(2-ethylhexyl) phthalate (DEHP) (also known as di-octyl phthalate or DOP), was the predominant *o*-DAP in children's products such as teethers, rattles, and soft toys (Wigle, 2003). When DEHP was found to be carcinogenic in laboratory rats and mice (NTP, 1982a), manufacturers voluntarily agreed to limit DEHP in pacifiers, teethers, and rattles to 3% by mass (ASTM F963-96, 1996). Generally, DEHP was replaced with another *o*-DAP, diisononyl phthalate (DINP), a likely alternative because it is less bioaccumulative than DEHP, was presumed to be less toxic, and is comparable to DEHP with regard to PVC compatibility (Ellenbecker et al., 2008; Wigle, 2003).

In 1997, two leaching studies commissioned by Greenpeace Germany observed migrations levels for DEHP and DINP from children's toys that exceeded the existing German guidelines, as well as exceeding the existing EU limit for total phthalate content (by mass) by 13 to 33 times. For example, DINP, identified more frequently than DEHP in the samples, was found comprising up to 40 percent (by mass) of these samples (Greenpeace, 1997). Studies like these increased concern from toy advocates, and subsequently, Greenpeace and twelve other non-governmental groups petitioned the U.S. Consumer Product Safety Commission (CPSC) (petition HP 99-1), calling for a ban on polyvinyl chloride (PVCs) in children's soft plastic toys based, in part, upon the potential health risks from DINP toxicity (BNET, 2003). Responding to this petition, a CPSC investigation from 1998-2002 concluded that DINP in children's articles did not present a significant health risk to children (Wind, 2002). A Chronic Hazard Advisory Panel (CHAP) convened by CPSC also concluded that DINP in children's products presents a minimal to non-existent risk of injury (Wind, 2002). In 1999, the European Commission enacted an emergency ban on the use of phthalates in PVC children's toys in 15 countries, due to concerns about the possible health risks of phthalate exposure (Greenpeace, 2003).

At the same time, in the United States, the American Council on Science and Health (ACSH) convened a panel to examine DINP safety in PVC toys. Headed by former Surgeon General Dr. C. Everett Koop, the panel concluded that, "DINP in flexible toys is unlikely to pose a health risk to children," although it did cite that younger animals appear to be more sensitive to the health effects of DINP than older animals (Noble,

1999). In 1999, at the request of CPSC, manufacturers voluntarily removed phthalates from teethers and rattles. Although DINP could still be used in toys, many manufacturers also removed DINP from toys (Chen, 2002). Nonetheless, some non-governmental organizations such as the New York Public Interest Research Group (NYPIRG), for example, continued to warn of the potential risks of DINP and other phthalates, urging consumers to call manufacturers directly to obtain content information for their products (NYPIRG, 2002).

Debate appeared to have ended in the European Union in 2005 when the European Commission banned DEHP, dibutyl phthalate (DBP), and butyl benzyl phthalate (BBP) in all toys and childcare articles, and DINP, diisodecyl phthalate (DIDP), and di-n-octyl phthalate (DNOP) from use in toys and childcare articles if those articles can be put in the mouth by children (EUROPA, 2005). Consequently, individual companies began removing phthalates from their PVC blends for children's products, and some individual U.S. states and local governments passed legislation to regulate their use (PBS, 2008). After heightened debate in the United States, the Congress passed the Consumer Product Safety Improvement Act 0f 2008 in August 2008 stating that the sale of children's toys or child care articles containing more than 0.1% of DEHP, DBP, or BBP is permanently prohibited, and the sale of children's toys that can be placed in a child's mouth or child-care articles containing concentrations of more than 0.1% of DINP, DIDP, or DNOP would be prohibited on an interim basis (U.S. Congress: PL 110-314).

1.3 Potential Phthalate Alternatives

In the global search for less toxic *o*-DAP alternatives for use in children's articles, several classes of chemicals have emerged. They have been suggested by both concerned interest groups and the plastics industry, and many are already under investigation for PVC compatibility and potential toxicity. Some of the most popular candidates include citrates, adipates, trimellitates, phosphates, benzoates, and vegetable oil derivatives.

Citrates

Citric acid, widely used in food and beverages, household cleaners, and pharmaceuticals, is also used by the plasticizer industry. When combined with alcohols of varying lengths, the resulting citrate esters can be used as solvents in products such as electrical casings, inks, hair sprays, and aerosol bandages (ECPI, 2009c). Several citrates, such as acetyl tri-n-butyl citrate (ATBC), have been approved by the FDA as plasticizers for food contact substances (FDA, 2002ab). ATBC is also a potentially useful alternative to phthalates in children's articles, and mouthing studies on humans have already begun taking place (Nikiforov, 2003 as cited in CSTEE, 2004). Conclusions by the European Union's Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) suggest that ATBC may be used for this purpose (CSTEE, 2004).

Adipates

Adipates are plasticizers with applications ranging from building material constituents (such as in concrete joint sealants and surface retarders) to plastics for medical and consumer applications (US Patent No. 4288354, 7037367, 5733562). Adipates consist of alcohols of similar chain length to those used in phthalate manufacture, esterified instead with adipic acid. These plasticizers have similar PVC compatibility as phthalates, but suffer from higher volatilities and higher migration rates, and are generally higher priced. As a result, it is not uncommon for adipates to be used in blends with phthalates to produce a compromise of properties (ECPI, 2009d). The most commonly used adipate for plasticizer applications, di(2-ethylhexyl) adipate (DEHA), can be found in a variety of home and office products, such as vinyl flooring, carpet backing, wood veneer, and coated fabrics (SCENIHR, 2007), as well as children's toys (Chen, 2002).

Trimellitates

Trimellitate esters, such as tris-(2-ethyhexyl) trimellitate (TOTM), are produced by the esterification of a range of alcohols with trimellitic anhydride (TMA). Trimellitates are significantly more viscous then the linear adipates or phthalates, with a lower volatility (Daman Organomers, 2003). The extraction and migration resistance of these materials are also significantly improved relative to the phthalates. Currently, large volumes of trimellitates are used in high specification electrical cable insulation and sheathing (ECPI, 2009e), and they have seen moderate use as an inert ingredient in pesticide formulations (Federal Register, 1998). However, there is no indication that trimellitates are used in children's articles.

Phosphates

Phosphoric acid esters, such as di(2-ethylhexyl) hydrogen phosphate (DEPHA) and tris(2-ethylhexyl)phosphate (TEHP), are not obvious PVC plasticizers, but their use in this industry may be growing, perhaps due to their improved fire retardancy relative to phthalates. The fire performance of PVC itself, relative to other polymeric materials, is very good due to its high halogen content, but the addition of plasticizers reduces flame resistance (ECPI, 2009f). If they prove to be of low toxicity, phosphates may find useful application as a phthalate alternative in children's articles.

Benzoates

Benzoic acid, used worldwide as a food preservative, can be combined with alcohols to form benzoate plasticizers. These compounds are used industrially as blends, or in combination with other plasticizers such as adipates or phthalates (Stanhope, 2000). Considered a safer alternative to phthalates, benzoate plasticizers have recently been suggested for use in so-called "sensitive" applications, such as children's articles (Lang and Stanhope, 2001). However, no evidence of current use in children's articles could be found, perhaps indicating a market slow to adapt benzoates for this purpose.

Vegetable Oil Derivatives

Epoxidized oils have the ability to replace phthalates in applications such as children's articles due to 1) their higher biodegradability compared to traditional plasticizers; 2) because they do not require metal stabilizers to supplement the plasticizer (as is often the case with traditional plasticizers); and 3) because many have already been approved as food contact substances. On a cost per pound basis, these vegetable oil-derived plasticizers generally tend to be more expensive than petrochemical plasticizers; however, they offer performance benefits – such as reducing the need for metallic stabilizers – which can make their overall economics favorable (ILSR, 1996).

A potential candidate for use in children's articles, epoxidized soybean oil (ESBO) has already been approved for use as a PVC plasticizer in gaskets and metal caps, such as for baby food jars (Weller et al., 2007). New to the market, COMGHA (Glycerides, Castor-oil-mono-, hydrogenated, acetates) also shows promise as a food contact substance. Marketed as Grindsted® SOFT-N-SAFE, this vegetable oil derivative was listed as one of the top eight potential DEHP substitutes by both the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks and the U.S. based Consumers for Competitive Choice (SCENIHR, 2007; Johnson, 2008).

1.4 Screening of Potential Alternatives

This section provides the methodology used to identify and select five potential phthalate plasticizer alternatives for further investigation. In subsequent sections of the report, these five compounds will be assessed for their physical/chemical properties, exposure potential, and toxicity.

1.4.1 Initial Pool and Selection of Eight Substitutes of Interest

In the initial phases of the investigation, approximately 20 compounds were identified as having the potential to replace *o*-DAPs in children's articles. Major candidates fell into one of the classes described above - citrates, adipates, trimellitates, phosphates, benzoates, and vegetable oil derivatives. Other alternatives included sebacates, sulfonic acids, aliphatic dibasic esters, chloroparaffin and sorbitol. The resulting broad list, compiled from PubMed and TOXNET database searches (see Appendix A), manufacturers' websites, and general internet searches, was narrowed to a list of eight suggested chemicals for further investigation, using a two-pronged ranking system. In this system, each chemical was scored on a scale of 1-5 with regard to 1) the likely potential for use as a PVC plasticizer in children's articles, and 2) the likely amount of toxicity information available on this chemical. The chemical's potential for use in children's articles was a qualitative decision based on the information available from literature and internet searches. The ranking of toxicity information was also somewhat qualitative, as it used the number of articles mentioning the chemical of interest, not the specific number of toxicological exposure studies or data sets available.

If evidence was found of a compound's current use in children's articles, then a 'potential substitute' ranking of 5 was assigned. Compounds that were weakly compatible with PVC, or for which no use data could be found, received a ranking of 1. Most compounds fell into the 2 to 4 range, with some applicability based on available data. For the initial toxicity ranking, the number of hits received using TOXLINE during September 2008 was the metric chosen. Those compounds that drew greater than 400 TOXLINE hits received a 'toxicity information' ranking of 5. Compounds with 100-400 hits received a 4, 40-100 hits received a 3, 10-40 hits received a 2, and fewer than ten hits received a 1.

A two-dimensional scatter plot was created to visualize the data (Figure 1-2). The x-axis of the graph indicates the *Potential for Use in Children's Articles* of a particular compound, while the y-axis indicates the *Amount of Toxicity Information Available* on the compound. Each compound appears as a single point on the graph. Visual inspection of the graph, coupled with more fine-tuned investigation of the compounds, aided in the selection of eight candidates of greatest interest. The following eight chemicals were selected to be further investigated as potential *o*-DAP substitutes:

- Acetyl tri-n-butyl citrate (ATBC) [77-90-7]
- Di(2-ethylhexyl) adipate (DEHA) [103-23-1]
- 1,2-Cyclohexanedicarboxylic acid, dinonyl ester, branched and linear (DINCH) [474919-59-0 and 166412-78-8].
- Phenyl esters of C10-C18 alkylsulfonic acids (Mesamoll®) [70775-94-9]
- Di(2-ethylhexyl) terephthalate (DEHT or DOTP) [6422-86-2]
- Trioctyltrimellitate (TOTM) [3319-31-1]
- Glycerides, Castor-oil-mono-, hydrogenated, acetates (COMGHA or AMG-HCO) [736150-63-3]
- Epoxidized soybean oil (ESBO or ESO) [8013-07-8]

Of particular interest to this investigation are ATBC and DEHA, which have been chemically identified in PVC specimens taken from children's soft plastic toys as early as 2002 (Chen, 2002). Currently, ATBC's main use is in medical tubing, although it has been approved for many food applications in the U.S., including the use as a flavoring substance (SCENIHR, 2007). In addition to its use in toys, DEHA can be found in a variety of home and office products, such as vinyl flooring, carpet backing, wood veneer and coated fabrics (SCENIHR, 2007). DINCH and Mesamoll are both recent additions to the market (by BASF and LAXNESS, respectively), developed specifically for use in so-called "sensitive applications" such as medical tubing and children's toys (Jobwerx, 2006; Plastmart, 2007). DEHT is used as a PVC plasticizer in a wide array of applications including toys, childcare articles and other consumer products, transportation and beverage closures (SCENIHR, 2007 – submission by Eastman Chemical Company). TOTM does not appear to be in use in children's articles at the present time. However, it is (along with ATBC, DEHA and DEHT) a high production volume chemical in the U.S. (HPVIS, 2008), and its potential use as an *o*-DAP substitute appears likely. Additionally, a significant amount of toxicity data regarding human and animal exposure to TOTM is available (75 TOXLINE hits).

Also, not yet used in children's articles, ESBO and COMGHA are both vegetable oil derived plasticizers. Currently, ESBO has found uses as a PVC plasticizer in gaskets and metal caps, such as for baby food jars (Weller et al., 2007). COMGHA is new to the market (Grindsted® SOFT-N-SAFE), and its manufacturer has recently requested FDA approval for its use as a food contact substance. COMGHA is said to exhibit a performance similar to DEHP and is intended for primary use in PVC (SCENIHR, 2007). It was listed as one of the top eight potential DEHP substitutes by both the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks and the U.S. based Consumers for Competitive Choice (CC4C, 2008; SCENIHR, 2007). Potential o-DAP substitutes that were not chosen for further investigation (such as sebacic acid and polyadipate) were excluded based on the combination of lack of toxicity information available and unclear evidence on their applicability for use as a PVC plasticizer.

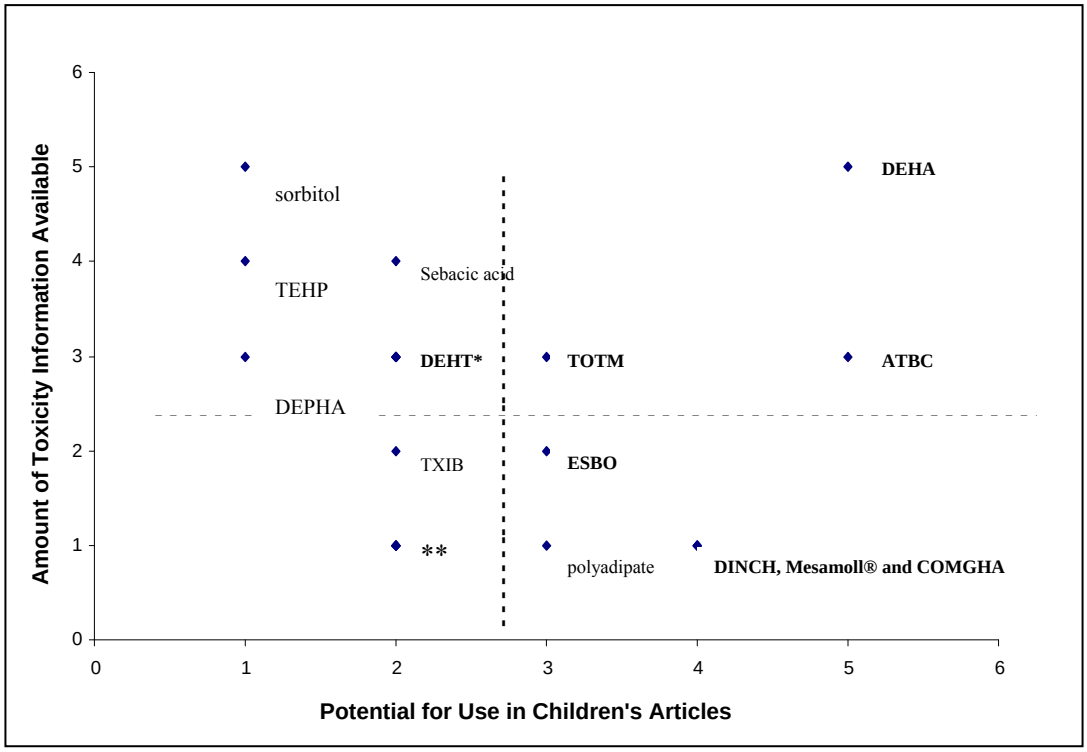

Figure 1-2. Potential Phthalate Substitutes for Use in Children's Articles. Chemicals were Ranked by Toxline Hits (scaled to y-axis) and Potential for Use in Children's Articles (subjective, x-axis).

*also includes aliphatic dibasic esters
**includes DOIP, benzoates and chloroparaffin

1.4.2 Toxicity Screening for Eight Substitutes

During the second phase of the investigation, toxicological screening was performed for the eight candidate chemicals and endpoints were summarized from studies identified in primary and secondary sources. Computer searches of the PUBMED, TOXLINE, TSCATS, CCRIS, DART/ETIC, GENE-TOX, HSDB, RTECS and EPA SRS databases were conducted, and titles and abstracts were evaluated. A complete description of each database is presented in Appendix A. In addition, the following secondary sources were checked for information pertinent to the human health toxicity of these chemicals:

- U.S. EPA IRIS, High Production Volume (HPV) Challenge Program, Drinking Water Health Advisories (DWHAs), Health Effects Assessment Summary Tables (HEAST);
- Agency for Toxicity Substances and Disease Registry (ATSDR) Toxicological Profiles;
- National Toxicology Program (NTP) documents;
- International Agency for Research on Cancer (IARC) Monographs;
- International Programme on Chemical Safety (IPCS) documents;
- Organisation for Economic Co-Operation and Development (OECD) Screening Information DataSets (SIDS); and
- 2007 European Commission Preliminary Report *The Safety of Medical Devices Containing DEHP-Plasticized PVC or Other Plasticizers on Neonates and Other Groups Possibly at Risk*.

A summary of the preliminary assessments of these eight chemicals follows (see below and Table 1-1).

Cancer Bioassays

Rat cancer bioassays are currently available for five of the eight *o*-DAP substitutes: ATBC, DEHA, DINCH, DEHT, and ESBO. No increased incidences of tumors were found in the rat bioassays for ATBC, DEHA, DEHT, and ESBO, but increased thyroid adenomas were found in the rat bioassay with DINCH. Only one mouse bioassay was identified – increased incidence of liver tumors (associated with increased peroxisome proliferation) was found in mice exposed to DEHA in the diet for 2 years.

Reproductive Toxicity Studies

One-generation or two-generation oral reproductive toxicity assays are available for six of the eight *o*-DAP substitutes: ATBC, DEHA, DINCH, DEHT, TOTM, and ESBO. No effects on reproductive performance were observed in any of these studies at doses up to about 1000 mg/kg-day, but decreased spermatocytes and spermatids were observed in rats exposed to TOTM at ≥300 mg/kg-day, and decreases in offspring body weight and litter weight and size were observed in rats exposed to DEHA at 1080 mg/kg-day. The NOAEL for these effects of DEHA is part of the basis for the IRIS reference dose (RfD) for DEHA.

Developmental Toxicity Studies

Oral developmental toxicity studies have been conducted in rats for six of the eight *o*-DAP substitutes: ATBC (a Russian study), DEHA, DINCH, DEHT, TOTM, and ESBO. The highest doses tested did not produce fetal developmental effects in rats gestationally exposed to ATBC, DINCH, DEHT, TOTM, or ESBO. Delayed ossification was the only fetal developmental effect observed in the rat developmental toxicity study with DEHA; the NOAEL for this effect is part of the basis for the IRIS RfD for DEHA. In addition, there are oral developmental toxicity studies in mice for ATBC (Russian study) and DEHT – no developmental effects were observed in these studies or in a rabbit gestational exposure study with DINCH.

Table 1-1. Oral Toxicity Summary for Eight Potential Substitutes

	Cancer Bioassay		**Reproductive Tox Studies**		**Developmental Tox Studies**	
Chemical	**Data Available**	**Negative Effect Observed**	**Data Available**	**Negative Effect Observed**	**Data Available**	**Negative Effect Observed**
ATBC	X		X		X	
DEHA	X	X	X	X	X	X
DINCH	X	X	X		X	
Mesamoll®						
DEHT	X		X		X	
TOTM			X	X	X	
COMGHA						
ESBO	X		X		X	

1.4.3 Selection of Five Priority Substitutes

From the preliminary toxicology assessments of eight potential substitutes, five chemicals were selected for more detailed analyses. To make this selection, first the oral toxicity data were summarized and presented alongside general use data for each of the eight potential substitutes under investigation (Table 1-1). It was observed that all eight chemicals could be considered potential alternatives to *o*-DAPs in children's articles due to their compatibility with PVC and their (presumed or determined) low toxicity. In particular, ATBC, DEHA, DINCH and DEHT are currently in use in children's toys (Chen, 2002; Merchant, 2005; SCENIHR 2007) and substantial amount of toxicological information is currently available on each of these chemicals. DEHT is in the phthalate family (full name di(2-ethylhexyl) terephthalate), but is not an *ortho*-phthalate, and thus is considered a viable *o*-DAP alternative for the purpose of this report. Mesamoll® and COMGHA are new to the market and recently approved for use in food contact substances (Plastmart, 2007; SCENIHR 2007), however, neither has been studied extensively for toxic effects. The remaining two chemicals - TOTM and ESBO - are both associated with a large amount of toxicological data and are PVC compatible. However, both are only being used currently in products not closely related to children's articles, such as electrical cables, fuel additives, adhesives, sealants, and inks.

Considering all of this, and with the goal of developing a broad, yet relevant, *o*-DAP alternative summary report, the following five chemicals were chosen for more detailed assessments in this report: ATBC, DEHA, DINCH, TOTM, and DEHT. In doing this,

over 150 articles were identified and reviewed, including peer reviewed journal articles, manufacturer's factsheets, EPA databases, international meeting reports, and foreign and domestic government agency documents. Consequently, these assessments were able to address current chemical use, potential use, physicochemical properties, and exposure and toxicology data for these five compounds, and comparisons were made with regard to DEHP and DINP where appropriate. The assessments are presented by chemical in the following five sections of this report.

2.0 Acetyl tri-n-butyl citrate (ATBC)

2.1 Use

Acetyl tri-n-butyl citrate (ATBC), produced from citric acid, is a High Production Volume (HPV) chemical under EPA's voluntary HPV program (HPVIS, 2008), indicating that one million pounds or more are either produced or imported into the U.S. each year. Its CAS number is [77-90-7] and synonyms include:

- tributyl, 2-acetylcitrate
- tributyl o-acetylcitrate
- 1,2,3-Propanetricarboxylic acid, 2-(acetyloxy)-, tributyl ester
- Citric acid, tributyl ester, acetate
- Citroflex® A-4
- dioctyl adipate (DOA)

(SCENIHR, 2007).

ATBC, a popular plasticizer for polyvinyl resins, is also permitted as a food additive and food contact substance (FDA, 2002ab). It is acceptable for use as a flavor additive in non-alcoholic beverages at 1ppm (Burdock, 1995), in the production of food-contact surfaces of resinous and polymeric coatings, and in paper/paperboard for use in contact with fatty foods (Sheftel, 2000).

In vinyl resins, ATBC can be found in medical plastics (pharmaceutical coatings and extra corporeal tubing), animal ear tags, and children's toys (HSDB, 2008). It is also used as a plasticizer in rubber and cellulosic resins (Ashford, 1994), as an ingredient in cosmetics, and as a component of adhesives, ink formulations, and pesticide inerts (HSDB, 2008; SCENIHR, 2007).

2.2 Physical/Chemical Properties

ATBC is an ester of citric acid (Figure 2-1), with chemical formula $C_{20}H_{34}O_{8.}$ Physical-chemical properties for this compound are highlighted in Table 2-1.

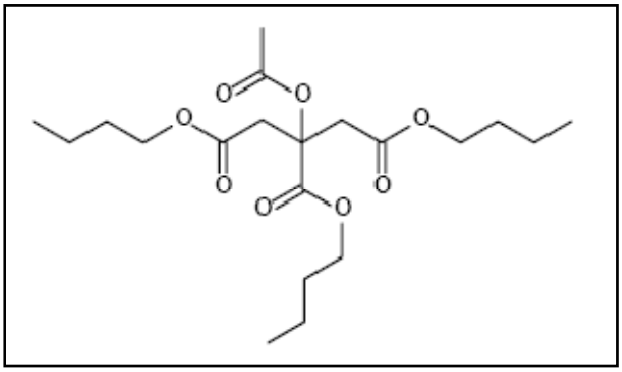

Figure 2-1. Structure of ATBC (SCENIHR, 2007)

ATBC is a colorless, transparent liquid that is soluble in alcohol and ether. It is soluble in water at 5 mg/L (temperature not specified), and has an estimated K_{oc} value of 1,800, indicating a readiness to adsorb to suspended solids and sediments. Volatilization from moist soil surfaces is not expected to be an important fate process based upon its estimated Henry's Law constant of 3.8×10^{-10} atm-cu m/mole. Additionally, ATBC is not expected to volatilize from dry soil surfaces based upon its low vapor pressure (HSDB, 2008).

If released into air, an estimated vapor pressure of 4.6×10^{-6} mm Hg at 25°C indicates that ATBC will exist in both the vapor and particulate phases in the ambient atmosphere. The vapor-phase ATBC will be degraded by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 27 hours. Particulate-phase ATBC will be removed from the atmosphere by wet and dry deposition (HSDB, 2008). An estimated BCF of 250 suggests that the potential for bioconcentration in aquatic organisms is moderate (HSDB, 2008).

Table 2-1. Physical-Chemical Properties of DEHP, DINP, and Potential *o*-DAP Alternatives (BASF, 2006; HPVIS 2008; HSDB 2008; SCENIHR 2007)

Name	MW	Wsol (mg/L)	K_{oc}	H (atm m^3/mol at 25°C)	Log K_{ow}	V_p (mm Hg at 25°C)	BCF L/kg
DEHP	390.56	0.285[a]	>87,420	1.3×10^{-7}	7.60	7.2×10^{-8}	115-851
DINP	418.62	0.2[b]	10,580	1.49×10^{-6}	n.a.	5.4×10^{-7}	1,500
ATBC	402.5	5.0[b]	1,800	3.8×10^{-10}	4.3[c]	4.6×10^{-6}	250
DEHA	370.57	0.78[c]	770,000	4.34×10^{-7}	>6.11	8.5×10^{-7} [d]	27
DINCH	424.7	<0.02[e]	n.a.	n.a.	10	9.75×10^{-7}[f]	189
TOTM	546.80	100[e]	350	4.4×10^{-7}	5.94[e]	3.9×10^{-11}	1-2.7
DEHT	390.54	4.0[d]	870,000	1.02×10^{-5}	5.72	2.14×10^{-5}	1,400,000

Wsol is the solubility of the chemical in water. K_{oc} is the organic carbon normalized solid-water partition coefficient in L/kg. H (atm m^3/mol) is the Henry's law constant. K_{ow} is the octanol-water partition coefficient. V_p is the vapor pressure. BCF is the bioconcentration factor. (Adapted from Remberger et al. 2005). See Appendix B for more detail.

[a] at 24°C
[b] temperature not specified
[c] at 22 °C
[d] at 20°C
[e] at 25°C
[f] at 50°C

2.3 Exposure

The general population may be exposed to ATBC via dermal contact with consumer products, oral contact via mouthing of products, such as children's toys, or by the ingestion of food containing this compound. In a review by Sheftel (2000), the migration of ATBC from food packaging material of cheese wrapped in ATBC-plasticized vinylidene chloride copolymer films was reported to be 6.1 ppm, or 2.0-8.0 mg/kg in the cheese itself after exposure to the film for 5 days at temperatures of 5°C. The concentration in similarly wrapped cake (after 5 days at 5°C) was reported to be 3.2 ppm.

Migration from plasticized vinylidene chloride-vinyl chloride copolymer film in fatty or water rich foods was found to be as low as 0.4 mg/kg after minimal contact during microwave cooking of a soup, and up to 79.8 mg/kg for use of the film during the microwave cooking of peanut-containing cookies. Migration of ATBC from plasticized polyvinylidene chloride-polyvinyl chloride films during microwave heating was determined to be 73.9 mg/L into olive oil after heating for 10 minutes, and 4.1 mg/L into water after heating for 8 minutes (Sheftel, 2000 and references therein). In Welle et al. (2005), ATBC was determined to have a higher leaching rate from medical tubing than DEHP (SCENIHR, 2007).

Occupational exposure to ATBC may occur through inhalation and dermal contact at workplaces where the compound is produced or used. The most recent worker exposure information available is a National Institute for Occupational Health and Safety (NIOSH) NOES Survey, 1981-1983, (NIOSH, 1983). It was statistically estimated that 106,668 workers (98,183 females) may have been exposed to ATBC in the U.S.

2.4 Toxicology

Data on the toxicity of acetyl tri-n-butyl citrate (ATBC) in humans and animals were obtained from primary source documents identified from an initial literature search conducted in October 2008. Databases searched included: PUBMED (+ cancer subset), TOXLINE (Special), TSCATS1/TSCATS2, CCRIS, DART/ETIC, GENE-TOX, HSDB, RTECS and EPA SRS. Safety evaluations by the World Health Organization (WHO, 2000), the European Commission (SCENIHR, 2007) and the Cosmetic Ingredient Review Panel (Johnson, 2002) were also reviewed for relevant toxicity data.

In addition, robust summaries for ATBC were obtained from the High Production Volume Information System (HPVIS) (U.S. EPA, 2008a). These summaries are submitted to the United States Environmental Protection Agency (U.S. EPA) under the High Production Volume (HPV) Challenge Program. A majority of the summaries provided in U.S. EPA (2008a) are based on unpublished source documents that could not be obtained under this effort. In these instances, the data provided in U.S. EPA (2008a) are used to the extent possible to characterize ATBC toxicity. It should be noted that effect incidence, magnitude and dose-dependence is often times not detailed in the robust summaries, so only qualitative statements on adverse effects can be made in these situations. Only data from summaries ranked as reliable under the HPV program were included in this toxicity characterization.

2.4.1 Absorption, Distribution, Metabolism, and Excretion

The toxicokinetics and metabolism of ATBC were studied in rats by Dow Chemical Company (1992). Absorption of ATBC from the gastrointestinal tract is rapid (half-time of 1 hour, peak blood levels 2-4 hours after dosing) and extensive (at least 67% of the administered dose) after oral exposure. ATBC is quickly and almost completely metabolized, primarily by hydrolysis to polar metabolites including acetyl citrate, monobutyl citrate, acetyl monobutyl citrate, dibutyl citrate and acetyl dibutyl citrate (two

isomers), along with several other unidentified metabolites. *In vitro* studies found that ATBC is metabolized by human serum and rat liver homogenates to citric, acetic, and butyric acids (Davis, 1991; Edlund and Ostelius, 1991). In the *in vivo* rat study, most of the absorbed radioactivity was rapidly eliminated from the blood with a half-life of 3.4 hours (Dow Chemical Company, 1992). Approximately 99% of the administered radioactivity was eliminated within 48 hours of dosing, primarily in the urine (59-70%) and feces (25-36%), with a small amount (2%) expired as CO_2. Only 0.4-1.3% remained in the carcass at 48 hours. In the urine, radioactivity was present in at least 9 metabolites; the major metabolite was thought to be monobutyl citrate. In the feces, unchanged ATBC represented about 7% of the dose, but at least 3 metabolites were also present.

2.4.2 Acute Toxicity

Studies on ATBC acute oral toxicity, acute dermal toxicity, skin irritation/sensitization, and eye irritation were available at the time this report was written. These studies are reviewed below.

Acute Oral Toxicity

Lethality of ATBC by acute oral exposure is low. Five Wistar rats given a single gavage dose of ATBC at dose levels ranging from 10-30 mL/kg (approximately 10,500-31,500 mg/kg) all survived through a 21-day observation period (LD_{50} >31,500 mg/kg) (Finkelstein and Gold, 1959). Cats were also tested; all 12 cats given a single gavage dose of ATBC at dose levels ranging from 30-50 mL/kg (approximately 31,500-52,500 mg/kg) survived through an 8-week observation period (LD_{50} >52,500 mg/kg) (Finkelstein and Gold, 1959). Shortly following dosing in this study, the oily dosing material began to leak from the rectums of both rats and cats. Rats appeared sluggish following dosing, but recovered during the course of the observation period. Cats showed signs of nausea and developed diarrhea, which subsided in less than 24 hours following dosing. Hematology and urinalysis examinations conducted at 2-week intervals for 2 months on two cats dosed with 52,500 mg/kg did not reveal any treatment-related changes (Finkelstein and Gold, 1959). No deaths were observed among rats and mice of both sexes given single doses of ATBC by gavage at 25,000 mg/kg (Larionov and Cherkasova, 1977).

Acute Dermal Toxicity

No sign of acute dermal toxicity was observed in guinea pigs following the application of undiluted ATBC to the skin at doses up to 1250 mg/kg (Larionov and Cherkasova, 1977; Johnson, 2002). Repeated application of 250 or 500 mg/kg was reported to cause reduced body-weight gain, increased liver weight, and decreased cerebral perfusion pressure, although no further data on methods or results were reported (Larionov and Cherkasova, 1977; Johnson, 2002).

Skin Irritation/Sensitization

ATBC was tested for dermal irritation and sensitization in 59 men and women volunteers ranging in age from 21 to 60 years (Hill Top Research, 1978, as cited in Johnson, 2002). There was no evidence of irritation in the initial patch tests, nor any reactions suggestive of contact sensitization in subsequent challenge tests. Tests in guinea pigs showed that ATBC was not very irritating to the skin, producing only faint erythema and/or edema in response to intradermal injection, and a nonsensitizer, producing barely perceptible erythema in challenge tests (Unilever Limited, 1976, as cited in Johnson, 2002).

Eye Irritation

ATBC (0.1 mL) was instilled into the left conjunctival sac of three male albino rabbits, with the contralateral eyes serving as controls (CTFA, 1998a, as cited in Johnson, 2002). Moderate erythema was observed in two of the three test subjects within 20 minutes. The erythema subsided in one of the rabbits after 5 hours, but persisted beyond 24 hours in the other. No irritation was observed in any rabbit at 48 or 72 hours post instillation. Larionov and Cherkasova (1977) did not observe any ocular irritation after instilling a single drop of undiluted ATBC into the conjunctival sac of one rabbit.

2.4.3 Repeated Dose Toxicity

Finkelstein and Gold (1959) performed a short-term feeding study in rats to evaluate the effect of oral exposure to ATBC on growth, hematology, and pathology. Mixed-sex groups of four immature Wistar rats were allowed free access to a diet containing 0, 5% or 10% ATBC for up to 6 weeks. Doses were approximately 0, 7620 or 15,240 mg/kg-day, using U.S. EPA (1988) reference values for weanling Wistar rats. Growth among rats fed the 5% ATBC diet exceeded controls. However, growth was reduced approximately 35% in rats fed the 10% ATBC diet. The high-dose rats also had frequent diarrhea. Treatment with ATBC had no effect on blood counts (measured prior to treatment and 4 and 8 weeks later) and gross or microscopic pathology (40 tissues examined at the end of the 8-week study period). The study identified a LOAEL of 15,240 mg/kg-day and NOAEL of 7620 mg/kg-day, based on reduced growth.

Finkelstein and Gold (1959) also performed a short-term feeding study on two cats. Each cat received 5 mL/kg-day ATBC (approximately 5250 mg/kg-day) via gavage for 2 months. An additional two cats served as controls. The treated cats developed diarrhea and demonstrated a 30% reduction in body weight relative to controls. No changes were observed in the appearance and behavior of the cats, or in urine, blood chemistry or blood count. The small group sizes in this study limit interpretation of these results.

In a range-finding study for a subchronic feeding study, Sprague-Dawley rats (5/sex/dose) were administered ATBC (purity>98%) in the diet at doses of 0, 1000, 2700 or 5000 mg/kg-day for 14 consecutive days (Jonker and Hollanders, 1990, as cited in U.S. EPA, 2008a). No rats died during the study. Transient dose-related reductions in body weights were reported among all dose groups. Body weights among high-dose rats

and mid-dose male rats remained slightly lower than control rats throughout the study. Food consumption remained lower among high-dose males throughout the study as well. Increased cytoplasmic eosinophilia accompanied by reduced glycogen content of periportal hepatocytes was observed in the livers of two mid-dose male rats and all of the high-dose rats. No further details of this study were available.

Based on the results of the range-finding study, Sprague-Dawley rats (20/sex/dose) were administered ATBC (purity >98%) in the diet *ad libitum* at doses of 0, 100, 300 or 1000 mg/kg-day for 13 weeks (Jonker and Hollanders, 1991, as cited in U.S. EPA, 2008a). No mortality or clinical signs were observed. Slight, non-significant reductions in mean body weights were noted among mid-dose female rats and among both male and female high-dose rats. Food consumption was slightly reduced in high-dose male rats. There were no changes in appearance or behavior, and functional observations of motor activity, sensory activity or autonomic activity revealed no treatment-related effects. Hematology, clinical chemistry and urinalysis results were unremarkable. Although some changes were reported by U.S. EPA (2008a), the magnitude and statistical significance of these apparent changes were not reported. Based on the absence of effects in both sexes for specific parameters, the lack of change among corresponding endpoints, and the lack of any corresponding histopathological changes, U.S. EPA (2008a) did not consider these changes to be related to treatment. Relative liver weights were reportedly increased among mid-dose male rats and both male and female high-dose rats. In addition, there was a slight increase in the relative kidney weights of high-dose male rats. However, statistical significance and magnitude were not reported. It is not clear if absolute organ weights were unchanged or not reported. Gross necropsy and histopathology did not reveal any treatment-related effects in the liver, kidneys or other organs. Metabolism studies in rats (oral feeding studies) and in rat liver homogenates reveal that ATBC is extensively absorbed and rapidly metabolized and excreted (CTFA, 1998b; Dow Chemical Company, 1992; Davis, 1991; Edlund and Ostelius, 1991). Thus, liver, and possibly kidney, enlargement is most likely an adaptive change occurring as a consequence of metabolic load.

Jonker and Hollanders (1991) observed slight changes in mean body weights, food consumption, hematology, clinical chemistry and urinalysis among high-dose rats and in some cases among mid-dose rats, as described above. However, these changes were either not considered to be adverse or not related to treatment with ATBC. Increased relative organ weights among high-dose rats were not accompanied by any biochemical or histopathological changes indicative of liver or kidney damage. Based on the findings summarized in U.S. EPA (2008a) for the subchronic study performed by Jonker and Hollanders (1991), the high dose of 1000 mg/kg-day appears to be a NOAEL due to the absence of toxicologically significant findings.

2.4.4 Chronic Toxicity/Carcinogenicity

Three groups of Sherman rats (20 rats/dose) (gender not specified) were allowed free access to a diet containing ATBC (99.4% purity) at concentrations of 200, 2000 or 20,000 ppm for 2 years (Soeler et al., 1950). Target doses were estimated to be 10, 100

and 1000 mg/kg-day. A fourth group of 40 rats was fed the control diet. Appearance and behavior of treated rats were similar to controls. During weeks 5 to 15, all treated groups exhibited a transient depression in growth rate, although no statistical difference from controls was found. In order to evaluate body weight further, Soeler et al. (1950) fed two additional groups of 10 rats each a diet containing ATBC at target doses of 100 or 1000 mg/kg-day for one year. A third group of 20 rats was fed the control diet. Similar reductions in body-weight gain were not observed in this study. Since the apparent effect on growth was not reproducible, it was not considered to be an effect of ATBC treatment. In the main study, mortality occurred in 20% of the treated rats (12/60) and the control rats (8/40) prior to study termination. Necropsy of the animals that died early revealed inflammatory disease of the lungs. Pulmonary lesions ranged from bronchitis to severe suppurative and infectious necrotizing pneumonitis. This suggests possible infection among the test animals. As shown in Table 2-2, lymphomas were observed in both control and treated rats. Based on the higher tumor incidence in control rats, these tumors are not considered to be related to treatment with ATBC. In conclusion, Soeler et al. (1950) did not observe any significant treatment-related effects in rats exposed to ATBC up to 1000 mg/kg-day in the diet for 2 years. Therefore, the NOAEL for this study is 1000 mg/kg-day. This study is of limited value as a cancer bioassay because group sizes were relatively small (20 per treated group and 40 in controls), 20% of animals died early from infection, and doses were inadequate (the high dose did not approach the maximum tolerated dose [MTD]) (Soeler et al., 1950).

Table 2-2. Incidence of Lymphomas in ATBC-Treated Rats[a]

Dose (mg/kg-day)	Lymphomas
0	6/40[b]
10	1/20
100	0/20
1000	2/20

[a]Soeler et al. (1950)
[b]Compiled from Table IV of the reference; the text of the reference reports the control incidence as 4/40

Soeler et al. (1950) also fed two mongrel dogs gelatin capsules containing 140 mg ATBC daily (approximately 7-10 mg/kg-day) for 2 years. No unusual hematology or urinalysis results were observed and no gross or microscopic abnormalities were found. However, the small number of treated dogs and lack of controls in this study limit interpretation of these results.

2.4.5 Reproductive/Developmental Toxicity

In a two-generation study provided as a robust summary in U.S. EPA (2008a) based on Robbins (1994), Sprague-Dawley rats (30/sex/dose) were administered ATBC (purity 99.4%) continuously in the diet at target doses of 0, 100, 300 or 1000 mg/kg-day. Males were exposed for 11 weeks prior to and during mating, and females were exposed for 3 weeks prior to mating, during mating and through gestation and lactation. Male and female pups from the F1 generation from each litter were exposed under similar conditions from weaning for 10 weeks prior to mating. F1 females were additionally

exposed through mating, gestation and lactation. Only tissues that appeared abnormal at necropsy were evaluated for histopathology. Actual doses were within 10% of target doses in both the F0 and F1 rats. No treatment-related clinical signs were observed in parental rats of either generation. Body weights of high-dose F0 females were significantly reduced at the end of pregnancy (GD21 or 22), but not at other times. Body weights were also reduced in F1 parental males from the mid- and high-dose groups in a manner that appeared to U.S. EPA (2008a) to be treatment-related. No further information was provided in U.S. EPA (2008a). Water consumption among high-dose rats from both the F0 and F1 generations was consistently lower than concurrent controls throughout the study. No effects were observed on mating, gestation or fertility of the F0 or F1 generations and no abnormalities were seen at necropsy. Slightly higher mortality and slightly reduced body weights were observed among offspring from the 300 and 1000 mg/kg-day dose groups compared to controls. U.S. EPA (2008a) suggests that these effects were a consequence of reduced water consumption among treated dams rather than a direct effect of treatment with ATBC. No other developmental abnormalities were observed among offspring. Based on the findings summarized in U.S. EPA (2008a) of the two-generation study performed by Robbins (1994), 100 mg/kg-day appears to be a NOAEL and 300 mg/kg-day a LOAEL for ATBC for reductions in body weights among F1 parental males. No reproductive or developmental effects directly attributable to ATBC were observed at doses up to 1000 mg/kg-day.

Another reproduction study was described in a robust summary provided in U.S. EPA (2008a) based on Chase and Willoughby (2002). F0 Han Wistar rats (25/sex/dose) were exposed to Citroflex A-4 (ATBC, 99.9% purity) continuously in the diet at target doses of 0, 100, 300 or 1000 mg/kg-day for 4 weeks prior to and during mating. F0 females were additionally exposed during gestation and lactation until the offspring were weaned on lactation day 21. Groups of F1 offspring (20/sex/group) were exposed to ATBC continuously in the diet at the same target doses as the parental animals for 13 weeks. An additional 10 F1 males and 10 F1 females were assigned to the control and high-dose group for a 4-week recovery period following the 13-week treatment period. Actual doses were within 3% of target doses. Although the general condition of parental animals was unaffected by treatment, it was noted that high-dose parental females had an increased incidence of yellow staining in the perigenital and sacral regions during treatment. No other effects were observed among F0 rats, and in particular no effects were observed on estrous cycles, mating performance, fertility or gestation. Although the number of implantations and litter size among high-dose rats were slightly lower than the control group, they were within the laboratory's historical control ranges. F1 males and females treated with 1000 mg/kg-day ATBC as adults demonstrated slight reductions in body-weight gain, and increases in liver weight and hepatic hypertrophy, compared to controls. Hepatic hypertrophy and increased liver weight resulting from the induction of metabolizing enzymes is an adaptive response; U.S. EPA (2008a) did not consider these effects to be toxicologically relevant. Weak peroxisome proliferation was measured in mid-dose males and high-dose males and females. As noted by U.S. EPA (2008a), peroxisome proliferation is a rodent specific effect that is not relevant to hazard characterization for humans. Slight variations in urinary composition and in plasma electrolyte concentrations (not further described) were observed at the higher dose levels.

However, the observed changes were within normal historical control ranges and were reversible, and no corresponding histopathological changes were observed. Based on the findings summarized in U.S. EPA (2008a) for the one-generation study performed by Chase and Willoughby (2002), this study appears to identify a NOAEL of 1000 mg/kg-day for systemic and reproductive toxicity.

In a study from the Russian literature, Larionov and Cherkasova (1977) administered ATBC (purity not reported) continuously in the diet to groups of male and female mice and rats (strains and group sizes not reported) at target doses of 0, 50 or 250 mg/kg-day for 1 year. During the ninth month of the study, animals from each group were cross-mated and embryotoxicity was evaluated. Slight, transient changes were observed in body weights, cerebral perfusion pressure, and hematology among high-dose animals, but no parameters differed substantially from controls towards the end of the study and these changes were considered by the researchers to be adaptive in nature. No changes were observed among low-dose animals. No effects were observed in male gonads from treated rats or mice and the spermatogenesis index for high-dose rats and mice was within the range for control animals. There was a decrease in desquamatosed spermatogenic epithelium in high-dose males. However, there was no effect on fertility or litter size. Offspring from high-dose animals weighed slightly more than offspring from control animals and were slightly longer on average. The physiological development of mice and rat pups appeared unaffected by treatment. Based on the available report, 250 mg/kg-day appears to be a NOAEL for both systemic and reproductive toxicity in this study. However, the lack of methodological details limits interpretation of these data.

2.4.6 Genotoxicity

Available data suggest that ATBC is not genotoxic. ATBC did not induce reverse mutation in various strains of *Salmonella typhimurium* (Gollapudi and Linscombe, 1988; Heath and Reilly, 1982; San and Wagner, 1991), forward mutation in L5178Y mouse lymphoma cells (Bigger and Harbell, 1991) or forward mutation at the HGPRT locus of Chinese hamster ovary (CHO) cells (Dow Chemical Company, 1991; Linscombe et al., 1991) in the presence or absence of metabolic activation in *in vitro* tests. ATBC was also negative in *in vitro* tests for chromosomal aberrations in rat lymphocyte cells (Dow Chemical Company, 1988; Linscombe et al., 1991) and an assay for unscheduled DNA synthesis in primary hepatocytes of male Han-Wistar rats treated with 800 or 2000 mg/kg of ATBC by gavage (Fellows, 1999).

2.5 Summary

ATBC is a High Production Volume chemical with previous FDA approval for use as a food contact substance (HPVIS, 2008). It has low solubility in water, and will exist in the ambient atmosphere in both the vapor and particulate phases. The estimated BCF suggests a moderate potential for this compound to bioconcentrate in aquatic organisms (HSDB, 2008). It has demonstrated a leaching rate higher than DEHP (SCENIHR, 2007), and is proven to migrate from food packaging material. Generally, consumers may be

exposed to ATBC via dermal contact with consumer products or by the ingestion of food containing this compound.

With regard to ATBC toxicity, no data were available on its effects in humans, except for one study that demonstrated that ATBC is not irritating and is non-sensitizing to human skin (Hill Top Research, 1978, as cited in Johnson, 2002). Acute oral toxicity is low based on studies where no lethality was observed at doses up to 25,000 mg/kg in mice, 31,500 mg/kg in rats and 52,500 mg/kg in cats (Finkelstein and Gold, 1959; Larionov and Cherkasova, 1977). In guinea pigs, there was no evidence of toxicity after a single dermal exposure to 1250 mg/kg, but repeated application of 250 or 500 mg/kg-day was reported to affect body and liver weight (Larionov and Cherkasova, 1977; Johnson, 2002). ATBC is not irritating or sensitizing to guinea pig skin (Unilever Limited, 1976, as cited in Johnson, 2002) and it is only slightly irritating to rabbit eyes (CTFA, 1998a, as cited in Johnson, 2002; Larionov and Cherkasova, 1977).

The key repeated-dose animal toxicity data for ATBC are summarized in Table 2-3. The most sensitive endpoint identified was reduced growth in adult F1 males in a 2-generation reproduction study (Robbins, 1994). The original report was not available, but U.S. EPA (2008a) reviewed the data and considered reduced growth in the 300 and 1000 mg/kg-day groups to be treatment-related. Reduced growth was also observed in other studies in rats and cats, albeit at much higher doses (Finkelstein and Gold, 1959).

There was no clear evidence of specific target organ toxicity of ATBC, although two studies reported results suggestive of a non-adverse, adaptive response to ATBC in the liver (increased liver weight and/or hepatic hypertrophy) and possibly the kidney (Jonker and Hollanders, 1991 and Chase and Willoughby, 2002, as cited in U.S. EPA, 2008a). A 2-year dietary cancer bioassay in rats was negative, but was probably not an adequate test of carcinogenicity because group sizes were relatively small (20 per treated group and 40 in controls), 20% of animals died early from infection, and doses were inadequate (the high dose did not approach the MTD) (Soeler et al., 1950). Dietary reproductive toxicity tests in rats and mice did not reveal any effects of ATBC on reproductive parameters, such as fertility, mating, spermatogenesis, or gestation, or postnatal developmental effects (Chase and Willoughby, 2002; Robbins, 1994; Larionov and Cherkasova, 1977).

Teratogenicity of ATBC has not been evaluated. ATBC is not genotoxic. Results were negative in tests for mutagenicity in bacteria (Gollapudi and Linscombe, 1988; Heath and Reilly, 1982; San and Wagner, 1991) and mammalian cells (Bigger and Harbell, 1991; Dow Chemical Company, 1991; Linscombe et al., 1991), unscheduled DNA synthesis in rat hepatocytes (Fellows, 1999), and chromosomal aberrations in rat lymphocytes (Dow Chemical Company, 1988; Linscombe et al., 1991). Therefore, further toxicity testing should include study of the teratogenicity of ATBC. Additionally, specific studies on leaching and migration from children's articles would aid in the analysis of its potential for human exposure from use in these products.

Table 2-3. Summary of Key Repeated-Dose Oral Toxicity Information for ATBC

Species, sex, number	Sex	Doses (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Subchronic Exposure									
Rat 4/group	M/F	0, 7620 or 15,240	Diet for 6 weeks	7620	15,240	15,240	Reduced growth	No effect on hematology or gross or microscopic pathology	Finkelstein and Gold, 1959
Rat, 20/sex/group	M/F	0, 100, 300 or 1000	Diet for 13 weeks	1000	NA	NA	NA	Minor changes in body and organ weights, urinalysis, hematology and clinical chemistry not adverse or not related to treatment	Jonker and Hollanders, 1991 (as cited in U.S. EPA, 2008a)
Chronic Exposure									
Rat, 20/group	NS	0, 10, 100 or 1000	Diet for 2 years	1000	NA	NA	NA	No effect on tumor incidence or non-cancer effects	Soeler et al., 1950
Reproductive/Developmental Toxicity									
Rat	M/F	0, 100, 300 or 1000	Diet during premating, mating, gestation and lactation periods for two generations	100 (systemic) 1000 (reproduction and developmental)	300 (systemic)	300 (systemic)	Reduced body weight in adult F_1 males	No adverse reproductive or developmental effects attributable to ATBC at any dose	Robbins, 1994 (as cited in U.S. EPA, 2008a)
Rat	M/F	0, 100, 300 or 1000	Diet during premating, mating, gestation and lactation periods for one generation	1000	NA	NA	NA	No adverse systemic, reproductive or developmental effects attributable to ATBC at any dose	Chase and Willoughby, 2002 (as cited in U.S. EPA, 2008a)
Rat/Mice	M/F	0, 50 or 250	Diet for one year, during mating, and through gestation	250	NA	NA	NA	No adverse systemic, reproductive or developmental effects attributable to ATBC at any dose	Larionov and Cherkasova, 1977

[a] Adjusted for continuous exposure

3.0 Di(2-ethylhexyl) adipate (DEHA)

3.1 Use

Di(2-ethylhexyl) adipate (DEHA) is a commonly used plasticizer in lubricants, glue, scotch-tape, and sealants (Remberger et al. 2005). DEHA is an EPA High Production Volume chemical, indicating an annual production volume or importation volume above 1 millions pounds in the U.S. (HPVIS, 2008). Unlike other adipates permitted for use as acidity regulator food additives, the U.S. FDA regulates that DEHA is only permissible as an indirect food additive as a component of adhesives (FDA, 1999; HSDB, 2008).

As early as 2002, DEHA's presence was detected in children's soft PVC articles (Chen, 2002). At this time, the Consumer Product Safety Commission's Directorate for Laboratory Sciences purchased 41 children's products from retail stores, one of which was analytically identified as containing DEHA (Chen, 2002). In addition to its use in toys, DEHA can be found in a variety of home and office products, such as vinyl flooring, carpet backing, wood veneer, and coated fabrics (SCENIHR, 2007).

3.2 Physical/Chemical Properties

DEHA is an ester of 2-ethylhexanol and adipic acid (Figure 3-1). Its chemical formula is $C_{22}H_{42}O_4$ and its CAS number is [103-23-1]. A common synonym is dioctyl adipate (DOA).

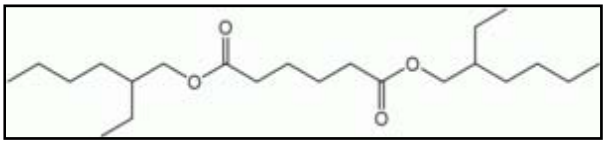

Figure 3-1. Structure of DEHA (SCEHIHR, 2007)

DEHA is an oily liquid, colorless and odorless (HSDB, 2008). Physical-chemical properties for this compound are highlighted in Table 3-1. The vapor pressure for DEHA indicates that in the atmosphere it may exist in both the gas and particle phases. It will be removed from the air via dry and wet deposition or via degradation primarily taking place through reactions with hydroxyl radicals. Direct photolysis is also a possible degradation route, because of functional groups on the molecule that absorb UV-light (HSDB, 2008).

DEHA is soluble in most organic solvents, including ethanol, ethyl ether, acetone, and acetic acid, and virtually insoluble in water (HSDB, 2008). DEHA has a relatively high K_{oc} value, indicating that it will sorb to organic carbon (Remberger et al., 2005). This, combined with its low vapor pressure, explains why DEHA is considered to be immobile when released to soil (HSDB, 2008). In the water environment, DEHA will sorb to particles and end up in the sediment, thus its transport via water is expected to be limited (HSDB, 2008). However, DEHA, like all adipates, is able to undergo hydrolysis, increasing its water solubility (HSDB, 2008). The BCF for DEHA is low, at 27 L/kg. In general, adipates, including DEHA, are fairly reactive substances, which readily degrade both in the environment and in organisms (Remberger et al., 2005).

Table 3-1. Physical-Chemical Properties of DEHP, DINP, and Potential *o*-DAP Alternatives (BASF, 2006; HPVIS 2008; HSDB 2008; SCENIHR 2007)

Name	MW	Wsol (mg/L)	K_{oc}	H (atm m^3/mol at 25°C)	Log K_{ow}	V_p (mm Hg at 25°C)	BCF L/kg
DEHP	390.56	0.285[a]	>87,420	1.3×10^{-7}	7.60	7.2×10^{-8}	115-851
DINP	418.62	0.2[b]	10,580	1.49×10^{-6}	n.a.	5.4×10^{-7}	1,500
ATBC	402.5	5.0[b]	1,800	3.8×10^{-10}	4.3[c]	4.6×10^{-6}	250
DEHA	370.57	0.78[c]	770,000	4.34×10^{-7}	>6.11	8.5×10^{-7} [d]	27
DINCH	424.7	<0.02[e]	n.a.	n.a.	10	9.75×10^{-7}[f]	189
TOTM	546.80	100[e]	350	4.4×10^{-7}	5.94[e]	3.9×10^{-11}	1-2.7
DEHT	390.54	4.0[d]	870,000	1.02×10^{-5}	5.72	2.14×10^{-5}	1,400,000

Wsol is the solubility of the chemical in water. K_{oc} is the organic carbon normalized solid-water partition coefficient in L/kg. H (atm m^3/mol) is the Henry's law constant. K_{ow} is the octanol-water partition coefficient. V_p is the vapor pressure. BCF is the bioconcentration factor. (Adapted from Remberger et al. 2005). See Appendix B for more detail.

[a] at 24°C
[b] temperature not specified
[c] at 22 °C
[d] at 20°C
[e] at 25°C
[f] at 50°C

3.3 Exposure

DEHA is used as a plasticizer in various food storage wraps and it has been shown to migrate into stored foods, thus the general population can be exposed through consumption of foods stored in plastic films (HSDB, 2008). For example, in a migration study by Petersen and Naamansen (1998), DEHA migration into fresh meat from food packaging was measured between 1and 40 mg/kg depending on fat content and number of times the meat was sliced and repacked in the DEHA containing film. The U.S. EPA Maximum Contaminant Level (MCL) for DEHA in drinking water is 0.4mg/L and the oral reference dose (RfD) is 0.6 mg/kg/day (US EPA, 2004). Fromme et al. (2007) quantified the median human dietary intake of DEHA as 0.7 µg/kg body weight using 27 female and 23 male subjects aged 14-60 years. The median, as well as the 95th percentile daily dietary intake, did not exceed the recommended tolerable daily intake (Fromme et al., 2007). In one-week duplicate diet samples provided by three Japanese hospitals, Tsumura et al. (2003) determined a total mean daily intake of DEHA as 12.5 micrograms. Inhalation of indoor air in office buildings using DEHA containing plastics is another route of human exposure (HSDB, 2008). Based upon indoor air monitoring of an office building, the representative indoor air concentration of DEHA was determined to be 2.0 ng/m^3; the source of the DEHA exposure was thought to be from plasticizer use (HSDB, 2008).

Widespread use of DEHA has made its investigation alongside phthalates in exposure and leaching studies commonplace (Cao, 2008; Fromme et al., 2007; Kueseng et al., 2007; Tsumura et al., 2003). Additionally, heavy and widespread use in food packaging and other industries has lead to widespread human exposure to this chemical (Remberger et al., 2005). In this study, conducted by the Swedish Environmental Research Institute, eight adipates were screened for in air, water, sediment, sludge, biota and human breast milk. DEHA was the only adipate frequently detected in samples. That is, it was detected in the majority of the samples, compared to the seven other adipates tested, five of which were not detected at all. Two were detected in sludge. No adipates, including DEHA, were detected in air or human breast milk (Remberger et al. 2005). DEHA metabolites were not investigated. No information has been found describing the exposure of children to DEHA, either from PVC articles or otherwise.

Occupational exposure to DEHA occurs during its production, its use as a plasticizer, and its use as a lubricant and functional fluid (IARC, 1982). Exposure can occur through dermal contact and inhalation (IARC, 1982). The NIOSH NOES Survey (NIOSH 1983) has statistically estimated that 15,636 workers (3,628 of these are female) are potentially exposed to DEHA in the U.S. For example, the average concentration of DEHA in the air of a meat-wrapping department of a supermarket, as a result of heating polyvinyl chloride film during meat packaging operations, was estimated to be 0.014 ppm (0.2 mg/cu m) (IARC, 1982).

3.4 Toxicology

Literature searches of the PUBMED, TOXLINE, TSCATS, CCRIS, DART/ETIC, GENE-TOX, HSDB, RTECS and EPA SRS databases were conducted in October 2008 for information relevant to the health effects of DEHA in humans and laboratory animals. The search strategy included CAS No. (103-23-1) and DEHA synonyms such as dioctyl adipate (DOP). Additional secondary sources checked for pertinent health effects information are listed in Section 1.4.2.

3.4.1 Absorption, Distribution, Metabolism, and Excretion

The disposition of DEHA in the body has been summarized by IARC (2000a) and SCENIHR (2007). Following oral exposure, DEHA in the gut is rapidly hydrolysed to mono-(2-ethylhexyl) adipate, adipic acid, and 2-ethylhexanol, which, along with unchanged DEHA are absorbed rapidly and completely within 24 hours. Once absorbed, DEHA and metabolites are widely distributed within the body. The highest levels were found in the gastrointestinal tract, muscle, liver, fat, blood, and kidney 6-12 hours after exposure in rats. Transplacental passage of DEHA has been demonstrated in pregnant mice. Elimination of DEHA and it metabolites is rapid, and occurs primarily via the urine. In humans, urinary metabolites of DEHA were excreted with an average half-time of 1.5 hours, and none were detected after 36 hours. Metabolites identified in human urine included (in decreasing quantities) 2-ethylhexanoic acid, 2-ethyl-5-hydroxyhexanoic acid, 2-ethyl-1,6-hexanedioic acid, 2-ethyl-5-ketohexanoic acid, and 2-ethylhexanol. In rats, adipic acid was the primary metabolite in urine, accounting for 20-

30% of the administered dose. In monkeys, the glucuronide of mono-(2-ethylhexyl) adipate was found in the urine. A small percentage of the administered dose (3% in rats) is excreted in the bile and undergoes enterohepatic circulation.

3.4.2 Acute Toxicity

Lethality of DEHA by acute exposure is low by all natural routes. Smyth et al. (1951) determined a single-dose oral range-finding LD_{50} value of 9110 mg/kg for DEHA in rats of unspecified strain and sex observed for 14 days. NTP (1982b) estimated LD_{50} values of 45,000 and 24,600 mg/kg in male and female F344 rats, respectively, given a single dose of DEHA by gavage in corn oil at levels ranging from 80 to 20,000 mg/kg (5/dose/sex) and observed for 14 days. Similar experiments in B6C3F1 mice yielded LD_{50} estimates of 15,000 mg/kg in males and 24,600 mg/kg in females (NTP, 1982b). Effects on endpoints other than mortality were not reported in any of these studies.

Acute inhalation data for DEHA were limited to the results of an acute inhalation test that found no mortality among rats exposed for 8 hours to air saturated with DEHA vapor (Smyth et al., 1951).

A single-dose dermal range-finding LD_{50} value of 16,300 mg/kg was determined for DEHA in rabbits observed for 14 days (Smyth et al., 1951). Information on the dermal exposure conditions in this study was not available. In an unpublished study, rabbits receiving a single application of DEHA to intact or abraded skin in doses of 3600 - 8700 mg/kg under occlusive conditions for 24 hours showed dose-related transient mild skin irritation (slight erythema), but no systemic effects, as evaluated by clinical signs, body weight, food consumption, hematology and urinalysis during the following 14 days (CTFA, 1967).

Skin and eye irritation were minimal in studies conducted by Smyth et al. (1951) in rabbits. A number of unpublished studies tested the dermal irritation and sensitization potential of DEHA in animals and humans; these have been evaluated in an authoritative assessment of the safety of DEHA as a cosmetic ingredient (Anonymous, 1984). Primary dermal irritation studies of DEHA alone or in cosmetic formulations in rabbits, as well as clinical patch tests of cosmetic formulations containing up to 9.0% DEHA in humans (including a 21-day cumulative irritancy test), indicated that DEHA is, at most, a weak skin irritant. The human patch tests of cosmetic products containing DEHA, as well as a study of unformulated DEHA in guinea pigs, also showed no induction of skin sensitization. Additionally, dermal phototoxicity tests of DEHA in humans and rabbits showed no phototoxic (primary irritant) or photoallergic reactions.

3.4.3 Repeated-Dose Toxicity

A number of repeated-dose oral studies of DEHA have been conducted in rats and mice. These studies mainly investigated the induction of peroxisome proliferation in the liver by DEHA, particularly mechanisms by which it can lead to the formation of hepatocellular tumors. Most of these studies were conducted in rats exposed to DEHA in

the diet for 1-4 weeks at one exposure level in the range of 1 - 2.5% (10,000 - 25,000 ppm), i.e., at dietary concentrations comparable to those tested in an NTP (1982b) chronic bioassay of DEHA in rats and mice and found to be hepatocarcinogenic in mice. A few of the studies tested mice, longer exposure durations (up to 13 weeks), multiple dietary exposure levels (ranging as low as 1500 ppm) and/or gavage exposure. Effects induced by DEHA in these studies are consistent with those of di(2-ethylhexyl)phthalate (DEHP) and other hepatic peroxisome proliferators in rats and mice (Cattley et al., 1998; Chevalier and Roberts, 1998; Doull et al., 1999; IARC 2000a, 2000b; Lake, 1995), and included liver enlargement due to hepatocellular hypertrophy and proliferation, increased replicative DNA synthesis, increased number and size of peroxisomes (ultrastructural effects), induction of peroxisomal and microsomal fatty acid-oxidizing enzymes, alterations in hepatic lipid metabolism including inhibition of cholesterolgenesis, and reduced serum/plasma cholesterol and triglyceride levels (Barber et al., 1987; Bell, 1983, 1984; Katoh et al., 1984; Kawashima et al., 1983a, 1983b; Keith et al., 1992; Lake et al., 1997; Moody and Reddy, 1978, 1982; Reddy et al., 1986; Takagi et al., 1990, 1992; Tomaszewski et al., 1986; Yanagita et al., 1987). Peroxisome proliferation is a rodent specific effect that is of questionable relevance to hazard characterization for humans (Cattley et al., 1998; Chevalier and Roberts, 1998; Doull et al., 1999; IARC, 2000a; Klaunig et al. 2003; Lake, 1995; Melnick 2001).

Studies not employing the specialized techniques required to detect peroxisome proliferation observed only increased weight in the liver. Kang et al. (2006) reported a large (50%) increase in relative liver weight and a decrease in body weight in male F344 rats exposed to 25,000 ppm (1570 mg/kg-day) DEHA in the diet for 4 weeks. There were no effects on serum indicators of hepatotoxicity (ALT, AST, GGT) or light microscopy of the liver. No hepatic changes were observed at 6000 ppm (318 mg/kg-day). Relative liver weight was also significantly increased without accompanying serum chemistry or histopathology changes in male and female Crj:CD (SD) rats given DEHA by gavage in corn oil at 1000 mg/kg-day, but not 200 mg/kg-day or lower, for 28 days or more (Miyata et al., 2006). The increases in liver weight in these studies were likely due to peroxisomal proliferation. Dietary 13-week studies performed by NTP (1982b) as dose range-finding studies for cancer bioassays in F344 rats and B6C3F1 mice (described below) did not include measurement of organ weights, but histopathological evaluations showed no effects in the liver, kidneys or other tissues of male or female F344 rats or B6C3F1 mice exposed to DEHA concentrations as high as 25,000 ppm (approximately 2500 mg/kg-day in rats and 4700 mg/kg-day in mice). Nabae et al. (2006) also reported no evidence of renal histopathology (or serum chemistry or urinalysis findings indicative of renal pathology) in male F344 rats exposed to 25,000 ppm (1570 mg/kg-day) DEHA in the diet for 4 weeks. In contrast, kidney lesions were observed by Miyata et al. (2006) in male, but not female, Crj:CD (SD) rats treated with 1000 mg/kg-day, but not 200 mg/kg-day or lower, of DEHA by gavage in corn oil for 28 days. The type of lesions (increased eosinophilic bodies and hyaline droplets) and pattern of occurrence (male rats only) suggest that this finding may be related to male rat specific alpha-2u-globulin nephropathy, which is not predictive of a renal effect in humans (U.S. EPA, 1991). Both Miyata et al. (2006) and Nabae et al. (2006) reported small increases in relative kidney

weight in treated rats. Miyata et al. (2006) found no effects on hematology or a functional observational battery (FOB) for neurological effects in treated rats.

3.4.4 Chronic Toxicity/Carcinogenicity

F344 rats (50/sex/dose) and B6C3F1 mice (50/sex/dose) were fed a diet containing 0, 12,000 or 25,000 ppm DEHA for 103 weeks and observed for an additional 1-3 weeks following the end of exposure (NTP, 1982b). Based on U.S. EPA (1988) reference values for food consumption and body weight for chronic exposure in F344 rats, estimated doses of DEHA in rats were 948 and 1975 mg/kg-day for the males and 1104 and 2300 mg/kg-day for the females (NTP, 1982b did not report food consumption). Clinical signs, survival, body weight, gross pathology, and histopathology of major tissues and organs and all gross lesions were evaluated. Mean body weights of the high-dose male and female rats were reduced throughout the study. At the end of the exposure period, the mean body weights of the high-dose males and females were approximately 12 and 22% lower than controls, respectively (as estimated from growth curves). No neoplastic or non-neoplastic lesions or other compound-related adverse effects were observed.

For mice in the NTP (1982b) study, estimated doses of DEHA, based on U.S. EPA (1988) reference values, were 2040 and 4250 mg/kg-day for both sexes. Mean body weights of low- and high-dose male and female mice were lower than controls throughout the study and the decreases were dose-related. Survival at the end of study in the control, low-dose and high-dose groups was 72, 64 and 82% in males and 84, 78 and 73% in females. Liver tumors were induced in both sexes. As shown in Table 3-2, incidences of hepatocellular adenomas or carcinomas (combined) were significantly increased in high-dose males and low- and high-dose females. No compound-related non-neoplastic lesions were observed in the liver or other tissues.

Table 3-2. Liver Tumor Incidence in DEHA Treated Mice[a]

Dose (mg/kg-day)	Hepatocellular Adenoma or Carcinoma	
	Males	Females
0	13/50	3/50
2040	20/49	19/50[c]
4250	27/49[b]	18/49[c]

[a]NTP (1982b)
[b]Significantly different from control at $p<0.05$
[c]Significantly different from control at $p<0.001$

Carcinogenicity results of chronic feeding studies of DEHA in rats and dogs were briefly and inadequately reported by Hodge et al. (1966). No compound-related tumors were induced in rats exposed to 0, 0.1, 0.5 or 2.5% (1000, 5000 or 25,000 ppm) DEHA in the diet for 2 years. These negative results are consistent with those of the NTP (1982b) rat study summarized above, which also tested DEHA in dietary concentrations up to 25,000 ppm. No tumors were found in dogs exposed to 0, 0.07, 0.15 or 0.2% (700, 1500 or 2000 ppm) DEHA in the diet for 1 year.

In other studies conducted by Hodge et al. (1966), C3H/AnF mice (50/sex/dose) were exposed to DEHA by dermal application or subcutaneous injection. In the dermal study, weekly application of 0.1 or 10 mg of DEHA in acetone to a clipped area of back skin under non-occlusive conditions for life caused no gross or histological evidence of tumor formation at the application site. In the subcutaneous study, a single 10 mg dose of DEHA caused no injection site tumors following lifetime observation.

3.4.5 Reproductive/Developmental Toxicity

DEHA has been suspected of having effects on the male reproductive system because it shares similarities in chemical structure and metabolism with DEHP, a well documented inducer of testicular toxicity and antiandrogenic effects in rats and other laboratory animals (SCENIHR, 2007; IARC, 2000b). Young animals are much more sensitive to DEHP testicular toxicity than adults, and male rats have been shown to be particularly susceptible to antiandrogenic effects of DEHP when exposed during the perinatal period (NTP-CERHR, 2005). In contrast to DEHP, DEHA has not shown any adverse reproductive effects in male rats exposed perinatally or for 4, 13 or 103 weeks from 5-11 weeks of age (Dalgaard et al., 2002, 2003; Kang et al., 2006; Miyata et al., 2006; Nabae et al., 2006, NTP, 1982b).

In general systemic toxicity studies, no histopathological effects were observed in the reproductive organs (testes, seminal vesicles, prostate, ovary or uterus) of male or female F344 rats or B6C3F1 mice that were exposed to DEHA in the diet at concentrations as high as 25,000 ppm for 13 weeks (~2500 mg/kg-day in rats and ~4700 mg/kg-day in mice) or 103 weeks (~2100 mg/kg-day in rats and ~4250 mg/kg-day in mice) (NTP, 1982b).

Studies by Nabae et al. (2006) and Kang et al. (2006) investigated the testicular toxicity of DEHA in greater detail. In each study, 11-week-old male F344 rats (6/dose) were exposed to DEHA in the diet at concentrations of 0, 6000 or 25,000 ppm for 4 weeks. Nabae et al. (2006) reported average intakes of 0, 318 and 1570 mg/kg-day. Evaluations included body weight, spermatogenesis (sperm number, motility and morphology abnormalities), and relative weight and histopathology of the testes, epididymes, prostate and seminal vesicles. Reduced body weight gain was reported in both studies at 1570 mg/kg-day. The only DEHA-related reproductive effect in either study was increased relative testes weight at 1570 mg/kg-day (9.3% higher than controls) reported by Nabae et al. (2006). This is not considered adverse because relative testes weight was increased rather than decreased (possibly secondary to reduced body weight) and not accompanied by abnormal spermatogenesis or testicular histopathology findings. Additionally, this effect was not induced by the same DEHA exposure in the Kang et al. (2006) study. Additional experiments by Kang et al. (2006) showed that the same DEHA exposures did not cause testicular toxicity in rats that were pretreated with thioacetamide to induce liver damage, in contrast to DEHP (25,000 ppm for 4 weeks), which caused testicular toxicity (e.g., seminiferous tubule atrophy and degeneration) that was enhanced by liver damage induced by thioacetamide. Additional experiments by Nabae et al. (2006) showed that the same DEHA exposures did not cause testicular toxicity in rats that were pretreated with

five consecutive weekly subcutaneous injections of folic acid to induce chronic renal dysfunction, in contrast to DEHP (25,000 ppm for 4 weeks), which caused testicular toxicity (e.g., decreased testicular weights, seminiferous tubule atrophy and diminished sperm counts) that was enhanced under conditions of renal dysfunction induced by folic acid. The high dose of 1570 mg/kg-day was a NOAEL for male reproductive toxicity of DEHA in these studies.

Both male and female reproductive endpoints were assessed in 8-week-old Crj:CD (SD) rats (10/sex/dose) given DEHA in corn oil by gavage at dose levels of 0, 40, 200 or 1000 mg/kg-day for at least 28 days (Miyata et al., 2006). Males were sacrificed on day 29 and females were sacrificed in the diestrus stage on days 30-34. Evaluations included estrus cycling in females (assessed daily from day 22 until the day of sacrifice), sperm morphology and number in males, and serum hormones (TSH, T3, T4, testosterone, FSH, LH and estradiol) and weight and histopathology of reproductive organs in both sexes. The reproductive and hormonal evaluations showed effects only in females. Ovarian follicle atresia (absence or disappearance by degeneration) was observed in 4/10 females at 1000 mg/kg-day (compared to 0/10, 0/10 and 0/9 females at 0, 40 and 200 mg/kg-day), and two of these four rats had a prolonged estrus cycle (estrous stage durations of 4 and 10 days). These effects are not conclusively DEHA-related due to the small numbers of affected animals. However, because a prolonged estrous stage was associated with histopathological changes in the ovary, the results suggest a NOAEL of 200 mg/kg-day and LOAEL of 1000 mg/kg-day for reproductive toxicity in female rats. A NOAEL of 1000 mg/kg-day and no LOAEL was identified for male reproductive toxicity in rats.

Dalgaard et al. (2002, 2003) studied the effects of perinatal exposure to DEHA in Wistar rat pups. In the dose-range finding study, dams (8/dose) were administered DEHA by gavage at dose levels of 0, 800 or 1200 mg/kg-day from gestation day (GD) 7 to postnatal day (PND) 17. Evaluations included maternal clinical signs and body weight during the dosing period, pregnancy length, number and size of litters, sex distribution, body weight of pups at birth and on PND 3, postnatal survival through PND 21, anogenital distance on PND 3 and areola/nipple retention on PND 13 in male pups, and weights of testes, epididymides, ventral prostate and seminal vesicles in male pups on PND 21. Statistically significant effects included decreased maternal body weight gain during GD 7-21, increased pregnancy length, and increased percentage of perinatal loss at 1200 mg/kg-day. Body weight of male and female pups was significantly decreased at birth at 1200 mg/kg-day and on PND 3 (only PND evaluated) at ≥800 mg/kg-day. The study found no antiandrogenic effects, but identified a LOAEL of 800 mg/kg-day and no NOAEL for developmental toxicity in rats based on decreased pup body weight. Maternal effects were reported only at 1200 mg/kg-day.

In the main study of perinatally exposed rats, dams (20/dose) were administered DEHA by gavage at dose levels of 0, 200, 400 or 800 mg/kg-day from GD 7 to PND 17 (Dalgaard et al., 2002, 2003). Evaluations included the endpoints assessed in the range finding study, as well as additional endpoints for onset of sexual maturation in both sexes, levels of reproductive hormones in males, sperm quality, weight and histopathology of male reproductive organs, and other organ weights. Statistically

significant effects included increased gestation length at 800 mg/kg-day, decreased body weight of male and female pups at 800 mg/kg-day, and a dose-related decrease in pup survival at ≥400 mg/kg-day. No antiandrogenic endpoints were affected. Relative liver weight was significantly increased in male offspring on PND 21 at 800 mg/kg-day but not as adults. The only statistically significant changes in adult male offspring were decreased body and adrenal weights at 800 mg/kg-day. This study found no antiandrogenic effects, but based on the increased postnatal deaths, identified a NOAEL of 200 mg/kg-day and LOAEL of 400 mg/kg-day for developmental toxicity in rats. Maternal effects were reported at 800 mg/kg-day.

DEHA and DEHP have the metabolite 2-ethylhexanol (2-EH) in common. Several studies used DEHA to investigate the hypothesis that 2-EH is responsible for some of the male reproductive effects of DEHP. In particular, if 2-EH causes these effects of DEHP, DEHA could hypothetically augment DEHP-induced changes in male reproductive endpoints when the two compounds are administered in combination, even though DEHA does not produce these effects on its own. In these studies, rats were administered either DEHP (300 or 700 mg/kg-day) or DEHP (750 mg/kg-day) in combination with DEHA (400 mg/kg-day) by gavage from GD 7 to PND 17 (Borch et al., 2004, 2005; Jarfelt et al., 2005). Exposure to DEHA alone was not tested. Examination of fetal, prepubertal and adult male offspring found that antiandrogenic and testicular effects of DEHP were not modulated by the administration of DEHA in combination with DEHP. Endpoints evaluated in these studies included weight and histopathology of reproductive organs, testicular apoptosis, anogenital distance and nipple retention, sperm number and motility, and reproductive hormones.

In an unpublished developmental toxicity study, Wistar-derived female rats (24/dose) were fed diets containing 0, 300, 1800 or 12,000 ppm DEHA from days 1-22 of gestation (ICI, 1988a). Average intake of DEHA was reported to be 0, 28, 170 or 1080 mg/kg-day. Maternal evaluations included clinical observations, body weight and food consumption throughout the study, and gross pathology following sacrifice on gestation day (GD) 22. Developmental endpoints included gravid uterus, litter and fetal weights, and numbers of corpora lutea, implantations (early and late intra-uterine deaths) and live fetuses. All fetuses were examined for gender, cleft palate, and external, visceral, skeletal and macroscopic brain abnormalities. Maternal effects occurred at 1080 mg/kg-day and consisted of statistically significant reductions in food consumption and body weight gain (-13%) throughout gestation. Fetal effects were observed at ≥170 mg/kg-day, and included several minor skeletal defects (e.g., partially ossified parietals of the skull) and variations indicative of slightly reduced ossification (e.g., partially ossified transverse process of the 7th cervical vertebrae) and two visceral variations involving the ureters (kinked ureter, slightly dilated ureter). The authors considered the ureter variations, as well as the reduced ossification as indicated by the minor skeletal defects and variations, to be the result of slight fetotoxicity. Based on the authors' interpretation of the results, this study identified a NOAEL of 28 mg/kg-day and LOAEL of 170 mg/kg-day for prenatal developmental toxicity in rats. U.S. EPA (2008b), however, considered the changes at 170 mg/kg-day to be non-adverse and classified this level as a NOAEL. Maternal effects were seen only at 1080 mg/kg-day.

Effects of DEHA on reproductive function were evaluated in an unpublished one-generation study in Wistar derived-rats (CEFIC, 1988; ICI, 1988b) that is incompletely summarized in a SIDS assessment (UNEP, 2000) and on IRIS (U.S. EPA, 2008b). Male rats (15/dose) and female rats (30/dose) were exposed to 0, 300, 1800 or 12,000 ppm DEHA in the diet for 10 weeks before mating, and apparently during the mating period in both sexes and gestation and lactation periods in females. The offspring were reared to PND 36. Based on the companion developmental toxicity study, doses were 0, 28, 170 or 1080 mg/kg-day. There were no clinical signs of toxicity or changes in body weight or feed consumption during the premating period, and no effects on male or female fertility were observed. Maternal body weight gain during gestation, as well as offspring weight gain, total litter weight and litter size throughout the post-partum period, were reduced at 1080 mg/kg-day. Postmortem examinations of the parental animals, apparently conducted in males at the end of the mating period and females after weaning of the offspring, showed increased absolute and relative liver weights in both sexes at 1080 mg/kg-day. No exposure-related histopathological changes occurred in the reproductive tissues of the parental males and females, and no exposure-related gross pathologic changes occurred in the offspring. Additional information on the scope of the organ weight and pathology evaluations was not provided in the available study summaries. The high-dose of 1080 mg/kg-day appears to have been a LOAEL for reduced maternal body weight gain during gestation and reduced litter size and weight that may have been secondary to the maternal effect. The NOAEL was 170 mg/kg-day.

3.4.6 Genotoxicity

DEHA was negative in a variety of *in vitro* and *in vivo* genotoxicity assays. When tested *in vitro*, DEHA did not induce gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 or TA1538 (Seed, 1982; Simmon et al., 1977; Zeiger et al., 1985), or in mouse lymphoma L5178Y cells (McGregor et al., 1988), in the presence or absence of exogenous metabolic activation. Additionally, urine from rats that were administered a daily 2000 mg/kg dose of DEHA by gavage for 15 days was not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 or TA1538 with or without metabolic activation (DiVincenzo et al., 1985). DEHA did not induce sister chromatid exchanges, micronuclei or chromosomal aberrations in cultured rat hepatocytes without exogenous metabolic activation (Reisenbichler and Eckl, 1993). When tested in cultured Chinese hamster ovary cells, DEHA did not induce sister chromatid exchanges with or without metabolic activation, although chromosomal aberrations were induced in the absence but not presence of metabolic activation (Galloway et al., 1987). DEHA was inactive in a BALB/c-3T3 cell transformation assay (Matthews et al., 1993).

In *in vivo* tests, bone marrow cells from mice that were administered DEHA by intraperitoneal injection had no induction of micronuclei with daily doses as high as 2000 mg/kg for 3 days (Shelby et al., 1993) or chromosomal aberrations with a single unspecified dose (Shelby and Witt, 1995). Feeding or injection of DEHA did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (Woodruff et al., 1985), although dominant lethal mutations were induced in male mice that were

administered a single high dose of DEHA (≥4700 mg/kg) by intraperitoneal injection (Singh et al., 1975). DNA synthesis was stimulated in hepatocytes from rats administered a single 3.78 mmol/kg (1401 mg/kg) dose of DEHA by gavage (Busser and Lutz, 1987) but not from mice gavaged with a single 1000 or 2000 mg/kg dose of DEHA (Miyagawa et al., 1995).

3.5 Summary

DEHA is a commonly used plasticizer whose presence has already been detected in children's soft PVC articles (Chen, 2002). It is characterized by low vapor pressure and low solubility in water (HSBD, 2008; Table 3-1). The BCF for DEHA is low, at 27 L/kg, however, it has structural similarities to other chemicals which have proven carcinogenic properties (HSDB, 2008). DEHA has been shown to migrate into stored foods, causing human exposure via ingestion (Fromme et al., 2007; Remberger et al., 2005; Tsumura et al., 2003). Inhalation and dermal exposure scenarios also arise, as DEHA can be found in a variety of home and office products (SCENIHR, 2007).

With regards to toxicity, a DEHA study in humans indicated that the chemical is not a potent skin irritant, and not a sensitizer; animal studies showed similar results (Anonymous, 1984; CTFA, 1967; Smyth et al., 1951). This was the only human data available for DEHA. The acute toxicity of DEHA is low by oral, inhalation or dermal exposure. Oral LD_{50} values ranged from 9110 to 24,600 mg/kg in rodents, no deaths were observed in rats after 8 hours exposure to air saturated with DEHA vapor, and a dermal LD_{50} of 16,300 mg/kg was determined in rabbits (NTP, 1982b; Smyth et al., 1951).

Available short-term and subchronic studies of systemic endpoints were of limited utility for hazard characterization in humans. Most of these studies investigated hepatic peroxisome proliferation induced by DEHA, which is a rodent-specific effect of questionable relevance to humans. Other studies reported only organ weight increases either related to peroxisome proliferation or of uncertain toxicological significance (Kang et al., 2006; Miyata et al., 2006; Nabae et al., 2006) or renal lesions in male rats suggestive of male rat specific alpha-2u-globulin nephropathy (Miyata et al., 2006), another effect that is not relevant to humans.

Although DEHA was found not to have testicular or antiandrogenic effects (Dalgaard et al., 2002, 2003; Kang et al., 2006; Miyata et al., 2006; Nabae et al., 2006), the chemical did produce other developmental/reproductive effects in several studies, including ovarian follicle atresia and prolonged estrus cycle in female rats (Miyata et al., 2006), increased postnatal mortality in rat pups exposed perinatally (Dalgaard et al., 2002, 2003), reductions in rat litter size and weight (ICI, 1988b), and minor skeletal and visceral variations in rat fetuses (ICI, 1988a) (see Table 3-3). The developmental effects in the gestational exposure studies occurred at lower doses than maternal effects in those same studies, indicating that the developing organism is a sensitive target for this chemical; the lowest LOAEL values in the database occurred in these studies (400 mg/kg-day with a NOAEL of 200 mg/kg-day for postnatal pup mortality, and 170-1080 mg/kg-day with a NOAEL of 28-170 mg/kg-day for fetal variations). U.S. EPA (2008b)

lists a chronic oral Reference Dose (RfD, verified in 1991) of 0.6 mg/kg-day for DEHA based on fetal variations in the ICI (1988a) study (using 170 mg/kg-day as the NOAEL) and reduced litter size and weight in the ICI (1988b) study.

DEHA has structural similarities to other chemicals, which have proven carcinogenic properties (HSDB, 2008). A cancer bioassay in rats was negative, while one in mice was positive, showing induction of liver tumors in both males and females (NTP, 1982b). Genotoxicity data from a variety of *in vitro* and *in vivo* mutagenicity and clastogenicity tests were primarily negative. It has been hypothesized that the observed mouse liver tumors are a result of peroxisome proliferation, and therefore, of questionable relevance to humans (Cattley et al., 1998; Chevalier and Roberts, 1998; Doull et al., 1999; IARC, 2000a; Lake, 1995, Melnick, 2001). Based on these considerations, IARC (2000a) concluded that DEHA was not classifiable as to its carcinogenicity in humans (Group 3). However, in a previous assessment verified in 1991, U.S. EPA classified DEHA in weight-of-evidence (WOE) Group C as a possible human carcinogen and calculated an oral slope factor (OSF) of 1.2E-3 $(mg/kg\text{-}day)^{-1}$ (U.S. EPA, 2008b).

Table 3-3. Summary of Key Repeated-Dose Oral Toxicity Information for DEHA

Species, sex, number	Sex	Doses (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Chronic Exposure									
Rat, 50/sex/ group	M/ F	M: 0, 948, 1975 F: 0, 1104, 2300	Diet for 2 years	948-1104	1975-2300	1975-2300	Reduced growth in males and females	Adequate cancer bioassay; no effect on incidence of tumors or non-cancer lesions	NTP, 1982b
Mouse, 50/sex/ group	M/ F	0, 2040, 4250	Diet for 2 years	NA	2040	2040	Reduced growth in males and females; increased incidence of liver tumors in females (tumors in males increased at high dose)	Adequate cancer bioassay. Basis for cancer assessment (WOE and OSF) on IRIS (U.S. EPA, 2008b).	NTP, 1982b
Reproductive/Developmental Toxicity									
Rat, 6/group	M	0, 318, 1570	Diet for 4 weeks	1570	NA	NA	NA	Study designed to investigate testicular effects	Nabae et al., 2006
Rat, 6/group	M	0, 318, 1570	Diet for 4 weeks	1570	NA	NA	NA	Study designed to investigate testicular effects	Kang et al., 2006
Rat 10/sex/ group	M/ F	0, 40, 200, 1000	Gavage in corn oil for at least 28 days	M: 1000 F: 200	M: NA F: 1000	M: NA F: 1000	M: NA F: Ovarian follicle atresia and prolonged estrus cycle	Study designed to investigate effects on hormones and reproductive organs in males and females	Miyata et al., 2006
Rat 20/group	F	0, 200, 400, 800, 1200	Gavage in peanut oil from GD 7 to PND 17	maternal: 400 pups: 200	maternal: 800 pups: 400	maternal: 800 pups: 400	maternal: increased gestation length pups: increased postnatal mortality	Study designed to investigate anti-androgenic and other developmental effects of perinatal exposure; no antiandrogenic effects observed	Dalgaard et al., 2002, 2003

Table 3-3. Summary of Key Repeated-Dose Oral Toxicity Information for DEHA

Species, sex, number	Sex	Doses (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Rat 24/group	F	0, 28, 170, 1080	Diet from GD 1-22	maternal: 170 fetal: 28-170	maternal: 1080 fetal: 170-1080	maternal: 1080 fetal: 170-1080	maternal: decreased body weight gain fetal: minor skeletal and visceral variations	Standard teratogenicity study. Basis (in part) for RfD on IRIS (U.S. EPA, 2008b)	ICI, 1988a
Rat 15M+ 30F/ group	M/ F	0, 28, 170, 1080	Diet from 10 weeks before mating through lactation	170	1080	1080	Decreased maternal body weight gain during gestation, litter size and weight, and offspring weight gain	Single generation reproductive study; complete report not available. Basis (in part) for RfD on IRIS (U.S. EPA, 2008b)	ICI, 1988b

[a] Adjusted for continuous exposure

4.0 1,2-Cyclohexanedicarboxylic acid, dinonyl ester (DINCH)

4.1 Use

Hexamoll® DINCH was recently developed by BASF (www.basf.com) for use as a PVC plasticizer and, specifically, to replace DEHP and DINP in products such as food contact applications, childcare articles, and children's toys (Jobwerx, 2006). Other targeted application areas include medical articles and shoes, as well as non-PVC applications such as adhesives, cosmetics, artificial leather, textile coatings, and erasers (BASF, 2007). DINCH has gained approval from the European Food Safety Authority (EFSA), the Japan Hygienic PVC Association (JHPA), and the German Institute for Risk Assessment (German BfR) for use as a food contact substance (BASF, 2008b).

According to the petitioner (presumably BASF) to the EFSA, DINCH is appropriately used as a plasticizer in PVC in concentrations up to 40%. It is used in PVC cling films for fresh meat packaging (10%), for aqueous food and fruits and vegetables (35%), artificial corks (35%), sealing gaskets for beverage containers (35%), flexible tubes for beverages (40%), in other foods (12%), and on conveyor belts for fatty foods (12%) (EFSA, 2006).

4.2 Physical/Chemical Properties

DINCH is a non-aromatic hydrogenated ester with chemical formula $C_{26}H_{48}O_4$. It appears under CAS number [474919-59-0] in the United States and Canada, and [166412-78-8] in the European Union (BASF, 2008a). DINCH is the non-aromatic analog to the ring hydrogenated ester DINP (Figure 4.1); they contain the same alcohol component. DINCH is produced by hydrogenation of DINP in the presence of a catalyst (Wilkes, 2005), and is said to be a suitable replacement to DINP due to its similar plasticizing performance. Additionally, mixtures of diisononyl esters of 1,2-cyclohexanedicarboxylic acid, whose isononyl radicals have a degree of branching from 1.2 to 2.0, are particularly suitable to replace DEHP in PVC applications (U.S. Patent Application 20080188601, 2008).

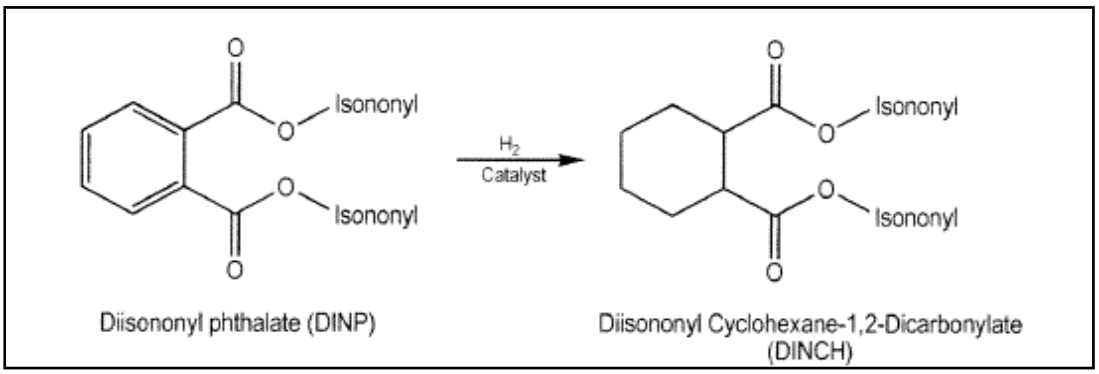

Figure 4-1. Conversion of DINP to DINCH

According to the manufacturer's technical leaflet (BASF, 2008a), DINCH is a "colorless, clear and practically anhydrous liquid with a hardly noticeable odor." It is soluble in common organic solvents, is essentially insoluble in water, and is miscible and

compatible with other monomeric plasticizers commonly used in PVC (BASF, 2008a). The manufacturer's Material Safety Data Sheet (MSDS) for DINCH (BASF, 2006) provides the physical-chemical properties for this compound displayed in Table 4-1.

Table 4-1. Physical-Chemical Properties of DEHP, DINP, and Potential *o*-DAP Alternatives (BASF, 2006; HPVIS 2008; HSDB 2008; SCENIHR 2007)

Name	MW	Wsol (mg/L)	K_{oc}	H (atm m^3/mol at 25°C)	Log K_{ow}	V_p (mm Hg at 25°C)	BCF L/kg
DEHP	390.56	0.285[a]	>87,420	1.3×10^{-7}	7.60	7.2×10^{-8}	115-851
DINP	418.62	0.2[b]	10,580	1.49×10^{-6}	n.a.	5.4×10^{-7}	1,500
ATBC	402.5	5.0[b]	1,800	3.8×10^{-10}	4.3[c]	4.6×10^{-6}	250
DEHA	370.57	0.78[c]	770,000	4.34×10^{-7}	>6.11	8.5×10^{-7} [d]	27
DINCH	424.7	<0.02[e]	n.a.	n.a.	10	9.75×10^{-7}[f]	189
TOTM	546.80	100[e]	350	4.4×10^{-7}	5.94[e]	3.9×10^{-11}	1-2.7
DEHT	390.54	4.0[d]	870,000	1.02×10^{-5}	5.72	2.14×10^{-5}	1,400,000

Wsol is the solubility of the chemical in water. K_{oc} is the organic carbon normalized solid-water partition coefficient in L/kg. H (atm m^3/mol) is the Henry's law constant. K_{ow} is the octanol-water partition coefficient. V_p is the vapor pressure. BCF is the bioconcentration factor. (Adapted from Remberger et al. 2005). See Appendix B for more detail.

[a] at 24°C
[b] temperature not specified
[c] at 22 °C
[d] at 20°C
[e] at 25°C
[f] at 50°C

DINCH has a vapor pressure of 9.75×10^{-7} mm Hg (25°C), indicating its ability to exist in the ambient atmosphere in both the gas and particle phases. Water solubility and log K_{ow} values for this compound indicate insolubility in water-based solutions. A BCF of 189 is considered moderate according to general EPA guidelines. The organic carbon normalized solid-water partition coefficient (K_{oc}) and Henry's Law Constant were not available for DINCH as of December, 2008.

4.3 Exposure

In 2006, specific information on DINCH migration was submitted to the European Food Safety Authority (EFSA) by its petitioner (presumably BASF). In this submission, migration of DINCH from PVC cling film containing 10-17.8% of DINCH into "food stimulants and foodstuffs" was said to be determined by Gas Chromatography/Mass Spectrometry (GC/MS). Results showed that DINCH migrates quantitatively into foods with high fat content; the migration rate of DINCH from cling wrap was 29 mg/dm^2 for sunflower oil (6h at 10°C and 144h at 20°C) and 27.5 mg/dm^2 for high fat cheese (10d at 5°C). All other products tested (fresh meats and low fat cheeses) were below the 10 mg/dm^2 European legal limit (EFSA, 2006).

Migration of DINCH from bottle closures containing a PVC sealing layer with 37% DINCH was determined by the petitioner for carbonated mineral water, grape fruit juice,

and orange lemonade. In all cases, migration into the aqueous beverages was low, in the range of 10-30 µg/kg. Results from a medical tubing migration study by Welle et al. (2005) determined that migration in a DINCH feeding system is considerably lower than for DEHP systems. No occupational exposure data was available. No biomonitoring studies could be found.

4.4 Toxicology

Literature searches of the PUBMED, TOXLINE, TSCATS, CCRIS, DART/ETIC, GENE-TOX, HSDB, RTECS and EPA SRS databases were conducted for information relevant to the health effects of DINCH in humans and laboratory animals. The search strategy included the two CASRNs as well as synonyms. Additional secondary sources checked for pertinent health effects information are listed in Section 1.4.2.

No published studies of DINCH were found. The only information located regarding the health effects of DINCH was found in the SCENIHR (2007) report, which contained summaries of unreferenced and unpublished studies submitted by BASF Corporation, and in an abstract/summary of one of these studies submitted by BASF Corporation to EPA under the Toxic Substances Control Act (TSCA) and identified in the search of the TSCATS database. An internet search that included the European Commission web site did not locate reports for any of the unpublished studies. Letters requesting copies of the unpublished studies were sent to the Public Health and Risk Assessment Group of the European Commission, as well as directly to BASF Corporation, but no responses to the letters were received as of December, 2008. The DINCH toxicity section in the SCENIHR (2007) report contains an introductory statement indicating that all included studies were performed under Good Laboratory Practice (GLP) conditions according to Organisation of Economic Co-operation and Development (OECD) guidelines.

4.4.1 Absorption, Distribution, Metabolism, and Excretion

The toxicokinetics and metabolism of DINCH have been summarized by SCENIHR (2007). DINCH is rapidly absorbed after oral administration, but absorption is saturable and incomplete. Absorption was estimated to account for 40-49% of the administered dose at the low dose tested, but only 5-6% at the high dose. Absorbed DINCH does not accumulate in the tissues. DINCH is metabolized initially through hydrolysis to the monoisononyl ester, which can be further metabolized in 2 ways, either by conjugation to glucuronic acid or by the hydrolysis of the mono ester to cyclohexane dicarboxylic acid. Elimination of DINP is rapid, with 80% of the radioactivity being eliminated within 24 hours and 90% within 48 hours. The primary route of elimination is the feces, mostly as unchanged parent compound. Absorbed DINCH is eliminated in the bile (primarily as the glucuronic acid conjugate of the monoisononyl ester) and the urine (primarily as cyclohexane dicarboxylic acid).

4.4.2 Acute Toxicity

The only acute toxicity values available for DINCH were provided in the SCENIHR (2007) summary of BASF studies (BASF, n.d.). Specially, acute LD_{50} values for DINCH in rats were >5000 mg/kg for oral exposure and >2000 mg/kg for dermal exposure (BASF, n.d.). DINCH was not an irritant in skin and eye irritation tests in rabbits and not a skin sensitizer in a guinea pig maximization test (BASF, n.d.). No additional information was provided in the SCENIHR (2007) summary of these studies.

4.4.3 Repeated-Dose Toxicity

A 28-day oral toxicity study of DINCH has been conducted (BASF, n.d.) but only minimal information on the study is provided in the SCENIHR (2007) summary. The species and type of oral exposure are not specified but are presumed to be rat, with diet presumed to be based on exposure concentrations of 0, 600, 3000 and 15,000 ppm and reported corresponding male/female doses of 0, 64/66, 318/342 and 1585/1670 mg/kg-day. The rat is the preferred species for testing according to OECD test guideline (TG) 407 (Repeated Dose 28-Day Oral Toxicity Study in Rodents). Based on OECD TG 407, the study likely evaluated 5 rats/sex/dose and endpoints that included clinical signs, body weight, food consumption, hematology, clinical chemistry, gross pathology, organ weights and histopathology. The only reported effects of DINCH were increased serum gamma-glutamyltransferase (GGT) and degenerated epithelial cells in the urine at the highest dose. No quantitative data or other details were provided for these effects. Based on increases in serum GGT and the presence of degenerated epithelial cells in the urine at 15,000 ppm (1585 mg/kg-day in males and 1670 mg/kg-day in females), SCENIHR (2007) identified 3000 ppm (318 mg/kg-day in males and 342 mg/kg-day in females) as a NOAEL. However, the toxicological significance of the observed changes is uncertain. SCENIHR (2007) considered these same changes to be non-adverse in their evaluations of subsequent longer-term studies (see below).

The repeated-dose toxicity of DINCH also was evaluated in a 90-day oral study (BASF, n.d.). The species and type of oral exposure are not specified in the SCENIHR (2007) summary, but are presumed to be rat with diets based on exposure concentrations of 0, 1500, 4500 and 15,000 ppm and reported corresponding male/female doses of 0, 107/128, 325/389 and 1102/1311 mg/kg-day. Again, the rat is the preferred species for testing according to OECD TG 408 (Repeated Dose 90-Day Oral Toxicity Study in Rodents). Based on information in the study summary and OECD TG 408, the study likely evaluated 10 rats/sex/dose and endpoints that included clinical signs, body weight, food consumption, sensory reactivity to stimuli of different types (e.g., auditory, visual and proprioceptive), grip strength and motor activity, ophthalmology, hematology, clinical chemistry, urinalysis, gross pathology, organ weights and histopathology. Effects included increases in liver weight, phase I and phase II enzymes in the liver, serum GGT and TSH (thyroid stimulating hormone), thyroid weight and hyperplasia/hypertrophy of the thyroid follicles.

No quantitative data or effect levels were provided for any of these effects, although they suggested a common mode of action of liver enzyme induction. This is causing thyroid effects via increased turnover of plasma thyroxin. Relative testes weights were increased at all dose levels but there was no dose-response relationship or histopathological changes in the testes or other parts of the male reproductive system. Other findings were blood and urinary tract transitional epithelial cells in the urine and alpha 2_u-globulin accumulation in the renal tubules of male rats. The latter effect is not considered relevant to humans because alpha 2_u-microglobulin is specific to the kidneys of male rats.

SCENIHR (2007) disregarded the liver and thyroid effects and identified effect levels based on renal effects. However, it is not clear that this was appropriate. Although induction of liver enzymes and an associated increase in liver weight by themselves would be considered an adaptive response to chemical exposure, the point at which these changes become of sufficient magnitude to produce hyperplasia/hypertrophy of thyroid follicles could be considered a LOAEL. Further, the only renal effects were alpha 2_u-globulin accumulation in males, which is known not to be relevant to humans, and epithelial cells in the urine, which is of uncertain toxicological significance and was considered by SCENIHR (2007) to be non-adverse in the absence of renal histopathology in the evaluation of the 2-year study (see below). The available study description provided insufficient information to independently determine effect levels.

Effects similar to those in the aforementioned 90-day study were observed in a two-generation reproduction study presumably conducted in rats (BASF, n.d.). As summarized in section 4.4.4, dietary exposure to DINCH caused increased serum GGT, decreased total bilirubin and increased liver, kidney and thyroid weights in F0 parental rats at 1000 mg/kg-bw, but not at ≤300 mg/kg-day. The authors reported that similar effects that were unspecified, except for increased thyroid weight and thyroid hypertrophy/hyperplasia, occurred in F1 parental rats at ≥300 mg/kg-day, but not at 100 mg/kg-day.

4.4.4 Chronic Toxicity/Carcinogenicity

A combined chronic toxicity/carcinogenicity study of DINCH was conducted in which Wistar rats (50/sex/dose) were orally exposed to dose levels of 0, 40, 200 or 1000 mg/kg-day for two years (BASF, 2005). The method of oral exposure is not specified in the available summaries of the study (BASF, 2005; SCENIHR, 2007). The study was conducted under OECD TG 453 (Combined Chronic Toxicity/Carcinogenicity Studies) (BASF, 2005), but this guidance does not indicate a preferred method of oral exposure. It is presumed that exposure was by diet based on likely consistency with the use of dietary exposure in the 28-day, 90-day and two-generation studies of DINCH. Based on OECD TG 453, the study likely evaluated endpoints that included clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights and histopathology. The main effects were increases in thyroid weight, follicular cell hyperplasia and follicular adenomas in male rats at ≥200 mg/kg-day and female rats at 1000 mg/kg-day. Quantitative data were provided only for the follicular cell adenomas (Table 4-2). The study did not report statistical significance.

Table 4-2. Incidence of Thyroid Gland Adenomas in DINCH-Treated Rats[a]

Dose (mg/kg-day)	Males	Females
0	3/50	1/50
40	5/50	3/50
200	11/50	3/50
1000	14/50	9/50

[a]BASF (2005)

The only other finding was the presence of urinary tract transitional epithelial cells in the urine at unspecified effect level(s), but this was considered by SCENIHR (2007) to be adaptive, as the effect was transitory and there were no histological lesions in the kidneys. Although SCENIHR (2007) argued that the observed thyroid effects, including tumors, are not relevant to humans, this is not consistent with the conclusions of the U.S. EPA (1998) Risk Assessment Forum. U.S. EPA (1998) concluded that rodent noncancer thyroid effects resulting from disruption of the thyroid-pituitary axis are presumed to pose a noncancer health hazard to humans and that rodent cancer effects resulting from the same mechanism may pose a cancer health hazard to humans. Based on the non-neoplastic effects in the thyroid, this study identified chronic toxicity NOAELs and LOAELs of 40 and 200 mg/kg-day in male rats and 200 and 1000 mg/kg-day in female rats.

4.4.5 Reproductive/Developmental Toxicity

A two-generation reproductive toxicity study was conducted using continuous dietary administration of DINCH at dose levels of 0, 100, 300 and 1000 mg/kg-day. The species is not specified in the SCENIHR (2007) summary of the study but is presumed to be rat because this is the preferred species for testing under OECD TG 416 (Two-Generation Reproduction Toxicity Study). Based on OECD TG 416, it is likely that F0 males and females were dosed for at least 10 weeks prior to mating, during mating and pregnancy, and through weaning of the Fl offspring. Similarly, weaned Fl offspring likely were dosed for at least 10 weeks before mating, during mating and pregnancy, and through weaning of the F2 offspring. Dose groups in both generations likely contained at least 20 males and 20 pregnant females. The available summary of the study indicates that evaluations included sperm parameters, fertility, reproductive performance, clinical chemistry, organ weights and histopathology in the F0 and/or F1 parental animals, and sexual maturation in the F1 generation. Based on OECD TG 416, additional evaluations likely included clinical observations, body weight gain, food consumption and estrous cycle length and normality in parental animals and offspring, and postnatal developmental toxicity endpoints (e.g., number and sex of pups, survival and weight of pups at birth through weaning, gross anomalies) in both generations. There were no effects on fertility or reproductive performance in the F0 or F1 parental animals or developmental toxicity in the F1 or F2 pups. Reported effects included increased serum GGT and decreased total bilirubin in F0 females, and increased liver, kidney and thyroid

weights in F0 males and females, at 1000 mg/kg-bw. Effects that were similar to those in the F0 generation, but unspecified except for increased thyroid weight and thyroid hypertrophy/hyperplasia, apparently occurred in F1 parental animals at ≥300 mg/kg-day. No quantitative data were provided for any of the effects. The high-dose of 1000 mg/kg-day appears to have been a NOAEL for reproductive and developmental effects in this study.

The previously summarized subchronic and chronic toxicity studies of DINCH apparently found no treatment-related effects on the weight or histopathology of reproductive organs in male/female rats exposed to oral doses as high as 1585/1670 mg/kg-day for 28 days, 1102/1311 mg/kg-day for 90 days or 1000/1000 mg/kg-day for 2 years.

The SCENIHR (2007) review includes a pre- and postnatal exposure developmental toxicity study of DINCH with an experimental design that apparently does not correspond to any current OECD test guideline. The design of this study appears to be similar to studies of DHEA and DEHP that focused on potential antiandrogenic effects in developing male rats. DINCH was orally administered to maternal animals from day 3 post-coitum to postnatal day (PND) 20 at dose levels of 0, 750 and 1000 mg/kg-day (BASF, n.d.). The species and method of oral exposure are not specified in the available summary (SCENIHR, 2007) but are likely to be rat and gavage. The only information on numbers of animals is that all male offspring and apparently 3 females/dose were raised to PND 100-105. Evaluations included anogenital distance (AGD) and anogenital index (AGI = AGD divided by body weight) on PPD 1, sexual maturation (assessed by testes descendance, balanopreputial separation, penis evaluation/inspection and vaginal opening), sperm parameters and weight and histology of testes. Small decreases (7-8% less than controls) in AGD in males and AGI in both sexes were observed on PND 1 at 1000 mg/kg-day, but these were not considered to be biologically significant because sexual maturation, sperm parameters and testicular weight and histology were not affected. Additionally, the effect on AGI is unlikely due to impaired androgen-dependent development because AGI was decreased to a similar extent in both sexes. This study identified an apparent NOAEL of 1000 mg/kg-day and no LOAEL for developmental toxicity in male and female rats.

Prenatal developmental toxicity was evaluated in rats and rabbits that were orally administered DINCH during gestation (BASF, n.d.). The type of oral exposure is not specified in the available summaries of these studies (SCENIHR, 2007), although gavage is the usual method of oral administration under these types of OECD TG 414-compliant studies (Prenatal Developmental Toxicity Study). In the rat study, DINCH was administered at dose levels as high as 1200 mg/kg-day (lower doses not specified) on gestational days (GD) 6-19. In the rabbit study, DINCH was administered at dose levels of 0, 100, 300 or 1000 mg/kg-day on GD 6-29. OECD TG 414 recommends that each test and control group should contain a sufficient number of rats or rabbits to result in approximately 20 females with implantation sites at necropsy. Based on OECD TG 414, as well as information provided in the summary of the rabbit study, evaluations in both species likely included maternal clinical signs, food consumption and body weight,

pregnancy status and gravid uterine weight, as well as corpora lutea, implantations, resorptions, live and dead fetuses, fetal sex and body weight, and fetal external, soft tissue and skeletal alterations. No effects were observed in either species, indicating that these studies identified apparent NOAELs of 1200 mg/kg-day in rats and 1000 mg/kg-day in rabbits, and no LOAEL in either species, for both maternal and developmental toxicity.

4.4.6 Genotoxicity

DINCH is not considered to be genotoxic. Specially, DINCH did not induce mutations in bacteria (*Salmonella typhimurium* or *Escherichia coli*) or Chinese hamster ovary cells *in vitro*, chromosomal aberrations in Chinese hamster V79 cells *in vitro*, or micronuclei in mouse bone marrow cells *in vivo* (BASF, n.d.). Additional information was not provided in the available summary of these genotoxicity studies (SCENIHR, 2007).

4.5 Summary

New to the market, DINCH lacks extensive exposure and toxicology data. It has a low migration rate and poor solubility in water (BASF, 2007). DINCH has been approved for use as a food contact substance, at times up to 40% by weight in PVC (EFSA, 2006). As the non-aromatic analog to DINP, DINCH is said to be a suitable direct substitute due to its similar plasticizing performance.

With regard to toxicity, there is no information on effects of DINCH in humans and animal studies were generally performed in orally exposed rats. The acute toxicity of DINCH is low, as shown by rat oral and dermal LD_{50} values of >5000 and >2000 mg/kg, respectively. DINCH was not irritating to skin and eyes in rabbits and was not a dermal sensitizer in guinea pigs.

Several toxicity studies on DINCH have been performed, but the results are available only as summaries prepared by the manufacturer. The summaries lack details, such as experimental design, the doses, and quantitative results. Short-term, subchronic, chronic and 2-generation reproductive oral studies in rats showed effects of DINCH on the liver, urinary tract and, in particular, thyroid. According to the authors, the hepatic effects appear to be mild and generally adaptive in nature, comprising induction of phase I and phase II enzymes in the liver and increases in liver weight and serum GGT with no accompanying histopathological changes or increases in other serum enzymes. The urinary tract effects also appear to be mild because they consisted of transitional epithelial cells and blood in the urine, had no accompanying urinalysis or histopathological changes, and were transient or reversible (i.e., were not evident after 2 years of exposure). The thyroid effects consisted of increases in serum TSH, thyroid weight, and follicular cell hypertrophy/hyperplasia and adenomas.

Table 4-3 summarizes the key data for DINCH. The lowest LOAELs were 200 and 300 mg/kg-day for thyroid effects in the 2-year and 2-generation reproduction studies. Corresponding NOAELs were 40 and 100 mg/kg-day. The 2-generation study in rats

showed no reproductive toxicity in either generation at doses as high as 1000 mg/kg-day. DINCH did not cause maternal or prenatal developmental toxicity in rats at doses as high as 1200 mg/kg-day on GD 6-19 or rabbits at doses as high as 1000 mg/kg-day on GD 6-19. DINCH also did not affect postnatal reproductive development in male offspring of rats that were exposed to doses as high as 1000 mg/kg-day during gestation and lactation (GD 3 - PND 20), as shown by no effects on sexual maturation, sperm parameters or testicular weight or histopathology. Additionally, there is no evidence that DINCH is genotoxic based on negative tests for mutations in bacteria and Chinese hamster ovary cells *in vitro*, chromosomal aberrations in Chinese hamster V79 cells *in vitro*, and micronuclei in mouse bone marrow cells *in vivo*.

Essentially all located information regarding the health effects of DINCH was found in the SCENIHR (2007) review of unreferenced and unpublished animal studies submitted by BASF Corporation. BASF Corporation also submitted an abstract/summary of one of these studies (the chronic toxicity/carcinogenicity study) to EPA under TSCA (BASF, 2005). The available summaries of these studies are brief and generally insufficient with respect to information on experimental design and results, particularly quantitative data and dose-response relationships. While DINCH is entering the market as a component of consumer products such as children's articles, the insufficiency of these study summaries preclude independent evaluation of the results and reliable identification of adverse effect levels.

Table 4-3. Summary of BASF (n.d., 2005) Oral Toxicity Studies of DINCH

Species	Number of Animals	Dose Levels (mg/kg-day)	Exposure Regimen	Apparent NOAEL[a] (mg/kg-day)	Apparent LOAEL[a] (mg/kg-day)	Critical Effects
Acute Exposure						
Rat	NS	NS	Single dose, likely gavage	NS	NS	LD_{50} > 5000 mg/kg
Repeated-Dose Toxicity						
Rat	NS, likely 5/sex/dose	0/0, 64/66, 318/342 or 1585/1670 in M/F	28 days, likely dietary	318 (M) 342 (F)	1585 (M) 1670 (F)	Increased serum GGT and degenerated epithelial cells in the urine. These effects of uncertain toxicological significance.
Rat	NS, likely 10/sex/dose	0/0, 107/128, 325/389 or 1102/1311 in M/F	90 days, likely dietary	NA	NA	Insufficient information to determine reliable effect levels.
Chronic Toxicity/Carcinogenicity						
Rat	50/sex/dose	0, 40, 200 or 1000 in both sexes	2 years, dietary	40 (M) 200 (F)	200 (M) 1000 (F)	Increased thyroid weight, follicular cell hyperplasia and follicular adenomas.
Reproductive/Developmental Toxicity						
Rat	NS, likely 20/sex/dose	0, 100, 300 or 1000	2 generations, dietary	100 1000	300 NA	Increased thyroid weight and follicular cell hypertrophy/hyperplasia in F1 parental rats. No reproductive or developmental toxicity in either generation.
Rat	NS	0, 750 or 1000	GD 3 – PND 20, likely gavage	1000	NA	No effects on sexual maturation, sperm, or testicular weight or histopathology in male offspring observed to PND 100 – 105.
Rat	NS, likely 20F/dose	≤1200[b]	GD 6 – 19, likely gavage	1200	NA	No maternal or developmental toxicity
Rabbit	NS, likely 20F/dose	0, 100, 300 or 1000	GD 6 – 29, likely gavage	1000	NA	No maternal or developmental toxicity

[a] NOAEL and LOAEL determinations based on limited information presented in SCENIHR (2008); studies were not presented in sufficient detail to permit independent evaluation.

[b] Doses below 1200 mg/kg-day not specified.

NS = not specified; NA = not applicable; GD = gestation day; PND = postnatal day

5.0 Trioctyltrimellitate (TOTM)

5.1 Use

Trioctyltrimellitate (TOTM) is known as the plasticizer of choice for high temperature applications, or when low volatility and high viscosity are important. TOTM is an EPA High Production Volume chemical (HPVIS, 2008) with an estimated global production of 40,000-100,000 tons/year (SCENIHR, 2007). Synonyms include tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate, triocyltrimellitate, tri(2-ethylhexyl)trimellitate, 1,2,4-benzenetricarboxylic acid, trioctyl ester, and tris(2-ethylhexyl) ester (SCENIHR, 2007).

When trimellitate esters, such as TOTM, are processed with PVC, their principle feature is low volatility, even under high temperatures. Consequently, TOTM's main use is in high specification electrical cable insulation and sheathing (ECPI, 2009e). Additionally, as a branched molecule, TOTM is more viscous than the essentially linear adipates and phthalates, and thus can be used where high viscosity is needed such as in gear lubricants and greases (Hatco, 2008), and in pesticide formulations as a release-rate control agent (Federal Register, 1998). The extraction and migration resistance of trimellitates are also significantly improved relative to phthalate plasticizers, leading to TOTM's recent use in dishwasher gaskets, medical tubing and photograph storage (SCENIHR, 2007). Due to its low volatility, high viscosity, and subsequently low migration rates, TOTM may be an alternative to *o*-DAP plasticizers in children's articles, although its use for this purpose has not yet been reported.

5.2 Physical/Chemical Properties

Trimellitate esters, such as TOTM, are produced by the esterification of a range of alcohols with trimellitic anhydride (TMA), which is similar in structure to phthalic anhydride with the exception of a third functionality on the aromatic ring (Figure 5-1). The presence of three alcohols makes trimellitates significantly more viscous then adipates or phthalates (Hatco, 2008).

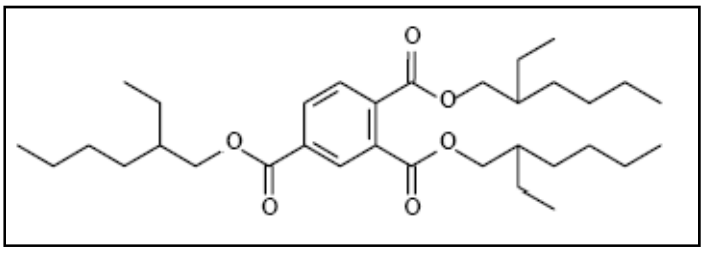

Figure 5-1. Structure of TOTM (SCENIHR, 2007)

TOTM is a yellow, oily liquid with chemical formula $C_{33}H_{54}O_6$ and CAS number [3319-31-1]. Physiochemical properties appear in Table 5-1. TOTM is soluble in water at 100mg/L (Table 5-1) and, if released into water, is expected to adsorb to suspended solids and sediment in water based upon an estimated K_{oc} value of 350. Volatilization from water surfaces or from moist soil surfaces is not expected to occur based upon an

estimated Henry's Law constant of 4.4 x 10^{-7} (HSDB, 2008). If released to air, an estimated vapor pressure of 3.9 x 10^{-11} mm Hg (25 ^{o}C) indicates that TOTM will exist solely in the particulate-phase in the ambient atmosphere (to be removed by wet and dry deposition). Volatilization from dry soil surfaces is not expected due to its low vapor pressure (HSDB, 2008). A measured BCF of less than 1 to 2.7 in carp suggest that bioconcentration in aquatic organisms is low (HSDB, 2008).

Table 5-1. Physical-Chemical Properties of DEHP, DINP, and Potential *o*-DAP alternatives (BASF, 2006; HPVIS 2008; HSDB 2008; SCENIHR 2007)

Name	MW (g/mole)	Wsol (mg/L)	K_{oc}	H (atm m^3/mol at 25^{o}C)	Log K_{ow}	V_p (mm Hg at 25^{o}C)	BCF L/kg
DEHP	390.56	0.285[a]	>87,420	1.3 x 10^{-7}	7.60	7.2 x 10^{-8}	115-851
DINP	418.62	0.2[b]	10,580	1.49 x 10^{-6}	n.a.	5.4 x 10^{-7}	1,500
ATBC	402.5	5.0[b]	1,800	3.8 x 10^{-10}	4.3[c]	4.6 x 10^{-6}	250
DEHA	370.57	0.78[c]	770,00	4.34 x 10 $^{-7}$	>6.11	8.5 x 10^{-7} [d]	27
DINCH	424.7	<0.02[e]	n.a.	n.a.	10	9.75 x 10^{-7}[f]	189
TOTM	546.80	100[e]	350	4.4 x 10^{-7}	5.94[e]	3.9 x 10^{-11}	1-2.7
DEHT	390.54	4.0[d]	870,000	1.02 x 10^{-5}	5.72	2.14 x 10^{-5}	1,400,000

Wsol is the solubility of the chemical in water. K_{oc} is the organic carbon normalized solid-water partition coefficient in L/kg. H (atm m^3/mol) is the Henry's law constant. K_{ow} is the octanol-water partition coefficient. V_p is the vapor pressure. BCF is the bioconcentration factor. (Adapted from Remberger et al. 2005). See Appendix B for more detail.

[a] at 24^{o}C
[b] temperature not specified
[c] at 22 ^{o}C
[d] at 20^{o}C
[e] at 25^{o}C
[f] at 50^{o}C

5.3 Exposure

The general population may be exposed to TOTM via dermal contact or ingestion if this chemical were to migrate out of a plasticized consumer product. However, based on its relatively high molecular weight and bulky structure, TOTM is expected to be resistant to migration. In a study by Kambia et al. (2001), less TOTM and less DEHP (combined, by weight) were released from hemodialysis tubing plasticized with a TOTM-DEHP combination, than DEHP released from hemodialysis tubing plasticized with DEHP only. The authors concluded that TOTM was a superior alternative to DEHP for use in medical devices because of its lower leachability. In a similar study by Flaminio et al. (1988), two groups of patients on chronic hemodialysis treatment were given TOTM plasticized tubing in place of the common PVC-DEHP blood tubing. Results showed less TOTM than DEHP leached from hemodialysis tubing. Thus, non-occupational dermal exposure to TOTM from a PVC based consumer product or medical device is expected to be lower relative to DEHP due to TOTM's lower migration rate. Additionally, non-occupational inhalation exposure to TOTM is also expected to be lower because of its very low vapor pressure (3.9 x 10^{-11} mm Hg).

Occupational exposure to TOTM may occur through inhalation and dermal contact with this compound at workplaces where it is produced or used (HSDB, 2008). However, TOTM is produced and used in closed systems, and occupational exposure time is said to be very short, limited to sampling and maintenance at the production facilities (SCENIHR, 2007).

5.4 Toxicology

Data on the toxicity of triocyltrimellitate (TOTM) in humans and animals were obtained from primary source documents identified from an initial literature search conducted in October 2008. Databases searched included: PUBMED (+ cancer subset), TOXLINE (Special), TSCATS1/TSCATS2, CCRIS, DART/ETIC, GENE-TOX, HSDB, RTECS and EPA SRS. Safety evaluations by the European Commission (SCENIHR, 2007) and the Toxics Use Reduction Institute (TURI, 2006) were also reviewed for relevant toxicity data.

In addition, robust summaries for TOTM from the High Production Volume Information System (HPVIS) (U.S. EPA, 2008c), the OECD SIDS Initial Assessment Report for SIAM 14 (UNEP, 2002), and the European Commission IUCLID Dataset for TOTM (European Commission, 2000) were reviewed. It should be noted that effect incidence, magnitude and dose-dependence are often times not detailed in the robust summaries, so only qualitative statements on adverse effects can be made in these situations.

5.4.1 Absorption, Distribution, Metabolism, and Excretion

The disposition of TOTM following oral exposure was studied in rats by Eastman Kodak Co. (1984). TOTM undergoes limited hydrolysis in the gastrointestinal tract to form 2-ethylhexanol and mono- and di-esters of trimellitic acid. The available data suggest that only 2-ethylhexanol and one of the mono esters are actually absorbed. Although limited in extent, absorption was relatively rapid, with a half-time of 0.7 hours. Absorbed 2-ethylhexanol undergoes additional oxidative metabolism in the body, but the mono-ester of trimellitic acid apparently does not. Following a single gavage dose in rats, most of the administered dose (75%) was eliminated in the feces over 6 days, primarily as unchanged parent compound. Small amounts of mono- and di-esters of trimellitic acid and unidentified polar metabolites were also present in feces. Another 16% of the dose was excreted in the urine (primarily as metabolites of 2-ethylhexanol), and 2% as expired CO_2. Only a trace amount of the dose was left in the tissues of animals after 6 days. The highest levels were in the liver and fat. Elimination in both the expired air and the urine was biphasic, with half-lives of 3-4 and 30-40 hours. Similarly, in rats administered ^{14}C labeled TOTM by intravenous injection, TOTM was cleared from the blood in a biphasic manner with half lives of 46.2 minutes and 5.34 days. The rapid decrease of plasma TOTM in the first phase of elimination is a result of the distribution to tissues including the liver, lung, and spleen rather than as a result of excretion; 72% of the administered dose was found in these tissues after 24 hours (Martis et al., 1987). The slow elimination of absorbed TOTM (only 21% of the i.v. dose in the feces and 3% in the urine after 14 days) suggests that TOTM has potential to accumulate in body tissues.

5.4.2 Acute Toxicity

Studies on TOTM acute oral, inhalation, and dermal toxicity, skin sensitization, and eye irritation were available at the time that this report was written. These studies are reviewed below.

Acute Oral Toxicity

Lethality of TOTM by acute oral exposure is low. No deaths were recorded among groups of 5 Sprague-Dawley-derived rats of each sex given a single dose of 2000 mg/kg of TOTM by gavage in corn oil and observed for two weeks (Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002), groups of 5 Sprague-Dawley-derived rats of each sex given a single dose of 5000 mg/kg of TOTM by gavage (use of vehicle not described) and observed for two weeks (Nuodex, 1983a), or groups of 2 Sprague-Dawley-derived rats of each sex given a single dose of 10 ml/kg (9850 mg/kg, based on a density of 0.985 g/cm^3) of TOTM by gavage (use of vehicle not described) and observed for two weeks (Ciba-Geigy, 1984a). The only effect reported in any of these studies was piloerection in the two male rats treated with 9850 mg/kg, which was seen 2-3 hours after treatment but not subsequently (Ciba-Geigy, 1984a). Eastman Kodak Co. (1983b) reported oral LD50 values of >3200 mg/kg for TOTM in both rats and mice, but no experimental details were provided.

Acute Inhalation Toxicity

Results of acute inhalation studies were not clear. No deaths occurred among a group of 5 male and 5 female Sprague-Dawley rats exposed via whole-body inhalation to 2600 mg/m^3 of TOTM (98.95% purity) aerosol (not further described) for 4 hours and observed for 14 days (Nuodex, 1983b). The test animals were all reported to have matted, drenched coats for the first 2 days, but no other visible effects. Necropsy revealed generalized lung involvement (reddening patches on lungs) of uncertain toxicological significance in 8/10 test animals. Eastman Kodak Co. (1983a,b) reported no deaths and only minimal irritation in rats (strain not identified) exposed to TOTM mist at 230 mg/m^3 for 6 hours, but more severe irritation and mortality (1-3 days after exposure) at 2640 and 4170 mg/m^3. No further details were available.

Acute Dermal Toxicity

No deaths or other toxic signs were observed in a group of 3 male and 3 female New Zealand albino white rabbits treated by application of 2.0 ml/kg TOTM (1970 mg/kg, based on a density of 0.985 g/cm^3) to the abraded skin under occlusion for 24 hours and observed for 14 days (Nuodex, 1983c). Eastman Kodak Co. (1983b) reported a dermal LD50 value of >20 ml/kg (19,700 mg/kg) for TOTM in guinea pigs, but no experimental details were provided.

Skin Irritation/Sensitization

TOTM was tested for dermal irritation and sensitization in 201 men and women volunteers ranging in age from 18 to 81 years (David et al., 2003). The chemical (1% v/v in acetone) was applied to the skin under a semi-occlusive patch for 3 consecutive weeks, and the reaction to a challenge application noted following a 2-week rest period. TOTM produced only minimal irritation in a handful of subjects at induction and similar results upon challenge (individuals responding to challenge were not the same as those showing irritation during induction). David et al. (2003) concluded that TOTM is non-irritating and non-sensitizing to humans.

Tests in animals determined that TOTM is only slightly irritating to rabbit (Ciba-Geigy, 1984b; Nuodex, 1981) and guinea pig skin (Nuodex, 1983d; Eastman Kodak Co., 1983a,b), and not sensitizing to guinea pig skin (Eastman Kodak Co., 1983a,b; Nuodex, 1983d).

Eye Irritation

TOTM (0.1 mL) was instilled into the right eyes of six young adult New Zealand White rabbits, with the left eyes serving as corresponding controls (Nuodex, 1983e). Only slight redness of the conjunctivae was observed during the first 2 days following treatment. No irritation was noted in the rabbit eyes 3 days post-instillation. Eastman Kodak Co. (1983a,b) also reported only slight, transient irritation in rabbit eyes following TOTM application.

5.4.3 Repeated-Dose Toxicity

Oral repeated-dose toxicity data for TOTM are available from several short-term gavage (Nuodex, 1983f; Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002; CMA, 1987; Hodgson, 1987) and feeding (CMA, 1986; Hodgson, 1987) studies in rats.

In a study submitted to the United Nations Environment Programme (UNEP) (2002) by the TOTM Consortium of Japan (a group of four Japanese corporations), Sprague-Dawley rats (5/sex/group) were administered TOTM (99% purity) via gavage in corn oil at 0 (vehicle control), 100, 300 or 1000 mg/kg-day daily for 28 days (Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002). No treatment-related effects were observed based on clinical signs, body weights, food and water consumption, hematology, clinical chemistry, urinalysis, organ weights or gross or histological pathology. A NOAEL of 1000 mg/kg-day was identified for both sexes. Although the full study report was not available for this review, UNEP considered the study to be reliable without restrictions (UNEP, 2002).

The other available studies were performed primarily to evaluate potential liver effects of TOTM, and especially those related to peroxisome proliferation, a well-known effect of di(2-ethylhexyl) phthalate (DEHP), which is structurally very similar to TOTM. For example, Male Fischer-344 albino rats (5/group) were administered TOTM (purity not

given) via gavage in corn oil at 0 (vehicle control) or 1000 mg/kg-day 5 days/week for 4 weeks (Nuodex, 1983f). No deaths occurred in either group. Body and organ weights (liver, kidney, brain, spleen, testes) in treated rats did not differ from controls. Triglyceride levels were significantly reduced in the treated rats compared to corn oil controls, but the toxicological significance of this finding is unclear. No other endpoints were investigated in this study.

In a short-term feeding study, Fischer-344 rats (5/sex/group) were fed TOTM (98% purity) at dietary levels of 0, 0.2, 0.67 or 2% for 28 days (CMA, 1986; Hodgson, 1987). Corresponding doses reported by the researchers were 0, 184, 642 and 1826 mg/kg-day for males, and 0, 182, 666 and 1641 mg/kg-day for females. Food consumption and body weight gain in treated rats did not differ significantly from controls. There were statistically significant reductions in red blood cell count and hemoglobin in both males and females even at the lowest dose group, but the changes were slight and a clear dose-response relationship was not determined. Serum chemistry analyses showed statistically significant increases in serum albumin in mid- and high-dose males and females, but again the changes were slight and not clearly related to dose. There was no effect of treatment on triglyceride levels. The only noteworthy effects on organ weights were statistically significant dose related increases in absolute and relative liver weight in both sexes in the mid- and high-dose groups (25-35% larger than controls at the high dose). This study included biochemical and electron microscopic assays for peroxisome proliferation. In the biochemical studies, TOTM produced significant dose-related increases in cyanide-insensitive palmitoyl CoA (pCoA) oxidation and carnitine acetyl transferase activity in the liver in both males and females and catalase activity in males, with some changes found even at the lowest dose group. Only the high-dose group and controls were examined for histopathology and electron microscopy. The only change in the liver by light microscopy was a slight reduction in cytoplasmic basophilia in 2/5 high-dose females; there were no treatment-related changes in other organs. Electron microscopy studies of the liver revealed slightly increased centrilobular and periportal peroxisomes in the high-dose group compared to controls. Thus, TOTM appears to be a PPAR agonist. While these effects produced by TOTM were similar in pattern to those produced by DEHP, TOTM was much less potent. The changes found in this study were all related to peroxisome proliferation. Peroxisome proliferation is a rodent specific effect that is of questionable relevance to hazard characterization for humans (Cattley et al., 1998; Chevalier and Roberts, 1998; Doull et al., 1999; IARC, 2000a; Klaunig et al. 2003; Lake, 1995, Melnick 2001). Therefore, for the purposes of this review, the high-dose of 1826 mg/kg-day is considered a NOAEL.

The same researchers conducted a 21-day gavage study that investigated many of these same endpoints (CMA, 1987; Hodgson, 1987). Fischer-344 rats (5/sex/group) were administered TOTM via gavage in corn oil at 0 (corn oil), 200, 700 or 2000 mg/kg-day for 21 days. There was no significant effect on body weight gain or feed consumption in treated rats. Serum triglyceride and cholesterol levels did not differ significantly from controls. Significant increases in absolute and relative liver weights were observed among female rats at all dose levels, but these changes did not increase with dose. Only slight, non-significant changes in liver weights were observed among male rats. The only

remarkable histological change was a reduction in the quantity of neutral lipid in the livers of all treated rats. Liver biochemistry revealed significant increases in pCoA activity at the high-dose in both males and females, and significant increases in lauric acid 12-hydroxylase activity in males at all dose levels. A slight increase in the number of hepatic peroxisomes was observed in high-dose males, but no change compared to controls was observed in females. For the purposes of this review, the high-dose of 2000 mg/kg-day is a NOAEL, as the only effects observed were related to peroxisome proliferation and not directly relevant to humans.

5.4.4 Chronic Toxicity/Carcinogenicity

No chronic toxicity studies were available for TOTM. CMA (1983) includes a description of an *in vivo* oncogenicity study conducted by the Food and Drug Administration (FDA) that found negative results for TOTM in strain A mice that have a propensity to form pulmonary adenoma. However, the lack of further detailed information limits the interpretation of these results.

5.4.5 Reproductive/Developmental Toxicity

In a reproductive toxicity study, Sprague-Dawley rats (12/sex) were administered TOTM (99% purity) via gavage at 0, 100, 300 or 1000 mg/kg-day for 46 days for males (including mating) and from 14 days prior to mating through day 3 of lactation for females (Japan Ministry of Health and Welfare, 1998, as cited in UNEP, 2002). No effects were observed in either sex on general appearance, body weights, food consumption, or weights of reproductive organs. No histological changes in ovaries from treated females were observed. Histological examination of the testes revealed decreases in spermatocytes and spermatids among mid- and high-dose males. There were no effects on reproductive ability, delivery of pups, maternal behavior of dams, or the viability, general appearance, birth weights or autopsy findings of offspring. A NOAEL of 100 mg/kg-day was identified for reproductive toxicity in males based on the decreases in spermatocytes and spermatids in male rats at 300 mg/kg-day.

Huntington Life Sciences (2002) evaluated both pre- and postnatal effects of TOTM in a gestational exposure study in Sprague-Dawley rats. Groups of 35 pregnant dams were administered TOTM (98.9%) via gavage in corn oil at 0 (vehicle control), 100, 500 or 1050 mg/kg on gestation days 6-19 for the prenatal teratology evaluation and on gestation day 6 through to lactation day 20 for the postnatal development evaluation. No significant effects on maternal body weights or gravid uterus weights were observed at any dose level during gestation or lactation. There was no significant difference between treated and control rats in regard to developmental parameters including the number of implantations, post-implantation loss, gestation length and index, litter size, fetal body weights, or offspring survival. There were apparent increases in the numbers of fetuses from treated dams exhibiting displaced testes, renal cavitation, and hydroureter compared to concurrent controls, but incidences were within historical control ranges for these findings. The only statistically significant finding was a slight increase in the number of male offspring from high-dose dams with retained areolar regions at post-natal day

(PND) 13 compared to offspring from control animals. However, by PND 18 the retained areolar regions were no longer present. This effect may represent a slight developmental delay, but was not considered to be toxicologically significant by the researchers. Therefore, the high-dose of 1050 mg/kg-day was identified as a NOAEL in this study for both maternal and developmental effects.

5.4.6 Genotoxicity

Available data suggest that TOTM is not genotoxic. TOTM did not induce reverse mutation in various strains of *Salmonella typhimurium* (U.S. EPA, 1983; Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002; Zeiger et al., 1988) or *Escherichia coli* strain WP2 (Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002), forward mutation at the HGPRT locus of Chinese hamster ovary (CHO) cells (CMA, 1985a), unscheduled DNA synthesis in primary rat hepatocytes (CMA, 1985b), or chromosomal aberrations in cultured Chinese hamster lung cells in the presence or absence of metabolic activation *in vitro*. TOTM was also negative for dominant lethal mutations *in vivo* in white Swiss mice (CMA, 1983). Urine from rats fed TOTM in the diet at 2000 mg/kg for 15 days did not induce mutagenic activity with or without metabolic activation in various strains of *Salmonella typhimurium* (Divincenzo et al., 1985).

5.5 Summary

As a branched molecule, TOTM is more viscous than the essentially linear adipates and phthalates, and its larger molecular weight and its bulky structure subsequently convey improved extraction and migration resistance. This has led to its use as a plasticizer for food contact materials and medical devices (Kambia et al., 2001; SCENIHR, 2007). Specifically, a study by Flaminio et al. (1988), showed less TOTM leached from haemodialysis tubing than from DEHP tubing. Additionally, a measured BCF of less than 1 to 2.7 in carp suggest that bioconcentration in aquatic organisms is low (HSDB, 2008). The general population may be exposed to TOTM through contact with products containing this chemical, such as lubricants and greases, pesticides, and medical tubing (SCENIHR, 2007).

With regard to toxicity, no data were available on the effects of TOTM in humans, except for one study that demonstrated that TOTM is not irritating and non-sensitizing to human skin (David et al., 2003). Acute oral toxicity is low based on studies where no lethality was observed at doses up to 9850 mg/kg in rats (Ciba-Geigy, 1984a; Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002; Nuodex, 1983a). The degree of toxicity by acute inhalation exposure is uncertain, as exposure to approximately 2600 mg/m^3 of TOTM aerosol produced no lethality in one study with a 4-hour exposure (Nuodex, 1983b), but reportedly produced severe irritation and mortality in another study with a 6-hour exposure (Eastman Kodak Co., 1983a,b). Acute dermal toxicity is low based on studies where no lethality was observed at doses of 1970 mg/kg in rabbits (Nuodex, 1983c) and 19,700 mg/kg in guinea pigs (Eastman Kodak Co., 1983a,b). TOTM is only slightly irritating to rabbit and guinea pig skin, and not sensitizing to

guinea pig skin (Ciba-Geigy, 1984b; Nuodex, 1981, 1983d; Eastman Kodak Co., 1983a,b). Studies in rabbits reported only slight eye irritation from TOTM instillation (Nuodex, 1983e; Eastman Kodak Co., 1983a,b).

Key available repeated-dose animal toxicity data for TOTM are presented in Table 5-2 and include short-term, reproductive and developmental toxicity studies. TOTM has only been found to cause minimal signs of toxicity in rats treated orally. The primary effects noted in the systemic toxicity studies were peroxisome proliferation and related effects in the liver (CMA, 1986, 1987; Hodgson, 1987). This is a rodent-specific effect of questionable relevance to humans. The only study that appeared to include a comprehensive assessment of toxicity found no effects of any type at doses up to 1000 mg/kg-day by 28-day gavage exposure (Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002). A single-generation study found no effects on reproductive function, but did report decreased spermatocyte and spermatid counts in males treated by gavage with 300 or 1000 mg/kg-day (Japan Ministry of Health and Welfare, 1998, as cited in UNEP, 2002). TOTM did not induce developmental effects in rats following gavage treatment during gestation (Huntington Life Sciences, 2002). Limited data in strain A mice suggest that TOTM is not carcinogenic (CMA, 1983). TOTM is not genotoxic; results were negative in tests for mutagenicity in bacteria and mammalian cells, unscheduled DNA synthesis in rat hepatocytes, chromosomal aberrations in Chinese hamster lung cells, and dominant lethal mutations *in vivo* in white Swiss mice (U.S. EPA, 1983; Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002; Zeiger et al., 1988; CMA, 1983, 1985a,b).

TOTM is lacking a key 2-year study that would allow it to be compared more comprehensively to the *o*-DAP plasticizers.

Table 5-2. Summary of Key Repeated-Dose Oral Toxicity Information for Trioctyltrimellitate (TOTM)

Species, sex, number	Sex	Doses (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Subchronic Exposure									
Rat 5/sex/ group	M/ F	0, 100, 300 or 1000	Gavage for 28 days	1000	NA	NA	NA	Based on robust summary; original report not available.	Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002
Rat 5/group	M	0 or 1000	Gavage 5 days/week for 4 weeks	1000	NA	NA	NA	Limited endpoints studies.	Nuodex, 1983f
Rat 5/sex/ group	M/ F	0, 184, 642 or 1826 (males) 0, 182, 666 or 1641 (females)	Diet for 28 days	1826	NA	NA	NA	Observed peroxisome proliferation and related effects of questionable relevance to humans.	CMA, 1986; Hodgson, 1987
Rat 5/sex/ group	M/ F	0, 200, 700 or 2000	Gavage for 21 days	2000	NA	NA	NA	Observed peroxisome proliferation and related effects of questionable relevance to humans.	CMA, 1987; Hodgson, 1987
Reproductive/Developmental Toxicity									
Rat 12/sex/ dose	M/ F	0, 100, 300 or 1000	Gavage for 46 day (including mating) for males and from 14 days prior to mating through lactation day 3 for females	100	300	300	Decreased spermatocytes and spermatides in testes of treated males	No effect on reproductive function or pup development.	Japan Ministry of Health and Welfare, 1998, as cited in UNEP, 2002

Table 5-2. Summary of Key Repeated-Dose Oral Toxicity Information for Trioctyltrimellitate (TOTM)

Species, sex, number	Sex	Doses (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Rat 35/group	F	0, 100, 500 or 1050	Gavage from gestation day 6-19 and gestation day 6 through lactation day 20	1050	NA	NA	NA	No signs of maternal toxicity. No signs of prenatal or postnatal developmental effects.	Huntington Life Sciences, 2002

[a] Adjusted for continuous exposure

6.0 Di(2-ethylhexyl) terephthalate (DEHT)

6.1 Use

Di(2-ethylhexyl) terephthalate (DEHT) is a U.S. EPA high production volume chemical, with production above 50 million pounds/year in the U.S. (SCENIHR, 2007). This chemical is listed under the U.S. EPA's Toxic Substances Control Act (TSCA) as 1,4-benzenedicarboxylic acid, di(2-ethylhexyl) ester, however, it is commonly referred to (informally) as either di(2-ethylhexyl) terephthalate or dioctyl terephthalate (DOTP) (McMillan, 2004). DEHT is produced by Eastman Kodak Company under the name Eastman 168 Plasticizer.

Because "phthalate" is part of one of the common names for DEHT, it can be confused with "phthalate esters" the common name for the class of compounds known as dialkyl *ortho*-phthalates *(o*-DAPs), discussed above. While *ortho*-phthalates contain two adjacent ring substitutions, *para*-phthalates, such as DEHT, have substitutions occupying positions 1 and 4 (located "across from" each other on the ring). Therefore, DEHT is not an *o*-DAP chemical, and thus is not subject to specific U.S. EPA or CPSC regulations aimed as these compounds. *Ortho*-phthalates are metabolized to a monoester form, which scientists generally agree to be the active metabolite (the cause of toxicological effects observed). In contrast, available data indicate that metabolism of DEHT (as reported by Eastman) does not lead to significant formation of a monoester (McMillan, 2004), suggesting that it may not have health effects similar to *ortho*-phthalates.

DEHT is compatible with cellulose acetate-butyrate, cellulose nitrate, polymethyl methacrylate, polystyrene, polyvinyl butyral, and polyvinyl chloride resins (HSDB, 2008). Essentially 100% of DEHT produced is used as a plasticizer and softener for these polymers (HSDB, 2008). It has a wide range of applications including beverage closures, and sealing materials used in construction joints (HSDB, 2008; SCENIHR, 2007). The 2007 European Commission Report (SCENIHR, 2007) states that it is used in children's toys and childcare articles, based on a submission from the DEHT manufacturer, Eastman Chemical Co. However, no specific toys or toy manufacturers were identified, so this remains unconfirmed.

6.2 Physical/Chemical Properties

DEHT is produced by transesterification of dimethylterephthalate with 2-ethylhexanol (HSDB, 2008). It is known by chemical formula $C_{24}H_{38}O_4$ and CAS number [6422-86-2].

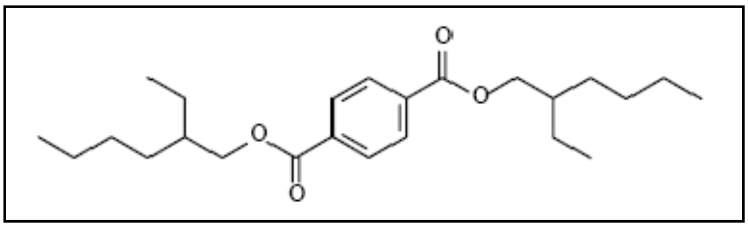

Figure 6-1. Structure of DEHT (SCENIHR, 2007)

Physiochemical properties appear in Table 6-1. DEHT is only soluble in water at 4.0 mg/L, and in the environment is expected to bind tightly to particulate matter and sediment in the water column based on its estimated K_{oc} value of 870,000, and is expected to be essentially immobile in soil (HSDB, 2008). According to a Henry's Law constant of 1.02 x 10^{-5} atm m^3/mole, DEHT will volatilize slowly from water surfaces and may also volatilize from moist soil surfaces. Biodegradation in soil is expected to be a major fate process for DEHT based on results for the structurally similar plasticizer DEHP, which undergoes aerobic and possibly anaerobic biodegradation (HSDB, 2008). If released to the atmosphere, DEHT will exist in both the vapor phase and the particulate phase based on an estimated vapor pressure of 2.14 x 10^{-5} mm Hg at 25 ^{o}C. Particulate-phase DEHT may be removed physically from air by wet and dry deposition (HSDB, 2008).

Based on an estimated BCF value of 1,400,000, DEHT should bioconcentrate in aquatic organisms. However, structurally similar DEHP has a measured BCF value of 637 with a depuration half-life of 38 days in sheepshead minnow, indicating that DEHT also may be readily metabolized by some organisms (HSDB, 2008).

Table 6-1. Physical-Chemical Properties of DEHP, DINP, and Potential *o*-DAP Alternatives (BASF, 2006; HPVIS 2008; HSDB 2008; SCENIHR 2007)

Name	MW	Wsol (mg/L)	K_{oc}	H (atm m^3/mol at 25^{o}C)	Log K_{ow}	V_p (mm Hg at 25^{o}C)	BCF L/kg
DEHP	390.56	0.285[a]	>87,420	1.3 x 10^{-7}	7.60	7.2 x 10^{-8}	115-851
DINP	418.62	0.2[b]	10,580	1.49 x 10^{-6}	n.a.	5.4 x 10^{-7}	1,500
ATBC	402.5	5.0[b]	1,800	3.8 x 10^{-10}	4.3[c]	4.6 x 10^{-6}	250
DEHA	370.57	0.78[c]	770,000	4.34 x 10^{-7}	>6.11	8.5 x 10^{-7} [d]	27
DINCH	424.7	<0.02[e]	n.a.	n.a.	10	9.75 x 10^{-7}[f]	189
TOTM	546.80	100[e]	350	4.4 x 10^{-7}	5.94[e]	3.9 x 10^{-11}	1-2.7
DEHT	390.54	4.0[d]	870,000	1.02 x 10^{-5}	5.72	2.14 x 10^{-5}	1,400,000

Wsol is the solubility of the chemical in water. K_{oc} is the organic carbon normalized solid-water partition coefficient in L/kg. H (atm m^3/mol) is the Henry's law constant. K_{ow} is the octanol-water partition coefficient. V_p is the vapor pressure. BCF is the bioconcentration factor. (Adapted from Remberger et al. 2005). See Appendix B for more detail.

[a] at 24^{o}C
[b] temperature not specified
[c] at 22 ^{o}C
[d] at 20^{o}C
[e] at 25^{o}C
[f] at 50^{o}C

6.3 Exposure

No information could be found on leaching or migration of DEHT from polymer resins. Additionally, no information was found regarding human exposure to DEHT, although exposure is presumed based on its presence in some consumer products. However, Eastman reports that "minimal consumer exposure is expected based on limited use in consumer products and low leaching of the compound out of the polymer matrix in its

major use as a plasticizer" (SCENIHR, 2007). With regard to occupational exposure, DEHT production utilizes a closed system; however, exposure could occur when the chemical is put into drums or during quality control (SCENIHR, 2007).

6.4 Toxicology

Data on the toxicity of DEHT in humans and animals were obtained from primary source documents identified from an initial literature search conducted in October 2008. Databases searched included: PUBMED (+ cancer subset), TOXLINE (Special), TSCATS1/TSCATS2, CCRIS, DART/ETIC, GENE-TOX, HSDB, RTECS and EPA SRS. Safety evaluations by the European Commission (SCENIHR, 2007) and the Toxics Use Reduction Institute (TURI, 2006) and a critical review of reproduction toxicity of phthalates (Fabjan et al., 2006) were also reviewed for relevant toxicity data.

6.4.1 Absorption, Metabolism, Distribution, and Excretion

Barber et al. (1994) studied the disposition of DEHT in rats treated by oral exposure. DEHT in the gut is hydrolyzed to terephthalic acid, 2-ethylhexanol and smaller amounts of the monoester mono(2-ethylhexyl) terephthalate (MEHT). Approximately one-half of the DEHT and metabolites are absorbed from the gut, with the remainder (primarily unchanged DEHT and small amounts of MEHT and its metabolites) passing through into the feces. Absorbed DEHT and metabolites are eliminated quickly, primarily in the urine. Metabolites identified in the urine included terephthalic acid (51%), 2-ethylhexanol and MEHT and metabolites, and glucuronic and sulphuric acid conjugates. A small amount of the absorbed dose is expired as CO_2. In all, 95% of the administered dose was eliminated within 24 hours after dosing. At sacrifice 6 days after dosing, only a small fraction of the administered dose remained in the carcass, primarily in the liver and fat.

6.4.2 Acute Toxicity

Studies on DEHT acute oral and dermal toxicity, skin sensitization, and eye irritation are reviewed below.

Acute Oral Toxicity

Eastman Kodak Co. (1975) reported an LD50 value of >3200 mg/kg DEHT in both rats and mice. No signs of mortality, irritation or distress were observed in either species during a 14-day observation period following oral treatment. No other details were reported for this study. The European Commission (SCENIHR, 2007) Safety Evaluation reported an oral LD50 of 5000 mg/kg, but did not provide a reference and no data matching this lethal dose were found during this review. A Russian study summarized in RTECS did not attain an LD50 in mice receiving DEHT up to 20,000 mg/kg, but the mice that did die during the study exhibited excitation followed by CNS inhibition (Timofiyevskaya, 1982).

Acute Dermal Toxicity

Eastman Kodak Co. (1975) reported a study in which DEHT at 5, 10 or 20 mL/kg (~4920, 9840 or 19,680 mg/kg based on a density of 0.984 g/mL) was applied to the depilated skin of guinea pigs under occluded conditions for 24 hours. No signs of systemic toxicity were reported during the 14-day observation period and the resulting 24-hour dermal LD50 in guinea pigs was >20 mL/kg (>19,680 mg/kg).

Skin Irritation/Sensitization

DEHT was tested for dermal irritation and sensitization in 203 men and women volunteers ranging in age from 18 to 81 years (David et al., 2003). Only one person demonstrated irritation, expressed as slight erythema, occurring on at least 4 occasions out of 9 exposures. This same individual exhibited a delayed reaction at challenge to DEHT. Another individual, who did not show signs of irritation in the initial patch test, did exhibit a reaction at 48 hours after challenge. David et al. (2003) concluded that DEHT is non-irritating and non-sensitizing to humans.

Tests in guinea pigs showed that undiluted DEHT was slightly irritating to the skin under occluded conditions for 24 hours and moderately irritating with repeated skin contact for 10 days (Eastman Kodak Co., 1975). In addition, DEHT has been shown to act as a sensitizer in guinea pigs, producing a strong skin sensitization reaction in 2/10 guinea pigs tested and a weak reaction in 6/10 guinea pigs (Eastman Kodak Co., 1975).

Eye Irritation

DEHT (0.1 mL) was instilled into the eyes of 6 albino rabbits for about a minute and a half, after which time the treated eyes of 3 of the rabbits were washed with distilled water (Eastman Kodak Co., 1975). Slight erythema was observed one hour after treatment in both washed and unwashed eyes. Twenty-four hours after treatment, this slight irritation was no longer observed and no other effects were seen during the 14-day observation period.

6.4.3 Repeated-Dose Toxicity

Studies on both oral and inhalation repeated dose toxicity were available. They are summarized below.

Oral Toxicity

In a short-term study, groups of 5 male albino rats were administered DEHT at 0, 0.1 or 1.0% in the diet 5 days/week for 2 weeks (Eastman Kodak Co., 1975). The researchers reported the high dose to be 890 mg/kg-day, but did not report a dose for the 0.1% level. No significant changes were observed based on body weight, hematology, serum chemistry, or organ weights. Microscopic findings indicated that 2/5 high-dose rats had tracheitis and bronchiolitis, and 1/5 high-dose rat also exhibited hemorrhage beneath the

hepatic capsule just before sacrifice. One control animal also demonstrated tracheitis, another demonstrated bronchiolitis, and two demonstrated interstitial pneumonia, indicating a possible infection among test animals. Therefore, although no treatment-related effects were observed in this study among rats fed a diet containing up to 890 mg/kg-day DEHT, the possible infection among test animals limits the interpretation of these results.

In a published short-term feeding study, Sprague-Dawley rats (5/sex/group) were administered DEHT at 0, 0.1, 0.5, 1.0, 1.2, or 2.5% continuously in the diet for 21 days (Topping et al., 1987). Doses were not reported by the researchers. Based on U.S. EPA (1988) reference values for body weight and food consumption of Sprague-Dawley rats, the estimated doses are 0, 86, 431, 861, 1033 and 2154 mg/kg-day for males and 0, 98, 490, 980, 1176 and 2450 mg/kg-day for females. Body weight gain was significantly reduced in both sexes in high-dose animals. These reductions corresponded to a significant reduction in feed consumption among this group. Feed consumption among rats fed DEHT in the diet at 1.2% was initially reduced compared to controls (first 3 days for males and first 10 days for females), but was statistically similar to controls for the remainder of the study, and body weight gain was similar to controls in this group.

Relative liver weights were significantly elevated over controls among high-dose rats of both sexes. Absolute liver weights in these rats were not significantly different from controls, indicating that the increases in relative liver weights were likely related to the reductions in body weight gain among high-dose rats. Relative liver weights among female rats fed diets containing 1.0 or 1.2% DEHT were also significantly elevated over controls, but to a lesser degree than among high-dose (2.5%) females.

Serum triglyceride levels among high-dose males were significantly elevated over controls at the end of the 21-day study. However, they were lower than males fed 0.5, 1 or 1.2% DEHT, and were not found useful in interpreting the effects of DEHT. High-dose females also exhibited significant increases in serum triglycerides over controls, but the difference in females was slight compared to the difference observed in males. Serum cholesterol levels were slightly but significantly elevated in high-dose animals over controls (2.1 vs. 1.8 mmol/L in males; 2.7 vs. 2.2 mmol/L in females). Topping et al. (1987) considered the triglyceride and cholesterol data of limited value because of the unclear dose-response in males that clearly differed from females for triglyceride levels and the relative lack of effect on cholesterol levels. High-dose animals also exhibited increases in liver enzymes and peroxisomes. However, Topping et al. (1987) concluded that since DEHT in the diet only caused liver effects at a level that severely decreased food consumption and weight gain, the findings based on liver enzymes and peroxisomes in high-dose animals are of doubtful significance since fasting alone has been implicated in altered lipid metabolism and the formation of hepatic peroxisomes (Ishii et al., 1980). Based on these findings, a NOAEL of 1.2% in diet (1033 mg/kg-day for males and 1176 mg/kg-day for females) and a LOAEL of 2.5% (2154 mg/kg-day for males and 2450 mg/kg-day for females) are identified, based on decreased body weight gain and feed consumption.

In a subchronic feeding study, Barber and Topping (1995) administered DEHT (~99% purity) at 0, 0.1, 0.5, or 1.0% continuously in the diet to groups of 20 male and female Sprague-Dawley rats for 90 days. Corresponding doses reported by the researchers were 0, 54, 277 and 561 mg/kg-day for males and 0, 61, 309 and 617 mg/kg-day for females. No mortality was observed and no significant changes occurred in mean feed consumption or body weight gain in either sex during the 90-day feeding study. Relative liver weights of high-dose animals were significantly increased over controls by 11 and 9% in males and females, respectively. Absolute liver weights were also increased in these animals, but the differences did not achieve statistical significance (9 and 7% in males and females, respectively). None of the other organs weighed were significantly different from controls.

Slight changes (<5% difference from controls) in hematology were observed in mid- and high-dose animals. In particular, hemoglobin concentration, hematocrit, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were statistically significantly decreased from controls among high-dose males. MCH was also statistically significantly decreased among mid-dose males. Statistically significant decreases in MCV and MCH were also observed in mid- and high-dose females. No other dose-related changes in hematology were observed. Barber and Topping (1995) determined that in the absence of any other indications of anemia, the changes seen in the mid-dose rats were not considered to be biologically significant. No significant dose-related changes were observed based on serum chemistry.

Microscopic examination did not reveal any significant treatment-related abnormalities. DEHT did not induce hepatic peroxisomes among groups of five male rats from the control and treatment groups compared to rats treated with a positive control (2-ethylhexanol) at 1000 mg/kg, 5 days/week for 3 weeks. Barber and Topping (1995) identified NOAELs of 277 and 309 mg/kg-day in males and females, respectively. This assignment was based on the minor effects seen on red blood cell parameters and slight enlargement of the livers among high-dose animals. However, the changes in hematology were of a low magnitude and have been shown to occur with age in normal Sprague-Dawley rats (Wolford et al., 1987). Also, U.S. EPA (2002) notes that slight increases in liver weights in the absence of additional indications of liver toxicity are most likely indicative of an adaptive change and do not indicate an adverse effect. Therefore, for the purposes of this review, NOAELs of 561 mg/kg-day in males and 617 mg/kg-day in females are identified.

Inhalation Toxicity

The only available inhalation data for DEHT come from a single short-term study in which five rats (strain not specified) were exposed to DEHT at 46.3 mg/m^3 on 8 hours/day, 5 days per week for 2 weeks (Eastman Kodak Co., 1983c). No significant effects were observed among rats based on hematology, serum chemistry or pathological examination. The lack of study details including a description of study design and procedures limits the interpretation of these results.

6.4.4 Chronic Toxicity/Carcinogenicity

Groups of F344 rats (50/sex/dose) were allowed free access to diets containing DEHT (>98% purity) at 0, 1500, 6000 or 12,000 ppm for 104 weeks (Deyo, 2008). Average daily doses reported by Deyo (2008) were 0, 79, 324 and 666 mg/kg-day for males and 0, 102, 418 and 901 mg/kg-day for females. Survival rates at the end of the 2 year study were equivalent to control rats for all treatment groups and even demonstrated a dose-related increase in survival percentage among female rats. Body weight gains among high-dose animals were significantly lower than controls during the course of the 2 year study. Mid-dose animals also demonstrated significant reductions in body weight gains compared to controls, but only during the first year of the study. Terminal body weights were only significantly different from controls among high-dose females. Deyo (2008) suggested that decreased body weight gains have been shown to enhance survivability of rats in chronic studies and suggests that this likely played a role in decreased mortality rates for females in this study.

Changes in hematology, clinical chemistry, and urinalysis were of minimal magnitude and biological significance, were confined to one sex in some cases, were often times within historical controls levels and were not accompanied by additional histological evidence of adverse effects (Deyo, 2008). Therefore, Deyo (2008) attributed changes in hematology, clinical chemistry, and urinalysis to the normal biological variability associated with geriatric animals. Absolute liver weights were not different from controls among any treatment group, but relative liver weights were significantly elevated among high-dose females compared to controls. Relative liver weights among high-dose males were elevated in comparison to controls but did not reach a level of statistical significance. The only corresponding adverse histological finding in livers occurred as an increase in the incidence of portal lymphoid foci among high-dose males surviving to study termination (15/26 vs. 8/29 controls). However, livers from male rats also showed a trend for a decreased incidence of periportal vacuolization. Absolute kidney weights were significantly decreased from controls among high-dose males and mid- and high-dose females. Relative kidney weights were significantly decreased from controls among low- and mid-dose males, but not high-dose males, and among mid-dose females (actually increased in high-dose females). Histology did not reveal any significant increases in kidney lesions and instead showed a trend for a decreased incidence of chronic progressive nephropathy and mineralization of the pelvic/papillary epithelium. Aside from liver and kidney weights, organ weight changes that attained statistical significance were regarded by Deyo (2008) as either a result of high individual variability or as secondary effects to changes in body weight.

Additional histological findings included an increased incidence of eosinophilic inclusions in the nasal turbinates and atrophy of the outer nuclear layer (ONL) of the retina among both sexes (Deyo, 2008). Specifically, significant increases in lesions of the nasal turbinates occurred among all of the early decedent high-dose females (12/23 controls) and among 33/36 high-dose females (17/27 controls) surviving to study termination. Deyo (2008) reported that these lesions were considered an exacerbation of an age-related finding and not of any toxicological significance. Atrophy of the ONL

occurred at a level of significance compared to controls among mid- and high-dose females combined across early decedents and survivors (Table 6-2). This change is a common degenerative change observed in geriatric albino rats, but since the effect was exacerbated and noted to occur in a dose-related manner in this study, Deyo (2008) further evaluated the potential significance of this effect. Deyo (2008) concluded that higher doses of DEHT exacerbate retinal ONL degeneration and identified a NOAEL of 324 mg/kg-day for males and of 102 mg/kg-day for females for this endpoint.

Table 6-2. Incidence of Lesions Among DEHT-Treated Rats[a]

Lesion	Dose (ppm)			
	0	**1500**	**6000**	**12,000**
Males				
ONL atrophy	2/50	4/50	4/50	7/50
Granular cell lymphomas	13/29	19/26[b]	16/29	8/26
Females				
ONL atrophy	9/50	14/50	27/50[c]	40/50[c]
Granular cell lymphomas	6/27	6/31	7/34	8/36

[a]Deyo (2008)
[b]Significantly different from control at $p<0.05$
[c]Significantly different from control at $p<0.01$

No significant differences were observed in the incidence of specific tumors between treated and control rats that died or were killed prior to study termination (data not shown) (Deyo, 2008). Among animals surviving to study termination, the only significant increase in tumor incidence was for large granular cell lymphomas in low-dose males. However, the incidence of this lesion decreased with increasing dose level as shown in Table 6-2 and is thus not considered to be related to treatment with DEHT.

6.4.5 Reproductive/Developmental Toxicity

In a two-generation reproduction study, Sprague-Dawley rats (30/sex/dose) were administered DEHT (purity >97%) continuously in the diet at target concentrations of 0, 0.3, 0.6 or 1.0% (Faber et al., 2007b). Males were exposed for at least 70 days prior to and during mating, and females were exposed for at least 70 days prior to mating, during mating and through gestation and lactation. Male and female pups from the F1 generation from each litter were exposed under similar conditions beginning on postnatal day (PND) 22. Average doses for F0 animals based on the mean calculated compound consumption for various periods during the study as reported by Faber et al. (2007b) were 0, 158, 316, and 530 mg/kg-day for males and 0, 273, 545, and 868 mg/kg-day for females. Similarly, average doses for F1 animals were 0, 208, 422 and 723 mg/kg-day for males and 0, 306, 630 and 1034 mg/kg-day for females. Reproductive parameters evaluated in this study included mating and fertility indices, estrous cycle lengths, pre-coital intervals, gestation lengths, gender ratios, live litter size, and postnatal survival. No adverse effects on reproduction were observed in either generation at any dose level. However, Faber et al. (2007b) did observe indications of systemic toxicity in both growing pups and adult animals as described below.

Among high-dose females, 3 F0 dams and 7 F1 dams died or were euthanized in extremis 2 to 8 days after weaning of the pups (Faber et al., 2007b). Pathology did not indicate a cause of death in these dams, but the timing of mortality (post-weaning) suggests that these deaths were related to treatment with DEHT (Faber et al., 2007b). Single male deaths not considered to be related to treatment by Faber et al. (2007b) occurred in the F0 control and mid-dose groups and in the F1 high-dose group. High-dose males of the F0 generation demonstrated significant reductions in mean weekly body weight gain (15-25%) during weeks 3 through 7, which resulted in a slight reduction (5%) in mean terminal body weights. Mid- and high-dose F1 males demonstrated lower mean birth weights compared to controls, and decreased growth before weaning resulting in reduced mean body weights throughout the generation. Feed consumption in these male rats was also slightly reduced (10%) during the first week after weaning for the mid-dose group and throughout the generation for the high-dose group.

No significant changes in sperm concentration, motility, or morphology were observed and no significant histological findings in males were reported (Faber et al., 2007b). Significant increases were observed in absolute (F0) and mean relative liver weights (both generations) among the mid- and high-dose females. However, no morphological changes indicative of liver damage were observed in either generation indicating that the observed increases in liver weights were most likely adaptive changes rather than adverse effects. The rate of maternal body weight gain through gestation, feed consumption, and mean maternal body weights on gestation day (GD) 20 and throughout lactation were significantly reduced in the high-dose F0 dams. Similar effects were observed among the high-dose F1 dams although the reductions in mean maternal body weights were found throughout gestation and were of greater severity than that observed in the F0 dams. Mean body weights and feed consumption among mid-dose F1 dams were also significantly reduced during lactation days 7-14. Reductions in postnatal pup body weights occurred at concentrations corresponding to reduced feed consumption among mid- and high-dose dams, indicating a possible secondary effect. However, Faber et al. (2007b) considered replication of reduced mean pup body weights from PND 14-21 in both the mid- and high-dose groups from both the F1 and F2 generations to possibly have been related to direct consumption of the treated feed by the pups or possible taste aversion.

No macroscopic findings attributable to parental exposure to DEHT were noted at the scheduled necropsy of F1 and F2 pups euthanized on PND 21 (Faber et al., 2007b). Changes unrelated to decreased body weights of the F1 and F2 pups included reduced mean relative spleen weight in the high-dose F1 males (13%) and the high-dose F2 males (8%) and females (11%), reduced mean relative thymus weight in the high-dose F2 females (12%), and increased mean relative brain weights for both sexes in the high-dose F1 (25%) and F2 (23-25%) pups and the mid-dose F1 females (12%). Based on the findings described above, this study identified a NOAEL of 530 mg/kg-day for reproductive toxicity and a NOAEL of 158 mg/kg-day for parental and pup systemic toxicity.

Two additional studies have been conducted in rats to evaluate the effect of DEHT on estrogenic activity in immature female rats (Faber et al., 2007a) and to evaluate the effects of DEHT on the male reproductive tract after perinatal exposure (Gray et al., 2000). One study, Faber et al. (2007a), performed a uterotrophic assay for evaluating estrogenic activity in rats by administering DEHT (purity >97%) to groups of 10 immature female Sprague-Dawley rats at 0, 20, 200 or 2000 mg/kg-day in corn oil by gavage daily on PND 19-21. In this study, an additional group of 10 immature female rats received 0.003 mg/kg-day 17α-ethinyl estradiol (EE) as a positive control under similar treatment conditions. No mortality, clinical signs or differences in mean body weights were observed. However, mean body weight gain in the high-dose group was reduced after the first day of dosing, which resulted in a 19% reduction in mean body weight gain over the entire treatment period (data not shown). No significant differences were observed in mean wet and blotted uterine weights or in the corresponding mean luminal fluid weight. The positive control group responded appropriately. Faber et al. (2000a) identified a NOAEL of 2000 mg/kg-day for estrogenic activity in rats.

The second study conducted in rats, Gray et al. (2000), administered DEHT (purity 98%) by gavage to groups of 8 pregnant Sprague-Dawley rats at 0 or 750 mg/kg-day in corn oil during the period of sexual differentiation in pups from GD14 to PND 3. No mortality or significant changes in maternal body weights was observed among treated dams and the number of live pups at birth was not affected by DEHT treatment. In addition, there were no significant reductions in mean pup weights at birth. Male offspring examined for signs of demasculinization did not show any indication of malformations along the male reproductive tract at 750 mg/kg-day. Gray et al. (2000) concluded that DEHT does not produce antiandrogenic effects in rats.

In a developmental toxicity study in Sprague-Dawley rats conducted by the same researchers that performed the two-generation reproduction toxicity study, DEHT (purity >97%) was fed to groups of 25 pregnant rats at 0, 0.3, 0.6 or 1.0% from GD 0-20 (Faber et al., 2007a). Corresponding doses reported by the researchers were 0, 226, 458 and 747 mg/kg-day. No effects were observed on feed consumption. A significant reduction in maternal body weight gain (10%) was observed among high-dose rats during GD 16-20 compared to the controls. However, mean maternal body weights were comparable to the control group throughout the entire treatment period. Significant reductions were also observed in the net body weights (5%) and net body weight gains (25%) of the high-dose rats. Gravid uterine weights in this group were similar to controls. These findings indicate that body weight changes are primarily maternal effects and not intrauterine. Significant increases in mean liver weights (8%) were observed among high-dose rats. Relative liver weights were not reported, but based on the terminal body weights they will also be elevated in high-dose rats over controls. This study identified a maternal LOAEL of 747 mg/kg-day and NOAEL of 458 mg/kg-day based on the reductions in mean and net maternal body weight gains.

Intrauterine growth and survival were unaffected by DEHT treatment at any dose level (Faber et al., 2007a). No differences in the overall total number of skeletal variations were observed between treatment groups and controls. However, there was an increase in

the number of fetuses with 14th rudimentary ribs among fetuses from the high-dose group. When evaluated on a litter proportional basis, this increase was significant (13.3% incidence in the high-dose group versus 5.1% among controls). Faber et al. (2007a) reports that the incidence of rudimentary 14th ribs among fetuses from the high-dose group was only slightly increased when compared to the range of values based on historical controls (2.11-12.01%). Faber et al. (2007a) also reports that rudimentary 14th ribs represent the most common skeletal developmental variation in laboratory rats and notes that this variation has been shown to represent transient changes that do not persist into adulthood. Faber et al. (2007a) identified a NOAEL of 747 mg/kg-day for developmental toxicity. However, since the incidence of rudimentary 14th ribs did exhibit a dose-related increase and was both statistically significantly elevated in the high-dose group compared to concurrent controls and elevated above the range of historical controls, this effect is considered a possible indication of developmental toxicity in this study. Therefore, for the purposes of this review, a NOAEL of 458 mg/kg-day is identified for developmental toxicity.

In a second developmental study in ICR mice, DEHT (purity >97%) was fed to groups of 25 pregnant mice at 0, 0.1, 0.3 or 0.7% from GD 0-18 (Faber et al., 2000a). Corresponding doses reported by the researchers were 0, 197, 592 and 1382 mg/kg-day. These doses were based on a dietary range-finding study that could not be obtained for this review (Knapp, 2005). No effects were observed on mean maternal body weights or body weight gains, or on feed consumption. No treatment-related effects were observed on net body weights, net body weight gains or gravid uterine weights compared to controls. Increased liver weights were noted in the mid- (8%) and high-dose (15%) mice compared to controls. The increased liver weight in the mid-dose mice was comparable to a mean control group value obtained in the range-finding study by Knapp (2005). Relative liver weights were not reported, but based on the terminal body weights it appears that they were elevated in mid- and high-dose mice over controls. Mean litter proportion of preimplantation loss in the mid-dose group was significantly higher compared to the controls (6.7% versus 3.0%). However, since this effect was not maintained in the high-dose group, it was considered by Faber et al. (2007a) to not be related to DEHT treatment. Overall, intrauterine growth and survival were unaffected by DEHT treatment at any dose level. Six fetuses in 2 litters of the mid-dose group exhibited tarsal flexure or cleft palate. Faber et al. (2007a) did not consider these external malformations to be treatment related, as they were clustered primarily in one litter and no corresponding malformations were observed in the high-dose group. Visceral developmental variations noted in single fetuses in the mid- and high-dose groups were similar to controls when evaluated on a litter proportional basis. Therefore, no significant malformations or variations were attributed to treatment with DEHT in mice in this study. Faber et al. (2007a) identified a NOAEL of 197 mg/kg-day for maternal toxicity based on increased liver weights and a NOAEL of 1382 mg/kg-day for developmental toxicity. No other evaluations to further elicit signs of liver damage in these mice were conducted by Faber et al. (2000a). However, without signs of additional adverse effects, the enlarged livers are likely adaptive changes to DEHT treatment rather than adverse effects (U.S. EPA, 2002). Therefore, for the purposes of this review, a NOAEL of 1382 mg/kg-day is identified for maternal toxicity.

6.4.6 Genotoxicity

Limited data suggest that DEHT is not genotoxic. A single study has shown that DEHT did not induce reverse mutation in various strains of *Salmonella typhimurium*, forward mutation at the HGPRT locus of Chinese hamster ovary (CHO) cells, or chromosomal aberrations in CHO cells with or without metabolic activation (Barber, 1994). Urine from rats fed DEHT in the diet at 2000 mg/kg for 15 days did not induce mutagenic activity with or without metabolic activation in various strains of *Salmonella typhimurium* (Divincenzo et al., 1985).

6.5 Summary

As a *para*-phthalate, DEHT is often compared to the *ortho*-phthalates with regards to physiochemical properties. However, this does not seem appropriate, especially in the case of BCF. For example, based on an estimated BCF value of 1,400,000, DEHT should bioconcentrate in aquatic organism. However, DEHP, which is structurally similar to DEHT, has an experimentally measured BCF value of only 637 (sheepshead minnow). Measured physical-chemical properties, such as water solubility, indicate that DEHT is relatively insoluble in water and likely to bind to particulate matter (HSDB, 2008). No information could be found on leaching or migration of DEHT from polymer resins or on any type of human exposure. It can be assumed that consumers may be exposed to DEHT via dermal contact to the extent that DEHT is used in consumer products containing this compound, including toys and childcare articles. Thus, the determination of leaching rates would greatly strengthen the assessment of this chemical.

With regard to toxicity, no data were available on the effects of DEHT in humans, except for one study that demonstrated that DEHT is not irritating and non-sensitizing to human skin (David et al., 2003). Limited data suggest that acute oral toxicity is low based on an LD50 of >3200 mg/kg in both rats and mice (Eastman Kodak Co., 1975). In guinea pigs, there was no evidence of systemic toxicity after a single dermal exposure to DEHT up to 20 ml/kg (Eastman Kodak Co., 1975). DEHT is irritating and sensitizing to guinea pig skin and is only slightly irritating to rabbit eyes (Eastman Kodak Co., 1975). DEHT did not illicit signs of sub-acute oral or inhalation toxicity in rats following 10-day exposures (Eastman Kodak Co., 1975, 1983c).

The key available repeated-dose animal toxicity studies for DEHT are presented in Table 6-3. There was no clear evidence of specific target organ toxicity of DEHT, although the subchronic, reproductive and developmental studies in rats and mice reported results suggestive of a non-adverse, adaptive response to DEHT in the liver (increased liver weight) (Barber and Topping, 1995, Faber et al., 2007a,b). Only minimal effects on red blood cells were observed following subchronic exposure to DEHT in rats (Barber and Topping, 1995). A 2-year dietary cancer bioassay in rats was negative (Deyo, 2008). However, rats dosed with DEHT up to 901 mg/kg-day in this study did experience decreases in body weight gains and exacerbation of retinal ONL degeneration (Deyo, 2008). Reduced body weight gain was also observed in a short-term oral study in rats (Topping et al., 1987) and in the reproduction and developmental feeding studies in rats

(Faber et al., 2007a,b). Topping et al. (1987) showed DEHT to be unpalatable at doses ≥ 2000 mg/kg-day.

In the reproductive toxicity study, reductions in feed consumption and maternal body weights of females consuming ≥ 458 mg/kg-day DEHT in the diet was correlated with decreased live pup birth weights, reduced postnatal pup body weights, and reduced pup body weight gains in both the F1 and F2 generations (Faber et al., 2007b). Direct consumption of a diet containing DEHT by these pups resulted in continued reductions in pup body weight gain later in lactation and after weaning. In comparison, mean fetal body weights were unaffected in dams consuming up to 747 mg/kg-day DEHT in the diet during gestation (Faber et al., 2007a). No reproductive effects based on fertility, mating, estrous cycle lengths, gestation lengths, gender ratios, liver litter size or postnatal survival were observed in rats during this study (Faber et al., 2007b). DEHT did not produce antiandrogenic effects in male rats (Gray et al., 2000) and did not affect estrogenic activity in female rats (Faber et al., 2007a). There was no evidence that DEHT caused increased incidence of external malformations of variations in rats or mice (Faber et al., 2007a,b). The incidence of rudimentary 14^{th} ribs was slightly elevated in fetuses from rats receiving DEHT at 747 mg/kg-day. Limited data suggest that DEHT is not genotoxic. Results were negative in tests for mutagenicity in bacteria and mammalian cells, and chromosomal aberrations in CHO cells (Barber, 1994) and there was no evidence of mutagenic substances excreted in the urine of rats dosed by gavage with DEHT (Divincenzo et al., 1985).

Table 6-3. Summary of Key Repeated-Dose Oral Toxicity Information for Di(2-ethylhexyl)terephthalate

Species, sex, number	Sex	Doses (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Subchronic Exposure									
Rat 20/group	M/F	0, 54, 277 or 561 (males) 0, 61, 309 or 617 (females)	Diet for 90 days	561 (male) 617 (female)	NA	NA	NA	Minor changes in organ weights and red blood cell parameters not considered adverse.	Barber and Topping, 1995
Chronic Exposure									
Rat 50/sex/ group	M/F	0, 79, 324 or 666 (males) 0, 102, 418 or 901 (females)	Diet for 104 weeks	324 (male) 102 (female)	666 (male) 418 (female)	666 (male) 418 (female)	Increased exacerbation of a retinal ONL degeneration and decreased body weight gains.	No effect on tumor incidence.	Deyo, 2008
Reproductive/Developmental Toxicity									
Rat 30/sex/ dose	M/F	0, 158, 316 or 530 (F0 males) 0, 273, 545 or 868 (F0 females) 0, 208, 422 or 723 (F1 males) 0, 306, 630 or 1034 (F1 females)	Diet prior to mating, during mating, and through gestation and lactation	158 (parental and developmental) 530 (reproductive)	316 (parental/ developmental) NA (reproductive)	316 (parental/ developmental) NA (reproductive)	Decreased parental and pup body weight gains.	Increased spleen and thymus weights were also observed in high-dose F1 and F2 pups. No effect on reproductive toxicity.	Faber et al., 2007b
Rat 10/group	F	0, 20, 200 or 2000	Gavage on postnatal days 19-21	2000	NA	NA	NA	No effects on estrogenic activity.	Faber et al., 2007a
Rat 8/group	F	0 or 750	Gavage from gestation day 14 to postnatal day 3	750	NA	NA	NA	No antiandrogenic effects were observed.	Gray et al., 2000

Table 6-3. Summary of Key Repeated-Dose Oral Toxicity Information for Di(2-ethylhexyl)terephthalate

Species, sex, number	Sex	Doses (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Rat 25/group	F	0, 226, 458 or 747	Diet on gestation days 0-20	458 (maternal and developmental)	747 (maternal/ developmental)	747 (maternal/ developmental)	Reductions in mean and net body weight gains, increased incidence of rudimentary 14th ribs.	Minor changes in organ weights not considered adverse.	Faber et al., 2007a
Mouse 25/group	F	0, 197, 592 or 1382	Diet on gestation days 0-18	1382 (maternal and developmental)	NA	NA	NA	Minor changes in organ weight not considered adverse.	Faber et al., 2007a

[a] Adjusted for continuous exposure

7.0 CONCLUSIONS

Since being introduced in the 1930's, dialkyl *ortho*-phthalates (*o*-DAPs) have been the leading plasticizer for PVC applications, such as household products and medical devices, as well as non-PVC applications such as inks, coatings and cosmetics. Recently, *o*-DAPs as a class have come under increasing scrutiny due to concerns about potential health effects in animal studies, which include reproductive and developmental toxicity, chronic organ toxicity, and cancer (IHCP, 2008; NTP-CERHR, 2006). Consequently, their use in children's articles has been under review. This report identifies the *o*-DAP substitutes that are currently being used in children's articles (or are probable future candidates) and summarizes available information on the potential risks associated with using these chemicals in this manner.

7.1 Need for Phthalate Alternatives

In the past, DEHP and DINP have constituted the majority of the six million ton plasticizer market (Arbeitsgemeinschaft, 2006), making their way into consumer products ranging from flooring to food contact substances. DEHP and DINP are not covalently bound to PVC. Thus, consumers may be exposed by handling PVC products, while children may be exposed when they suck or chew toys or other articles made from PVC. Additionally, for those undergoing medical care, plasticizers can be encountered through contact with medical tubing, blood bags, IV bags, and catheters.

Following the 2005 European Union ban on DEHP, DINP, and several other *o*-DAPS for use in toys and childcare articles (EUROPA, 2005), consumers and corporations began searching for alternatives to *o*-DAPs. After the United States Congress passed the Consumer Product Safety Improvement Act in August 2008 stating that the sale of children's toys or child care articles containing more than 0.1% of DEHP, BBP, and DBP are permanently prohibited, and the sale of children's toys that can be placed in a child's mouth or child care articles containing concentrations of more than 0.1% of DINP, DIDP, or DNOP, would be prohibited on an interim basis (Kamalick, 2008), change appeared inevitable. The CPSIA also directs the Consumer Product Safety Commission to convene a Chronic Hazard Advisory Panel to investigate the potential health effects of phthalates and phthalate substitutes

7.2 Summary of Potential Alternatives

In this report, five chemicals were identified as the most likely alternatives to *o*-DAPs in children's articles based on a variety of factors which included their compatibility with PVC. This review focused on the amount and quality of exposure and toxicity data available on the chemical, lowest hazard (NOAELs and cancer effects), low leaching rate, and previously approved uses, such as in food contact substances. Current data limitations are pointed out below. Additionally, comparisons are made between these candidates with regard to both the strength and the implications of available exposure and toxicity data.

Exposure

When measuring consumer chemical exposure, significant variables include the physical and chemical properties of the substance, the type of product (and material) in which it is incorporated and, subsequently, the extent to which the chemical will leak or migrate from the product. With regard to plasticizers incorporated into children's articles, properties of the chemical such as water solubility may indicate the ability of the substance to migrate from the product into a child's saliva. Similarly, vapor pressure indicates the chemical's propensity to volatilize from the surface of products (presumably after leaching has already occurred). A property such as bioconcentration factor (BCF) indicates the chemicals propensity for being metabolized (low BCF value) or bioaccumulated (high BCF value).

The physical-chemical properties of DEHP, DINP, and the five potential *o*-DAP alternatives chosen for review, appear in Table 7-1. Water solubility is low for all of these chemicals, with the exception of TOTM. The estimated BCF is particularly high for DEHT, but for the other alternatives is lower than values observed for DEHP and DINP, indicating the potential for these chemicals to be metabolized by organisms.

Table 7-1. Physical-Chemical Properties of DEHP, DINP, and Potential *o*-DAP Alternatives (BASF, 2006; HPVIS 2008; HSDB 2008; SCENIHR 2007)

Name	MW	Wsol (mg/L)	K_{oc}	H (atm m^3/mol at 25°C)	Log K_{ow}	V_p (mm Hg at 25°C)	BCF L/kg
DEHP	390.56	0.285[a]	>87,420	1.3×10^{-7}	7.60	7.2×10^{-8}	115-851
DINP	418.62	0.2[b]	10,580	1.49×10^{-6}	n.a.	5.4×10^{-7}	1,500
ATBC	402.5	5.0[b]	1,800	3.8×10^{-10}	4.3[c]	4.6×10^{-6}	250
DEHA	370.57	0.78[c]	770,000	4.34×10^{-7}	>6.11	8.5×10^{-7} [d]	27
DINCH	424.7	<0.02[e]	n.a.	n.a.	10	9.75×10^{-7}[f]	189
TOTM	546.80	100[e]	350	4.4×10^{-7}	5.94[e]	3.9×10^{-11}	1-2.7
DEHT	390.54	4.0[d]	870,000	1.02×10^{-5}	5.72	2.14×10^{-5}	1,400,000

Wsol is the solubility of the chemical in water. K_{oc} is the organic carbon normalized solid-water partition coefficient in L/kg. H (atm m^3/mol) is the Henry's law constant. K_{ow} is the octanol-water partition coefficient. V_p is the vapor pressure. BCF is the bioconcentration factor. (Adapted from Remberger et al., 2005). See Appendix B for more detail.

[a] at 24°C
[b] temperature not specified
[c] at 22 °C
[d] at 20°C
[e] at 25°C
[f] at 50°C

In addition to the physical/chemical parameters presented above, measured migration rate data are available for select chemicals. When available, these were the most informative measures used to assess potential exposure. For example, DEHA has been shown to migrate from food wraps and films, and the median human dietary intake has been estimated at 0.7 µg/kg body weight in human studies (Fromme et al., 2007). Another food wrap constituent, DINCH, has been shown to migrate into foods with high fat

content such as oils and high fat cheeses at rates above the 10 mg/dm^2 European legal limit (EFSA, 2006). It is not clear whether plasticized materials are used for food contact in the U.S. All other foods tested were below the European threshold. Additionally, results from a medical tubing migration study characterized migration in a DINCH feeding system as considerably lower than in DEHP systems (Welle et al., 2005).

TOTM, of relatively high molecular weight and with a bulky structure, is expected to be resistant to migration. Several studies have concluded that TOTM is a superior alternative to DEHP for use in medical devices because of its lower leachability (Flaminio et al., 1998; Kambia et al., 2001). Additionally, non-occupational inhalation exposure to TOTM is also not expected because of its very low vapor pressure (3.9 x 10^{-11} mm Hg). ATBC is the only candidate that appears to have a higher leaching rate than that of DEHP, as determined from a study of its migration from PVC films (Sheftel, 2000). No information could be found regarding the leaching or migration of DEHT from polymer resins. This represents a gap in the field of research for *o*-DAP alternatives.

Toxicity

In order to evaluate chemical toxicity, criteria such as the number, type, and quality of studies performed on each chemical were considered. Additionally, hazard information, as well as dose-response information (e.g., NOAEL and LOAEL values), for a variety of non-cancer endpoints, as well as carcinogenicity data, were evaluated. Chemicals were compared based on these parameters, with the intention that the compounds with lower apparent toxicity would be appropriate potential candidates for *o*-DAP alternatives in children's articles.

Overall, a substantial amount of toxicity information was currently available on these five chemicals. However, no published studies of DINCH were found. The only information located regarding the health effects of DINCH was found in the SCENIHR (2007) report, which contained summaries of unreferenced and unpublished studies submitted by BASF Corporation, and in an abstract/summary of one of these studies submitted by BASF Corporation to EPA under the Toxic Substances Control Act (TSCA) and identified in the search of the TSCATS database. Of these studies, the lowest LOAELs were reported by BASF to be 200 and 300 mg/kg-day for thyroid effects in the 2-year and 2-generation reproduction studies. Corresponding NOAELs were 40 and 100 mg/kg-day. The 2-generation study in rats showed no reproductive toxicity in either generation at doses as high as 1000 mg/kg-day, as reported by BASF.

Data are available on the subchronic, chronic, reproduction and developmental toxicity of DEHT. Limited data from this research suggests that acute oral toxicity is low based on an LD50 of >3200 mg/kg in both rats and mice (Eastman Kodak Co., 1975). For repeated-dose animal toxicity, there was no clear evidence of specific target organ toxicity of DEHT, although the subchronic, reproductive and developmental studies in rats and mice reported results suggestive of a non-adverse, adaptive response to DEHT in the liver (increased liver weight) (Barber and Topping, 1995, Faber et al., 2007a,b). A 2-year dietary cancer bioassay in rats was negative (Deyo, 2008). In the reproductive

toxicity studies, reductions in feed consumption and maternal and pup body weights were observed; however, no reproductive effects based on fertility, mating, estrous cycle lengths, gestation lengths, gender ratios, liver litter size or postnatal survival were observed in rats during this study (Faber et al., 2007a,b).

Alternatively, DEHA appears to have the largest amount of high-quality toxicity data available, including two 2-year chronic exposure studies. While a cancer bioassay in rats was negative, one in mice was positive, showing induction of liver tumors in both males and females (NTP, 1982b). It has been hypothesized that the observed mouse liver tumors are a result of peroxisome proliferation, and therefore, of questionable relevance to humans (Cattley et al., 1998; Chevalier and Roberts, 1998; Doull et al., 1999; IARC, 2000a; Lake, 1995, Melnick, 2001). Based on these considerations, IARC (2000a) concluded that DEHA was not classifiable as to its carcinogenicity in humans (Group 3). However, in a previous assessment verified in 1991, U.S. EPA classified DEHA in weight-of-evidence (WOE) Group C as a possible human carcinogen and calculated an oral slope factor (OSF) of 1.2E-3 $(mg/kg\text{-}day)^{-1}$ (U.S. EPA, 2008b). The acute toxicity of DEHA is low by oral, inhalation or dermal exposure (Table 3-3) (NTP, 1982b; Smyth et al., 1951). The U.S. EPA has set a Maximum Contaminant Level (MCL) for DEHA in drinking water at 0.4mg/L and the oral reference dose (RfD) at 0.6 mg/kg/day (U.S. EPA, 2004).

For TOTM, acute oral toxicity is low based on studies where no lethality was observed at doses up to 9850 mg/kg in rats (Ciba-Geigy, 1984a; Japan Ministry of Health and Welfare, 1996, as cited in UNEP, 2002; Nuodex, 1983a) and the key reproductive study found no effects on reproductive function, but did report decreased spermatocyte and spermatid counts (Japan Ministry of Health and Welfare, 1998, as cited in UNEP, 2002). TOTM did not induce developmental effects in rats following gavage treatment during gestation (Huntington Life Sciences, 2002) and limited data in strain A mice suggest that TOTM is not a lung carcingoen (CMA, 1983). However, this chemical is lacking a key 2-year chronic toxicity study.

Of the five chemicals, ATBC appears to be the least toxic as indicated by a relatively high NOAEL and lack of cancer effects. For ATBC, acute oral toxicity is very low, based on studies where no lethality was observed at doses up to 25,000 mg/kg in mice, 31,500 mg/kg in rats and 52,500 mg/kg in cats (Finkelstein and Gold, 1959; Larionov and Cherkasova, 1977). In guinea pigs, there was no evidence of toxicity after a single dermal exposure to 1250 mg/kg, but repeated application of 250 or 500 mg/kg-day was reported to affect body and liver weight (Larionov and Cherkasova, 1977; Johnson, 2002).

In repeated-dose studies, there was no clear evidence of specific target organ toxicity of ATBC, although two studies reported results suggestive of a non-adverse, adaptive response to ATBC in the liver (increased liver weight and/or hepatic hypertrophy) and possibly the kidney (Jonker and Hollanders, 1991 and Chase and Willoughby, 2002, as cited in U.S. EPA, 2008a). A 2-year dietary cancer bioassay in rats was negative, although perhaps not an adequate test of carcinogenicity because group sizes were relatively small (20 per treated group and 40 in controls), 20% of animals died early from

infection, and doses were inadequate (the high dose did not approach the MTD) (Soeler et al., 1950). Thus, the usefulness of this 2-year study is severely limited due to several deficiencies. Dietary reproductive toxicity tests in rats and mice did not reveal any effects of ATBC on reproductive parameters, such as fertility, mating, spermatogenesis, or gestation, or postnatal developmental effects (Chase and Willoughby, 2002; Robbins, 1994; Larionov and Cherkasova, 1977).

Furthermore, ATBC has been approved by the U.S. Food and Drug Administration (FDA) for use as a food additive and food contact substance (FDA, 2002a,b), while DEHA is permissible as an indirect food additive as a component of adhesives (FDA, 1999). DINCH has gained approval from the European Food Safety Authority (EFSA), the Japan Hygienic PVC Association (JHPA), and the German Institute for Risk Assessment (German BfR) for use as a food contact substance (BASF, 2008b), and is waiting approval from the FDA. TOTM and DEHT have no such approvals at this time.

Conclusions

Through an investigation of current and potential use, exposure, and toxicity data, this report presented reviews of five viable alternatives to *o*-DAPs in children's articles. Four of the five chemicals chosen for review have been cited as already being used in children's articles - ATBC, DEHA, DINCH and DEHT (Chen, 2002; Merchant, 2005; SCENIHR, 2007). The fifth, TOTM is currently only being used in products not closely related to children's articles, such as electrical cables, fuel additives, adhesives, sealants, and inks. However, like the others, TOTM is compatible with PVC – the most popular resin for children's soft plastic toys and other articles – and thus a likely *o*-DAP alternative (Adams, 2001).

Of the five chemicals presented in this review, TOTM appears to have the lowest migration potential; however no mobility data were available for DEHT. Additionally, probably because it is new to the plasticizer market, DINCH lacks extensive exposure and toxicology data, but does appear to have low migration rates and poor solubility in water, earning it approval from several governments to be used as a food contact substance (BASF, 2007).

Overall, a significant amount of toxicity information is currently available on these five chemicals (Table 7-2), although the quality of some studies is questionable. No published studies of DINCH were available. Acute oral toxicity for ATBC appears to be the lowest of the five chemicals (Finkelstein and Gold, 1959; Larionov and Cherkasova, 1977), and it has been approved by the U.S. Food and Drug Administration (FDA) for use as a food additive and food contact substance (FDA, 2002a,b).

In chronic exposure studies performed in rats, NOAELs and LOAELs were highest for DEHA at 948 (M) and 1104 (F) mg/kg-day, and 1975 (M) and 2300 (F) mg/kg-day, respectively. This was followed closely by ATBC, with a NOAEL of 1000 mg/kg-day and no LOAEL reached in the only chronic study available. DEHT had NOAELs from 324 to 102 mg/kg-d and LOAELs from 418 to 666 mg/kg-d for males and females,

respectively. The DINCH manufacturer reported NOAELs of 40 to 200 mg/kg-d and LOAELs of 200 to 1,000 mg/kg-d for males and females. No such study was available for TOTM.

Table 7-2 Summary of Available Repeated Dose Studies

Chemical	Study Type			
	Subchronic	**Chronic**	**Reproductive**	**Developmental**
ATBC	Y	?[a]	Y	N
DEHA	N	Y	Y	Y
DINCH	Y	Y	Y	Y
TOTM	?[b]	N	Y	Y
DEHT	Y	Y	Y	Y

Y, study available; N, study not available; ?, available study was inadequate.

[a] Small n; no Maximum Tolerable Dose (MTD) reported; respiration infection.

[b] Small n.

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APPENDIX A

Explanation of Databases Utilized

During the second phase of the investigation, toxicological screening was performed for eight candidate chemicals and endpoints were summarized from studies identified in primary and secondary sources. Computer searches of the PUBMED, TSCATS, RTECS and EPA SRS databases, as well as TOXNET databases, including TOXLINE, CCRIS, DART/ETIC, GENE-TOX, and HSDB, were conducted. Please see the list below for a full explanation of each database.

PUBMED

PubMed, a service of the U.S. National Library of Medicine (NLM), includes over 18 million citations from MEDLINE (NLM's Medical Literature Analysis and Retrieval System) and other life science journals for biomedical articles dating back to 1948. PubMed also provides access to out-of-scope citations (e.g., articles on plate tectonics or astrophysics) from certain MEDLINE journals, primarily general science and chemistry journals, for which the life sciences articles are indexed for MEDLINE, as well as citations that precede the date that a journal was selected for MEDLINE indexing. PubMed includes links to full text articles and other related resources, and can be accessed for free online at www.pubmed.gov.

TSCATS

The Toxic Substance Control Act Test Submission Database (TSCATS) was developed by SRC for the EPA in 1985. It is a central system for the collection, maintenance, and dissemination of information on unpublished technical reports submitted by industry to the EPA under the Toxic Substances Control Act (TSCA). Studies on over 8,000 chemicals are categorized into three broad subject areas (health effects, environmental effects, and environmental fate). Searches can be conducted using these subject areas plus additional indexing terms from the controlled vocabulary of testing protocol describing observations (i.e., species, duration of study, etc.). The database can be accessed online at http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384.

RTECS

Registry of Toxic Effects of Chemical Substances (RTECS) is a compendium of data extracted from the open scientific literature. The data are recorded in the format developed by the RTECS staff and arranged in alphabetical order by prime chemical name. Six types of toxicity data are included in the file: (1) primary irritation; (2) mutagenic effects; (3) reproductive effects; (4) tumorigenic effects; (5) acute toxicity; and (6) other multiple dose toxicity. Specific numeric toxicity values such as LD50, LC50, TDLo, and TCLo are noted as well as species studied and route of administration used. For each citation, the bibliographic source is listed, thereby enabling the user to access the actual studies cited. No attempt has been made to evaluate the studies cited in

RTECS and the user has the responsibility of making such assessments. Instructions on accessing RTECS can be found at http://www.cdc.gov/niosh/rtecs/RTECSaccess.html.

EPA SRS

The U.S. EPA Substance Registry Services (SRS) is EPA's consolidated registry of monitored and regulated substances. The database includes information on chemical identification and properties, including synonyms, CASRNs, chemical structure, chemical formula, and molecular weight. The database can be accessed online at http://www.epa.gov/srs/.

TOXNET Databases

TOXNET (the TOXicology Data NETwork) is a cluster of databases covering toxicology, hazardous chemicals, environmental health and related areas managed by the Toxicology and Environmental Health Information Program (TEHIP) in the Division of Specialized Information Services (SIS) of the National Library of Medicine (NLM). TOXNET offers features such as relevancy ranking, and flexible sorting and downloading options. Databases within the network include TOXLINE, DART/ETIC, GENE-TOX, and HSDB (see descriptions below).

TOXLINE

The TOXLINE database (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE) is the NLM's bibliographic database for toxicology, providing comprehensive coverage of the biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals from 1965 to the present. TOXLINE contains over 3 million citations, almost all with abstracts and/or index terms and CAS Registry Numbers. TOXLINE references are drawn from various sources organized into component subfiles which are searched together but which may be used to limit searches as well. The database covers much of the standard journal literature in toxicology, complemented with references from an assortment of specialized journals and other sources listed below:

- Standard biomedical/toxicology journal literature, including PubMed and MEDLINE.
- Special journal and other research literature, including the Developmental and Reproductive Toxicology (DART®) and International Labor Office (CIS) databases.
- Technical reports and research projects, including the Federal Research in Progress (FEDRIP), Toxic Substances Control Act Test Submissions (TSCATS), Toxicology Document and Data Depository (NTIS), and Toxicology Research Projects (CRISP) databases.
- Archival collection (no longer being updated), including Aneuploidy (ANEUPL), Environmental Mutagen Information Center File (EMIC), Environmental Teratology Information Center File (ETIC), Epidemiology Information System (EPIDEM), Hazardous Materials Technical Center (HMTC), Health Aspects of Pesticides Abstract Bulletin (HAPAB), International Pharmaceutical Abstracts

(IPA), NIOSHTIC (NIOSH), Pesticides Abstracts (PESTAB), Poisonous Plants Bibliography (PPBIB), Swedish National Chemicals Inspectorate (RISKLINE), and Toxicological Aspects of Environmental Health (BIOSIS) databases.

CCRIS

The Chemical Carcinogenesis Research Information System (CCRIS) is a toxicology data file of NLM's TOXNET. It is a scientifically evaluated and fully referenced data bank, developed and maintained by the National Cancer Institute (NCI), and containing over 9,000 chemical records with carcinogenicity, mutagenicity, tumor promotion, and tumor inhibition test results. Data are derived from studies cited in primary journals, current awareness tools, NCI reports, and other special sources. Test results have been reviewed by experts in carcinogenesis and mutagenesis. CCRIS is accessible, free of charge, via TOXNET at http://toxnet/nlm.nih.gov.

DART/ETIC

The Developmental and Reproductive Toxicology/Environmental Teratology Information Center (DART®/ETIC) database is the component of NLM's TOXNET exclusively containing references to developmental and reproductive toxicology literature. It covers teratology and other aspects of developmental and reproductive toxicology, and contains over 200,000 references to literature published since 1965. DART/ETIC is funded by the U.S. Environmental Protection Agency, the National Institute of Environmental Health Sciences, the National Center for Toxicological Research of the Food and Drug Administration, and the NLM. DART/ETIC is accessible, free of charge, via TOXNET at http://toxnet.nlm.nih.gov.

GENE-TOX

The GENE-TOX database, part of the NLM's TOXNET, was created by the U.S. Environmental Protection Agency (EPA) through the GENE-TOX program. The program works to select assay systems for evaluation, review data in the scientific literature, and recommend proper testing protocols and evaluation procedures for these systems. The GENE-TOX database contains genetic toxicology (mutagenicity) test data, resulting from expert peer review of the open scientific literature, on over 3,000 chemicals. It can be accessed, free of charge, via TOXNET at http://toxnet.nlm.nih.gov.

HSDB

Also part of NLM's TOXNET, the Hazardous Substances Data Bank (HSDB) focuses on the toxicology of about 5,000 potentially hazardous chemicals. It contains information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, and related areas. All data are referenced and derived from a core set of books, government documents, technical reports and selected primary journal literature. The data is organized into individual chemical records, and entries are peer-reviewed by the Scientific Review Panel (SRP), a committee of experts in the major

subject areas within the data bank's scope. HSDB be accessed, free of charge, via TOXNET at http://toxnet.nlm.nih.gov.

APPENDIX B

Explanation of Physico-chemical Parameters

The organic carbon normalized solid-water partition coefficient (K_{oc}), also known as the organic carbon adsorption coefficient, is defined as the ratio of the chemical's concentration in a state of sorption (i.e. adhered to soil particles) and the solution phase (i.e. dissolved in the soil water). K_{oc} is crucial for estimating a chemical compound's mobility in soil and the prevalence of its leaching from soil. For a given amount of chemical, the smaller the K_{oc} value, the greater the concentration of the chemical in solution. Thus, chemicals with a small K_{oc} value are more likely to leach into groundwater than those with a large K_{oc} value (http://www.acdlabs.com/products/phys_chem_lab/logd/koc.html).

Henry's law, one of the gas laws formulated by William Henry, states that "at a constant temperature, the amount of a given gas dissolved in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid (http://en.wikipedia.org/wiki/Henry's_law)." Henry's Law Constants characterize the equilibrium distribution of dilute concentrations of volatile, soluble chemicals between gas and liquid phases (http://www.epa.gov/athens/learn2model/part-two/onsite/esthenry.htm).

The octanol/water partition coefficient (K_{ow}) is defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. In recent years, this coefficient has become a key parameter in studies of the environmental fate of organic chemicals. It has been found to be related to water solubility, soil/sediment adsorption coefficients, and bioconcentration factors for aquatic life. Because of its increasing use in the estimation of these other properties, K_{ow} is considered a required property in studies of new or problematic chemicals (http://www.pirika.com/chem/TCPEE/LOGKOW/ourlogKow.htm).

The bioconcentration factor (BCF) is the concentration of a particular chemical in a tissue per concentration of chemical in water (reported as L/kg). This property characterizes the accumulation of pollutants through chemical partitioning from the aqueous phase into an organic phase, such as the gill of a fish. The scale used to determine if a BCF value is high, moderate or low will depend on the organism under investigation. The U.S. EPA generally defines a high potential BCF as being greater than 5,000; a BCF of moderate potential as between 5,000 and 100; a low potential BCF as less than 100 (http://en.wikipedia.org/wiki/Bioconcentration_factor; http://sitem.herts.ac.uk/aeru/footprint/en/Quest/ecotox.htm).