Screening Assessment for the Challenge

Hexanedioic acid, bis(2-ethylhexyl) ester (DEHA)

Chemical Abstracts Service Registry Number
103-23-1

Environment Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of hexanedioic acid, bis(2-ethylhexyl) ester (or DEHA), Chemical Abstracts Service Registry Number 103-23-1. The substance DEHA was identified in the categorization of the *Domestic Substances List* as a high priority for action under the Challenge initiative under the Chemicals Management Plan, as it was determined to present greatest potential for exposure of individuals in Canada and was considered to present a high hazard to human health, based upon classification by other agencies on the basis of carcinogenicity. The substance did not meet the ecological categorization criteria for persistence or bioaccumulation, but did meet the criteria for inherent toxicity to aquatic organisms.

According to information reported under section 71 of CEPA 1999, DEHA was manufactured in Canada in 2006 at quantities between 1 million and 10 million kilograms. Approximately 250 000 kg of DEHA was imported into Canada in the same reporting year. The majority of information submitted under section 71 of CEPA 1999 indicated that DEHA is used as a plasticizer. Globally, this substance is primarily used as a plasticizer in the flexible vinyl industry and may be used in flexible polyvinylchloride (PVC) food packaging (cling film). Sources of exposure of the general population of Canada are expected to be environmental media, food (as a result of migration from food packaging), and consumer products containing DEHA (including cosmetics and personal care products, auto interior protectants, heavy-duty hand cleansers, and lubricants).

As DEHA was classified with regards to its potential carcinogenicity by international agencies, this health effect was examined in this screening assessment. Increased liver tumours were observed in female mice, occurring at mid and high doses, but not in rats. The proposed mode of tumour induction is not considered to operate in humans and the observed tumours are therefore considered to be of limited relevance to human health risk characterization. Additionally, while the mode of induction has not been fully elucidated, consideration of the available information on genotoxicity indicates that DEHA is not likely to be genotoxic. Accordingly, a threshold approach is used to characterize risk to human health.

The critical effect for characterization of risk to human health for DEHA is developmental toxicity (increased postnatal deaths observed in rats). Based on a comparison of estimated exposures to DEHA in Canada to the critical effect levels for developmental effects, and taking into account the uncertainties in the databases on exposure and effects, it is considered that the resulting margins of exposure resulting from use of certain cosmetics and personal care products are potentially inadequate.

On the basis of the potential inadequacy of the margins between estimated exposures to DEHA and critical-effect levels, it is concluded that DEHA is a substance that is entering or may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

The low water solubility of DEHA, as well as its tendency to partition to particles and lipids (fat) of organisms, indicates that it will predominantly reside in soil and sediment when released to the environment. Despite its tendency to partition to lipids, DEHA appears to have a

low bioaccumulation potential, likely due to rapid metabolism. Both empirical and modeled data demonstrate that DEHA biodegrades in water, and that it is also not expected to persist for long periods in air, sediment, or soil. Acute toxicity studies generally report no effects to aquatic organisms at the water solubility limit, but there is potential for chronic toxicity, particularly for invertebrates.

A comparison of the predicted no-effect concentration with concentrations measured in Canadian surface water and effluents, as well as realistic worst-case estimated exposure concentrations determined for site-specific industrial releases to water, suggests that harm to aquatic organisms is possible at many locations in Canada.

On the basis of ecological hazard and estimated exposures, it is concluded that DEHA is entering or may be entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. DEHA does not meet the criteria for persistence or bioaccumulation as set out in the *Persistence and Bioaccumulation Regulations*.

Based on the information available, it is concluded that DEHA meets one or more of the criteria set out in section 64 of CEPA 1999.

This substance will be considered for inclusion in the *Domestic Substances List* inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or to human health.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce in Canada; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE) and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance hexanedioic acid, bis(2-ethylhexyl) ester (or DEHA) was identified as a high priority for assessment of human health risk because it was considered to present GPE and had been classified by other agencies on the basis of carcinogenicity. The Challenge for this substance was published in the *Canada Gazette* on September 26, 2009 (Canada 2009a, 2009b). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information pertaining to the substance were received.

Although DEHA was determined to be a high priority for assessment with respect to human health, it did not meet the ecological categorization criteria for persistence or bioaccumulation at that time.

Screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of CEPA 1999. Screening assessments examine scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution.[1]

[1] A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) Challenge is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of the regulatory framework for the Workplace Hazardous Materials Information System

This final screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to June 2010 for the health sections and July 2010 for the ecological sections of the document. Key studies were critically evaluated; modelling results have also been used to reach conclusions.

Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight-of-evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The final screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

This final screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. Both the human health and ecological portions of this assessment have undergone external written peer review and consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Gradient Corp., including Cathy Petito Boyce, Leslie Beyer, and Chris Long. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. While external comments were considered, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. Approaches used in the screening assessments under the Challenge have been reviewed by an independent Challenge Advisory Panel.

The critical information and considerations upon which the final assessment is based are summarized in the following report.

[WHMIS] for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA 1999 does not preclude actions being taken under other sections of CEPA or other Acts.

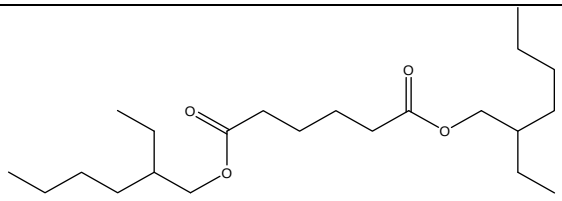
Substance Identity

Substance Name

Hexanedioic acid, bis(2-ethylhexyl) ester is also commonly known as di(2-ethylhexyl) adipate or DEHA. For the purpose of this assessment, this substance will be referred to as DEHA. Information on the identity of DEHA is summarized in Table 1.

While DEHA is often referred to by the archaic name dioctyl adipate (DOA) in technical literature, an isomer of DEHA with unbranched aliphatic chains is also called dioctyl adipate, and has its own CAS RN 123-79-5. This assessment specifically addresses DEHA as defined as CAS RN 103-23-1, and does not include CAS RN 123-79-5. Additionally, the name, dioctyl adipate, has been changed to diethylhexyl adipate in the International Cosmetic Ingredient Directory (CIR 2006; CTFA 2008).

Table 1. Substance identity for DEHA

Chemical Abstracts Service Registry Number (CAS RN)	**103-23-1**
DSL name	**Hexanedioic acid, bis(2-ethylhexyl) ester**
National Chemical Inventories (NCI) names[a]	*Hexanedioic acid, bis(2-ethylhexyl) ester* (AICS, ASIA-PAC, ENCS, PICCS, SWISS, NZIoC, TSCA) *Bis(2-ethylhexyl) adipate* (EINECS, PICCS) *Hexanoic acid bis(2-ethylhexyl) ester* (ECL) *Adipate, di (2-ethylhexyl)* (PICCS) *Dioctyl adipate* (PICCS)
Other names	*Adimoll DO; Adipic acid, bis(2-ethylhexyl) ester; Adipol 2EH; ADO; ADO (lubricating oil); Arlamol DOA; Bisoflex DOA; Crodamol DOA; Dermol DOA; Di(2-ethylhexyl) adipate; Diacizer DOA; Diethylhexyl adipate; DOA; Effomoll DA; Effomoll DOA; Ergoplast AdDO; Flexol A 26; Hatcol 2908; Hexanedioic acid, 1,6-bis(2-ethylhexyl) ester; Hexanedioic acid, bis(2-ethylhexyl) ester; Jayflex DOA 2; K 3220; Kodaflex DOA; Lankroflex DOA; Monoplex DOA; NSC 56775; Octyl adipate; Plasthall DOA; Plastomoll DOA; Reomol DOA; Sansocizer DOA; Sicol 250; SP 100; SP 100 (solvent); Truflex DOA; USS 700; Vestinol OA; Vistone A 10; Wickenol 158; Witamol 320*
Chemical group (DSL Stream)	Discrete organics
Major chemical class or use	Esters
Major chemical sub-class	Alkyl adipates
Chemical formula	$C_{22}H_{42}O_4$
Chemical structure	

SMILES[b]	O=C(OCC(CCCC)CC)CCCCC(=O)OCC(CCCC)CC
Molecular mass	370.58 g/mol

[a] National Chemical Inventories (NCI). 2007: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Commercial Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); NZIoC (New Zealand Inventory of Chemicals); PICCS (Philippine Inventory of Chemicals and Chemical Substances); SWISS (Swiss Giftliste 1 and Inventory of Notified New Substances); and TSCA (Toxic Substances Control Act Chemical Substance Inventory).

[b] Simplified Molecular Input Line Entry System

Physical and Chemical Properties

The experimental and estimated physical and chemical properties of DEHA that are relevant to its environmental fate are presented in Table 2. Key studies for which experimental data were reported were critically reviewed for validity for some of these properties.

Table 2. Physical and chemical properties for DEHA

Property	Value[a]	Reference
Physical form	Light coloured, oily liquid	HSDB 1983–
Melting point (ºC)	-67.8*	US EPA 2008, 2010
	-76	European Commission 2000
	-11 to 108 (modelled)	MPBPVP 2008
Boiling point (ºC)	417*	US EPA 2008, 2010
	379 (modelled)	MPBPVP 2008
Density (kg/m^3)	922 (0.922 g/mL)	HSDB 1983–
	924 (0.924 g/cm^3)	European Commission 2000
Vapour pressure (Pa)	1.1×10^{-4} (8.5×10^{-7} mm Hg*,[b])	Felder et al. 1986
	4.3×10^{-4} (modelled)	MPBPVP 2008 (Modified Grain Method)
Henry's Law constant ($Pa\cdot m^3/mol$)	4.4×10^{-2} (0.33 torr·L/mol; 4.34×10^{-7} $atm\cdot m^3/mol$*,[b]; at 20ºC)	Felder et al. 1986
	13 (calculated[c]; at 20ºC)	HENRYWIN 2008
	2.2, 5.2 (modelled[d]; at 25ºC)	HENRYWIN 2008

Property	Value[a]	Reference
Log K_{ow} (Octanol-water partition coefficient) (dimensionless)	> 6.1	Felder et al. 1986
	8.12* (modelled)	KOWWIN 2008
Log K_{oc} (Organic carbon-water partition coefficient) (dimensionless)	4.18	Felder et al. 1986
	~5.9	OECD 2005
	4.6 – 5.3 (modelled)	KOCWIN 2008
Log K_{oa} (Organic carbon-air partition coefficient) (dimensionless)	12.9 (modelled)	KOAWIN 2008
Water solubility (mg/L)	0.78[e] (at 22°C)	Felder et al. 1986; OECD 2005
	< 0.5	European Commission 2000
	0.23[f]	OECD 2005
	0.0055[g] (at 20°C)	Robillard et al. 2008
	< 0.005[h]	OECD 2005
	0.0032[i,*] (at 20°C)	Letinski et al. 2002
Other solubilities (g/L)	Soluble in most organic solvents; insoluble or very slightly soluble in glycerine and glycols	HSDB 1983–
	Soluble in ethanol, ethyl ether, acetone, and acetic acid	HSDB 1983–

* Indicates selected value for modelling in EPIsuite (2008); preference is given to experimental values of acceptable quality.
[a] Values in parentheses represent the original ones as reported by the authors or as estimated by the models. All values are experimental values unless otherwise noted.
[b] Method details not completely described in report; OECD (2005) state that this vapour pressure value was calculated from a measured vapour pressure at 200°C. For Henry's Law constant determination, di(2-ethylhexyl)[^{14}C]adipate was used.
[c] Calculated using the vapour pressure reported by Felder et al. (1986) and the water solubility reported by Letinski et al. (2002).
[d] Group method, bond method.
[e] Determined using deionized water but technique not defined by the author (Felder et al. 1986). Determined using the vigorous shake-flask technique (OECD 2005).
[f] Determined using the vigorous shake-flask technique; in saltwater.
[g] Determined using the slow-stir method; in moderately hard water and pH 7.9.
[h] Determined using a separator column technique.
[i] Determined using the slow-stir method; carbon treated well water; 50 mg/L of mercuric chloride added as a microbial inhibitor.

Models based on quantitative structure–activity relationships (QSARs) were used to generate data for some of the physical and chemical properties of DEHA. These models are mainly based on fragment addition methods (i.e., they rely on the structure of the chemical). The modelling program pK_aDB from ACD/pK_aDB (2005) predicts that this substance is not ionizable at environmentally relevant pH. Since the structure of this substance is easily modelled, the QSAR values are viewed with relatively high confidence. The modelled values shown in Table 2 generally support the experimental values.

Letinski et al. (2002) and Robillard et al. (2008) determined the water solubility of DEHA using the slow stir method. This method was determined to provide more reliable water solubility measurements (for a group of substances, including DEHA) because the formation of emulsions was avoided. Traditional methods using the vigorous shake-flask technique resulted in the formation of micelles or emulsions, making it difficult to remove undissolved chemical from the water phase. Water solubilities determined using the vigorous shake-flask technique, thus, tend to overestimate solubilities compared with those reported using the slow stir method. The water solubility reported by Letinski et al. (2002) has been used in modelling other properties for DEHA. Although the solubility value of Letinski et al. (2002) is considered the most reliable, there is nevertheless some uncertainty associated with all water solubility estimates.

Sources

DEHA is an anthropogenic substance and does not naturally occur in the environment. It is produced by an esterification reaction of adipic acid and 2-ethylhexanol in the presence of a catalyst such as sulfuric acid or *p*-toluenesulfonic acid.

DEHA is a high production volume (HPV) chemical in the United States (US EPA 2010) and in the European Union (ESIS c1995–2010). According to information submitted under section 71 of CEPA 1999, 1 – 10 million kilograms of DEHA were manufactured in Canada in 2006 (Environment Canada 2010a). The total quantity reported to be imported into Canada in the same year above the reporting threshold of 100 kg/year was approximately 250 000 kg (Environment Canada 2010a).

The national aggregate production quantity for DEHA in the United States was 10–50 million pounds (approximately 4 550 – 22 700 tonnes) in each of the 1986, 1990 and 2002 reporting cycles, and 50–100 million pounds (approximately 22 700 – 45 400 tonnes) in each of the 1994, 1998 and 2006 reporting cycles under the U.S. Environmental Protection Agency's Inventory Update Reporting program (US EPA 1986–2006).

Uses

Globally, DEHA is used primarily as a plasticizer in the flexible vinyl industry and widely used in flexible polyvinylchloride (PVC) food film (cling film). Aliphatic plasticizers consisting of adipic acid esters (adipate plasticizers), such as DEHA, are used either alone or together with other plasticizers in food packaging materials to incorporate low-temperature flexibility in PVC formulations (Bizzari et al. 2009). When it is mixed with other plasticizers, it is commonly

blended with bis(2-ethylhexyl) phthalates (DEHP) and di(isooctyl)phthalate (DIOP) at variable concentrations (IARC 2000).

A plasticizer is a substance that causes an increase in the flexibility and workability of the polymer when added to a polymer. PVC is the most widely plasticized polymer due to its excellent compatibility with plasticizers. While PVC without a plasticizer is used in rigid polymer applications such as pipes and window profiles, with the addition of plasticizer, PVC can be applied to other applications as food film, cable insulation, and floorings. Although a rigid polymer may be internally plasticized by chemically modifying the polymer or monomer, the common practice of plasticizing a polymer is by the external addition of a plasticizer where the plasticizers are not chemically bound to the polymers (Cadogan and Howick 2000; Fromme et al. 2002).

Alcohols of similar chain length to those used in phthalate manufacture can be esterified with adipic acid rather than phthalic anhydride to produce adipate plasticizers. The adipates in PVC applications lead to improved low temperature performance relative to phthalates due to their lower inherent viscosities. This property allows its prevalent use in food packaging, such as cling wrap for meat. Adipates used are typically in the C8 to C10 range as in the case for DEHA. Due to their relatively higher volatilities, migration rates, and cost relative to phthalates, adipates are often used in blends with phthalates to produce a compromise of properties. DEHA is classified as a secondary plasticizer due to its limited solubility and compatibility with PVC, and it is used mostly in conjunction with other primary plasticizers (Cadogan and Howick 2000; OECD 2005; Bizzari et al. 2009).

Adipates, especially DEHA, are primarily used in meat and food wrap (Bizzari et al. 2009). In the past, typical cling wrap formulations contained up to 22% DEHA; however, due to concerns over plasticizer migration into foods, DEHA content has declined to 8–10% by replacement with mainly bio-based plasticizers in conjunction with adipic acid-based polymeric plasticizers. Such combinations have been used in special food-grade PVC film, as well as in other food applications including tubes, hoses and conveyor belts in the food industry (Cadogan and Howick 2000; OECD 2005; Bizzari et al. 2009). The main uses of PVC packaging in Canada are in beef and poultry processing plants, for selected fruits and vegetables, repackaging of cheese in supermarkets, in fast food outlets and food distributors such as food caterers and cafeterias (2010 Personal communication from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

The Acceptable Daily Intake (ADI), 0.5 mg/kg-bw per day, of DEHA was originally established by the Food Directorate, Health Canada, in 1976 based on a two-year feeding study in rats and it is still valid to date. DEHA may be found in a heat-seal ink system intended to be used on the exterior of laminated structures, however, no food contact is expected from this use. It was also found in one polystyrene product used in the middle layer of a laminate structure and one lubricant product where no direct contact with food is expected. (April 2010 Personal communication from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

DEHA is listed under the U.S. Food and Drug Administration (US FDA) Code of Federal Regulations Title 21 in sections: 175.105 (adhesives), 177.1200 (cellophane), 177.1210 (closures with sealing gaskets for food containers), and 178.3740 (plasticizers in polymeric substances), indicating that it is approved as an indirect food additive as a component of

adhesives, cellophane food wrap, closures with sealing gaskets for food containers, water-insoluble hydroxyethyl cellulose film and plasticizers in polymeric substances (US FDA 2007a, 2007b, 2007c, 2007d, 2007e).

According to the information submitted under section 71 of CEPA 1999, the majority of DEHA manufactured and imported to Canada in 2006 was for use as a plasticizer (Environment Canada 2010a). Other reported uses submitted under section 71 of CEPA 1999 include, but are not limited to, adhesives and sealants for automobile manufacturing (Environment Canada 2010a). Other than its use as a plasticizer, global uses of DEHA include as a solvent and as a component of functional (hydraulic) fluid and aircraft lubricants (European Commission 2000), in the processing of nitrocellulose and synthetic rubber, and in plasticizing polyvinyl butyral, cellulose acetate butyrate, polystyrene and dammar wax (IARC 2000).

Based on the available information, consumer products containing DEHA in Canada include cosmetic and some personal care products, auto interior protectant, heavy-duty hand cleanser, and lubricant.

DEHA is used in cosmetic products, as a plasticizer, emollient or solvent (Gottschalck and McEwen 2004). In Canada, approximately 300 products containing DEHA have been notified to the Cosmetic Notification System (CNS), including skin moisturizer and cleanser, facial makeup, and bath preparation products (CNS 2010). Products intended for use by children were not identified in the Cosmetic Notification System (CNS 2010)

DEHA is a formulant (non-active ingredient) found in pesticides, which are regulated under the *Pest Control Products Act* in Canada (PMRA 2005). There are 5 registered pesticide products in Canada containing DEHA as a plasticizer. Recent reassessment of DEHA, a List 1 formulant, concluded it is acceptable for use as a plasticizer in cattle ear tags within the current concentration range. Other proposed uses would require additional data (April 2010 Personal communication from Pest Management Regulatory Agency, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

DEHA is not listed in the Drug Products Database as a medicinal ingredient in pharmaceutical drugs or veterinary products (DPD 2010). However, it is listed in the Therapeutic Products Directorate's internal Non-Medicinal Ingredients Database as a non-medicinal ingredient present in a sunscreen (March 2010 Personal communication from Therapeutic Products Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). DEHA is listed in the Natural Health Products Ingredients Database as an acceptable non-medicinal ingredient for use as a plasticizer or skin-conditioning emollient or solvent in natural health products (NHPID 2010). However, as DEHA is not listed in the Licensed Natural Health Products Database, it is not present in any currently licensed natural health products (LNHPD 2010).

Releases to the Environment

Most plasticizers are not chemically bound to the polymers and can migrate from plastic products during normal use and following their disposal (Fromme et al. 2002). Since plastic formulations, such as those used with PVC, can contain up to 40% plasticizer by weight

(Graham 1973; Wypych 2004), even a gradual loss of plasticizer can become a very significant source of environmental contamination.

In Canada, DEHA may be released to the environment during its manufacture, distribution, and industrial use, and from consumer use and disposal of finished products. According to the information submitted under section 71 of CEPA 1999, the majority of DEHA released to the environment in 2006 was to air (Environment Canada 2010a).

The National Pollutant Release Inventory (NPRI) reported the total on-site releases and total off-site disposals of DEHA from industrial sources, which are summarized in Table 3. NPRI data confirm that release of DEHA is mainly to air, as reported under section 71 of CEPA 1999 (Environment Canada 2010a; Environment Canada 2008).

Table 3. NPRI release and disposal data for DEHA, 2000–2008[a]

Year	On-site releases (kg)				Total on-site releases (kg)	Total off-site disposals (kg)
	To air	To water	To land	To unspecified compartment		
2008	1 400			–	1 400	6 100
2007	654	–	–	9	663	3 900
2006	1 800	–	–	–	1 800	6 900
2005	2 300	–	–	–	2 300	13 000
2004	2 000	–	–	400	2 400	114 000
2003	1 700	–	–	500	2 200	37 000
2002	652	–	–	148	1 100	13 000
2001	608	–	–	392	1 000	36 000
2000	1	–	–	451	452	47 000

[a]The NPRI reporting threshold for this substance is the manufacturing, processing or otherwise use of this substance in a quantity that is equal to or greater than 10 000 kg, and the concentration by weight of the substance is equal to or greater than 1%.

Environmental Fate

Level III fugacity modelling (EQC 2003) simulates the distribution of a substance in a hypothetical evaluative environment according to chemical partitioning, reactivity and inter-media transport processes. The mass-fraction values shown in Table 4 represent the net effect of these processes under conditions of continuous release when a non-equilibrium "steady-state" has been achieved (i.e., Level III).

Based on its physical and chemical properties (Table 2), the results of Level III fugacity modelling (Table 4) suggest that DEHA is expected to predominantly reside in soil and sediment, depending on the compartment of release. These results are reflective of DEHA's low experimental water solubility (0.0032 mg/L), high experimental and estimated log K_{ow}

values (>6.1 and 8.12, respectively) and high estimated log K_{oc} values (4.2–5.9), as well as its degradation.

Table 4. Results of the Level III fugacity modelling (EQC 2003)

	Percentage of substance partitioning into each compartment			
Substance released to:	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	4.5	1.8	77.7	16.0
Water (100%)	0.1	10.2	1.5	88.2
Soil (100%)	0	0	100	0

If released to air, DEHA may exist in both the vapour and particulate phases, based on a gas/particle partitioning model for semi-volatile organic compounds (HSDB 1983–). Low amounts of DEHA are predicted to partition into air (Table 4), which may be followed by subsequent removal by wet and dry deposition and/or degradation reactions with hydroxyl radicals.

Estimated log K_{oc} values suggest that DEHA is expected to have high adsorptivity to soil (i.e., it is expected to be immobile). According to fugacity modelling, this substance will mainly reside in the soil, if released to this compartment (Table 4). The experimental and estimated Henry's Law constants (4.4×10^{-2}–13 $Pa\cdot m^3/mol$) suggest that it would have some potential for volatilizing from moist soil surfaces. DEHA volatilization from dry soil surfaces is not expected to be an important fate process based upon its low experimental vapour pressure of 1.1×10^{-4} Pa.

If released into water, DEHA is expected to strongly adsorb to suspended solids and sediment based upon high estimated log K_{oc} values. Some volatilization from water surfaces may occur based upon experimental and estimated Henry's Law constants. Fugacity modelling predicts that if water is the receiving medium, DEHA is expected to mainly partition to sediment (Table 4).

These results suggest that soil and sediment would act as sinks for DEHA released into the environment.

Persistence and Bioaccumulation Potential

Environmental Persistence

The available experimental data on the persistence of DEHA in water are presented in Table 5a. These studies include ready biodegradation tests and inherent biodegradation tests (evaluating primary and ultimate biodegradation), which generally provide favourable conditions for biodegradation (e.g., acclimation and nitrification) as compared to ready biodegradation tests.

Table 5a. Empirical degradation data for DEHA

Medium	Fate process	Degradation value	Degradation	Reference

			endpoint / units	
Biotic				
Water	Primary Biodegradation[a]	82% 83% (55.1% $ThCO_2$)	ThOD; 28 days (different methods)	Huls AG 1996a, 1996b
Water	Primary Biodegradation (10 individual strains of bacteria, yeast, fungi)	"moderate degradation"	Measurement of DEHA and metabolites; 14 days	Nalli et al. 2006a
Water	Primary Biodegradation (7 individual strains of bacteria, yeast, fungi)	"significant degradation"	Measurement of DEHA and metabolites; 14 days	Nalli et al. 2006a
Water	Primary Biodegradation (soil bacterium)	90%	16 days	Nalli et al. 2006b
Water	Primary Biodegradation (fungi, yeast)	"moderate" and "significant" (75–100%)	8 days	Gartshore et al. 2003
Water	Primary biodegradation[b] (acclimated, semi continuous activated sludge)	73%, 92% (+-8%, 4%)	Loss per day (5 mg vs. 20 mg DEHA/day)	Saeger et al. 1976
	Ultimate biodegradation[c] (acclimated activated sludge)	82%, 94%	$ThCO_2$ evolution; 35 days (different methods)	Saeger et al. 1976
Water	Ultimate Biodegradation (ready biodegradability)	71%	%BOD; 28 days	CHRIP c2011

$ThCO_2$ – theoretical carbon dioxide
ThOD – theoretical oxygen demand
[a] Biodegradation of 82% = BOD test for insoluble substances ISO 10708. Biodegradation of 83% = Modified Sturm test. Test substance: Vestinol OA.

[b] From a local domestic sewage plant; acclimated 3 weeks.
[c] Biodegradation of 82% = Gledhill shake-flask method; set up is similar to the Sturm test but with smaller vessels and different initial seed concentrations; 37.4 mg/L DEHA. Biodegradation of 94% = Modified Sturm test; currently referred to as the OECD method 301B test, with the exception of acclimated activated sludge; 20.1 mg/L DEHA.

Abiotic degradation of DEHA may occur through photolysis and hydrolysis (Howard 1991; HSDB 1983–; OECD 2005). DEHA reacts rapidly with hydroxyl radicals, with calculated half-lives of 2.6 to 26 hours for a range of polluted to unpolluted air, calculated from its rate constant that was determined using a structure estimation method (Howard 1991; Table 5b). These values are similar to the AOPWIN model-predicted atmospheric oxidation half-life value of 5 hours (Table 5b). This substance may also undergo direct photolysis, because the compound contains a functional group that can absorb light at > 290 nm (HSDB 1983–).

However, DEHA is unreactive to peroxy radicals (RO_2) and is unreactive to ozone (O_3) (Howard 1991). With an atmospheric degradation half-life of no more than ~1 day by reaction with hydroxyl radicals, DEHA is not considered to persist in air. Consequently, long-range transport in air is not likely to be a concern for DEHA.

Although DEHA may be expected to hydrolyze at basic pH (similar to other diesters, Felder et al. 1986; US EPA 1984a), the rate of hydrolysis is considered slow to negligible at environmental pHs (US EPA 2008). The predicted hydrolysis half-lives of 3.2 years (pH 7) and 117 days (pH 8) calculated using a structure estimation method (Table 5b) support this analysis.

Based on the available experimental data (Table 5a), the biodegradation of DEHA in water appears to occur fairly quickly, with significant primary degradation occurring within days to a few weeks.

A mechanism has been confirmed for the biodegradation of DEHA by *Rhodococcus rhodochrous* (Nalli et al. 2002; Horn et al. 2004; Nalli et al. 2006b). Nalli et al. (2006b) demonstrated a mole balance calculation for the degradation of DEHA (initial amount of ~10 g), showing that approximately 10% of DEHA remained in the liquid phase after 16 days. Detailed analysis of the fate of all of the components in the DEHA system showed that at most, 2% of DEHA was mineralized after 400 h (~16 days) under ideal growth conditions. The first step in the degradation process is the enzymatic hydrolysis of the ester bonds in DEHA (Sauvageau et al. 2009). These data suggest that DEHA undergoes substantial primary biodegradation under aerobic conditions.

Nalli et al. (2002) have shown that DEHA can be degraded by *R. rhodochrous* when it is growing on a primary carbon source. The DEHA initial concentration was 1 000 mg/L, and the substance completely disappeared over the course of the first 60 hours (test spanned 5 days and metabolites were observed). The degradation of DEHA results in a few metabolites (Nalli et al. 2002, 2006a,b,c; Grochowalski et al. 2007), including 2-ethylhexanoic acid.

Gartshore et al. (2003) have shown that DEHA was significantly degraded (primary degradation; 75–100% loss of parent compound) by two species of *Aspergillus* and moderately degraded by *Candida bombicola* (no % loss given) over a period of 8 days.

Several strains of common soil bacteria (7 species), yeast (6 species) and fungi (2 species) were grown in the presence of different plasticizers (including DEHA at 2 500 mg/L) for a period of 2 weeks (Nalli et al. 2006a). Of the 18 strains/species tested, 17 of the tests resulted in moderate to significant primary biodegradation (qualitatively determined), indicating that the majority of the microbes tested were able to degrade DEHA. The degradation of DEHA by *Bacillus subtilis* was studied in the presence of surfactants, which resulted in the sequestering of metabolites in mixed micelles, thereby reducing their bioavailability for further degradation (Grochowalski et al. 2007). Berk et al. (1957) found that adipic acid diesters containing 12 or more carbons supported fungal growth. The ability of yeast cultures to utilize adipic acid esters was demonstrated by Osmon et al. (1970). Sabev et al. (2006) demonstrated a 4% loss in weight of polyvinyl chloride over 10 months in a field study with buried plastic. There were 92

fungal morphotypes isolated from grassland soil and 42 from forest soil that were able to clear DEHA agar.

In Saeger et al. (1976), the rapid primary and essentially complete (ultimate) degradation of DEHA to CO_2 and water observed in a 35-day semi-continuous activated sludge (SCAS) procedure and CO_2 evolution tests, respectively, suggest that mixed microbial populations in the environment will rapidly degrade DEHA, with a half-life much shorter than 182 days.

A ready biodegradation test for DEHA was performed according to the test methods of the Ministry of International Trade and Industry in Japan (MITI) set out by the Organisation for Economic Co-operation and Development (OECD) Test Guideline 301C (i.e., MITI-I-OECD TG 301C), with results indicating ready biodegradability (CHRIP c2011). The 28-day test resulted in a biochemical oxygen demand of 71%. This test also indicates that the ultimate degradation half-life in water is likely to be much shorter than 182 days (6 months) and that the substance is therefore not likely to persist in this environmental compartment. Ready biodegradability tests conducted on a number of other diesters also indicate the potential for these compounds to degrade relatively rapidly in the environment (US EPA 2008).

Although experimental data on the degradation of DEHA are available and preferable, a QSAR-based weight-of-evidence approach (Environment Canada 2007) was also applied using the degradation models shown in Table 5b below. Data from predictive approaches may be used to strengthen and support the existing experimental data as an additional line of evidence. In the case of DEHA, model results are consistent with the experimental data and add to the weight of evidence indicating that the ultimate biodegradation half-life of this substance in water is significantly less than 182 days.

Table 5b. Modelled degradation data for DEHA

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
AIR			
Ozone reaction	AOPWIN 2008[a]	n/a[b]	
Atmospheric oxidation	Polluted to unpolluted air; (structure estimation method)[c] Howard 1991	2.6 to 26 hours	<2
	AOPWIN 2008[a]	$t_{1/2}$ ~ 5 hours	<2
WATER			
Hydrolysis	HYDROWIN 2008[a]	$t_{1/2}$ = 3.2 years (pH 7) $t_{1/2}$ = 117 days (pH 8)	n/a
Primary biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[a] Sub-model 4: Expert Survey (qualitative results)	4.3[d] "biodegrades fast"	<182

Ultimate biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[a] Sub-model 3: Expert Survey (qualitative results)	3.3[d] "biodegrades fast"	<182
Biodegradation (aerobic)	BIOWIN 2008[a] Sub-model 5: MITI linear probability	0.9[e] "biodegrades very fast"	<182
Biodegradation (aerobic)	BIOWIN 2008[a] Sub-model 6: MITI non-linear probability	0.9[e] "biodegrades very fast"	<182
Biodegradation (aerobic)	TOPKAT 2004 Probability	1[e] "biodegrades very fast"	<182
Biodegradation (aerobic)	CATABOL c2004–2008 % BOD (biological oxygen demand)	% BOD = 63 "biodegrades fast"	<182

[a] EPIsuite (2008) using SMILES notation in Table 1; for HYDROWIN, the model notes that fragments on this compound are not available from the fragment library so substitutes have been used.
[b] Model does not provide an estimate for this type of structure.
[c] Uses a base-catalyzed second-order hydrolysis rate constant of 0.07 L/mole-sec estimated using a structure estimation method.
[d] Output is a numerical score from 0 to 5.
[e] Output is a probability score.

Using an extrapolation ratio of 1:1:4 for a water:soil:sediment biodegradation half-life (Boethling et al. 1995), the ultimate biodegradation half-life in soil is also < 182 days and the half-life in sediments is < 365 days (based on a half-life in water that is expected to be < 90 days, given the experimental and modelled data). Therefore, DEHA is not considered to persist in soil and sediment.

Based on the empirical data and taking into account supporting modelled data (Tables 5a and 5b), DEHA does not meet the persistence criteria in air, soil, water or sediment (half-life in air ≥ 2 days, half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

The log K_{ow} value, on its own, suggests that DEHA has the potential to accumulate in aquatic organisms, although this was not confirmed in a fish bioconcentration study by Felder et al. (1986). These authors performed a 28-d uptake and 14-d depuration study on the bluegill sunfish according to US EPA and ASTM procedures. The nominal exposure concentration in the flow-through test was 0.20 mg/L of [^{14}C] DEHA (which was confirmed by radio-analysis before test fish were introduced to the test chambers). Groups of 130 fish were transferred to the control and test chambers, and observed for mortality and unusual behaviour at 0 h and every 24 hours during the 28-d exposure period. Water and fish (muscle filet and viscera portions) were sampled at 4 h and 1, 3, 7, 14, 21 and 28 d during the uptake period. On day 28,

the addition of the test substance was stopped and the fish were exposed to flowing uncontaminated well water for an additional 14 d. Water and fish were sampled on days 29, 31, 35, 38 and 42 and analyzed in a similar fashion as the uptake period. A whole-fish bioconcentration factor (BCF) of 27 was observed for bluegill sunfish exposed to 0.250±0.08 mg/L [^{14}C] DEHA at the end of the test (day 28). DEHA appeared to reach equilibrium in the fish on day 7. The depuration half-life for DEHA in this organism was less than 1 day. As the measured BCF was based on [^{14}C] determinations and not on the measured concentration of DEHA in fish tissue, some of the [^{14}C] activity may have been attributable to DEHA metabolites. In addition, the BCF could have been overestimated since the exposure concentration used to calculate the experimental bioaccumulation value is about 100 times greater than the substance's water solubility limit. However, even if the water solubility concentration is used in the BCF calculation, the BCF would be significantly below the bioaccumulation criterion of BCF ≥ 5000.

Although an experimental BCF value for DEHA was available, a predictive approach was applied using available BAF and BCF models as shown in Table 6 below. According to the *Persistence and Bioaccumulation Regulations* (Canada 2000) a substance is bioaccumulative if its BCF or BAF is ≥ 5000; however measures of BAF are the preferred metric for assessing bioaccumulation potential of substances. This is because BCFs may not adequately account for the bioaccumulation potential of substances via the diet, which predominates for substances with log K_{ow} > ~4.0 (Arnot and Gobas 2003). Kinetic mass-balance modelling is in principle considered to provide the most reliable prediction method for determining the bioaccumulation potential because it allows for correction for metabolic transformation as long as the log K_{ow} of the substance is within the log K_{ow} domain of the model.

Table 6: Modelled bioaccumulation data for DEHA

Test organism	Endpoint[a]	Value wet weight (L/kg)	Reference
Fish	BAF (corrected)	47	Arnot and Gobas 2003 (Arnot-Gobas middle trophic level)
Fish	BCF (corrected)	7	Arnot and Gobas 2003 (Arnot-Gobas middle trophic level)
Fish	BCF (corrected)	7	CPOPS 2008
Fish	BCF	957	BCFBAF 2008

[a] Values used in modelling with EPIsuite (2008) are indicated with an asterisk in Table 2. The water solubility of 0.78 mg/L was used in the CPOPs model.

BCF and BAF estimates, corrected for potential biotransformation, were generated using the BCFBAF model (EPIsuite 2008). Metabolic rate constants were derived using structure activity relationships described further in Arnot et al. (2008a, 2008b and 2009). Since metabolic potential can be related to body weight and temperature (Hu and Layton 2001, Nichols et al. 2007), the BCFBAF model further normalizes the k_M for a 10g fish at 15^{o}C to the body weight of the middle trophic level fish in the Arnot-Gobas model (184 g) (Arnot et al. 2008b). The

middle trophic level fish was used to represent overall model output as suggested by the model developer and is most representative of fish weight likely to be consumed by an avian or terrestrial piscivore. After normalization routines, the k_M for a 10g fish at 15°C is estimated to be 2.3 days^{-1}. Therefore, the rate of metabolism for this substance is relatively fast, indicating that this substance is not likely to be bioaccumulative.

The available evidence indicates that DEHA is expected to have a low bioaccumulation potential, despite its relatively high experimental log K_{ow} value, most likely because this substance is rapidly metabolized. All BCFs and the BAF are significantly less than 5000. Based on the available empirical and modelled values corrected for metabolism, and considering evidence for metabolic potential, DEHA does not meet the bioaccumulation criteria (BCF or BAF $\geq$ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

Ecological Effects Assessment

In the Aquatic Compartment

The acute and/or chronic toxicity of DEHA has been tested using four species of fish, eight species of freshwater and marine invertebrates, two species of green algae, as well as some microorganisms. Both benthic and pelagic organisms have been tested. A summary of experimental ecological effects data is presented in Table 7. Many of the values are reported as cited in OECD (2005).

Table 7. Empirical aquatic toxicity data for DEHA

Test organism	Type of test	Endpoint	Value* (mg/L)	Reference
Fish				
Bluegill sunfish *Lepomis macrochirus*	Acute (96 hours, static)	LC_{50}	>0.78 (no effects)	Felder et al. 1986
Fathead minnow *Pimephales promelas*	Acute (96 hours, static)	LC_{50}	>0.78 (no effects)	Felder et al. 1986
Rainbow trout *Oncorhynchus mykiss*	Acute (96 hours, static)	LC_{50}	>0.78 (no effects)	Felder et al. 1986
	Acute (96 hours, static)[a]	LC_{50}	54–110 (actual bounds)	Hrudey et al. 1976
Carp *Cyprinus carpio*	Acute (96 hours, semi-static)[b]	LC_{50}	>1.6 (no effects)	Huls AG 1996c[c]
Invertebrates				
Midge larvae *Chironomus*	Acute (96 hours, flow-	LC_{50}	>0.73 (no effects)	Springborn Life Sciences 1989a

riparius	through)			
Amphipod *Gammarus fasciatus*	Acute (96 hours, flow-through)	LC_{50}	>0.73 (no effects)	Springborn Life Sciences 1989a
Isopod *Assellus sp*.	Acute (96 hours, flow-through)	LC_{50}	>0.73 (no effects)	Springborn Life Sciences 1989a
Midge larvae *Chironomus tentans*	Acute (96 hours, static)	LC_{50}	>0.78 (no effects)	Felder et al. 1986
Water flea *Daphnia magna*	Acute (48 hours, static)	EC_{50}	0.66 (immobilization)	Felder et al. 1986
	Acute (48 hours, static)[b]	EC_{50}	>1.6 (no effects)	Huls AG 1996d[c]
	Chronic (21 days, flow-through)[d]	EC_{50}	>0.0032 (no effects)	CHRIP c2011
	Chronic (21 days, semi-static)	EC_{50}	>0.0044 (average; no effects)	Robillard et al. 2008
	Chronic (21 days, flow-through)[e]	MATC	0.035** (0.024–0.052)	Felder et al. 1986
	Chronic (21 days, semi-static)	EC_{50}	>0.77 (no effects)	Huls AG 1996d[c]
Mysid shrimp *Mysidopsis bahia*	Acute (96 hours, flow-through)	LC_{50}	>0.23 (no effects)	Springborn Life Sciences 1989b
Grass shrimp *Paleomonetes pugio*	Acute (96 hours, flow-through)	LC_{50}	>0.23 (no effects)	Springborn Life Sciences 1989b
Amphipod *Ampelisca abdita*	Acute (96 hours, flow-through)	LC_{50}	>0.23 (no effects)	Springborn Life Sciences 1989b
Algae				
Green alga *Pseudokirchneriella subcapitata*	Chronic (96 hours, static)	EC_{50}	>0.78 (no effects)	Felder et al. 1986
Green alga *Scenedesmus subspicatus*	Chronic (72 hours, static)[b]	EC_{50}	>1.4 (no effects)	Huls AG 1996e[c]
Microorganisms				
Microtox assay	Acute (5 minutes)	EC_{50}	1000 (no effects)	Nalli et al. 2002
Activated sludge	Chronic (assumed; no	EC_{50}	>352 (no effects)	Huls AG 1996f

	time period given) [b]			

LC_{50} – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.
EC_{50} – The concentration of a substance that is estimated to cause some effect on 50% of the test organisms.
NOEC(L) – The No Observed Effect Concentration (Level) is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls.
LOEC(L) – The Low Observed Effect Concentration (Level) is the lowest concentration in a toxicity test causing a statistically significant effect in comparison to the controls.
MATC – The maximum allowable toxicant concentration, generally presented as the range between the NOEC(L) and LOEC(L) or as the geometric mean of the two measures.

* Most of reported test concentrations exceed the water solubility limit (0.0032 mg/L).
** The critical toxicity value used to derive a probable no effects concentration.
[a] The authors noted that resulting mortality times were random (precluding calculation of an LC_{50}) and which suggested something other than a consistent chemical toxic action.
[b] Only concentration tested; or the highest concentration tested in the case of activated sludge.
[c] Test substance: Vestinol OA.
[d] Additional data included: 72 h NOEC growth inhibition = 50 mg/L for green algae (1999); 48-h EC_{50} immobilization >50 mg/L for daphnia (1999); 21 d NOEC reproduction = 14 mg/L for daphnia (1999); 96-h acute LC_{50} >50 mg/L for fish (1999).
[e] [^{14}C]DEHA concentration measured at days 0, 4, 7, 14, and 21 with a mean measured concentration of 92% of nominal.

Most of the acute toxicity studies on aquatic organisms indicate no effects at the highest concentrations tested – i.e., at concentrations >0.23 mg/L (higher than the water solubility limit for this substance; Table 7). However, DEHA was acutely toxic to two of the species tested, both with reported test concentrations measured above the water solubility limit. In one study, rainbow trout were exposed to DEHA concentrations ranging from 54–420 mg/L, with 30–55% mortality reported (Hrudey et al. 1976). The authors noted that DEHA exhibited significant self-emulsifying characteristics, allowing for direct emulsification and testing without the use of any carrying agents or stabilizers. The relatively high concentrations of test emulsions enhanced their instability, resulting in globules of the test compound over time. Therefore, it was suggested by the authors that the test emulsions may have killed the fish primarily due to a physical coating effect on the fish. In the second study, a 48-hour LC_{50} concentration of 0.66 mg/L was reported for *D. magna* (Felder et al. 1986). Although the test concentrations in the study by Felder et al. (1986) were also above the water solubility limit, the authors did not report that toxicity was due to any physical effect.

The available data indicate a concern for chronic toxicity to aquatic organisms at DEHA concentrations below about 0.1 mg/L. Two chronic toxicity studies were performed on *D. magna* and two species of green algae (Table 7). Robillard et al. (2008) performed a 21-day chronic *D. magna* limit test at an average exposure of 0.0044 mg/L in laboratory diluent water. These authors also reported the water solubility of DEHA as 0.0055 mg/L using the slow-stir method, and according to the authors, test concentrations were chosen to avoid insoluble test material and physical entrapment of organisms. No adverse effects on survival, growth or reproduction were observed in the DEHA-treated organisms. However, this study was deemed unreliable because the measured initial concentration of DEHA in the test solution at the time of renewal varied from 0.00165 to 0.00832 mg/L. More importantly, when test concentrations were measured three times just prior to renewal, the concentration of DEHA had decreased to very low levels (<0.00009 mg/L) during 24 h in the test chamber in the presence of daphnids and food. The authors note that it was reasonable to expect that DEHA would adsorb to the food in the exposure chambers, given its physical-chemical properties and a reported partition

coefficient for di(2-ethylhexl) phthalate between water and algae-plankton (this substance has a similar water solubility and log K_{ow} to DEHA).

Another chronic toxicity study using *D. magna* also measured survival, growth and reproduction over a 21-day flow-through test (Felder et al. 1986) conducted according to the American Society for Testing and Materials (ASTM) procedures. Radio-labelled DEHA was used in the experiment. [^{14}C]DEHA concentrations were measured at days 0, 4, 7, 14, and 21. The mean measured concentrations were 92% of nominal and averaged 0.014, 0.024, 0.052, 0.087 and 0.18 mg/L. All treatments and controls were conducted in quadruplicate with 10 first-instar daphnids (less than 24 h old) in each of the test chambers. The daphnids were fed 15–30 ml of a *S. capriconutum* suspension three times daily and 2 ml of trout chow suspension once daily. A MATC geometric mean was determined to be 0.035 mg/L. Results from this study were considered acceptable for the critical toxicity value (CTV) (see robust study summary in Appendix 1), which is used in deriving a predicted no-effects concentration (PNEC; described later in this report). This chronic value reported by Felder et al. (1986) is also used in the OECD SIDS assessment report for DEHA (OECD 2005) to derive a PNEC for aquatic organisms.

The CTV (0.035 mg/L) is considered acceptable since it lies within a factor of ten of acceptable water solubility estimates. This ten-fold factor is used to account for variability and uncertainties in the experimental estimates of water solubility and inherent toxicity, and the fact that co-solvents exist in the natural environment that may ultimately affect the solubility and bioavailability of a substance. The two studies reporting acceptable water solubility estimates for DEHA (0.0032–0.0055 mg/L) used the slow-stir method. Furthermore, in assessing the ecological risks of a substance, other modes of action (e.g., physical effects) that would have the potential to be manifested in the natural environment may also be considered. Therefore, the results of aquatic toxicity tests that are conducted above a substance's water solubility limit may provide useful information in this respect.

Modelled predictions for aquatic toxicity were performed for DEHA, as predictive approaches provide an additional line of evidence. ECOSAR (2008) results for the ester class indicated that the chemical may not be soluble enough to cause acute effects and that the log K_{ow} cut-off of the model was marginally exceeded. Therefore, no acute effects at saturation were predicted. However, predicted chronic toxicity values (reported as ChV values) were below the water solubility (with the exception of one endpoint). These included predictions for esters: fish (32–33-day) 0.0003 mg/L, daphnid (21-day) 0.002 mg/L, and green algae 0.006 mg/L. Predictions of ChV values for neutral organics included: fish 0.0002 mg/L, daphnid 0.0006 mg/L, and green algae 0.014 mg/L. The TOPKAT model results were also considered reliable with an LC_{50} of 0.0011 mg/L predicted for Fathead minnow (although computed logP value exceeds the range spanned by the training set). These predictions generally support the empirical data discussed above.

The available toxicity data indicate a concern for chronic toxicity of this substance. Therefore, the critical toxicity value selected for deriving the PNEC was the experimental 21-day MATC for survival, reproduction and growth in *D. magna* of 0.035 mg/L (Felder et al. 1986).

In Other Environmental Compartments

Only one study was available that evaluated the effects of DEHA in soil. Earthworms were exposed to DEHA amended quartz sand and soil for 7 days and 14 days, with reported LC_{50}s of >1000 mg/kg and 865 mg/kg, respectively (Huls 1996g; as reported in OECD 2005). No ecological effects studies were found for this compound in sediment.

No ecological effects studies were found for DEHA in air.

An equilibrium partitioning approach (Di Toro et al. 1991) using the critical toxicity study (MATC for *D. magna*) chosen from the available aquatic toxicity data was used to estimate the CTV for sediment-dwelling organisms, as shown below.

$$CTV_{sediment} = f_{oc} \cdot K_{OC} \cdot MATC_{aquatic}$$

where:

- f_{OC} is 0.02, a standard value for organic carbon content given in Mackay (1991); and
- K_{OC} (Table 2; average taken of log K_{OC} of 4.9)
- $MATC_{aquatic}$ for *D. magna* (Table 7)

Therefore:

$$CTV_{sediment} = 0.02 \times 79\,500 \text{ L/kg} \times 0.035 \text{ mg/L}$$

$$= 55.7 \text{ mg/kg dry wt}$$

This approach assumes that toxicity to sediment-dwelling organisms is directly proportional to the unbound substance dissolved in sediment pore water and is applicable to those sediments with >0.2% organic carbon. The CTV for sediment-dwelling organisms is 55.7 mg/kg dry wt and can be used to estimate the predicted no-effects concentration in sediment.

Ecological Exposure Assessment

DEHA is an ingredient in a number of industrial and consumer products and is used in high volumes in Canada (Environment Canada 2010a), as well as throughout the United States (US EPA 2010) and the European Union (ESIS c1995–2010). It is used in a wide variety of plastic applications, particularly where flexibility is required at low temperatures (e.g., cling wraps for food). Most plasticizers are not chemically bound to the polymers and can migrate from plastic products during normal use and following their disposal (Fromme et al. 2002). Since plastic formulations, such as those used with PVC, can contain up to 40% plasticizer by weight (Graham 1973; Wypych 2004), even a gradual loss of plasticizer can become a very significant source of environmental release. Adipates in general are also used in a large number of products and applications, and as an example, Sweden reported 158 chemical products containing DEHA in 2003 (IVL SERI 2005).

This substance may be released to the environment through the manufacturing of DEHA, industrial and consumer uses, and disposal of various products containing DEHA. The processing of wastewater through wastewater treatment plants may result in either the release of DEHA to the aquatic environment and/or its concentration in wastewater biosolids (Barnabé et al. 2008; Beauchesne et al. 2008). Disposal of products or biosolids, or use of biosolids (treated wastewater sludge) in soil amendments containing this substance could result in releases to the environment through direct application to soil, leaching from landfill (where leachate is not collected) and/or waste incineration.

Data concerning concentrations of DEHA in the Canadian environment and elsewhere have been identified (Table 8). Canadian environmental monitoring data provides the most pertinent evidence for exposure of organisms in Canada.

Table 8. Concentrations of DEHA in the environment

Medium	Location; year	Concentration	Reference
Water/Effluent (mg/L)			
Melted snow	Montreal, Québec; 2004	0.15	Horn et al. 2004[a]
Landfill leachate	Montreal, Québec; 2004	0.025	
River water	Montreal, Québec; 2004	0.014	
Creek water	Montreal, Québec; 2004	0.0058	
Tap water	Montreal, Québec; 2004	0.0051	
Influent; wastewater treatment plants[b]	Montreal, Québec; 2005	6.17	Barnabé et al. 2008
	Québec, Québec; 2005	4.6	Barnabé et al. (unpublished data)
	Gatineau, Québec; 2005	5.8	
	Drummondville, Québec; 2005	0.05	
	Granby, Québec; 2005	0.65	
	Victoriaville, Québec; 2005	1.2	
	Thetford Mines, Québec; 2005	8.0	

Effluent; wastewater treatment plants[b]	Montreal, Québec; 2005	0.147	Barnabé et al. 2008
	Québec, Québec; 2005	0.65	Barnabé et al. (unpublished data)
	Gatineau, Québec; 2005	5.9	
	Drummondville, Québec; 2005	nd	
	Granby, Québec; 2005	0.033	
	Victoriaville, Québec; 2005	1.0	
	Thetford Mines, Québec; 2005	0.003	
Rivers, bays, lakes	Various locations in US; 23 sites	0.00025–0.001	Felder et al. 1986[c]
Great Lakes	Great Lakes, US	0.000 01–0.007	Strosher and Hodgson 1975
Rivers	Various locations in US	0.0003–0.30	Wypych 2004
Streams	1999-2000 US Geological Survey reconnaissance; 139 streams across US	0.01 (maximum) (0.003 median)	Kolpin et al. 2002[d]
Water; canals & marshes	Kavala, northern Greece; January 2003; 8 sites	130–870 ng/L	Grigoriadou et al. 2008
Sediment/Sludge (mg/kg)			
River sediment	Montreal, Québec; 2004	4.4	Horn et al. 2004[a]
Homogenized sludge (or primary)	Montreal, Québec; 2005	34	Barnabé et al. 2008
Press-filtered sludge (or dewatered)	Montreal, Québec; 2005	340	
Granules (dried sludge)	Montreal, Québec; 2005	19.3	
Primary sludge	Québec, Canada; 2005	4–69	Beauchesne et al. 2008
Secondary sludge	Québec, Canada; 2005	24–743	
Thickened sludge	Québec, Canada; 2005	74–111	
Digested sludge	Québec, Canada; 2005	97–149	
Dewatered sludge	Québec, Canada; 2005	64–340	
Dried sludge	Québec, Canada; 2005	19	
Sediment	Sweden; 13 samples	68–520 µg/kg	IVL SERI 2005[e]
Sludge	Sweden; 16 samples	0.11–0.18	
Air			
Open burn smoke of	Chile; 2005	67.6 ng/mg smoke	Simoneit et al. 2005

roadside litter		particles	
Open burn smoke of landfill trash	Chile; 2005	28.5 ng/mg smoke particles	
Air	Sweden; 12 samples	0.02–0.6 ng/m^3	IVL SERI 2005[e]
Biota			
Fish	Sweden; 12 samples (muscle)	5–23 µg/kg fresh weight	IVL SERI 2005[e]

nd = not detected
[a] Undisturbed snow was sampled from a green space in downtown Montreal. River water and sediment samples were collected within 2m of the shoreline of the St. Lawrence River at the downstream end of the island of Montreal. Water samples were taken from a creek that drains an industrial area on the Island of Montreal and passes through parkland (Bois-de-Liess Park, Montreal, PQ). Landfill leachate was collected from the Miron landfill site, inside the boundaries of the city of Montreal, and sampled from a pipe that delivered the leachate collected from the landfill to an aeration basin.
[b] Listed in decreasing order of population served.
[c] Sites included both industrialized and relatively non-industrialized sites involving a survey of major rivers, Chesapeake and San Francisco Bays and Lakes Huron, Michigan, Ontario and Superior. Only 7% of the water samples analyzed contained DEHA and results for sediments were unreliable due to poor recovery rates.
[d] Note that this substance was routinely detected in lab blanks.
[e] The Swedish national screening program included measurements at sites with potential point sources, diffuse sources (wastewater treatment plants), urban sites as well as background sites. A total of 125 samples were taken.

Measured concentrations in a range of media have been reported as summarized in Table 8. Horn et al. (2004) investigated the concentrations of common plasticizers (including DEHA) and their metabolites in precipitation, surface waters and river sediment near Montreal, Québec. River water and landfill leachate had the highest concentrations of DEHA, while relatively high concentrations were also measured in sediments, as would be expected given this chemical's physical and chemical properties. The river water and sediment samples were collected in the St. Lawrence River at the downstream end of the island of Montreal. The concentration of DEHA in river water reported in this study is similar to the upper end of ranges reported for monitoring studies across the United States, which also included some impacted water bodies (Kolpin et al. 2002; Wypych 2004).

In addition, DEHA has been measured in the influents, effluents and sludges of wastewater treatment plants (WWTPs) (Barnabé et al. 2008; Beauchesne et al. 2008; Harrison et al. 2006; Nasu et al. 2001; Paxeus 1996), in grey wastewater (Eriksson et al. 2003) and in landfill leachates (Horn et al. 2004; Paxeus 2000). The data from seven WWTPs in Québec are summarized in Table 8.

Barnabé et al. (2008) studied plasticizers and their degradation products in the process streams at the Montreal WWTP, which provides primary treatment with some physical-chemical removal processes. Relatively high concentrations of DEHA were measured in separate sewer system influents (10.3 mg/L in the north influent – serving a predominantly residential population, and 3 mg/L in the south influent; the influent concentration in Table 8 represents the average influent). The authors note that DEHA was strongly associated with oily solids and droplets suspended in the influent wastewaters, thus making it likely that the samples collected were inhomogeneous and that amounts of this substance in the streams at the Montreal plant

may have been over-estimated. Regardless, DEHA was present in much higher concentrations than two other more commonly used phthalate plasticizers that were also measured in the process streams. These results indicate that the sources of DEHA through urban wastewaters are significant and that DEHA must be more mobile and/or leach out of products more readily than the two other phthalate plasticizers (Barnabé et al. 2008).

Despite the significant removal rate of DEHA following primary and physico-chemical treatment (98%) at the Montreal WWTP, DEHA was measured in the effluent at 0.147 mg/L (Barnabé et al. 2008). Much of the solid materials removed could not be analyzed and therefore, it was not possible to complete a mass balance. Also, given the physicochemical nature of the treatment process and the relatively short time scale of treatment, it is unlikely that the decrease in DEHA concentration was primarily due to biodegradation. However, if one considers daily mass flows (represented by the day of sampling in 2005), then 320 kg of DEHA are released per day in the Montreal effluent and 87 kg/day are removed to the dewatered sludge (Barnabé et al. 2008).

Concentrations of DEHA were measured in the influent, effluent and sludge of six other WWTPs in Québec equipped with biological treatment systems and varying hydraulic retention times (Barnabé et al. unpublished data). The industrial contribution (overall) to influent was determined to be <5% at three of these plants (Québec City, Gatineau, Victoriaville), 49% at the Granby WWTP, 60% at the Drummondville WWTP, and was not available for the Thetford Mines WWTP. Concentrations of DEHA ranged from 0.05–8 mg/L in the influents and not detected–5.9 mg/L in effluents. DEHA was also measured in the sludges of these WWTPs with concentrations ranging from 4–743 mg/kg in primary, secondary, digested, dewatered or dried sludges (Beauchesne et al. 2008; Barnabé et al. unpublished data).

Industrial Release

The aquatic exposure of DEHA resulting from industrial activities is expected if the substance is released from industrial use to a WWTP and the treatment plant subsequently discharges its effluent to a receiving water body. The concentration of the substance in the receiving water near the discharge point of the WWTP is used as the predicted environmental concentration (PEC) in evaluating the aquatic risk of the substance. It can be calculated using the equation

$$C_{water-ind} = \frac{1000 \times Q \times L \times (1-R)}{N \times F \times D}$$

where

$C_{water\text{-}ind}$ is aquatic concentration resulting from industrial releases, mg/L
Q is total substance quantity used annually at an industrial site, kg/year
L is loss to wastewater, fraction
R is wastewater treatment plant removal rate, fraction
N is number of annual release days, days/year
F is wastewater treatment plant effluent flow, m^3/day
D is receiving water dilution factor, dimensionless

A site-specific exposure analysis was conducted for the aquatic compartment at 8 industrial sites which are identified as being involved with the highest quantities of DEHA based on the information collected from the CEPA section 71 survey (Environment Canada 2010a). These 8 sites include one DEHA manufacturer, seven DEHA industrial users and one DEHA container cleaning operation. Each site consists of one or two facilities and involves a quantity of this substance in the range of 10 000 to 10 000 000 kg per year. The selection of these sites is based on a general assumption that the quantity released is proportional to the quantity used, manufactured or transported and that these sites represent sites with the highest potential for risk.

In this site-specific exposure analysis (Environment Canada 2010b), it was assumed that the facility or facilities at each site discharge their wastewater to a local WWTP, which subsequently releases its effluent to a receiving water body. The predicted environmental concentration (PEC) in the receiving water was estimated based on the concentration in the effluent by applying a dilution factor of up to 10 depending upon the flow characteristics of the receiving water body. The concentration in the effluent was estimated based on the estimated proportional loss of the substance to wastewater, the WWTP removal efficiency and the WWTP effluent flow. The loss to wastewater from each facility was estimated to be 0.16% for DEHA manufacturers or industrial users and 0.2% for container cleaning facilities (OECD 2009). An assumption for days of operation of 250 days/year was also used in the estimation, which is typical for small or medium sized facilities. The WWTP removal rate is assumed to be zero in the case of unknown treatment and estimated by a computer model (ASTreat 2006) to be 57.1% for primary treatment and 85.4% for secondary treatment. The effluent flow of a WWTP is considered proportional to the population served and was in the range of 2 000 to 350 000 m^3 per day for the sites considered.

Based on the above assumptions, the PECs are estimated to be in the range of 0.01 to 73.13 µg/L for these 8 industrial scenarios.

Consumer Release

Monitoring data provide evidence that DEHA is being released to WWTPs and subsequently to the aquatic environment (see Table 8), which does not appear to be explained solely by industrial activities that may be releasing DEHA to WWTPs (according to the authors of those related studies). Given that there was insufficient information on quantities of DEHA-containing consumer products being used, a quantitative consumer release modelling scenario could not be developed.

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine various supporting information and develop conclusions based on a weight-of-evidence approach and using precaution as required under CEPA 1999. Lines of evidence considered include results from risk quotient calculations, as well as information on persistence, bioaccumulation, toxicity, sources and fate of the substance.

The high Canadian manufacture and importation volumes of DEHA, information on the uses of DEHA, its presence in WWTP effluents in Canada, as well as measured concentrations in the Canadian environment, indicate potential for widespread and continual release into, and occurrence in, the Canadian environment. Once released into the environment, this substance will partition mainly to sediment and soil, but will also be found in the water column either dissolved or as an emulsion.

DEHA is not expected to be persistent in air, water, soil or sediment as defined in the *Persistence and Bioaccumulation Regulations*. This substance is also not expected to bioconcentrate or bioaccumulate in aquatic organisms, based on one fish bioconcentraton study and modelled data for fish that indicate these organisms rapidly metabolize this substance. The majority of acute toxicity studies report no acute effects at the water solubility limit, which is much less than 1 mg/L. In one case where acute lethality was observed in rainbow trout, the toxic mechanism may have been a physical effect, which is considered to be ecologically relevant. Invertebrates, on the other hand, appear to be more sensitive to this substance in the water column, given the available acute and chronic toxicity data. There is concern over the potential for chronic toxicity to aquatic organisms (chronic LOEC <0.1 mg/L) as available toxicity data indicate that adverse effects may occur at chronic exposure levels near or below the estimated water solubility limit for DEHA. The substance is metabolized in fish and excreted fairly rapidly, thus there is not as much concern for potential chronic toxicity in fish.

Given the concern for chronic toxicity to invertebrates, a PNEC was derived by dividing the chronic toxicity (MATC) value of 0.035 mg/L (the most sensitive valid experimental value) for *D. magna*, by an assessment factor of 10 to extrapolate from the laboratory to a predicted no-effects concentration in the field. The resulting PNEC value is 0.0035 mg/L. This PNEC value is the same value recommended in the OECD SIDS assessment document (OECD 2005), which used the same study, chronic value, and assessment factor as above.

A risk quotient analysis integrating monitoring results and realistic estimates of exposure in Canada with toxicity information (calculated as PEC/PNEC) was performed for the water and sediment media to determine whether there is potential for ecological harm in Canada. The PECs and associated risk quotients for Canadian scenarios are summarized below in Table 9.

Table 9. Summary of risk quotient analyses for DEHA

Exposure scenario	Predicted environmental concentration (PEC; mg/L or mg/kg)	Measured environmental concentration (PEC; mg/L or mg/kg)	Risk Quotient (PEC/PNEC or measured concentration / PNEC)
Aquatic – water (PNEC = 0.0035 mg/L)			
Montreal, Québec; river water[a]		0.014	4
Montreal, Québec; creek water[a]		0.006	1.7
Montreal, Québec; melted snow[a]		0.15	43
Montreal, Québec; landfill leachate[a]		0.025	7.2

Montreal, Québec; tap water[a]		0.0051	1.5
Montreal, Québec; WWTP effluent[b,d]		0.015	4.3
Quebec, Québec; WWTP effluent[c,d]		0.065	19
Gatineau, Québec; WWTP effluent[c,d]		0.59	169
Drummondville, Québec; WWTP effluent[c,d]		n/a	n/a
Granby, Québec; WWTP effluent[c,d]		0.0033	0.9
Victoriaville, Québec; WWTP effluent[c,d]		0.1	29
Thetford Mines, Québec; WWTP effluent[c,d]		0.0003	0.1
Scenario 1 – manufacture[e]	0.023		6.6
Scenario 2 – container cleaning[e]	0.002		0.6
Scenario 3 – manufacture[e]	0.073		21
Scenario 4 – industrial use[e]	0.011		3.2
Scenario 5 – industrial use[e]	0.004		1.1
Scenario 6 – industrial use[e]	0.001		0.2
Scenario 7 – industrial use[e]	0.001		0.2
Scenario 8 – industrial use[e]	0.000 01		0.003
Aquatic – sediment (PNEC = 5.6 mg/kg)			
Montreal, Québec; bed sediment St. Lawrence River[a]		4.4	0.8

[a] Horn et al. (2004); the St. Lawrence River site was at the downstream end of the Island of Montreal with river water and sediment samples taken within 2 m of the shoreline; the creek drained an industrial area on the Island of Montreal, which passed through parkland. Undisturbed snow was sampled from a green space in downtown Montreal. Landfill leachate was collected from the Miron landfill site and sampled from a pipe that delivered the leachate collected from the landfill to an aeration basin.
[b] Barnabé et al. (2008); PEC calculated using the measured concentration in effluent (Table 8) with an applied dilution factor of 10 to account for dilution by the receiving water.
[c] Barnabé et al. (unpublished data); n/a = not available as DEHA was not detected in effluents. PEC calculated using the measured concentration in effluent (Table 8) with an applied dilution factor of 10 to account for dilution by the receiving water.
[d] Listed in decreasing order of population served.
[e] Site-specific industrial release and exposure analysis developed in this report; see section on Ecological Exposure Assessment.

Measured concentrations of DEHA in river water and creek water near Montreal, compared with the PNEC, resulted in risk quotients of 4 and 1.7, respectively. PECs were also calculated using the measured concentration of DEHA in effluents at a number of WWTPs in Québec, and dividing by a dilution factor of 10 to estimate the concentration in the receiving water (similar to the approach used in the site-specific industrial release scenarios). These analyses resulted in risk quotients of concern (those above 1) of 4.3 to 169 in the receiving environment near four of the WWTPs monitored. Therefore, harm to aquatic organisms is possible at these sites.

The model-based, site-specific industrial release and exposure analyses yielded PECs of 0.00001 to 0.073 mg/L for eight sites handling the highest quantities of DEHA. The risk quotients for these eight sites ranged from 0.003 to 21 for this substance, with 4 sites having a risk quotient above 1. Therefore, harm to aquatic organisms is anticipated at these sites.

Based on the previously estimated $CTV_{sediment}$ of 55.7 mg/kg dry wt, and dividing by an assessment factor of 10 to account for lab to field extrapolation and interspecies variation, the PNEC for sediment-dwelling organisms would be 5.6 mg/kg. Using the sediment concentration data of 4.4 mg/kg reported by Horn et al. (2004) for a site near Montreal, Québec, a risk quotient for sediment at this site is calculated to be 0.8.

The information above indicates that DEHA has the potential to cause ecological harm in Canada.

Uncertainties in Evaluation of Ecological Risk

In assessing the bioaccumulation potential of this substance, limited empirical data were available. The exposure concentration used to calculate the experimental bioaccumulation value is above the substance's water solubility limit. However, even the adjusted value would be significantly below the bioaccumulation criteria of BCF ≥ 5000. Also, the rate of metabolism for DEHA is relatively fast, indicating that this substance is not likely to be bioaccumulative.

Uncertainties related to the potential for exposure of aquatic organisms to this substance are recognized, although measured concentrations near Montreal and predicted environmental concentrations based on effluent concentrations at a number of WWTPs in Québec are comparable. Overall industrial contributions to influents of the WWTPs were estimated, but it is not known the degree to which DEHA concentrations in effluents can be attributed to either industrial activities or consumer use of products containing DEHA. Industrial exposure models were also used to compliment the empirical concentration data available, with realistic worst-case assumptions being made when determining potential releases.

The significance of soil and sediment as important media of exposure is not well addressed by the toxicological effects data available, which apply primarily to pelagic aquatic exposures. DEHA partitions to sediment and ends up in wastewater biosolids, as demonstrated by reported concentrations in wastewater sludge from WWTPs in Québec. Therefore, there is the potential for this substance to be transferred to soil through land application of biosolids, if the biosolids are not sent to landfill or incinerated.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media and Food

Multimedia intake estimates were derived primarily from available North American data. Upper-bounding estimates of daily intake of DEHA from environmental media and food for all age groups are summarized in Appendix 2. The total estimates ranged from 1.6 μg/kg body weight (kg-bw) per day for breast milk-fed infants (0 – 6 months old) to 143 μg/kg-bw per day for children (5 – 11 years old). Food was estimated to be the highest contributor to the total intake for most age groups except for breast milk-fed and formula-fed infants[2] (0 – 6 months old).

Environmental Media

Limited data on measured concentrations of DEHA in environmental media in Canada or elsewhere were identified. While release of DEHA to the environmental media was reported to be mainly to air (refer to Release to the Environment section), its persistence in air is considered low based on its physical and chemical properties and estimated half-life of less than or equal to 2 days (refer to Table 5b).

One U.S. study was identified for measured concentrations of DEHA in indoor air and dust sampled in 120 homes in Cape Cod, Massachusetts. The maximum concentration of DEHA in indoor air reported in this study was 66 ng/m^3 (6.6 x 10^{-5} mg/m^3). The study also reported a median DEHA concentration of 9.0 ng/m^3 with the limit of detection (LOD) of 3 ng/m^3 (Rudel et al. 2003). Both maximum and median values reported in this study were higher than the value reported in another study (2.0 ng/m^3), which measured the level in office building indoor air in 1986 (Wescheler and Shields 1986). The higher value of 66 ng/m^3 was used in the estimate of total daily intake.

DEHA is relatively insoluble in water and is expected to partition to sediment in the aquatic environment as predicted by fugacity modelling (Table 4). It is also expected to strongly adsorb to suspended solids and sediment based upon high estimated log K_{oc} values, therefore it is expected that concentrations of DEHA in drinking water available for consumption by the general population would be low.

Two Canadian studies were identified to report measured concentrations of DEHA in drinking water; one study monitored levels in tap water (Horn et al. 2004) while the other reported bottled water measurements (Cao 2008). A higher concentration was measured in tap water (5.1 μg/L) than in bottled water, however, the limit of detection (LOD) and sample number were not clearly indicated in the report. In the first study, tap water was sampled continuously

[2] Non-formula fed infants refers to infants who are given solid foods instead of breast milk or infant formula.

from the Montreal water distribution system. A total of 44.3 L, at a flow rate of 1 L per hour was passed through 100 mL of HPLC grade chloroform. No further details are provided in the study report (Horn et al. 2004). In the bottled water study, a total of 11 samples were analyzed, and included both carbonated and non-carbonated water, contained in glass, polycarbonate, and PET bottles. DEHA was not detected in any of the samples, with a method detection limit of 17 ng/L (± 4.78%).

Other studies of tap water, bottled water, and finished water from a water treatment plant in the U.S. and elsewhere reported concentrations of DEHA ranging from 0.010 to 1.7 μg/L (Sheldon and Hites 1979; US EPA 1994; Schmid et al. 2008). Some of the bottled water measurements were done under extreme conditions such as exposure to sunlight at 60°C, where the maximum concentration of DEHA measured was 0.046 μg/L (Schmid et al. 2008).

DEHA was also measured in surface water in Canada at concentrations ranging from 5.8 to 150 μg/L (Horn et al. 2004). In the U.S. and Europe, the reported maximum concentration of DEHA in surface water ranged from 0.03 to 300 μg/L (Gusten et al. 1974; Strosher and Hodgson 1975; Sheldon and Hites 1978, 1979; Lin et al. 1981; DeLeon et al. 1986; Penalver et al. 2001; Kolpin et al. 2002; Wypych 2004). The U.S. Geological Survey in 1999 – 2000 reported a maximum DEHA concentration of 10 μg/L with a median concentration of 3 μg/L in 139 streams across the U.S. (Kolpin et al. 2002).

The highest DEHA concentration in drinking water from the two Canadian studies (5.1 μg/L) was used to derive a conservative estimate of total daily intake. This was also the highest DEHA level in drinking water within the dataset. This level is below an international drinking water guideline for DEHA of 80 μg/L established by the World Health Organization (WHO 1996), a maximum contaminant level (MCL) in drinking water of 400 μg/L established by the U.S. EPA (US EPA 1998), and the State drinking water guideline established in Maine at 292 μg/L (Maine CDC 2008). The U.S. FDA Code of Federal Regulations Title 21; 21CFR 165.110 also lists DEHA with an allowable level of 400 μg/L in bottled water (US FDA 2003).

No studies were identified for DEHA concentrations in soil, while one U.S. study reported its concentration in dust in 119 homes. The maximum DEHA concentration was reported to be 391 μg/g with a median of 5.97 μg/g, minimum of 0.935 μg/g, and a method reporting limit of 0.4 μg/g (Rudel et al. 2003). One Canadian study was identified which reported the concentration of DEHA in river sediment at 4.4 mg/kg (Horn et al. 2004). Elsewhere, DEHA was detected, but not quantified in sediment samples collected from Lake Jusan and bottom material samples collected from Mutsu Bay, Japan (Ishizuka 1995).

The maximum concentration of DEHA at 391 μg/g in dust from the U.S. study was used as a surrogate for the concentration of DEHA in soil in the estimates of daily intake.

Food

Migration of DEHA from food wrapping PVC films has been extensively studied in various countries, especially for fatty foods such as cheese and meat (Till et al. 1982; Castle et al. 1987; MacLeod and Snyder 1988; Mercer et al. 1990; Gilbert et al. 1988; Page and Lacroix 1995;

Petersen et al. 1995; Petersen and Briendahl 2000; Goulas et al. 2000; Fankhauser-Noti et al. 2006; Fankhauser-Noti and Grob 2006; Goulas et al. 2008). In a limited number of the studies identified, the concentration of DEHA was measured in various food items in μg/g (mg/kg). These studies were included in the critical dataset for estimating food intake of DEHA (Startin et al. 1987; Harrison 1988; Page and Lacroix 1995; Goulas et al. 2000; Petersen and Briendahl 2000; Fankhauser-Noti and Grob 2006). It has been shown that migration of DEHA to food increases with length of contact time, temperature of storage and exposure (including microwave heating), exposed contact area between food and PVC film wrapping containing DEHA, DEHA content in the wrapping, as well as fat and moisture content of food (Startin et al. 1987; Harrison 1988; Page and Lacroix 1995; OECD 2005).

In order to derive estimates of daily intake of DEHA from food for the Canadian general population, results reported in a Canadian study (Page and Lacroix 1995) were selected over measurements in food from other countries. In the absence of Canadian data, data from other countries were included in the estimates.

The Canadian study by Page and Lacroix (1995) reports levels of various plasticizers present in selected food packaging and as migrants in various food items. The food items selected were those which were likely to be packaged in plasticized materials, including foods packaged in flexible plastic film by the retailer or manufacturer, or in bottles or jars with plasticized cap or lid liners. Also included were food items which may have contacted plasticized transport tubing or storage tanks. A total of 260 samples of selected packaged food items, as well as 99 samples of available food composites, were sampled between 1987 and 1989, and were analyzed for phthalate plasticizers and DEHA. An analysis was done both on a whole food basis (concentration of DEHA reported in μg/g food) and exposed surface area basis (μg/cm^2). DEHA concentrations in non-contacting or 'core' samples, obtained for several of the meat and chicken samples, were less than 0.4 μg/g in all cases, while higher concentrations were measured close to the surface (Page and Lacroix 1995). PVC film used for food packaging in the survey was analyzed and found to contain 11.5 to 20.5 % DEHA with an average of 16.3 %.

Fourteen types of cheese in contact with food wrapping film were analyzed in this Canadian study, of which the highest value was measured at 310 μg/g (cheddar-marble) and used for the estimate of intake of DEHA from cheddar cheese. Low concentrations of DEHA were reported in food items with low fat content, such as fruits and vegetables. Similarly, for most food items which are not likely to be packaged in PVC film wrappings, such as eggs, nuts and seeds, sugar, soft drinks and alcohols, DEHA was generally not detected. Not all detection limits were reported in the study; for these cases the lowest detected value was assumed to be the detection limit; food items in which no DEHA was detected were assumed to contain a concentration equivalent to half of the detection limit (Page and Lacroix 1995).

Concentrations of DEHA in baby food and infant formula were reported in a Danish study (Petersen and Briendahl 2000). It was described that processing equipment such as plasticized tubing, surface coatings and gaskets used in the food industry which are in direct contact with foods were identified as potential sources for exposure. In this study, different types of ready-to-use baby food (11 samples) or formulae (11 samples) were sampled in retail shops and analyzed before their last day of use. For baby food, different types of baby food such as fruit, cereals, rice mixed with fruit or meat mixed with vegetables were represented. DEHA was not

detected in any of the samples. In infant formula which were sold either as a powder to be mixed with water or ready-to-use, DEHA was measured in two samples at 0.02 and 0.05 μg/g. The highest detection limit of 0.03 μg/g for baby food and the higher value of 0.05 μg/g for infant formula were used to derive the intake estimates in the absence of Canadian data (Petersen and Briendahl 2000).

For environmental media and food exposures, food constitutes the main portion of the estimated total daily intake of DEHA for most age groups, with estimates of exposure ranging from 0.6 μg/kg-bw per day for formula-fed infants (0 – 6 months old) to 142 μg/kg-bw per day for children age 5 – 11 years old. No data were identified for DEHA in breast milk.

Uncertainties

Confidence in the estimates of exposure to DEHA in environmental media is moderate. Although there were limited Canadian data on the concentration of DEHA in environmental media, the values used to estimate daily intake were from recent measurements in Canada and the U.S and where the highest concentrations reported.

High uncertainty is associated with the estimates of exposure from food due to the limitation of the data and lack of recent Canadian food survey information. Where available, Canadian data were used to derive food intake estimates of DEHA relevant to the Canadian context, however, it was recognized that higher concentrations of DEHA were reported in some food items in other countries, mainly the U.K. (Goulas et al. 2000; Harrison 1988; Startin et al. 1987). While using the lower values from the Canadian study may result in underestimating exposure, there are indications that both the concentration of DEHA in packaging materials and the number of food packaging materials that contain DEHA may have decreased since the time these studies were conducted; in which case, total intake of DEHA via migration from food packaging would have also decreased.

In addition, other reported estimates of daily intake of DEHA from food are lower than the estimates derived in the current assessment, ranging approximately from 1 to 100 μg/kg-bw per day (Fromme et al. 2007: Petersen and Breindahl 2000; Loftus et al. 1994; Tumura et al. 2001, 2003; OECD 2005). In these studies, the intake of DEHA was determined via analysis of whole diet samples and/or measurement of urinary metabolites.

While the derived food exposure estimates are likely conservative, it is recognized that there are uncertainties associated with the lack of data identifying levels of DEHA in consumer prepared food stored in contact with PVC film, as well as microwave reheated precooked meals and prepared foods from supermarkets and take-away food outlets, which were not included in the derivation of exposure estimates. It is recognized that such an approach taken may have underestimated actual exposure to the general population of Canada.

Consumer Products

The main use of DEHA is as a plasticizer in PVC plastics. As a consequence, DEHA may be found in various consumer products. According to information submitted under section 71 of

CEPA 1999 as well as from publically available sources, DEHA is present in heavy-duty hand cleanser, lubricant, and auto interior protectant (Clorox 2008; K-G Packaging 2008; Jig-A-Loo Canada Inc. 2009; Environment Canada 2010a). It is also used in cosmetics and personal care products (CNS 2010).

Based on the physical and chemical properties of DEHA (low vapour pressure, high molecular weight, high K_{ow}, and low water solubility), inhalation of DEHA is not likely, and the main route of exposure during use of consumer products is considered to be via dermal contact. Inhalation during use of pump spray products is not considered likely based on the particle size (CIR 2006). Absorption of DEHA through the skin is expected to be limited, based on consideration of its physical and chemical properties (e.g., molecular weight).

Cosmetic and Personal Care Products

Exposure to DEHA from use of personal care products, including cosmetics, was estimated using ConsExpo 4.1 (ConsExpo 2006) for the products found in the CNS database (CNS 2010). Only dermal exposure was estimated for the majority of products based on the physical and chemical properties of DEHA as well as the types of products known to contain DEHA. A summary of upper-bounding estimates of chronic exposure for use of each product, as well as the aggregated exposure estimates for use of multiple products are presented in Table 10, while the details of the exposure scenarios are summarized in Appendix 3. Exposure estimates were based on the ranges of upper-bounding concentrations reported to CNS (CNS 2010). Aggregated exposure estimates were summarized for adult females and males separately to capture the difference in product types used specifically by each gender (i.e., after-shave lotion for adult male). For rinse-off products such as hair shampoo, hand cleanser and shaving cream, retention factors were applied as appropriate (refer to Appendix 3 for details).

For frequently used products contributing to chronic exposure to DEHA, such as skin moisturizers and facial and eye makeup, the predominant contribution to total exposure was from skin moisturizers (0.2–13.6 mg/kg-bw per day) for both adult females and adult males. The upper-bounding estimate of combined use of multiple products resulted in an applied dose of 0.7–22.0 mg/kg-bw per day for an adult female and 0.6–18.6 mg/kg-bw per day for an adult male (Table 10). Overall, the upper-bounding estimates of combined use of multiple cosmetic and personal care products by an adult resulted in an applied dose of 0.6–22.0 mg/kg-bw per day.

Table 10. Summary of chronic dermal exposure estimates of DEHA from use of personal care products for an adult [a]

Product	Concentration range (%)[b]	Frequency (/yr)	Chronic external applied dose (mg/kg-bw per day)
Skin Moisturizer – body	0.1 – 6	730	0.23 – 13.56
Face Cream	0.1 – 10	730	0.03 – 3.38
Foundation – female only	0.3 – 17.9	365	0.03 – 2.02
Hair Conditioner	0.1 – 3	260	0.05 – 1.63

Concealer – female only	10 – 30	365	0.21 – 0.63
Deodorant	0.3 – 1	473	0.06 – 0.22
Makeup remover – female only	1 – 3	730	0.07 – 0.21
Hair Shampoo	0.1 – 1	260	0.02 – 0.20
After shave lotion – male only	0.1 – 3	365	0.02 – 0.51
Perfume	1 – 3	730	0.03 – 0.08
Hand cleanser	0.3 – 1	730	$1.4 – 4.8 \times 10^{-3}$
Shaving Preparation – male only	0.1 – 3	365	$3 – 9 \times 10^{-4}$
Total – female			**0.74 – 21.95**
Total – male			**0.58 – 18.59**

[a] Modelled using ConsExpo 4.1 (RIVM 2006) with default assumptions unless otherwise noted in Appendix 3.
[b] Concentrations of DEHA as reported on the Cosmetics Notification System (CNS 2010)

For cosmetic and personal care products that are used less frequently, such as bath preparation and body shimmer, exposure was estimated per use of product (Table 11). The highest upper-bounding exposure estimates resulted from the use of bath preparation products, which ranged from 0.2 to 7.2 mg/kg-bw of applied dose per use.

Table 11. Summary of acute dermal exposure estimates of DEHA by an adult from use of cosmetic and personal care products[a]

Product	Concentration range (%)[b]	Acute external applied dose (mg/kg-bw)[c]
Bath Preparation	0.1 – 30	0.24 – 7.2
Body shimmer	1 – 3	0.49 – 1.5
Sunscreen	0.84 [d]	1.2
Hair perm lotion (including fixing lotion)	0.1 – 1	0.11 – 1.1
Face mud mask	1 – 3	0.28 – 0.85
Manicure Preparation (nail polish)	0.1 – 10	$7x10^{-4} – 7x10^{-2}$

[a] Modelled using ConsExpo 4.1 (RIVM 2006) with default assumptions unless otherwise noted in Appendix 3.
[b] Concentrations of DEHA as reported on the Cosmetics Notification System unless otherwise noted (CNS 2010).
[c] Acute external applied dose is reported per application.
[d] July 2010 Personal communication from Therapeutic Products Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced.

Low exposure was estimated via other routes of exposure for two products containing DEHA, lipstick and nail polish (CNS 2010). Both products contained DEHA at 0.1–10% (w/w). Oral exposure from use of lipstick resulted in a chronic external applied dose of $5.6x10^{-4}$ to $5.6x10^{-2}$ mg/kg-bw per day, inhalation exposure from use of nail polish resulted in a range of mean event concentrations from $5.2x10^{-6}$ to $5.6x10^{-4}$ mg/m^3 during use of the product. Details of these exposure estimates are summarized in Appendix 3b (oral route) and Appendix 3c (inhalation route).

Other Consumer Products

Based on the available information, exposure to DEHA via consumer product use was estimated for the products summarized in Table 12, which were identified as being sold on the Canadian market (Clorox 2008; K-G Packaging 2008; Jig-A-Loo Canada Inc. 2009; Environment Canada 2010a; 2010 Personal communication from Risk Management Bureau, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; 2010 unreferenced).

Exposure estimates during use of these consumer products were derived using ConsExpo 4.1 (ConsExpo 2006). The resulting estimates of dermal exposure (external), as well as concentrations in air where applicable, are summarized in Table 12. The inputs and assumptions used in ConsExpo 4.1 modelling of each of the consumer product scenarios are provided in Appendix 4.

Table 12. Summary of estimated air concentration, inhalation dose and dermal exposure (external) to DEHA during use of consumer products

Consumer Product	DEHA in product (% w/w)	Inhalation		Dermal – external exposure (mg/kg-bw)
		mean event concentration (mg/m^3)	Dose (mg/kg-bw)	
Tapping lube	30 - 60 %[a]	N/A	N/A	0.21 - 0.43
Heavy duty hand cleanser	< 1 %[b]	N/A	N/A	0.26
Auto interior protectant – wipe	< 1 %[c]	N/A	N/A	0.13
Auto interior protectant – spray	< 1 %[d]	$1.5x10^{-3}$	$3.6x10^{-6}$	0.004

Abbreviation: kg-bw, kilogram body weight.
[a] K-G Packaging 2008
[b] Jig-A-Loo Canada Inc. 2009
[c] Personal communication from Risk Management Bureau, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; 2010 unreferenced)
[d] Clorox 2008

Two available reports from the Danish Environmental Protection Agency (Danish EPA) indicate other types of products may contain this substance (Danish EPA 2002; Danish EPA 2008).

DEHA was measured at 38 and 40 mg/kg in one of four clay samples tested for oven baking in Denmark. DEHA was the only softener detected as a minor component in this sample while phthalates were detected at 16–24 % in all four clay samples (Danish EPA 2002).

Another study conducted by the Danish EPA analyzed marker pens, glitter glue, acrylic paint, and shrink plastic as potential sources of exposure for children during use of hobby products for children. DEHA was detected in marker pens from a discount store, at 0.35 mg/g (orange) and 0.32 ± 0.02 mg/g (purple) with the detection limit ranging from 0.01–0.1 mg/g. DEHA

was not detected in the other 13 markers analyzed. The maximum exposure was estimated to be 0.00012 mg/kg-bw per day via oral intake by sucking fingers or on the marker pen (Danish EPA 2008).

Exposure estimates were not derived for these products as it is highly uncertain as to whether they are available on the Canadian market.

Uncertainties

Confidence in the modelled estimates of exposure from consumer products including cosmetic and personal care products is moderate to high, as the information on concentrations of DEHA in these products is Canadian-specific. There may be other DEHA containing consumer products which were not taken into consideration in this assessment due to limited availability of Canadian-specific information.

It is recognized that there is uncertainty associated with the use of models to estimate general population exposure to DEHA from the use of cosmetics. A biomonitoring study measuring levels of a DEHA metabolite in urine was identified, however, it was not considered to be representative of current general population use of DEHA containing products in Canada (EPFMA 1998). The default parameter values in ConsExpo (ConsExpo 2006) were based on upper-bound scenarios which consider a general population who frequently uses consumer products. It is recognized that there is uncertainty associated with the use of model parameters which are not Canadian-specific, however, derived estimates of consumer exposure are likely to be conservative.

Health Effects Assessment

A summary of available health effects information is presented in Appendix 5.

The U.S. Environmental Protection Agency (US EPA 1994[3]) has classified DEHA as a Class C (possible human) carcinogen. A classification of Group 3 (not classifiable as to its carcinogenicity to humans) was given by the International Agency for Research on Cancer (IARC 1982, 2000). These classifications were based principally on observations of increased liver tumours in female mice, but not in either sex of rats. The European Commission (1999) considered the cancer risk of environmental exposure to DEHA to be minimal. DEHA is being reassessed under the IRIS program of the US EPA (1994).

Chronic toxicity and carcinogenicity studies of DEHA were conducted in Fischer 344 rats and B6C3F1 mice. In mice, depression of growth rates was observed at the two highest doses (3222 and 8623 mg/kg-bw per day in females, 2659 and 6447 mg/kg-bw per day for males) for

[4]A toxicological review of DEHA is not available with the US EPA IRIS summary.

both sexes after oral administration of DEHA in the diet for 104 weeks (NTP 1982; US EPA 1984b; Kluwe et al. 1985). Except for liver tumours (carcinomas and adenomas combined) in females at both dose levels, no histopathological changes were observed. Carcinogenic responses were not observed in other organs examined. No treatment-related increase in tumours, neoplastic nodules or hepatocellular carcinomas was found in rats after 106 weeks of exposure (Hodge et al. 1966; NTP 1982; Kluwe et al. 1985). No tumours were reported in a 1-year study with dogs after oral administration of 0.2% DEHA in the diet (equivalent to 50 mg/kg-bw per day, based on Health Canada 1994) (stated as unpublished data; no other information provided in Hodge et al. 1966). There was also no evidence of carcinogenicity in a skin painting study using C3H mice dermally administered 0, 0.1, or 10 mg of DEHA (equivalent to 0, 3.3, or 333 mg/kg-bw per day, based on Health Canada 1994) in 0.20 mL of acetone once weekly until death (maximum total of 293 or 30667 mg/kg-bw lifetime doses in males, and 327 or 33667 mg/kg-bw lifetime doses in females, respectively, based on Health Canada 1994) (Hodge et al. 1966; US EPA 1994). No other non-neoplastic effects were observed even at the highest dose administered; however, few endpoints were measured (average cage weights, gross autopsies). As such, this study is inappropriate for use in risk characterization. The lowest oral critical non-neoplastic effect level in a chronic toxicity study was 1500 mg/kg-bw per day based on decreased rate of body weight gain in Fischer 344 rats after 106 weeks administration of DEHA in the diet (NTP 1982). Long-term inhalation studies using DEHA were not identified.

It is proposed that the liver tumourigenicity of DEHA is a function of peroxisome proliferation (Reddy et al. 1980). Peroxisome proliferators (PP) are a diverse group of compounds that cause hepatic hypertrophy and hyperplasia, increased peroxisome number and volume, induction of palmitoyl-CoA (Coenzyme A) oxidation and lauric acid hydroxylase activity, and lead to rodent liver tumourigenesis after chronic high-dose administration (Dirven et al. 1992; DeLuca et al. 2000; Klaunig et al. 2003). Data have been presented suggesting that the stimulation of DNA synthesis by PPs may be more important in the carcinogenic process than is the proliferation of peroxisomes *per se* (Marsman et al. 1988; Yang et al. 2007). Other proposed mechanisms whereby PPs induce liver tumours in rodents include oxidative stress, increased growth of preneoplastic lesions, and inhibition of apoptosis (IARC 1995; Lake 1995). Liver enlargement induced by PPs results from both hyperplasia and hypertrophy. The hyperplastic response is seen within the first few days of PP administration (review by Lock et al. 1989). The available evidence indicates that peroxisome proliferation in rodent liver is mediated by activation of PP-activated receptor-α (PPARα), which is a member of the steroid hormone receptor superfamily (Klaunig et al. 2003).

The differences in sensitivity between humans, non-human primates, and rodents towards PPs have been extensively reviewed (Bentley et al. 1993; Doull et al. 1999; US EPA 2003; Peters et al. 2005). Cultured hepatocytes from these species, excluding rodents, have been unresponsive to a variety of PPs. No study specifically examining the effects of DEHA on human hepatocytes was identified. Although not all studies are consistent, PPARα expression in human liver may be much lower than that observed in mice (approximately one-tenth) (Palmer et al. 1998; Klaunig et al. 2003; Peters et al. 2005; Peters 2008). Liver biopsies from human epidemiological and volunteer studies have documented that evidence for hepatic peroxisome proliferation is not convincing (reviewed in Bentley et al. 1993).

More recently, two different transgenic PPARα-humanized mouse models have been generated demonstrating that while PPs can activate human PPARα expression, the mitogenic and hepatocarcinogenic effects do not occur (Cheung et al. 2004; Morimura et al. 2006). It was suggested that the difference in species' responses may be due to species-specific regulation of a microRNA (Shah et al. 2007; Peters 2008). It must be noted, however, that based on findings from the chronic study in both rats and mice, it is not entirely clear that the observed tumours are solely due to peroxisome proliferation because this effect has been observed in both rats and mice, but tumours have only been noted in female mice due to oral administration of DEHA. In a report published by the Office of Prevention, Pesticides and Toxic Substances (OPPTS), the US EPA concluded that although humans possess functional PPARα and its receptor can be activated by PPs, humans appear to be refractory to the important events associated with the induction of liver tumours through this mechanism (US EPA 2003).

A number of short-term repeated dose studies have shown DEHA induces changes indicative of peroxisome proliferation in the liver of rats when the compound is orally administered at doses generally higher than 300 mg/kg-bw for 7 to 42 days. Dose-dependent changes included reduced body weight gain, increased relative liver and kidney weights, reduction in serum triglyceride, cholesterol levels, and phosphotidylcholine:phosphotidylethanolamine ratios, and increases in hepatic fatty-acid binding protein, catalase, carnitine acyl transferase, stearoyl-CoA desaturation, hepatic phospholipid levels, and 8-hydroxydeoxy-guanosine activities, as well as evidence of peroxisome proliferation (palmitoyl-CoA oxidation, cell proliferation) and hypolipidemia (Mason Research Institute 1976; Moody and Reddy 1978; Kawashima et al. 1983a, 1983b; CMA 1982a, 1986, 1989, 1995; Bell 1984; Yanagita et al. 1987; Takagi et al. 1990; Keith et al. 1992; European Commission 2000). DEHA also acts as a PP in mice via the oral route (Keith et al. 1992; CMA 1989; European Commission 2000). In these studies, changes similar to those in rats were observed; they also reported induction of fatty-acid translocase, fatty-acid transporter protein, fatty-acid binding protein in liver, and a reduction in spleen weights, as well as higher cholesterol levels in blood (CMA 1989; Motojima et al. 1998).

The lowest LOAEL for rats from short-term repeated-dose studies was based on an increase in liver weights in female Fischer 344 rats when administered 0.6% DEHA in the diet for 3 weeks (equivalent to 309 mg/kg-bw per day, based on Health Canada 1994). An increase in lauric acid 12-hydroxylase activity in male rats and peroxisome proliferation in both sexes were also observed at this dose (CMA 1986). However, no histopathological effects of the liver were noted.

Subchronic studies in rodents demonstrated similar treatment-related effects to those observed in short-term repeated dose studies. The lowest oral LOEL was found in female Fischer 344 rats (five per group) based on observations of increased lauric acid 11- and lauric acid 12-hydroxylation, an effect of peroxisome proliferation, at 282 mg/kg-bw per day (0.3% DEHA) at weeks 1 and 13 when administered DEHA in the diet for 1, 4, or 13 weeks (Lake et al. 1997). Other observations included increased palmitoyl-CoA oxidation, decreased body weights, increased relative liver and kidney weights, and hepatocellular replication at 577 mg/kg-bw and higher in rodents treated with DEHA via the oral route for 13 weeks (Smyth et al. 1951; Lake et al. 1997).

Evidence available to date indicates that PPARα-induced liver carcinogenesis is not likely to occur in humans, and that the effects reported in short-term and subchronic studies and subsequent tumours found in chronic studies related to peroxisome proliferation after exposure to DEHA would not be relevant for risk characterization to human health.

The lowest critical-effect level in a short-term oral toxicity study not directly related to peroxisome proliferation was 617 mg/kg-bw per day based on evidence of lower body weights and increased relative liver weights in male Fischer 344 rats after oral administration of DEHA for 3 weeks (CMA 1982a). A similar previously mentioned study found reduced cytoplasmic basophilia in livers along with increased relative and absolute liver weights in male Fischer 344 rats at this dose level after oral administration daily for 3 weeks (CMA 1986).

The lowest critical-effect level in a short-term dermal study was 2060 mg/kg-bw per day in rabbits. When DEHA was administered via the dermal route for 14 days, a reduction in weight gain was observed along with laboured breathing and lethargy at this dose (Hazleton Laboratories 1962). Short-term repeated-dose inhalation studies using DEHA were not identified.

The lowest critical-effect level in a subchronic oral toxicity study not directly related to peroxisome proliferation was 700 mg/kg-bw per day in rats and mice. Exposure of animals to DEHA for up to 90 days resulted in reduced body weight gain (at least 10%) for male Fischer 344 rats at this dose level (700 mg/kg-bw per day or 12500 ppm) and higher in feed for rats and 700 mg/kg-bw per day (3100 ppm) and higher in feed for B6C3F1mice. No compound-related histopathologic effects or reductions in feed consumption were noted (data not shown) (NTP 1982). Subchronic inhalation toxicity studies using DEHA were not identified.

However, it should be noted that there were no adverse effects observed in dogs after a 2-month oral administration of DEHA. The dogs (number and strain not identified) were fed 2000 mg/kg-bw per day DEHA in the diet, and had only a transient loss of appetite with no changes in blood, urine, or histopathology (Patty 1963).

The potential genotoxicity of DEHA has been assessed in a multitude of *in vitro* and *in vivo* assays. There was no indication of genotoxicity in almost all *in vitro* tests in both bacterial and mammalian cell systems (Simmon et al. 1977; US EPA 1981, 1984a, 1984c; CMA 1982b, 1982c, 1982d; Litton Bionetics, Inc. 1982a, 1982b, 1982c, 1982d; Seed 1982; Eastman Kodak Co.1984a; Microbiological Associates 1984; DiVincenzo et al. 1985; Zeiger et al. 1985; Barber et al. 1987; Galloway et al. 1987; McGregor et al. 1988; Reisenbichler and Eckl 1993; European Commission 2000). *In vivo* studies in rodents and *Drosophila* were mainly negative for genotoxicity (CMA 1982e; von Däniken et al. 1984; Woodruff et al. 1985; Shelby et al. 1993; Shelby and Witt 1995). Unscheduled DNA synthesis (UDS) studies reported positive results, but these occurred at relatively high doses in mice (single gavage dose of 2000 mg/kg-bw based on maximum tolerated dose) and rats (approximately 1401 mg/kg-bw) (Büsser and Lutz 1987; Miyagawa et al. 1995). Takagi et al. (1990) observed slight, but statistically significant increases in 8-hydroxydeoxyguanosine (8-OH-dG), an indicator of oxidative DNA damage, in Fischer

344 rat livers after oral administration of 2.5% DEHA in diet (equivalent to 1286 mg/kg-bw per day; based on Health Canada 1994). Consideration of the above mentioned available information indicates that DEHA is not likely to be genotoxic.

The potential for DEHA to adversely affect fertility has been investigated in some reproductive toxicity studies, mostly in rats. Most of these studies reported no effects on reproduction, lactation, spermatogenesis, or relative reproductive organ (uterus, ovaries, testes, epididymides, prostate, seminal vesicles) weight with reduction in maternal weight gain as an effect via the oral route (Le Breton 1962; Kang et al. 2006; Miyata et al. 2006; Nabae et al. 2006). DEHA also does not induce antiandrogenic effects similar to those observed in DEHP (Borch et al. 2002, 2006; Dalgaard et al. 2003) nor does it induce any testicular effects (NTP 1982; Kang et al. 2006; Miyata et al. 2006; Nabae et al. 2006).

Two female Crl:CD (SD) rat studies reported maternal reproductive effects as measured by increased atresia of the large follicle, decreases in currently formed corpus luteum, increases in estrus cycle length, and the presence of follicular cysts in groups fed DEHA at the mid-dose (1000 mg/kg-bw per day) and higher (Miyata et al. 2006; Wato et al. 2009). There was also a significant decrease in implantation rate and number of live embryos, and an increase in pre-implantation loss rate at the highest dose (2000 mg/kg-bw per day). Another oral study found a reduction in maternal weight gain, but also observed reduction of offspring weight gain, total litter weight, and litter size after both male and female Wistar-derived rats were administered 1080 mg/kg-bw per day of DEHA in the diet for 10 weeks prior to mating through to day 36 postpartum (ICI 1988a).

The lowest LOAEL reported for reproductive toxicity was 800 mg/kg-bw per day based on prolonged gestation period (by 1 day, but statistically significant) and decreased maternal body weight gain in a study where female Wistar rats were administered DEHA at doses of 0 to 800 mg/kg-bw per day by oral gavage from gestational day (GD) 7 to postnatal day (PND) 17 (Dalgaard et al. 2003). DEHA also induced a dose-related increase in postnatal death at 400 and 800 mg/kg-bw per day in this study. The LOAEL for developmental toxicity (postnatal death) was determined to be 400 mg/kg-bw per day. DEHA also induced a permanent decrease in surviving offspring body weight at 800 mg/kg-bw per day.

Another developmental toxicity study examining the effects of DEHA through oral exposure during gestation (0, 300, 1800, 12000 ppm) observed increases in pre-implantation foetal loss, higher incidence of skeletal variations (reduced ossification), kinked or dilated ureters, and a reduction in maternal body weight gain and food consumption in female Wistar-derived rats (ICI 1988b). The study NOAEL was at the 1800 ppm feed level (160 mg/kg bw per day) based on food consumption.

The weight of evidence from consideration of the data from Wato et al 2009. Dalsgard et al 2003 and ICI 1998b together support a lowest NOAEL of 200 mg/kg bw per day administered by gavage for developmental toxicity. Examinaton of the data set shows postnatal death is the effect of concern at 400 mg kg bw day , the next higher dose. This DEHA value of 200 mg/kg bw per day has previously been established as the study NOAEL, based on the same effects, by the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR,2008).

A summary of the critical-effect levels relevant to risk characterization for human health are presented in Table 13.

Table 13. Summary of relevant critical effect levels (LOAELs).

Endpoint	LOAEL (mg/kg-bw per day)	Critical effect(s)
Short-term repeated-dose toxicity	617 (oral)	Lower body weights, increased (relative and absolute) liver weights, and catalase activity as well as reduced cytoplasmic basophilia in the liver (CMA 1982a, 1986).
	2060 (dermal)	Decreased body weight gain, lethargy, and laboured breathing (Hazleton Laboratories 1962).
Subchronic toxicity (oral)	700	Decreased body weight gain (10%) (NTP 1982).
Chronic toxicity (oral)	1500	Decreased body weight gain (NTP 1982).
Reproductive toxicity (oral)	800	Decreased body weights and prolonged gestation period (Dalgaard et al 2003).
Developmental toxicity (oral)	400 (NOAEL = 200)	Dose-related increase in postnatal deaths (Dalgaard et al 2003; SCENIHR 2008).

Estrogenic, androgenic, and thyroid hormone activities were evaluated in several *in vitro* and *in vivo* bioassays. The estrogenic potential of DEHA was negative in the estrogen receptor (ER)-mediated luciferase (*luc*) reporter gene system in ER-*luc* male mice as well as in all tissues, including placenta and foetuses, of pregnant female mice (Ter Veld et al. 2008, 2009). There was also no significant *luc* activity observed in human breast MVLN cells *in vitro* after exposure to DEHA (Ghisari et al. 2009). An aryl hydrocarbon receptor (AhR) AhR-CALUX assay in mouse hepatoma (Hepa1.12cR) cells as well as an AR- CALUX assay in the chinese hamster ovary (CHO-K1) cells showed no treatment related effects (Krüger et al. 2008). An *in vitro* yeast two-hybrid assay was negative (Nishihara et al. 2000), and the ability of DEHA to elicit a uterotrophic response *in vivo* was also negative in ovariectomized Sprague-Dawley rats (JPIA 1998). An *in vitro* bioassay based on thyroid hormone-dependent cell proliferation (T-Screen) was positive at low potency, but this assay is not used extensively nor is it a validated assay (Ghisari et al. 2009; May 2010 Personal communication from Environmental Health Science Research Bureau to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). An *in vitro* tritiated 17ß-estradiol receptor binding study was inconclusive (Jobling et al 1995).

The oral metabolism of DEHA has been characterized in humans where six male volunteers were given DEHA (~0.5 mg/kg-bw) in corn oil. 2-Ethylhexanoic acid (2- EHA) was the

only metabolite found in the plasma and it appeared soon after dosing in all subjects; the peak concentrations of approximately 1.6 μg/cm^3 occurred between 1 and 2 hours. The rate of elimination from plasma was also rapid and was estimated to be around 0.42 hour, corresponding to an elimination half-life of 1.65 hours. The measured urinary metabolites accounted for a total of 12.1% (range, 8.7 to 16%) of the administered dose with the main metabolite being 2-EHA (average of 8.6% fraction of administered deuterium label), the majority being eliminated within 24 hours (Loftus et al. 1993). The authors suggested that the pre-systemic hydrolysis of DEHA by the gastrointestinal (GI) tract in humans and subsequent hepatic oxidation processes result in the formation 2-EHA, which then appears in the plasma.

Ingested DEHA showed similar metabolism in a range of animal species. Radioactivity from orally administered ^{14}C-labelled DEHA was widely distributed in tissues of rodents for 6-12 hours after exposure, but was not retained (Takahashi et al. 1981; Bergman and Albanus 1987). Absorption studies in mice indicated rapid absorption after dosing with peak levels reached at 1 and 3 hours. The contents of the GI tract contained DEHA, mono-(2-ethlyhexyl)adipate (MEHA), and 2-ethylhexanol (2-EH) (CMA 1984). Takahashi et al (1981) suggested that when DEHA is orally administered, a significant amount is hydrolyzed in the stomach prior to absorption. DEHA did not migrate to endocrine organs, bone, lymphatic tissues, cartilage, connective tissue, muscle, respiratory tract, or nervous tissue in the mouse or rat (Bergman and Albanus 1987). Disposition studies in mice indicated that 95-102% (effectively 100%) of the administered radioactivity from a single dosing was eliminated in the urine, feces, and expired air within 24 hours post-dosing (CMA 1984). Approximately 90% was excreted in the urine and 7-8% in the feces. In rats, only 0.5% of the oral dose remained after 96 hours. Monkeys also eliminated the majority of radioactivity in the urine, but had a higher fecal elimination than did mice (CMA 1984). The half-life of DEHA was 6 minutes in rat small intestinal mucous membrane homogenates and a small percentage of the administered dose (0.3% in rats) was excreted in the bile and entered enterohepatic circulation (Takahashi et al. 1981; Eastman Kodak Co. 1984b; Bergman and Albanus 1987). However, the authors did not provide justification for this claim.

There are species differences in the biotransformation of DEHA. Urinary metabolites from mice consisted of 2-EHA, its glucuronide conjugate, 5-hydroxy-EHA, and the diacid diEHA (CMA 1984). In rats, DEHA is cleaved into the MEHA and adipic acid and less glucuronide-conjugated metabolite than in mice (Takahashi et al. 1981; CMA 1984; Bergman and Albanus 1987). Monkeys excrete mainly MEHA, 2-EH, 2-EHA, and glucuronide-conjugated metabolites (CMA 1984; BUA 1996), whereas humans excrete mainly 2-EHA (Loftus et al. 1993).

The confidence in the health effects database in for DEHA is considered to be moderate to high, as there was adequate information to address effects that may be of concern and to identify critical endpoints based on oral exposures. However, there were limited studies via the dermal route and no repeated-dose or long-term studies via the inhalation route.

Characterization of Risk to Human Health

Carcinogenicity was considered in the health effects assessment for DEHA, because the substance had been classified as a possible human carcinogen by the US EPA (1994). Increased incidences of liver tumours were observed in female mice in lifetime studies. However, these were seen only at mid and high concentrations (3222 and 8623 mg/kg-bw per day) of DEHA (NTP 1982). Consideration of the available information on genotoxicity indicates that DEHA is not likely to be genotoxic. Although a mode of action has not been fully elucidated, reviews on rodent tumours suggest that the increased incidence of liver tumours in female mice following treatment with DEHA results from a mechanism that does not operate in humans, i.e., a mechanism based on enhanced activation of peroxisome proliferators (Cattley et al. 1998; Klaunig et al. 2003). Based on this evidence, as well as the fact that mouse liver tumours were observed only at high doses and evidence that DEHA is not likely to be genotoxic, a threshold approach is used to assess risk to human health.

Analysis of the literature and assessments by other international agencies (US EPA, OECD) confirmed that the critical effects of exposure to DEHA were developmental. The lowest LOAEL for developmental toxicity is 400 mg/kg-bw per day based on a dose-related increase in postnatal deaths. This LOAEL is based on mortality, which implies that there would be other less severe effects due to treatment occurring below this dose prior to death that were not measured in this or any other study identified (Dalgaard et al. 2003). Based on the lack of reported effects in fetuses and/or developing rats at doses lower than 400 mg/kg-bw per day, the NOAEL of 200 mg/kg-bw per day is used for the characterization of risk to human health in this assessment.

The lowest dermal LOAEL, based on one repeated-dose study, was 2060 mg/kg-bw per day when DEHA was administered to rabbits for 14 days. The only other reported dermal repeated-dose study (chronic, Hodge et al. 1966) was not suitable for risk characterization.

The main contributor in the estimate of total daily intake of DEHA is expected to be food for most age groups in the general population. Comparison between the lowest NOAEL for developmental effects at 200 mg/kg-bw per day with the highest upper-bounding intake estimate (0.14 mg/kg-bw per day) results in a margin of exposure (MOE) of 1400. This MOE is considered to be adequately protective of human health, taking into account the uncertainties in the databases on exposure and effects.

The general population may also be exposed to DEHA during the use of consumer products containing this substance. The principal route of such exposure is considered to be dermal contact based on its physical and chemical properties as well as the types of products containing this substance.

The chronic internal dose of DEHA from use of cosmetic and personal care products may be estimated by applying a dermal absorption factor to the externally applied dose. Preliminary results from a Health Canada *in vitro* dermal absorption study indicated that less than 1% of the applied amount of DEHA was passed through the skin and detected in the receptor fluid from an application of a roll-on deodorant, while a higher portion was found to be bound in skin (November 2010; Personal communication from Environmental Health Research Science

Bureau to Existing Substances Risk Assessment Bureau; unreferenced). Although CIR also indicates that less than 1% of DEHA is likely to be absorbed through skin based on its solubility, no supporting experimental data is provided (CIR 2006). Therefore, while dermal absorption of DEHA is expected to be low based on its physical and chemical properties (low water solubility and high K_{ow}), given the uncertainty associated with the skin-bound portion, a dermal absorption of 10% is considered appropriate and adequately conservative for use in this assessment. A value of 10% for dermal absorption is also in agreement with the predicted value estimated using the method by Kroes et al. (2007), which is based on substance specific physical and chemical properties (molecular weight, K_{ow}, and water solubility) (Kroes et al. 2007).

Applying a dermal absorption value of 10% to the estimated external applied dose for daily use of cosmetic and personal care products containing DEHA (0.6–22.0 mg/kg-bw per day) results in a chronic internal dose estimated to range from 0.06 to 2.05 mg/kg-bw per day. Comparison between the NOAEL for developmental effects of 200 mg/kg-bw per day with the estimate of potential exposure from daily use of cosmetic and personal care products (0.06–2.2 mg/kg-bw per day) results in MOEs ranging from 91 to 3300. MOEs in the lower end of the range are not considered to be adequately protective of human health, considering the severity of effect (postnatal death) at the next highest dose in the reproduction and developmental effects database , as well as the uncertainties in the health effects and exposure databases.

Use of other cosmetic and personal care products that are not used on a daily basis (e.g, bath salts, nail polish, body shimmer) resulted in exposure estimates ranging from $7x10^{-4}$ to 7.15 mg/kg-bw per application. A 2-week dermal study on rabbits was used as a surrogate for acute critical effects in the absence of an acute dermal study. Comparing the short-term (2 weeks) dermal LOAEL from this study (2060 mg/kg-bw per day) to the exposure estimates from infrequent use of cosmetic and personal care products resulted in MOEs of 300 to 2 900 000. These MOEs are considered to be adequately protective of human health, taking into account uncertainties in the health effects and exposure databases.

Use of other consumer products such as auto protectants and heavy-duty hand cleansers resulted in exposure estimates ranging from 0.004 to 0.43 mg/kg-bw per application. Comparison of the LOAEL from the rabbit dermal study (2060 mg/kg-bw per day) to the upper-bound estimates of the range of exposure estimates during the use of the consumer products containing DEHA resulted in MOEs ranging from 4800 to 515 000. Thus, based on a “per event” use of these consumer products, the resulting MOEs are considered to be adequately protective of human health, taking into account the uncertainties in the databases on exposure and effects.

Uncertainties in Evaluation of Risk to Human Health

This screening assessment does not include a full analysis of the mode of induction of effects, including cancer, of DEHA. The available toxicity dataset is essentially limited to animal studies. In addition, there is no route-specific information available concerning reproductive toxicity and developmental toxicity via the dermal or inhalation routes and route-to-route

extrapolation is therefore required. Additionally there are no studies by any route of administration on immunotoxicity or neurodevelopmental toxicity of DEHA. Thus, critical-effect levels determined in this screening assessment are limited by the toxicity database and by uncertainties in the interpretation of the biological significance of effects, including uncertainties in the interpretation of intraspecies and interspecies variation.

Confidence in the exposure estimates for environmental media and food is moderate to high. because concentrations of DEHA in environmental media used to derive exposure estimates were based on North American studies. Higher uncertainty is associated with food estimates in the absence of recent Canadian food survey data. Based on the available information, the estimated total daily intake may underestimate or overestimate actual exposures of the general population in Canada to DEHA.

Uncertainty in the modelled estimates of exposure from consumer products is moderate based on the Canada-specific information on presence and concentration of DEHA in products. However, there is uncertainty in the use of default values that are not specific to Canada in the consumer exposure model. Overall, a wide range of MOEs resulted from estimates of exposure during the use of consumer products containing DEHA including cosmetic and personal care products. Additional product-specific information would reduce uncertainty associated with exposure.

There is uncertainty associated with the selection of a dermal absorption value of 10%. Preliminary results from an *in vitro* dermal absorption study indicated low transfer of DEHA through skin into a receiver solution, but high levels of residues bound to the skin and may translocate with time into the systemic compartment. There is additional uncertainty as the *in vitro* dermal absorption study data is limited to one type of product (deodorant) while DEHA is found in various other consumer products e.g body lotion that could result in greater dermal exposures . However, the use of 10% dermal absorption is considered appropriate when the physical and chemical properties of DEHA are taken into account. It is noted that10% is also the absorption value estimated using the Kroes method (Kroes et al. 2007). This method is based on the maximum flux at which a substance can cross the skin when it is maintained in a saturated solution on the surface. Considering DEHA is not at a saturated concentration in cosmetic and personal care products, use of the maximum flux may overestimate dermal absorption. On the other hand, transdermal accelerant properties of certain chemicals have been demonstrated to increase rates of absorption; therefore, the estimated dermal absorption may also be an underestimated value for some cosmetic and personal care products with formulations that possess such properties.

Conclusion

Based on the information presented in this final screening assessment, it is concluded that DEHA is entering or may be entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. DEHA does not meet the criteria for persistence or bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

On the basis of the potential inadequacy of the margins between estimated exposures to DEHA and critical-effect levels, it is concluded that DEHA is a substance that is entering or may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that DEHA meets one or more criteria under section 64 of CEPA 1999.

This substance will be considered for inclusion in the Domestic Substances List inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment, and, where appropriate, the performance of potential control measures identified during the risk management phase.

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Appendix 1. Robust Study Summary

Chronic toxicity of DEHA to *Daphnia magna* (Felder et al. 1986)

No	Item	Weight	Yes/No N/A	Specify Details
1	**Reference: Felder et al. (1986)**			
2	Substance identity: CAS RN	N/A	N	
3	Substance identity: chemical name(s)	N/A	Y	Dioctyl adipate or di(2-ethylhexyl) adipate
4	Chemical composition of the substance	2	Y	Structure given
5	Chemical purity	1	Y	Commercial-grade & [^{14}C]carbonyl-labelled material
6	Persistence/stability of test substance in aquatic solution reported?	1	Y	
	Method			
7	Reference	1	Y	
8	OECD, EU, national, or other standard method?	3	Y	ASTM procedures
9	Justification of the method/protocol if a non-standard method was used	2	N/A	
10	GLP (good laboratory practice)	3	N/A	
	Test organism			
11	Organism identity: name	N/A	Y	*Daphnia magna*
12	Latin or both Latin and common names reported?	1	Y	
13	Life cycle age / stage of test organism	1	Y	First-instar daphnids (< 24 h old)
14	Length and/or weight	1	N/A	
15	Sex	1	N/A	
16	Number of organisms per replicate	1	Y	Ten; all treatments and controls conducted in quadruplicate
17	Organism loading rate	1	N	Not reported, but assume according to ASTM procedures
18	Food type and feeding periods during the acclimation period	1	N	Not reported, but assume according to ASTM procedures
	Test design / conditions			
19	Test type (acute or chronic)	N/A	Y	Flow-through chronic

20	Experiment type (laboratory or field)	N/A	Y	Lab
21	Exposure pathways (food, water, both)	N/A	Y	Water
22	Exposure duration	N/A	Y	21 days
23	Negative or positive controls (specify)	1	Y	Solvent control (although 'solvent' not reported for chronic study, it was indicated that [^{14}C]DEHA in acetone was used in the bioconcentration study)
24	Number of replicates (including controls)	1	Y	All treatments and controls conducted in quadruplicate
25	Nominal concentrations reported?	1	Y	
26	Measured concentrations reported?	3	Y	Mean measured concentrations were 92.1% of nominal and averaged (±1 SD) 0.014(±0.003 SD), 0.024 (±0.006 SD), 0.052 (±0.006 SD), 0.087 (±0.020 SD), and 0.18 (±0.020 SD) mg/L.
27	Food type and feeding periods during the long-term tests	1	Y	15 to 30 m/L of a *S. capricornutum* suspension three times daily and 2 mL of trout chow suspension once daily
28	Were concentrations measured periodically (especially in the chronic test)?	1	Y	Days 0,4,7, 14 and 21
29	Were the exposure media conditions relevant to the particular chemical reported? (e.g., for the metal toxicity - pH, DOC/TOC, water hardness, temperature)	3	Y	Well water (aerated, filtered and disinfected by UV exposure) was used with a hardness of 250±25 mg/L, an alkalinity of 350±25 mg/L, a pH of 8.1 to 8.3, dissolved oxygen from 6.2 to 8.6 mg/L, and a specific conductance of 700 $\mu\Omega^{-1}$/cm.
30	Photoperiod and light intensity	1	N	Not reported, but assume according to ASTM procedures
31	Stock and test solution preparation	1	N	Not reported, but assume according to ASTM procedures
32	Was solubilizer/emulsifier used, if the chemical was poorly soluble or unstable?	1	N	
33	If solubilizer/emulsifier was used, was its concentration reported?	1	N/A	
34	If solubilizer/emulsifier was used, was its ecotoxicity reported?	1	N/A	
35	Monitoring intervals (including observations and water quality parameters) reported?	1	Y	
36	Statistical methods used	1	Y	MATC reported

	Information relevant to the data quality			
37	Was the endpoint directly caused by the chemical's toxicity, not by organism's health (e.g. when mortality in the control >10%) or physical effects (e.g. 'shading effect')?	N/A	Y	No indication by authors that observed effects were due to physical effects.
38	Was the test organism relevant to the Canadian environment?	3	Y	
39	Were the test conditions (pH, temperature, DO, etc.) typical for the test organism?	1	Y	
40	Do system type and design (static, semi-static, flow-through; sealed or open; etc.) correspond to the substance's properties and organism's nature/habits?	2	Y	
41	Was pH of the test water within the range typical for the Canadian environment (6–9)?	1	Y	
42	Was temperature of the test water within the range typical for the Canadian environment (5–27°C)?	1	Y	
43	Was toxicity value below the chemical's water solubility?	3	Y	Based on water solubility (0.78 mg/L) determined as part of this study. Based on measured concentrations reported (see line 26), the lower concentrations and the MATC reported in this study are within a factor of ten of acceptable water solubility estimates, as determined in this assessment report.
	Results			
44	Toxicity values (specify endpoint and value)	N/A	Y	MATC range = 0.024 to 0.052 mg/L based on statistical analyses of adult mean length, survival and young adult per adult per reproduction day.
45	Other endpoints reported – e.g., BCF/BAF, LOEC/NOEC (specify)?	N/A	Y	
46	Other adverse effects (e.g., carcinogenicity, mutagencity) reported?	N/A	N	
	Score:	**97.1**		
	Environment Canada reliability code (1,2 or 3):	**1**		
	Reliability category (high, satisfactory, low):	**High confidence**		

Appendix 2. Upper-bounding estimates of daily intake of DEHA by various age groups of the general population in Canada

Route of exposure	Daily intake (µg/kg-bw per day)							
	0–0.5 years[a,b,c]			0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
	Breast milk fed[a]	Formula fed[b]	Not formula fed[c]					
Ambient air[i]	0.002	0.002	0.002	0.005	0.004	0.002	0.002	0.002[c]
Indoor air[j]	0.016	0.016	0.016	0.035	0.027	0.015	0.013	0.011
Drinking water[k]	N/A	0.54	0.20	0.23	0.18	0.10	0.11	0.11
Food and beverages[l]	N/A	0.64	20.95	139.73	141.68	94.52	104.95	76.73
Soil[m]	1.58	1.56	1.56	2.52	0.82	0.20	0.17	0.16
Total intake	1.58	2.77	22.67	142.35	142.60	94.76	105.16	76.93

[a] No data were identified on concentrations of DEHA in breast milk.

[b] Assumed to weigh 7.5 kg, breathe 2.1 m^3 of air per day, drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed), and ingest 30 mg of soil per day (Health Canada 1998).

[c] For exclusively formula-fed infants, intake from water is synonymous with intake from food. The concentration of DEHA in water (5.1 µg/L) used to reconstitute formula was based on the level reported in drinking water in Canada (Horn et al. 2004). No data on concentrations of DEHA in formula were identified for Canada while the maximum concentration of DEHA in infant formula was reported to be 0.05 µg/g in Denmark (Petersen and Breindahl (2000). Approximately 50% of non-formula-fed infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990).

[d] Assumed to weigh 15.5 kg, breathe 9.3 m^3 of air per day, drink 0.7 L of water per day, and ingest 100 mg of soil per day (Health Canada 1998).

[e] Assumed to weigh 31.0 kg, breathe 14.5 m^3 of air per day, drink 1.1 L of water per day, and ingest 65 mg of soil per day (Health Canada 1998).

[f] Assumed to weigh 59.4 kg, breathe 15.8 m^3 of air per day, drink 1.2 L of water per day, and ingest 30 mg of soil per day (Health Canada 1998).

[g] Assumed to weigh 70.9 kg, breathe 16.2 m^3 of air per day, drink 1.5 L of water per day, and ingest 30 mg of soil per day (Health Canada 1998).

[h] Assumed to weigh 72.0 kg, breathe 14.3 m^3 of air per day, drink 1.6 L of water per day, and ingest 30 mg of soil per day (Health Canada 1998).

[i] No Canada-specific data on concentrations of DEHA in ambient air were identified. The calculation was based on the maximum concentration in indoor air identified in a U.S. study, 66 ng/m^3 (Rudel et al. 2003). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[j] No Canada-specific data on concentrations of DEHA in ambient air were identified. The calculation was based on the maximum concentration in indoor air identified in a U.S. study, 66 ng/m^3 (Rudel et al. 2003). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[k] Based on the maximum concentration of DEHA found in drinking water in Canada, 5.1 µg/L (Horn et al. 2004).

[l] Based on studies measuring DEHA in food, presumed to have migrated from food wrapping (Startin et al. 1987; Harrison 1988; Page and Lacroix 1995; Petersen and Briendahl 2000). In order to derive estimates of daily intake of DEHA from food for the Canadian general population, results reported in a Canadian study (Page and Lacroix 1995) were selected over measurements in food from other countries. In the absence of Canadian data, data from other countries were included in the estimates. When DEHA was measured but not detected, half of the limit of detection (LOD) was used. If no LOD was provided, the lowest detected level of DEHA in that food category was taken as the LOD. The following values were used for each food item:

Dairy products: Cheese – cheddar, marble (310 µg/g; highest value amongst cheddar): cheddar, old (190 µg/g; cheddar, mild (120 µg/g)); processed cheese and cottage cheese (not detected) (Page and Lacroix 1995).

Fats: Cooking fats, salad oil (not detected); magarine (not detected) (Page and Lacroix 1995).

Fruits and fruit products: Pineapples (not detected); grapes (0.4 µg/g); plums and prunes – fresh (0.34 µg/g); watermelons (0.8 µg/g), citrus fruit – canned, citrus juice – fresh, citrus juice – canned, apples – raw, apple products – canned, bananas, cherries – fresh, grape juice – bottled, peaches – fesh, pears – fresh, pears – canned, melons, strawberries and blueberries (Page and Lacroix 1995). Grapefruits (3 µg/g) (Startin et al. 1987).

Vegetables: Red cabbage (1.3 µg/g), sweet pepper (3.1 µg/g), lettuce (1.2µg/g), mushroom (0.4 µg/g), broccoli (not detected), potatoes (not detected), cucumber (not detected), baked beans – cans (not detected), beets – plastic bags, cans (not detected) (Page and Lacroix 1995).

Cereal products: White bread, whole wheat bread, wheat flour, rolls and biscuits, cakes, cookies, crackers, cereals, rice, pasta - dry (not detected),rolls and biscuits (1 ug/g), danish pastry and doughnuts (22 µg/g), pancakes (0.1 µg/g), spinach pie – cold (160 µg/g), pizza – cold (12 µg/g), muffins (0.53 µg/g), rice – dry (1 µg/g) (Page and Lacroix 1995).

Meat and poultry: Veal cutlets, cold cuts – luncheon meat, luncheon meat – canned (not detected), beef steak (9.1 µg/g), ground beef (9.5 µg/g), pork – fresh (3.5 µg/g), pork – cured (1.5 µg/g), chicken breast (14 µg/g), chicken breast – no skin (1.4 µg/g), cooked ham (2.2 µg/g) (Page and Lacroix 1995). Lamb – fresh (11 µg/g) (Harrison 1988).

Fish: Smoked salmon fillet (220 µg/g), freshwater fish (0.3 µg/g), canned fish and shellfish (not detected) (Page and Lacroix 1995).

Infant formula (0.05 µg/g) and baby food (0.03 µg/g) were based on the reported value in the Danish study (Petersen and Briendahl 2000).

Miscellaneous food: Garlic in oil (115 µg/g) (Frankhauser-Noti and Grob 2006).

DEHA was not detected in most food items in soups, eggs, nuts and seeds, sugar, soft drinks and alcohols (Page and Lacroix 1995). For beer, a level of 0.07 µg/g from draft beer samples was used (Harrison (1988) because the Page and Lacroix study sampled bottled beer where DEHA is not expected to be found (Page and Lacroix 1995).

In these goups, the highest value from other studies was used (0.07 µg/g for beer) (Harrison 1988).

[m] No Canada-specific data on concentrations of DEHA in soil were identified. One Canadian study reported concentrations of DEHA in river sediment at 4.4 mg/kg (Horn et al. 2004). The maximum concentration of DEHA in house dust identified in the literature, which was 391 µg/kg from a study conducted in the USA in 2003 (Rudel et al. 2003), was used to estimate the upper-bounding estimate of daily intake from soil.

Appendix 3. Upper-bounding exposure estimates to DEHA in personal care products using ConsExpo 4.1 (ConsExpo 2006)

(a) Exposure estimates via dermal route

Product	Scenario	Assumptions[a]	External applied dose[b]
Chronic Exposure Estimates			**(mg/kg-bw per day)**
Skin moisturizer	Body lotion	Concentration of DEHA = 0.1–6% Exposure frequency: 730 times per year Exposed area: 16 925 cm^2 (Health Canada 1995) Amount product applied: 8 g[d]	0.226–13.6
Face cream (antiwrinkle preparation, barrier cream)	Face cream	Concentration of DEHA = 0.1–10% Exposure frequency: 730 times per year Exposed area: 637 cm^2 (Health Canada 1995) Amount product applied: 1.2 g[d]	0.0338–3.38
Foundation	Foundation	Concentration of DEHA = 0.3–17.9% Exposure frequency: 365 times per year Exposed area: 637 cm^2 (Health Canada 1995) Amount product applied: 0.8 g	0.0338–2.02
Hair conditioner	Hair conditioner	Concentration of DEHA = 0.1–3% Exposure frequency: 260 times per year Exposed area: 1.55E3 cm^2 (Health Canada 1995) Retention factor of 10% was applied[c] Amount product applied: 54 g[d]	0.054–1.63
Facial makup-concealer	Foundation	Concentration of DEHA = 10–30% Exposure frequency: 365 times per year Exposed area: 50 cm^2 (Health Canada 1995) Amount product applied: 0.15 g	0.211–0.634
Deodorant (stick)	Deodorant	Concentration of DEHA = 0.3–1% Exposure frequency: 365 times per year Exposed area: 240 cm^2 (estimated) Amount product applied: 1.2 g[d]	0.0608–0.219
Skin cleanser – face	Makeup remover/ cleansing lotion	Concentration of DEHA = 1–3% Exposure frequency: 730 times per year Exposed area: 637 cm^2 (Health Canada 1995) Retention factor of 10% was applied[c] Amount product applied: 2.5 g[d]	0.0705–0.211
Hair shampoo	Hair shampoo	Concentration of DEHA = 0.1–1% Exposure frequency: 260 times per year Exposed area: 1.55E3 cm^2 (Health Canada 1995) Retention factor of 10% was applied[c] Amount product applied: 20 g	0.020–0.20
After shave lotion	After shave lotion	Concentration of DEHA = 0.1–3% Exposure frequency: 365 times per year Exposed area: 319 cm^2 (Health Canada 1995) Amount product applied: 1.2 g	0.0169–0.507
Perfume stick	Deodorant	Concentration of DEHA = 1–3% Exposure frequency: 730×/year	0.0282–0.0846

Product	Scenario	Assumptions[a]	External applied dose[b]
		Exposed area: 20 cm^2 (estimated) Amount product applied: 0.1 g[d]	
Hand cleanser	Skin cleanser	Concentration of DEHA = 0.3–1% Exposure frequency: 730 times per year Exposed area: 910 cm^2 (Health Canada 1995) Retention factor of 1% was applied[c] Amount product applied: 1.7 g[d]	0.0014–0.0048
Shaving cream	Shaving cream	Concentration of DEHA = 0.1–0.3% Exposure frequency: 365 times per year Exposed area: 305 cm^2 (Health Canada 1995) Retention factor of 1% was applied[c] Amount product applied: 2 g	0.00028–0.00085
Acute Exposure Estimates			**(mg/kg-bw per event)**
Bath salts	Bath preparation (salt-cube)	Concentration of DEHA = 0.1–30% Exposed area: 16 925 cm^2 (Health Canada 1995) Retention factor of 0.1% was applied[c] Amount product applied: 16 925 g	0.238–7.15
Body shimmer		Concentration of DEHA = 1–3% Exposure frequency: 10 times per year Exposed area: 8.37×10^3 cm^2 (Health Canada 1995) Amount product applied: 3.5 g	0.494–1.48
Sunscreen	Sunscreen lotion	Concentration of DEHA = 0.84 %[e] Exposure frequency: 75 times per year Exposed area: 16 925 cm^2 (Health Canada 1995) Amount product applied: 9.7 g[d]	1.15
Hair perm lotion	Hair waving preparation	Concentration of DEHA = 0.1–1% Exposure frequency: 4 times per year Exposed area: 637 cm^2 (Health Canada 1995) Retention factor of 10% was applied[c] Amount product applied: 80 g	0.113–1.13
Face mud mask	Face pack	Concentration of DEHA = 1–3% Exposure frequency: 104 times per year Exposed area: 637 cm^2 (Health Canada 1995) Retention factor of 10% was applied[c] Amount product applied: 20 g	0.282–0.846
Manicure preparation (nail polish)	Nail polish	Concentration of DEHA = 0.1–10% Exposed area: 4 cm^2 (Health Canada 1995) Amount product applied: 0.05 g	0.000705–0.0705

[a] All assumptions were ConsExpo default assumptions (RIVM 2006) unless otherwise noted. In addition, the following assumptions were applied to all scenarios:
- body weight of 70.9 kg for an adult
- uptake fraction of 1 was used to account for external applied dose
- exposure type of "direct dermal contact" for instant application (ConsExpo 2006)
- concentrations of DEHA as reported on the Cosmetics Notification System (CNS 2010)

[b] Chronic external applied dose calculated through amortization over a year to estimate daily exposure dose.

[c] Retention factor was applied for rinse-off products (2006 Cosmetics Exposure Workbook, New Substances Assessment and Control Bureau, Health Canada).

[d] Calculated by multiplying the product amounts as stated in RIVM 2006 with the ratio of the surface area of the affected body surface as reported in Health Canada 1995 with that of RIVM 2006.
[e] July 2010 Personal communication from Therapeutic Products Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced.

(b) Exposure estimates via oral route

Product	Assumptions[a]	Estimated chronic exposure (mg/kg-bw per day)
Lipstick	Concentration of DEHA = 0.1–10% Exposure frequency: 1.46×10^3 times/year Exposure type: Direct intake (ConsExpo 2006) Amount product ingested: 0.01 g Body weight: 70.9 kg	Chronic external oral dose[b]: 5.64×10^{-4} – 5.64×10^{-2}

[a] All assumptions were ConsExpo default assumptions (RIVM 2006) except for the following:
- body weight of 70.9 kg for an adult
- uptake fraction of 1 was applied to account for external applied dose
- concentrations of DEHA as reported on the Cosmetics Notification System (CNS 2010)

[b] Chronic oral dose calculated through amortization over a year.

(c) Exposure estimates via inhalation route

Product	Scenario	Assumptions[a]	Estimated acute exposure (per application)
Manicure preparation (nail polish)	Nail polish	Concentration of DEHA = 0.1–10% Amount product applied: 0.05 g Uptake fraction: 100% Body weight 70.9 kg (Health Canada 1995)	Mean event concentration: 5.2×10^{-6} to 5.6×10^{-4} mg/m^3 Acute external applied does: 4.1×10^{-9} to 4.4×10^{-7} mg/kg-bw

[a] All assumptions were ConsExpo default assumptions (RIVM 2006) except for the following:
- body weight of 70.9 kg for an adult
- uptake fraction of 1 was applied to account for external applied dose
- concentrations of DEHA as reported on the Cosmetics Notification System (CNS 2010)

Appendix 4. Upper-bounding exposure estimates to DEHA in consumer products using ConsExpo 4.1 (ConsExpo 2006)

Consumer product	Assumptions	Estimated exposure
Auto interior protectant - spray	Concentration: <1% (Clorox 2008). Inhalation exposure during application of the product (e.g., from spraying) and dermal exposure after spraying as the consumer, using a cloth, wipes the product from surfaces are estimated. **Inhalation** Adapted from ConsExpo 4.1 All purpose spray cleaner (RIVM 2006) **Exposure to spray:** - Exposure duration: 15 min (estimated) - Auto interior volume: 2.4 m^3 (US EPA 1986) - Ventilation rate: 12.5 times per hour (US EPA 1986) - Mass generation rate: 0.78 g/second (RIVM 2006) - Spray duration: 1.38 minute (US EPA 1986) - Airborne fraction: 0.2 (RIVM 2006) - Weight fraction of non-volatile: 0.25 (Clorox 2008) - Density of non-volatile: 1.8 g/cm^3 (RIVM 2006) - Auto interior height: 1 m (estimated) - Inhalation cut-off diameter: 15 µm (RIVM 2006) - Inhalation rate = 16.2 m^3/day (Health Canada 1998) **Dermal** Adapted from exposure to vinyl upholstery cleaner (US EPA 1986) The mass of product on skin per event, M_{skin}, was estimated with the equation below: $M_{skin} = SA_{skin} \times FT \times \rho$ where: SA_{skin} (exposed skin area*) is 15 cm^2 (Health Canada 1995) FT (film thickness on skin) is 2.03×10^{-3} cm (US EPA 1986) ρ (density of product) is 0.99 g/cm^3 (US EPA 1986) * assumed for finger tips while wiping with a cloth after spraying; assumed that each finger tip has an area of 1.5 cm^2 (1 cm × 1.5 cm); the total fingertip area is 15 cm^2 (1.5 cm^2 × 10). $M_{skin} = (15\ cm^2) \times (2.03 \times 10^{-3}\ cm) \times (0.99\ g/cm^3)$ $M_{skin} = 0.030\ g = 30\ mg$ Dermal exposure during application was estimated with the following assumptions: WF = weight fraction of DEHA in product = 0.01 EV = number of events per day = 1 (US EPA 1986) AF = absorption factor = 1 BW = 70.9 kg (Health Canada 1998) Acute dermal exposure $= \frac{M_{skin} \times WF \times AF}{BW} = \frac{30mg \times 0.01 \times 1}{70.9kg - bw} = 0.004\ mg/kg\text{–}bw$	**Inhalation** Mean event concentration of DEHA inside the car during application of auto interior protectant = 0.002 mg/m^3 Acute dose = 3.63×10^{-6} mg/kg-bw **Dermal** Acute dose = 0.004 mg/kg-bw

Auto interior protectant – wipe	Concentration: <1% *. Dermal exposure during application of the product is estimated. **Dermal** Same approach was taken as for "auto interior protectant – spray" with the following parameters. SA_{skin} (exposed skin area; both palms): 455 cm^2 (Health Canada 1995) FT (film thickness on skin): 2.03×10^{-3} cm (US EPA 1986) ρ (density of product): 0.99 g/cm^3 (US EPA 1986) M_{skin} = (455 cm^2) × (2.03×10^{-3} cm) × (0.99 g/cm^3) M_{skin} = 0.914 g = 914 mg WF = weight fraction of DEHA in product = 0.01 AF = absorption factor = 1 BW = 70.9 kg (Health Canada 1998) Acute dermal exposure per event $= \frac{M_{skin} \times WF \times AF}{\text{BW.}} = \frac{914\text{mg} \times 0.01 \times 1}{70.9\,\text{kg}}$ $= 0.129$ mg/kg–bw * assumed for finger tips while wiping with a cloth after spraying; assumed that each finger tip has an area of 1.5 cm^2 (1 cm × 1.5 cm); the total fingertip area is 15 cm^2 (1.5 cm^2 × 10).	**Dermal** Acute dose = 0.13 mg/kg-bw
Jig-A-Clean (heavy-duty hand cleanser)	Concentration: <1% (Jig-A-Loo Canada, Inc. 2009). **Dermal** Same approach was taken as for "auto interior protectant – spray" with the following parameters. SA_{skin} (exposed skin area; both hands): 910 cm^2 (Health Canada 1995) FT (film thickness on skin): 2.03×10^{-3} cm (US EPA 1986) ρ (density of product): 1.0 g/cm^3 (Jig-A-Loo Canada, Inc. 2009) M_{skin} = (910 cm^2) × (2.03×10^{-3} cm) × (1.0 g/cm^3) M_{skin} = 1.8473 g WF = weight fraction of DEHA in product = 0.01 AF = absorption factor = 1 BW = 70.9 kg (Health Canada 1998) Acute dermal exposure per event $= \frac{M_{skin} \times WF \times AF}{BW} = \frac{1.8473 \times 10^3\,mg \times 0.01 \times 1}{70.9kg - bw}$ $= 0.26055$ mg/kg–bw	**Dermal** Acute dose = 0.26 mg/kg-bw
Tapping lube	Concentration: 30–60% (K-G Packaging 2008) **Dermal** Same approach was taken as for "auto interior protectant – spray" with the following parameters. SA_{skin} (exposed skin area*): 3 cm^2 (Health Canada 1995) FT (film thickness on skin): 15.88×10^{-3} cm (US EPA 1986) ρ (density of product): 1.06 g/cm^3 (K-G Packaging 2008)	**Dermal** Acute dose = 0.21–0.43 mg/kg-bw

	* assumed for two finger tips as a conservative estimate of unintentional contact; assumed that each finger tip has an area of 1.5 cm^2 (1 cm × 1.5 cm); the total exposed area of 3 cm^2 (1.5 cm^2 × 2). M_{skin} = (3 cm^2) × (15.88 × 10^{-3} cm) × (1.06 g/cm^3) M_{skin} = 0.0505 g = 50.5 mg WF = weight fraction of DEHA in product = 0.30–0.60 AF = absorption factor = 1 BW = 70.9 kg (Health Canada 1998) Acute dermal exposure per event WF = 0.30; $\frac{M_{skin} \times WF \times AF}{BW.} = \frac{50.5mg \times 0.30 \times 1}{70.9\,kg} = 0.214$ mg/kg–bw WF = 0.60; $\frac{M_{skin} \times WF \times AF}{BW} = \frac{50.5mg \times 0.60 \times 1}{70.9\,kg} = 0.427$ mg/kg–bw	

Appendix 5. Summary of health effects information for DEHA

Endpoint	Lowest effect levels[a] / results
Animal studies	
Acute toxicity	**Lowest oral LD_{50} (rat)** = 5600 mg/kg-bw (NTP 1982; European Commission 2000). **Other oral LD_{50}s** = 9110 mg/kg-bw (rats) (Smyth et al. 1951); 12 900 mg/kg-bw (guinea pigs) (Lefaux 1968). **Lowest inhalation LC_{50} (rat, 4 hours)** = >900 mg/m^3 (>59 ppm) (Vandervort and Brooks 1975). (Additional study using saturated DEHA vapour for 8 hours on rats reported no mortality; Smyth et al. 1951). **Lowest dermal LD_{50} (rabbit, 24 hours)** = >8670 mg/kg-bw (Kolmar Research Center 1967; Mason Research Institute 1976). **Other dermal LD_{50} (rabbit)** = 15 029 mg/kg-bw (Smyth et al. 1951).
Short-term repeated-dose toxicity	**Lowest oral LOAEL (rat) =** 309 mg/kg-bw per day based on peroxisome proliferation in both sexes, increased liver weights in females, and increased lauric acid 12-hydroxylase activity in males in Fischer 344 rats (five per sex per group) dosed at 0, 0.1, 0.6, 1.2, or 2.5% DEHA (equivalent to 0, 51.4, 308.6, 617, or 1286 mg/kg-bw per day; based on Health Canada 1994) daily in the diet for 3 weeks. Other effects observed were reduced cytoplasmic basophilia in livers of males at 617 mg/kg-bw per day (along with increased absolute and relative liver weights) and in both sexes at 1286 mg/kg-bw per day, increased mitotic activity and focal necrosis in the liver of both sexes, and significantly higher levels of microsomal proteins as well as lower body weights and cytoplasmic eosinophilia in livers of males. Male rats fed 1286 mg/kg-bw per day of DEHA had lower feed consumption compared with controls. Occasional lower body weights were also noted for male rats fed 51.4 and 617 mg/kg-bw per day DEHA (CMA 1986). **Other oral LOAELs (rat)** = 617 mg/kg-bw per day based on evidence of lower body weights in males, increased catalase activity, and liver weights at this dose (CMA 1982a). Fischer 344 rats (12 per sex per group) were administered 1, 0.1, 1.2, and 2.5% DEHA (0, 51, 617, and 1286 mg/kg-bw/day, Health Canada 1994) in diet, daily for 3 weeks followed by 2 weeks of recovery. Males at the mid and high doses had lower body weights, whereas the females were unaffected. No clinical signs of toxicity were noted. Relative liver weights were significantly higher at the mid and high doses groups and no changes were noted in the low dose group. Triglyceride levels in mid and high dose males at 1 week and high dose males at 3 weeks were significantly lower than in the control group. Catalase activity was significantly higher in mid and high dose groups beginning at week 1. Activity remained high even after recovery. Hepatocellular hypertrophy was noted in high dose males at 1 and 3 weeks. Hypertrophy was noted only in a few high dose females at 3 weeks. No lesions were found after recovery. Cholesterol levels were lower at 1 and 3 weeks, but no differences were noted at the 2 week recovery compared with controls (CMA 1982a).

	Other oral LOAELs (rat) = 514 mg/kg-bw per day based on evidence of significantly decreased plasma cholesterol levels at 2 and 4 weeks oral administration, but not at 7 weeks at this dose (Bell 1984). Upjohn:TUC rats were administered 1% DEHA (514 mg/kg-bw per day, Health Canada 1994) for 2, 4, and 7 weeks. Author suggested that plasma cholesterol synthesis was diminished by DEHA (Bell 1984). These effects were not persistent. **Other oral studies:** Several rodent studies observed non-persistent increases in liver weights, palmitoyl-CoA activity, and cell proliferation (without histopathological effects); increases in kidney weights, peroxisome proliferation, and/or hepatocellular hypertrophy (in only a few animals) at doses ranging from 6.2 to 62 mg/kg-bw per day in rodents (CMA 1989, 1995). DEHA orally administered at doses generally higher than 500 mg/kg-bw per day for 7 to 42 days produced various effects related to peroxisome proliferation (Moody and Reddy 1978; Kawashima et al. 1983a, 1983b; Takagi et al. 1990; Keith et al. 1992; Motojima et al. 1998; European Commission 2000). A 2-month study where dogs (number and strain not identified) were fed 2000 mg/kg-bw per day DEHA in their diet observed only a transient loss of appetite with no changes in blood, urine, or histopathology (Patty 1963). **Lowest dermal LOAEL** = 2060 mg/kg-bw per day based on decreased body weight gain, lethargy, and laboured breathing in male (strain not indicated) rabbits (four per group) exposed to 0, 410, or 2060 mg/kg-bw per day (5 times/week on shaved abdomen) for 2 weeks (Hazleton Laboratories 1962). The liver and kidneys were examined microscopically. One animal in the 2060-mg/kg-bw group had slightly altered cytology of the liver parenchymal cells (basophilic granulation with enlarged and hyperchromatic nuclei). No other microscopic changes were noted (Hazleton Laboratories 1962). No inhalation studies were identified.
Subchronic toxicity	**Lowest oral LOEL** = 282 mg/kg-bw per day (0.3% DEHA) based on increased lauric acid 11- (at week 1) and lauric acid 12-hydroxylation activities (at weeks 1 and 13) in female Fischer 344 rats (five per group) administered 0, 0.15, 0.3, 0.6, 1.2, 2.5, or 4.0% DEHA in diet (equal to 0, 144, 282, 577, 1135, 2095, or 3140 mg/kg-bw per day) for 1, 4, or 13 weeks. No effects were observed at 144 mg/kg-bw per day. Reduction in body weight occurred at 2095 mg/kg-bw per day and above after 4 and 13 weeks. Significant increases in liver weight were observed at 1135 mg/kg-bw per day and above after 1 week and at 577 mg/kg-bw per day after 13 weeks. Lauric acid 11-hydroxylation for the groups dosed with 282, 577, 1135, and 2095 mg/kg-bw were significantly higher than that for the control at week 1. Lauric acid 12-hydroxylation for the 282, 577, 1135, and 2095-mg/kg-bw dose groups were significantly higher than that for the control at weeks 1 and 13. Hepatocellular replication (measured by BrdU) increased during week 1 at 1495 mg/kg-bw per day, but was not

	sustained at weeks 4 and 13. Palmitoyl-CoA oxidation was higher than in the controls for 577 mg/kg-bw per day at each time period (Lake et al. 1997). **Lowest oral LOAEL (mice)** = 700 mg/kg-bw per day (3100 ppm in diet) based on evidence of weight gain depression (10% or more) for male mice at this dose. Male and female B6C3F1 mice were administered 0, 1600, 3100, 6300, 12 500, and 25 000 ppm DEHA (0, 400, 700, 1300, 2800, or 7000 mg/kg-bw per day, US EPA 1994) in the diet for 13 weeks (10 per group). Weight gain depression was 13% or more for females fed 1300 or 7000 mg/kg-bw per day. No compound-related histopathologic effects or reduction in feed consumption were observed (NTP 1982). **Other oral LOAEL (rat) =** 700 mg/kg-bw per day (12 500 ppm DEHA in diet) based on evidence of reduced weight gain in male rats (11%) at this dose. Male and female Fischer 344 rats were administered 0, 1600, 3100, 6300, 12 500, and 25 000 ppm DEHA (0, 100, 200, 400, 700, or 1500 mg/kg-bw per day, US EPA 1994) in the diet for 13 weeks (10 per group). Weight gain in female rats was decreased by 8% at the 1500-mg/kg-bw dose level, and by at least 11% in male rats at the 700-mg/kg-bw and 1500-mg/kg-bw dose levels. Neither compound-related histopathology nor a reduction in feed consumption were noted (NTP 1982). **Other oral LOAELs** = 808 mg/kg-bw per day based on liver enzyme induction (i.e. microsomal lauric acid 11- and 12-hydroxylase activities) in a 13-week mouse study (Lake et al. 1997), and 2920 mg/kg-bw per day based on reduced growth and food consumption, altered organ weight (either kidney or liver; increase or decrease not specified), and microscopic lesions observed in either the liver, kidney, or testis (specific organ not indicated) in a 13-week rat study (Smyth el al. 1951). No dermal or inhalation studies were identified.
Chronic toxicity/ carcinogenicity	**Oral studies:** Fischer 344 rats (50 per sex per dose) and B6C3F1 mice (50 per sex per dose) were administered 0, 12 000, or 25 000 ppm DEHA (equal to 0, 860, or 1674 mg/kg-bw per day in female, and 0, 697, or 1509 mg/kg-bw per day in male rats; 0, 3222, or 8623 mg/kg-bw per day in female, and 0, 2659, or 6447 mg/kg-bw per day for male mice) in the diet for 104 weeks (mice) and 106 weeks (rats). Except in the liver, where tumours (carcinoma and adenoma combined) developed in female mice, no histopathological changes were observed (NTP 1982; US EPA 1984b; Kluwe et al. 1985). Although hepatocellular carcinomas and adenomas (combined) were also increased in male mice, the US EPA noted that this combined incidence value did not differ greatly from historical controls and time-to-tumour analysis showed no significant differences between control and treated males (US EPA 1994). No treatment-related increase in tumours, neoplastic nodules, or hepatocellular carcinomas was found in rats other than a decrease in the occurrence of fibroadenomas of the mammary glands in females (see Endocrine Disruption *in vivo* and *in vitro*

	section below). **Non-neoplastic LOAEL**s = 1500 mg/kg-bw per day based on decreased body weight gain in rats; 6447 mg/kg-bw per day based on decreased body weight gain in mice (NTP 1982). **Other Studies**: Rats (strain and sex not reported) were administered 0, 0.1, 0.5, or 2.5% (equivalent to 0, 51.4, 257, or 1286 mg/kg-bw per day, based on Health Canada 1994) DEHA in diet for 2 years. No compound-related increase in tumour incidence was noted (Hodge et al. 1966). No tumours were reported in a 1-year study with dogs after oral administration of 0.2% DEHA in diets (equivalent to 50 mg/kg-bw per day; based on Health Canada 1994) (stated as unpublished data). No other information provided (Hodge et al. 1966). **Dermal study:** C3H mice were administered 0, 0.1, and 10 mg DEHA in 0.2 mL acetone (equivalent to 0, 3.3, or 333 mg/kg-bw, based on Health Canada 1994) once weekly to a 3 × 3-cm shaved area in the scapular region until death (average of 64 weeks for males; 44 weeks for females). The maximum total number of doses in a lifetime were 293 representing 30 667 mg/kg-bw in males, and 327 and 33 667 mg/kg-bw in females (based on Health Canada 1994). There were no gross or histopathological changes in the skin in any of the mice and no treatment-related significant increase in tumours in the organs examined (no detail on which organs were examined) (Hodge et al. 1966). No inhalation studies were identified.
Reproductive toxicity	**Lowest LOAEL for reproductive toxicity =** 1000 mg/kg-bw per day based on increased atresia of the large follicle, decreases in relative ovary weight and currently formed corpus luteum, increases in estrus cycle length, and the presence of follicular cysts in female Crl:CD (SD) rats exposed by gavage to 0, 200, 1000, or 2000 mg/kg-bw per day in a one-generation study (males were untreated; females treated from 2 weeks before mating until gestational day 7 or 14). There was a decrease in relative ovary weight at 2000 mg/kg-bw dose at the 2-week (but not 4 week) time point in a corresponding repeated dose study (Wato et al 2009). **LOAEL for systemic toxicity** = 1000 mg/kg-bw per day, based on a significant increase in relative liver and kidney weights with associated histopathology (eosinophilic change of proximal tube in the kidney) (Wato et al 2009). There was a reduction in body weight gain before mating in females at a 2000-mg/kg-bw dose after 4 weeks treatment with DEHA in a corresponding repeated-dose study (Wato et al 2009). **LOAEL for developmental toxicity** = 1000 mg/kg-bw per day based on a significant increase in post-implantation loss rate. There was a significant decrease in implantation rate and live embryos and an increase in pre-implantation loss rate at 2000 mg/kg-bw

	(Wato et al. 2009). **Additional Study:** **LOAEL for maternal toxicity** = 1000 mg/kg-bw per day based on disturbance of the estrous cycle and increased follicle atresia in female Crl:CD (SD) rats (10 per sex per dose) orally administered 0, 40, 200, and 1000 mg/kg-bw per day of DEHA by gavage for 28 days from 8 weeks of age (Miyata et al. 2006). **Other oral studies:** A one-generation study using (Alpk:APfSD) Wistar-derived rats where both male and females (15 males and 30 females per group) were given 0, 300, 1800, or 12 000 ppm (equal to 0, 28, 170, or 1080 mg/kg-bw per day) DEHA in the diet for 10 weeks before mating and subsequently throughout pregnancy until day 36 post partum (approximately 18–19 weeks exposure). No effects were seen on male or female fertility. At 1080 mg/kg-bw per day, there was evidence of decreased body weight gain in dams during gestation, increased (relative and absolute) liver weight in both sexes, and decreases in pup body weight gain, total litter weight, and litter size (ICI 1988a; US EPA 1994). A multigenerational study was done with rats given 100 mg/kg-bw per day of DEHA in the diet. For four successive generations, no substance-specific influence on reproduction rate, lactation, or growth was reported (no further details supplied; Le Breton 1962). No dermal or inhalation studies were identified.
Developmental toxicity	**Lowest LOAEL for developmental toxicity** = 400 mg/kg-bw per day based on a dose-related increase in postnatal deaths ($P = 0.0118$ based on linear regression analyses) in an oral study in which pregnant female Wistar rats were dosed by gavage from gestation day 7 through to lactation day 17 to 0, 200, 400, or 800 mg/kg-bw per day DEHA. Pairwise analysis (compared with control group) showed that the increase was statistically significant at 800 mg/kg-bw per day ($P < 0.05$; $P = 0.0003$, regression analysis using binomial linear model with overdispersion). A permanent decrease in offspring body weight and adrenal weight was also observed at 800 mg/kg-bw per day as well as increased relative liver weights in adult male offspring. **LOAEL for reproductive toxicity** = 800 mg/kg-bw per day based on decreased body weights and prolonged gestation period in dams (Dalgaard et al. 2003). **NOAEL** for developmental toxicity for this study is 200 mg/kg-bw per day. Additional Study: **LOAEL for developmental and maternal toxicity** = 1080 mg/kg-bw per day based on increased pre-implantation loss and slight fetal toxicity (reduced ossification and kinked or dilated ureters) and a reduction of maternal weight gain and food consumption in pregnant female (Alpk:APfSD) Wistar-derived rats (24 per dose) fed 0, 300, 1800, or 12 000 ppm (equal to 0, 28, 170, or 1080 mg/kg-bw per day) DEHA in the diet from gestational day 1 to day 22 (ICI 1988b). Although the NOAEL

	for this study (170 mg/kg-bw) is lower than the above-mentioned study (200 mg/kg-bw), it was an unpublished report, incompletely described as well as cited differently by several sources and therefore not used for risk characterization (cited as: ICI 1988 by US EPA 1992; Hodge 1991 [in BUA 1996] by IARC 2000; CEFIC 1988 by OECD 2005). No dermal or inhalation studies were identified.
Effects on the Endocrine system *in vivo* and *in vitro*	***In vivo*** **ER-mediated luciferase (*luc*) reporter assay** **Negative:** No induction of *luc* activity by DEHA in both oral and intraperitoneal (i.p.) exposure in the examined tissues, including placenta and fetuses in mice administered single doses of 0, 30, or 100 mg/kg-bw (Ter Veld et al. 2008, 2009). **Uterotrophic assay** **Negative**: Ovariectomized Sprague-Dawley rats were treated orally with DEHA by intubation with 0 or 1000 mg/kg-bw per day DEHA for 3 days. No increase in uterine weight was observed following treatment (JPIA 1998). **Other studies**: There was one effect found in the endocrine or endocrine-responsive organs of rats in the 2-year rat study conducted by Kluwe et al. (1985). There was a decrease in the occurrence of fibroadenomas of the mammary glands in female rats receiving DEHA at 860 and 1674 mg/kg-bw per day. No compound-related effects of this nature were observed in the 2-year mouse study. ***In vitro*** **ER transactivation assay** **Negative:** MVLN cells (a human breast cell line [MCF-7] that has been transfected with the firefly luciferase gene) did not produce any significant activity in the luciferase (*luc*) reporter gene system after administration of 1×10^{-10} to 5×10^{-5} M concentrations of DEHA (Ghisari et al. 2009). **AhR-CALUX Assay** **Negative:** Mouse hepatoma (Hepa1.12cR) cells at concentrations ranging from 1×10^{-10} to 1×10^{-4} M DEHA in DMSO alone and with co-treatment with 60 pM TCDD (Krüger et al. 2008). **AR-CALUX assay** **Negative**: Chinese hamster ovary (CHO-K1) cells at concentrations ranging from 1×10^{-10} to 1×10^{-4} M DEHA in DMSO alone with and without co-treatment with 25 pM R1881 (Krüger et al. 2008). **Yeast two-hybrid assay** **Negative:** DEHA did not bind to estrogen receptors (ERα) with coactivator (TIF2) in *Saccharomyces cerevisiae* Y190 up to the concentration of 1 mM (Nishihara et al. 2000). **Tritiated 17ß-estradiol receptor binding** **Inconclusive:** DEHA bound to the receptor, but did not activate the

	receptor in two human breast cell lines (ZR-75 and MCF-7). Whether this inhibitory effect was due to direct competition was not determined. Concentrations as high as 1 mM may have approached the limits of solubility and, therefore, no accurate estimations of the affinity of DEHA for the receptor could be determined (Jobling et al. 1995). **T-Screen assay** **Positive:** DEHA was administered at concentrations up to 5×10^{-5} M in GH3 cells (a rat pituitary tumour cell line) and was found to significantly stimulate cell proliferation, but at low potency. Co-treatment of GH3 cells with T3-EC_{50} (positive T3 control) potentiated the T3-induced GH3 cell proliferation compared with the T3 control indicating an additive effect (Ghisari et al. 2009).
Genotoxicity and related endpoints *in vivo*	**Micronuclei** **Negative:** B6C3F1 Mice; three daily doses by i.p. injection of 0 to 5000 mg/kg-bw (CMA 1982e; Shelby et al. 1993). **Chromosomal aberration** **Negative**: B6C3F1 mouse bone marrow; three daily doses by i.p. injection (Shelby and Witt 1995). **Covalent DNA binding** **Negative**: NMR1 female mouse liver after 4-week administration of 2090 mg/kg-bw per day of DEHA in diet (von Däniken et al. 1984). **Oxidative DNA Damage** **Positive:** Slight, but statistically significant increases in 8-hydroxydeoxy-guanosine (8-OH- dG), which is an indicator of oxidative DNA damage in liver after 1 and 2 weeks in male 6-week-old F-344 rats in the diet at concentrations of 0 to 2.5 % DEHA (1286 mg/kg-bw per day, based on Health Canada 1994) (Takagi et al. 1990). **Unscheduled DNA synthesis** **Positive:** Stimulated DNA synthesis in liver with doubling dose of 0.7 mmol/kg (378 µmol/kg-bw or 1401 mg/kg-bw) in Fischer 344 rats after single oral administration by gavage. Authors suggest that this is a 'false positive' (Büsser and Lutz 1987). **Positive:** In hepatocytes of male B63C1 mice 39 hours after a single, oral gavage administration at 2000 mg/kg-bw (dose range 0, 1000, and 2000 mg/kg-bw) (Miyagawa et al. 1995). **Dominant Lethal mutation** **Positive:** Dose-related increase in dominant lethal mutations as measured by early fetal deaths in male Harlan/ICR Albino Swiss mice (premeiotic and postmeiotic stages of spermatogenesis without controls) at the two highest doses (4.6 and 9.2 g/kg-bw) (Singh et al. 1975). **Sex-linked recessive lethal mutation** **Negative**: Male *Drosophila* sp. treated with DEHA (0 or 5000 ppm by

	injection or 0 or 20 000 ppm by feeding) resulted in 30% mortality. After treatment, males were mated and three broods were used for analysis. There was no difference in number of wild type male offspring numbers between control and treated groups (Woodruff et al. 1985).
Genotoxicity and related endpoints *in vitro*	**Bacterial tests:** ***Ames test (mutagenicity)*** **Negative:** *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538 with and without rat liver S9 activation (Simmon et al. 1977; CMA 1982b; Litton Bionetics, Inc. 1982a; Seed 1982; Eastman Kodak Co. 1984a; Zeiger et al. 1985). **Negative:** *S. typhimurium* TA98, TA100, TA1537, and TA1538 with and without rat liver S9 activation when exposed to urine from male Sprague-Dawley rats orally administered 2000 mg/kg of DEHA daily for 15 days (DiVincenzo et al. 1985). **Mammalian cell mutation** **Negative:** Mouse lymphoma L5178Y cells with and without S9 activation (CMA 1982c; Litton Bionetic, Inc. 1982b; McGregor et al. 1988). **Chromosomal aberration** **Negative:** Female Fischer 344 rat hepatocytes with and without activation **(**Reisenbichler and Eckl 1993). **Positive:** Chinese hamster ovary cells without activation at 0 and 40 to 400 µg/mL (Galloway et al. 1987). This study did not address cytotoxicity. **Sister chromatid exchange** **Negative:** Chinese hamster ovary cells with and without activation (Galloway et al. 1987; Reisenbichler and Eckl 1993). **Micronuclei** **Negative**: Female Fischer 344 rat hepatocytes with and without activation (Reisenbichler and Eckl 1993). **Unscheduled DNA synthesis (UDS)** **Negative**: Rat hepatocytes (no information on metabolic activation) (CMA 1982d; Litton Bionetics, Inc. 1982d). **Cell transformation** **Negative:** Mouse BALB/3T3 cells with and without activation at concentrations from 0 to 12.5 µg/mL (US EPA 1981, 1984a, 1984c; Litton Bionetics 1982c; Microbiological Associates 1984; Barber et al. 1987). **Cytogenetic Assay** **Negative:** Human lymphocytes at 0, 10, 50, and 100 µg/mL with and without activation (European Commission 2000).
Irritation	**Skin irritation** **No irritation**: In mice exposed weekly, uncovered, of up to 5% DEHA in acetone until death (Hodge et al. 1966); in rabbits, uncovered (Smyth et al.

	1951). **Mild irritation**: In rabbits, covered application for 24 hours (CTFA 1967). **Eye irritation:** No irritation after application of 0.1 mL DEHA into eyes of rabbits (CTFA 1967), but slight irritation with 0.5 mL application (Smyth et al. 1951).
Sensitization	**Not sensitizing:** In guinea pigs after i.p. injection of 10 males with 0.1% DEHA in oil three times per week for 3 weeks and challenged after 2 weeks (Kolmar Research Centre 1967) or in rabbits (2/4) after a neat dermal application with a 2-week challenge (Mallette and von Haam 1952).
Human studies	
Irritation	**Slight to no skin irritation:** No irritation observed after neat application of DEHA in 15–30 individuals (sex and age not reported) (Mallette and von Haam 1952). Of 151 individuals, two had skin irritation after application of product with 9% DEHA for 48 hours three times per week for 3 weeks (CTFA 1976) and slight irritation was observed in subjects administered 0.175% DEHA for 24 hours daily for 21 days (HTR 1978).
Sensitization	**Not sensitizing:** In 15–30 individuals from a neat liquid application with a challenge application after 2 weeks (sex and age not reported) (Mallette and von Haam 1952) and in 151 humans after an application of the product with 9% DEHA for 48 hours, three times a week for 3 weeks followed by a challenge application 2 weeks later with a 48-hour patch (CTFA 1976).
Metabolism	Six adult males were given 46 mg deuterium-labelled DEHA (~0.5 mg/kg-bw) in corn oil in a volunteer study. 2-EHA appeared in the plasma soon after dosing in all subjects (peak concentrations: 1.6 µg/cm^3 between 1 and 2 hours). The rate of elimination from plasma was estimated to be 0.42 hour (half-life of 1.65 hours). Urinary metabolites accounted for a total of 12.1% (range, 8.7 to 16%) of the administered dose with 2-EHA as the major metabolite (average of 8.6%). The fate of the remainder was not determined (Loftus et al. 1993).

[a] Definitions: LD_{50}, median lethal dose; LOAEL, lowest-observed-adverse-effect level; NOAEL, no-observed-adverse-effect level.