Screening Assessment for the Challenge

Hexanoic acid, 2-ethyl-

Chemical Abstracts Service Registry Number
149-57-5

Environment Canada
Health Canada

September 2011

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 hexanoic acid, 2-ethyl- (or 2-ethylhexanoic acid), Chemical Abstracts Service Registry Number 149-57-5[1]. This substance 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 Challenge. 2-Ethylhexanoic acid (2-EHA) was identified as a high priority as it was considered to pose greatest potential for exposure (GPE) of individuals in Canada and is classified by the European Commission on the basis of developmental toxicity. The substance did not meet the ecological categorization criteria for persistence, bioaccumulation potential, or inherent toxicity to aquatic organisms.

According to information reported under section 71 of CEPA 1999, 2-EHA was not manufactured in Canada in 2006 above the reporting threshold of 100 kg but was imported into the country in a total quantity ranging from 100 000 to 1 000 000 kg in 2006. The major use of 2-EHA is in the preparation of metal salts used in various applications including as drying agents in paint and inks. 2-EHA is also used to produce an ester used as a plasticizer. 2-EHA is primarily an industrial intermediate whereby the resulting derivatives are contained in the finished products.

Data were identified for 2-EHA concentrations in the Canadian environment (water and sediment), as well as concentrations in influents, effluents, and biosolids from a number of municipal wastewater treatment plants in Québec, Canada. In 2006, the majority of 2-EHA in Canada was sent to non-hazardous, off-site waste management facilities. Limited data were available regarding concentrations of 2-EHA in food.

The critical human health effect associated with exposure to 2-EHA is developmental toxicity, based on observations in experimental animals. In addition, effects on the liver and stomach and reduced body-weight gain were observed following repeated-dose exposures to 2-EHA and 2-ethylhexanol, which is metabolized extensively to 2-EHA. The margins between upper-bounding estimates of exposure from environmental media and food and consumer products (alkyd paint) and critical effect levels in experimental animals are considered adequate to address uncertainties in the health effects and exposure databases.

On the basis of the adequacy of the margins between upper-bounding estimates of exposure to 2-EHA and critical effect levels, it is concluded that 2-EHA is a substance

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that is not 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.

2-Ethylhaxanoic acid is a highly soluble substance that primarily exists in its ionized (negatively charged) form in water at environmentally relevant pHs. Empirical and modelled data demonstrate that 2-EHA biodegrades quickly in the environment and has a low potential to accumulate in the lipid tissues of organisms. Acute and chronic toxicity values indicate that the substance is moderately toxic to aquatic organisms (acute LC_{50} or EC_{50} >1.0 mg/L and <100 mg/L). Realistic estimates of exposure were determined for site-specific industrial releases and consumer releases to water. The predicted environmental concentrations in water of this substance (as well as actual concentrations measured in Canadian river water and effluents) are estimated to be below the predicted no-effect concentration for sensitive aquatic organisms, resulting in risk quotients lower than 1.

On the basis of its low ecological hazard and conservatively estimated releases of 2-EHA, it is concluded that the substance is not 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 or that constitute or may constitute a danger to the environment on which life depends. 2-EHA 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 2-EHA does not meet any 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.

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 hexanoic acid, 2-ethyl- (or 2-ethylhexanoic acid) 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 developmental toxicity. 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 2-ethylhexanoic acid (2-EHA) was determined to be a high priority for assessment with respect to human health, it did not meet the categorization criteria for persistence, bioaccumulation or inherent toxicity to aquatic organisms.

Screening assessments focus on information critical to determining whether a substance meets the criteria 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.[2]

[2] 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

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 ecological and human health sections. 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.

The ecological and human health portions of this assessment have undergone external, written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Joan Strawson (Toxicology Excellence for Risk Assessment [TERA]), Dr. Michael Jayjock (The Lifeline Group) and Dr. Chris Bevans (CJB Consulting). Additionally, the draft of this screening assessment was subject to a 60-day public comment period. Although external comments were taken into consideration, the final content and outcome of the screening 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 below.

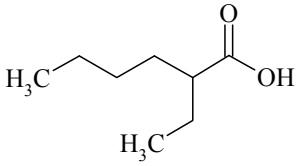
limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) Challenge Batches 1-12 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of the regulatory framework for the Workplace Hazardous Materials Information System (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

For the purposes of this document, this substance will be referred to as 2-EHA, which has been derived from the inventory name hexanoic acid, 2-ethyl. Information on the identity of 2-EHA is summarized in Table 1.

Table 1. Substance identity for 2-EHA

Chemical Abstracts Service Registry Number (CAS RN)	**149-57-5**
DSL name	**Hexanoic acid, 2-ethyl-**
National Chemical Inventories (NCI) names[a]	*Hexanoic acid, 2-ethyl-* (AICS, ASIA-PAC, ENCS, PICCS, SWISS, NZIoC, TSCA) *2-ethylhexanoic acid* (EINECS, ECL, PICCS) *Ethyl hexanoic acid, 2-* (PICCS) *2-ethylhexanoic acid* (*EHA*) (PICCS)
Other names	(±)-*2-Ethylhexanoic acid; α-Ethylcaproic acid; α-Ethylhexanoic acid; 2-Butylbutanoic acid; 2-Ethyl hexanoic acid; 2-Ethyl-1-hexanoic acid; 2-Ethylcaproic acid; 2-Ethylhexoic acid; 3; Heptanecarboxylic acid; Butylethylacetic acid; Caproic acid, α-ethyl-; Ethylhexanoic acid; NSC 8881; Octylic acid*
Chemical group (DSL Stream)	Discrete organics
Major chemical class or use	Organic – acids / esters
Major chemical sub-class	Not available
Chemical formula	$C_8H_{16}O_2$
Chemical structure	
SMILES[b]	O=C(O)C(CCCC)CC
Molecular mass	142.212 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

Experimental and estimated physical and chemical properties of 2-EHA that are relevant to its environmental fate are presented in Table 2.

Models based on quantitative structure–activity relationships (QSARs) were used to generate data for some of the physical and chemical properties of 2-EHA. These models are mainly based on fragment addition methods (i.e., they rely on the structure of the chemical) (except for WSKOW 2008). Most of the models accept only the neutral (i.e., un-ionized) form of a chemical as input (in SMILES form). However, this substance is ionic with an estimated pKa of 4.82, which means that at environmentally relevant pHs (6 to 9) it will exist largely to entirely in the ionized form (94 to 100%, respectively) as a result of giving up the proton from the hydroxyl group. The log D and water solubility values predicted using the ACD/PhysChem Suite (2009) are dependent on pH, thus accounting for the ionizing characteristics of this substance. The experimental log K_{ow} value agrees well with the log D_{ow} value at pH 3, where the neutral form predominates. At pH 6–8, the ionized (negatively charged) form predominates and, thus, the log D_{ow} values are lower. All other physical and chemical property values in Table 2 refer to the neutral form of this substance and the influence of its ionic nature on these properties is further discussed in the section on Environmental Fate.

Table 2. Physical and chemical properties for the neutral form of 2-EHA (unless otherwise indicated)

Property	Type	Value[a]	Temperature °C	Reference
Physical form	Colourless to yellow liquid			BASF 2009; Eastman 2010
Melting point (°C)	Experimental	-60*, -118.4		European Commission 2000; US EPA 2001, 2010; BASF 2009
	Modelled	38		MPBPVP 2008 (mean value)
Boiling point (°C)	Experimental*	223–229		European Commission 2000; US EPA 2002, 2010; Eastman 2010
	Modelled	234		MPBPVP 2008

Property	Type	Value[a]	Temperature °C	Reference
Density (kg/m^3)	Experimental	905–910 (0.905–0.91 g/cm^3)	20	European Commission 2000; US EPA 2010
Vapour pressure (Pa)	Experimental*	1.33–<10	20	European Commission 2000; US EPA 2001, 2010
	Modelled	12.8	25	MPBPVP 2008 (mean value)
Henry's Law constant ($Pa \cdot m^3/mol$)	Experimental*	0.29	20	EPIsuite 2008
	Modelled[b]	0.30, 0.37 (bond versus group)	25	HENRYWIN 2008
Log K_{ow} (octanol-water partition coefficient) (dimensionless)	Experimental[c]	2.6–2.7*	25	European Commission 2000
	Modelled	2.96		KOWWIN 2008
Log K_{oc} (organic carbon-water partition coefficient) (dimensionless)	Modelled[d]	1.4–1.7		KOCWIN 2008
Log D[e] (distribution coefficient) (dimensionless)	Modelled (Log D_{ow}; octanol-water)	2.6, 1.4, 0.4, -0.5 (pH 3, 6, 7, 8, respectively)		ACD/PhysChem Suite 2009
	Modelled (Log D_{oc}; Organic carbon-water)	2.8, 1.6, 0.6, 0 (pH 3, 6, 7, 8, respectively)		ACD/PhysChem Suite 2009

Property	Type	Value[a]	Temperature °C	Reference
Water solubility (mg/L)	Experimental[f]	1400 (pH ca. 3.3)	20–25	BASF 2009; HSDB 1983– ; US EPA 2010
		2000*–2500 (0.2–0.25% by weight; pH ca. 3.3)	20–25	HSDB 1983– ; Kyowa Hakko 2009; US EPA 2010
	Modelled[g]	2865	25	WSKOW 2008
		2350, 37 240, 1 000 000 (pH 3, 6, 7.5, respectively)		ACD/PhysChem Suite 2009
Other solubilities	Soluble in ethyl ether, carbon tetrachloride; slightly soluble in ethanol			HSDB 1983–
pK_a (acid dissociation constant) (dimensionless)	Modelled	4.82	25	ACD/PhysChem Suite 2009

***** Values used in modelling with EPIsuite (2008); including boiling point of 226°C and vapour pressure of 4 Pa.

[a] Values in parentheses represent the original ones as reported by the authors or as estimated by the models.

[b] Henry's Law constant is calculated using experimental values for vapour pressure and water solubility of 0.03 mmHg and 2000 mg/L (HENRYWIN 2008).

[c] The partition coefficient was determined using the OECD guideline 107 partition coefficient (n-octanol/water) flask-shaking method. According to the method, measurements should be made on ionizable substances only in their non-ionized form (free acid or free base) produced by the use of an appropriate buffer.

[d] As noted by the model, K_{oc} may be sensitive to pH and includes fragment corrections for organic acid.

[e] Log D – distribution coefficient taking into account the presence of the ionic species; represents a net amount of the neutral and ionic forms expected to partition into the lipid or organic carbon phases at a given pH.

[f] All references for water solubility values include note that it is strongly acidic or give pH ca. 3.3. At this pH, the substance is almost entirely in its neutral form (97%, according to ACD/PhysChem Suite 2009). BASF (2009) noted that it is immiscible in water. USEPA (2010) includes information submitted to HPVIS program. The value of 2000 mg/L is used to model other properties.

[g] WSKOW (2008) uses the experimental values for log K_{ow} (2.6) and melting point (-60 C). The ACD/PhysChem Suite (2009) water solubility predictions are dependent on pH, taking into account the ionizing characteristics of this substance.

In addition, the substance 2-EHA is a chiral molecule, which means it is non-super imposable on its mirror image (enantiomers). Therefore, the two enantiomers of this substance may have different biological effects.

Sources

2-EHA does not occur naturally in the environment and in North America it is produced from n-butanal (Bizzari et al. 2009). Aldol condensation of two molecules of n-butyraldehyde produces 2-ethyl-2-hexenal; upon reduction of the alkene, 2-ethylhexanal is produced. 2-Ethylhexanal is a versatile intermediate: reduction of the aldehyde produces 2-ethylhexanol, a component of plasticizers such as diethylhexylphthalate (DEHP) and diethylhexyl adipate (DEHA) and oxidation of the aldehyde produces the substance 2-EHA; see Figure 1 for details (HSDB 1983–; Billig 2003; Bizzari et al. 2009).

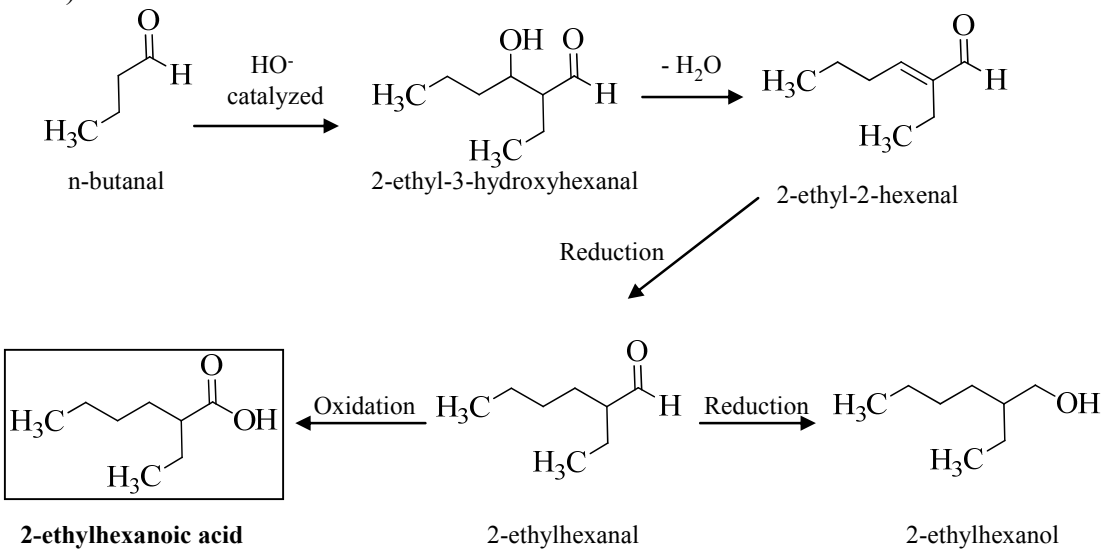


Figure 1. Synthesis of 2-EHA

Detection of 2-EHA in environmental media, foods and consumer products may also be due to leaching and/or transformation of other chemicals in finished products. For example, 2-EHA can be released from 2-ethylhexanoate salts and esters, owing to dissociation of the ions and ester hydrolysis, respectively. 2-EHA can also come from degradation of 2-ethylhexanol containing esters, which can occur in the environment as well as in humans (Figure 2).

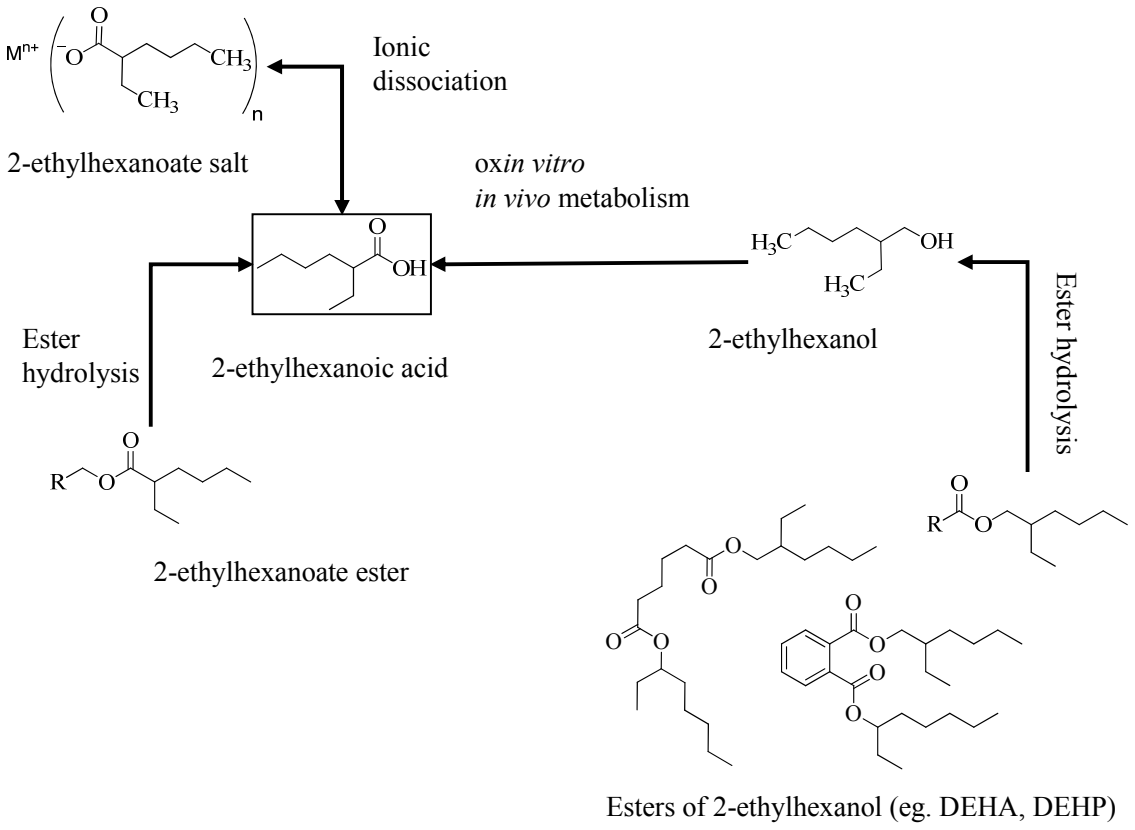


Figure 2. Sources of 2-EHA from environmental media, foods, and the use of finished products.

Based on a survey conducted under section 71 of CEPA, 1999, no Canadian companies reported manufacturing 2-EHA above the 100 kg/year threshold in 2006 (Environment Canada 2010a). Results from the same survey indicated that a total quantity between 100 000 and 1 000 000 kg of this substance was imported into Canada in 2006 (Environment Canada 2010a). Many companies submitting 2006 information also reported importing or using 2-EHA above thresholds in 2008 (Environment Canada 2010a). According to Bizzari et al. (2009), Canadian imports of 2-EHA were 500 000 kg in 2007 and 400 000 kg in 2008, primarily from the USA. 2-EHA is a high production volume (HPV) chemical in the United States (US EPA 2010) and in the European Union (ESIS c1995–2010).

Uses

The primary use of 2-EHA is in the preparation of metal salts that are used as drying agents in paints, inks, varnishes, lacquers, and enamels, and are gelling agents for hydrocarbons (CCOHS 1997; Cragg 2001; Billig 2003; Bizzari et al. 2009). The most common metal salts produced from 2-EHA in the USA are those containing cobalt, manganese, zirconium, calcium, and zinc (Bizzari et al. 2009). The lead, cobalt, manganese, and zinc salts (soluble in hydrocarbons) serve as drying agents for lacquers

and enamels. The iron, nickel, and cobalt salts are used as stabilizers for silicones. The copper salt is a fungicide for marine and other applications. On contact with water these salts are expected to dissociate into free metal and free acid moieties (US EPA 2002).

2-EHA is also used to produce esters (e.g., 2-ethylhexanoate ester) that are used in the production of plasticizers, in particular for polyvinyl butyral (PVB) resins, which are used in automotive windshields, architectural applications and vinyl products, including resilient vinyl flooring. PVB resins are also used in the production of polyvinyl chloride (PVC) (CCOHS 1997; Bizzari et al. 2009). The neopolyol esters of 2-EHA are used in the manufacture of synthetic lubricants, which are used in residential and commercial refrigerators and air conditioners with minor amounts being used in automotive applications (Bizzari et al. 2009).

2-EHA may also be used: as an oxidation catalyst during the manufacture of propylene oxide/styrene from ethylbenzene; as a catalyst promoter in the production of various polyester products including low-density polyethylene; as a catalyst in polyurethane foam; as a corrosion inhibitor in antifreeze; and in wetting agents, gel thickeners, emulsifiers, and fungicides (CCOHS 1997; Bizzari et al. 2009).

2-EHA is of particular importance in the production of alkyd resins used for baking enamels because of their exceptional stability (even at temperatures over 200°C), as well as their good weathering and aging stability. The acid and its derivatives are also used in the manufacture of lubricants, detergents, flotation aids, and corrosion inhibitors, as catalysts for polyurethane foaming, for solvent extraction, and for dye granulation (HSDB 1983–). In addition, 2-EHA may be used as a chemical intermediate in pharmaceuticals, dyes, flavourings, and fragrances (BASF 2007; Dow 2008; Eastman 2008).

According to submissions made under section 71 of CEPA 1999, approximately 386 000 kg of 2-EHA were used in Canada in 2006 (Environment Canada 2010a). Reported uses in Canada in 2006 included: as a viscosity adjustor in industrial coatings, to control ash-clogging in incinerator boilers, in mill and temper rolling oils, in flotation reagents, in industrial cleaners, lubricants and sealants, as a neutralizing agent in polyol resins ultimately used in foams, and in various other industrial applications (Environment Canada 2010a). 2-EHA was also reported as being used in products that may be available to the general public including as an ingredient in paint driers, in liquid and spray paints, and as an additive to antifreeze. In addition, 2-EHA was identified as an impurity in unsaturated polyester resins (Environment Canada 2010a).

In Canada, 2-EHA is a List 2 formulant that can be found in seven non-food pesticide products, five of which are discontinued and whose registrations will expire over the next 2 years. Four of these are antimicrobial tree dressings and one is a siding stain and preservative. One of the remaining products is approved to manufacture products only destined for export (2010 emails from Pest Management Regulatory Agency to Risk Management Bureau, Health Canada; unreferenced). According to the Canadian Cosmetic Notification System, 2-EHA is listed as an ingredient in two temporary tattoo

products (CNS 2010). 2-EHA is not listed on Health Canada's Cosmetic Ingredient Hotlist, a list of substances that are restricted or prohibited in cosmetics (Health Canada 2010).

In Canada, stannous 2-ethylhexanoate (CAS RN 301-10-0) may be used as a starting material for components that could possibly be found in coatings for cans and polystyrene trays, and zirconium 2-ethylhexanoate (CAS RN 22464-99-9) may be used as a starting material for components that could possibly be found in coatings, paint driers, and inks (2010 emails from Foods Directorate Health Canada to Risk Management Bureau, Health Canada; unreferenced). It should also be noted that according to the Food and Drug Regulations, no person shall sell any food in a package that has been manufactured from a polyvinyl chloride formulation containing an octyltin chemical (Canada 1978).

Releases to the Environment

Information reported under section 71 of CEPA 1999 indicated that for 2-EHA, approximately 1500 kg of this substance were released into the environment in 2006, primarily to air. Responses to the section 71 notice also reported a transfer of between 100 and 1 000 kg of 2-EHA as hazardous or recycled waste and approximately 23 000 kg as non-hazardous waste to off-site waste management facilities in 2006 (Environment Canada 2010a). Potential releases to water from both industrial and consumer use of products containing 2-EHA are further discussed in the Ecological Exposure Assessment section later in this report.

2-EHA may also be released from the biodegradation of plasticizers such as DEHP and DEHA (see Figure 2). Soil microbes readily oxidize 2-ethylhexanol to 2-EHA; however, the branched acid is degraded less readily (Nalli et al. 2002, 2006).

Information on the release and disposal of 2-EHA in Canada has not been reported through the National Pollutant Release Inventory (NPRI) to be above the reporting thresholds (Environment Canada 2008).

Environmental Fate

Based on its physical and chemical properties (Table 2), its ionic characteristics and varied uses, 2-EHA is expected to be found primarily in water as a result of releases to the environment. Sediment and soil would tend not to be sinks for 2-EHA if it was released to water or soil (Staples 2001).

If released to the aquatic environment, 2-EHA is expected to remain in the water column owing to its high water solubility and low estimated log K_{oc}. In addition, this substance is almost completely ionized at environmentally relevant pHs. The estimated acid dissociation constant (pK_a) of 4.82 indicates that this substance primarily exists in its ionized (base or anionic) form in water, by giving up the proton from the hydroxyl group.

The proportion of base form is greater than 94%, at a pH range of 6–9 (Environment Canada 2010b). Adsorption characteristics would be influenced by its ionic nature, and thus this substance would have limited affinity for suspended solids and would not tend to accumulate in bed sediments.

Similarly, if released to soil, this substance would have limited affinity for organic matter (which generally has a net negative charge) but could bind to some degree to positively charged soil particles (e.g., nitrogen containing complexes, metals). As a result, 2-EHA is expected to be moderately to highly mobile in soils.

When released to air, 2-EHA is not expected to remain in this compartment, and given its physical-chemical properties as an ionic substance, removal can occur due to both rain and photo-oxidation reactions. The air-water distribution is influenced by ambient pHs and 2-EHA's pK_a and would effectively result in negligible transfer of this substance into the air phase from other compartments at an environmentally relevant pH range. The low experimental Henry's Law constant suggests that the neutral form of 2-EHA would have low volatility from water and moist soil surfaces. The substance's Henry's law constant would be anticipated to be much lower than that of the neutral form under typical ambient pH conditions, given the expected predominance of the ionized form in the environment. However, its experimental vapour pressure for the neutral form is moderate suggesting that this form may volatilize to some degree from dry acidic soil surfaces.

Persistence and Bioaccumulation Potential

Environmental Persistence

Tables 3a and 3b present the available biodegradation data, which indicate the half-life of 2-EHA in water, soil and sediment is likely to be much shorter than 182 days (6 months) and that the substance is not likely to persist in those environmental compartments.

Based on the available experimental data (Table 3a), the aerobic biodegradation of 2-EHA in water and sediment appears to occur fairly quickly. Model results were consistent and also predicted that this substance would biodegrade quickly in water (Table 3b). Decreases of 4 to 50% in initial 2-EHA concentrations ranging from 5.1 mg/L to 67.8 mg/L were observed after 21 days incubation in an aerobic mixed bacterial culture obtained from trench leachate at two waste disposal sites (Francis 1982). Waggy (1994) reported an aerobic biodegradation value of 83% (theoretical biochemical oxygen demand or ThBOD at 20 days) in an activated sludge (non-acclimated) after 20 days, with concentrations of 2-EHA of 3, 7, and 10 mg/L used. Companies reporting to the European Commission (2000) also indicated that this substance is rapidly degraded, with >95 to 100% ultimate degradation reported over 3 to 5 days in an activated sludge. In all of these cases, the original studies were not obtainable and data are presented as cited in other reports.

Table 3a. Empirical degradation data for 2-EHA

Medium	Fate process	Degradation value	Degradation endpoint	Reference
Aerobic				
Water	Primary biodegradation (mixed bacterial culture from trench leachate)[a]	4	% degradation; 21 days (5.1 mg/L 2-EHA)	Francis 1982
Water	Primary biodegradation (mixed bacterial culture from trench leachate)[b]	16, 24	% degradation; 21 days (67.8 mg/L 2-EHA; nitrogen amended)	Francis 1982
Water	Primary biodegradation (mixed bacterial culture from trench leachate)[b]	50	% degradation; 21 days (with acclimation, 59.5 mg/L 2-EHA)	Francis 1982
Water	Ultimate biodegradation (activated, non-acclimated sludge)[c]	60, 76, 83	$\%ThBOD_{5,10,20\ days}$[d] (2.44 g O_2/g 2-EHA)	Waggy 1994
Water	Ultimate biodegradation (activated sludge)	>95, 100	% degradation; 5 days (COD[e]) and Zahn-Wellens test, 3 days (TOD)	European Commission 2000
Anaerobic				
Water	Ultimate biodegradation (anaerobic digester sludge)	92.3	%COD average removal; 15 days (8200 mg/L 2-EHA)	Yap et al. 1992
Water	Ultimate biodegradation (anaerobic digester sludge)	98	% removal; 2 days; chemical analysis (1 mg/L 2-EHA)	Chua and Chen 1995
Water	Ultimate biodegradation (various digested sludge)	~100	% mineralization; 12 days; (36 g 2-EHA)	Mosche 2004
Sediment	Ultimate biodegradation (soft clay, deep river sediment)	>98	% removal; 15 days; chemical analysis (2.3 g/L 2-EHA)	Chua et al. 1998, 2001

[a] At a low-level radioactive waste disposal site in Maxey Flats, Kentucky; as cited in Syracuse Research Corporation's biodegradation file; measured concentrations, pH 7, 28°C.
[b] At a low-level radioactive waste disposal site in West Valley, New York; as cited in Syracuse Research Corporation's biodegradation file; measured concentrations, pH 7, 28°C.
[c] As cited in USEPA (2001, 2010); similar to OECD Guideline 301D; concentrations of 3, 7, and 10 mg/L used.

[d] ThBOD = theoretical biochemical oxygen demand
[e] COD = chemical oxygen demand

2-EHA also completely degrades in anaerobic systems (Chua and Chen 1995; Chua et al. 1995, 1998, 2001; Yap et al. 1992). Yap et al. (1992) designed an anaerobic biofilter to degrade a high strength simulated pharmaceutical wastewater containing 2-EHA (8200 mg/L initial concentration). The optimal performance of the biofilter was attained at 1.1 days hydraulic retention time (HRT), where the average chemical oxygen demand (COD) removal efficiency over 15 days was 92.3%. Periodic chemical analyses often showed less than 70 mg/L 2-EHA in the effluent. Chua and Chen (1995) developed a novel adsorption-anaerobiosis column system that effectively removed a concentration of 1000 mg/L of 2-EHA from contaminated water at an HRT of 2 days. In studying the degradation of surfactants, Mosche (2004) demonstrated almost complete anaerobic mineralization of 2-EHA using different inocula (digested sewage sludge, digested organic waste, and biofilm). 2-EHA (36 g) was added to biomass suspensions and concentrations were monitored. The substance disappeared after 12 days, and after a second addition of 36 g of the substance at this time, the added 2-EHA disappeared within the subsequent 5 days. The ultimate degradation of 2-EHA in anaerobic sediment of the Pearl River, southern China was studied *in vitro* with enrichment shake-flask cultures (Chua et al. 1998, 2001). Over the course of 15 days, almost all of the initial concentration of 2-EHA (2300 mg/L) was degraded, which was determined using theoretical values from chemical reaction stoichiometry. Chemical concentrations, methane and carbon dioxide levels were measured. The anaerobic degradation pathway of 2-EHA has been elucidated by Chua et al. (1995, 1996).

In other studies, various wastewater treatment systems have demonstrated the removal of 2-EHA, but such results may not necessarily be attributable to biodegradation, depending on the processes used and retention times. Also, some plasticizers present in the influents may also degrade to this substance over the course of these processes. The process streams and residues of a sewage treatment plant (STP) in Montreal, Québec, were investigated by Barnabé et al. (2008). Given the relatively short retention period of this treatment facility, which incorporates primary and physicochemical treatment steps, 2-EHA declined by 59% compared with influent concentrations and was still detected in the effluent at a concentration of 0.0148 mg/L. In another study, six other sewage treatment plants in Québec (equipped with various biological treatment systems) were studied and 2-EHA was measured in almost all sampled influents, effluents and sludge (Barnabé et al., unpublished data; see the Ecological Exposure Assessment section of this document for a summary). Ng et al. (1989) treated pharmaceutical wastewaters containing 2-EHA using a two-stage batch system, which effectively reduced this substance to non-detectable levels in less than 6 days. Finally, a combination of anaerobic treatment followed by aerobic treatment of tannery wastewater resulted in the complete removal of short-chain carboxylic acids, which included 2-EHA in the untreated wastewater at concentrations between 0.1 to 1 mg/L (Reemtsma and Jekel 1997).

Although experimental data on the degradation of 2-EHA are available, a QSAR-based weight-of-evidence approach (Environment Canada 2007) was also applied with the degradation models shown in Table 3b. Model results are generally consistent with the

empirical information, indicating relatively rapid primary and ultimate biodegradation of 2-EHA.

Table 3b. Modelled degradation data for 2-EHA

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
AIR			
Atmospheric oxidation	AOPWIN 2008[a]	$t_{1/2}$ ~ 16 hours	<2
Ozone reaction	AOPWIN 2008[a]	n/a[b]	
WATER			
Hydrolysis	HYDROWIN 2008[a]	n/a[b]	
Primary biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[a] Sub-model 4: Expert Survey (qualitative results)	4.3[c] "biodegrades fast"	<182
Ultimate biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[a] Sub-model 3: Expert Survey (qualitative results)	3.5[c] "biodegrades fast"	<182
Biodegradation (aerobic)	BIOWIN 2008[a] Sub-model 5: MITI linear probability	0.6[d] "biodegrades fast"	<182
Biodegradation (aerobic)	BIOWIN 2008[a] Sub-model 6: MITI non-linear probability	0.8[d] "biodegrades fast"	<182
Biodegradation (aerobic)	TOPKAT 2004 Probability	1[d] "biodegrades very fast"	<182
Biodegradation (aerobic)	CATABOL c2004–2008 % BOD (biological oxygen demand)	% BOD = 59 "biodegrades fast"	<182

[a] EPIsuite (2008) using SMILES notation in Table 1.

[b] n/a: not available. Model does not provide an estimate for this type of structure.

[c] Output is a numerical score from 0 to 5.

[d] Output is a probability score.

When an extrapolation ratio of 1:1:4 for a water:soil:sediment biodegradation half-life (Boethling et al. 1995) is used, the ultimate degradation half-life in soil is also <182 days and the half-life in sediments is <365 days (based on an ultimate degradation half-life in water that is expected to be <90 days). This indicates that 2-EHA is not persistent in soil or sediment.

Abiotic degradation of 2-EHA, including indirect photolysis and hydrolysis, will not play a significant role in the environmental fate of this substance. Although this substance is not expected to reside in air, if released to air, the substance will react with hydroxyl radicals, with an estimated degradation half-life of 16 hours (Table 3b). The substance is not expected to react appreciably with other photo-oxidative species in the atmosphere (such as O_3), nor is it likely to degrade via direct photolysis as predicted from the models in Table 3b and because that the substance does not contain chromophores that absorb at wavelengths greater than 290 nm (HSDB 1983–). The substance does not contain

functional groups expected to undergo hydrolysis. Based on its short degradation half-life by reaction with hydroxyl radicals this substance is not considered to be persistent in air.

Based on the good agreement between empirical and modelled data (Tables 3a and 3b), there is a consistent line of evidence to suggest that 2-EHA 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

Experimental log K_{ow} values for 2-EHA suggest that this chemical has a low potential to bioaccumulate (see Table 2).

No experimental bioaccumulation factor (BAF) and/or bioconcentration factor (BCF) data for 2-EHA were available, so a predictive approach was applied with available BAF and BCF models as shown in Table 4. 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. BCFs may not adequately account for the bioaccumulation potential of substances via the diet, which predominates for substances with log K_{ow} greater than ~4.0 (Arnot and Gobas 2003). The log K_{ow} for 2-EHA is ~2.7. 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.

BCF and BAF estimates for the neutral form of the substance, corrected for potential biotransformation or not, were generated with the BCFBAF model. This represents a worst-case condition for this substance (EPIsuite 2008) since it is expected to be present mainly in the less bioavailable, ionized form in the environment. Metabolic rate constants (k_M) were derived by means of structure activity relationships described further in Arnot et al. (2008a, 2008b, 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 10-g fish at 15°C to the body weight of a fish in 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. The k_M calculated with the BCFBAF QSAR for a 10-g fish at 15°C is ~1.3, which suggests a substantial rate of whole-body biotransformation even when further normalized to a 184-g fish (k_M = 0.6 days^{-1}); this is consistent with the chemical structure.

Table 4. Modelled bioaccumulation data for 2-EHA

Test organism	Endpoint	Wet weight value (L/kg)	Reference
Fish	BAF (neutral form)	31.3 (with metabolism)	Arnot and Gobas 2003 (Arnot-Gobas middle trophic level)
		50.7 (no metabolism)	
Fish	BCF (neutral form)	31.3 (with metabolism)	Arnot and Gobas 2003 (Arnot-Gobas middle trophic level)
		47.5 (no metabolism)	
Fish	BCF (corrected for metabolism)	135	CPOPs 2008
Fish	BCF [a] (ionizable organics)	1.12	Fu et al. 2009
Fish	BCF (accounts for ionization potential)	3.2	BCFBAF 2008

[a] The regression equation for strong acids (pH 6) is log BCF = 0.34 logD_{ow} + 0.65; log D_{ow} at pH 6 = 1.37.

All estimated BCFs and the BAF are much less than the 5000 threshold. The lowest BCFs were approximately 1 to 3 L/kg. These BCF values, which were estimated to account for ionization potential, were also much lower than those BCF or BAF values estimated for the neutral form of the substance. The available modelled evidence thus indicates that 2-EHA has a low bioaccumulation potential, which is consistent with 1) its low experimental log K_{ow} value of 2.7 (for the neutral form), 2) the almost complete ionization of this substance in water at ambient pHs and 3) its expected fast rate of metabolism in fish.

Based on the available information, 2-EHA does not meet the bioaccumulation criterion (BCF or BAF $\geq$ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

The acute and chronic toxicity of 2-EHA has been tested in five species of fish (including one test on embryos), an amphibian, an invertebrate, a green alga, a marine hydroid, a freshwater polyp, and bacteria. A summary of the experimental ecological effects is presented in Table 5.

Table 5. Empirical aquatic toxicity data for 2-EHA

Test organism	Test type	Endpoint	Value (mg/L unless indicated otherwise)	Reference
Fish				
Fathead minnow *Pimephales promelas*	Acute (96 hours, static)	LC_{50}[a]	70 (pH 5.3–5.5)[b]	US EPA 2001, 2010
	Chronic (7 days)	IC_{25} (decreased body weight)	23.0 (12–25)	Horn et al. 2004
Carp *Cyprinus carpio*	Acute (45 hours)	NOEL	>117 mg/kg-bw[c] (no effects)	European Commission 2000
Rainbow trout *Oncorhynchus mykiss*	Acute (96 hours)	LC_{50}	150 (110–220)	Horn et al. 2004
	Acute (48–96 hours, static)	LC_{50}	180 (nominal)	European Commission 2000
Pumpkinseed *Lepomis gibbosus*	Acute (48–96 hours, static)	LC_{50}	270 (nominal)	European Commission 2000
Zebrafish *Brachydanio rerio*, embryos	Chronic[d] (31 hours)	MATC[e]	8.65*	Herrmann 1993
Amphibians				
African clawed frog *Xenopus laevis*, embryos	Acute (96 hours, renewal)	EC_{50} (teratogenesis)	47.5 (44–51)	Dawson 1991
	Acute (96 hours, renewal)	LC_{50}	645.5 (496–759)	Dawson et al. 1996
Invertebrates				
Water flea *Daphnia magna*	Acute (48 hours)	EC_{50}[f] (immobilization)	85.4 (79.8–91.4) (nominal; 31.25–500 mg/L tested)	US EPA 2001, 2010
	Acute (48 hours)	LC_{50}	120 (0–430)	Horn et al. 2004
	Acute (24–48 hours)	EC_{50} (immobilization)	85.4–116.6	European Commission 2000
	Chronic (21 days)	NOEC	25	BASF 2009
Algae				
Green alga	Chronic	EC_{50}[b]	49–61	US EPA 2001,

Scenedesmus subspicatus	(72 hours)	(biomass and growth rate)		2010
	Chronic (96 hours)	EC_{50}[b] (biomass and growth rate)	41–44	US EPA 2001, 2010
Other animals				
Marine hydroid *Hydractinia*	Acute (48 hours)	MATC (embryogenesis)	57.7	Berking 1991
	Acute (24 hours)	EC_{50} (metamorphosis)	1000	Berking 1991
Freshwater polyp *Hydra*	Acute (2 days)	EC_{50} (head regeneration)	10.8	Berking 1991
Microrganisms				
Microtox assay	Acute (5 minutes)	EC_{50} (light generation)	43	Nalli et al. 2002
Pseudomonas putida	Chronic (17 hours)	EC_{50} (respiration inhibition)	110	European Commission 2000
	Chronic (30 minutes)	EC_{50} (respiration inhibition)	670	European Commission 2000
Activated sludge	Chronic (30 minutes)	EC_{20} (respiration inhibition)	650	European Commission 2000
Rhodococcus rhodochrous	Chronic (200 hours)	EC_{50} (growth, reproduction)	>288.4 No effects	Nalli et al. 2006

***** Value used to calculate the predicted no effects concentration.

[a] LC_{50} – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.

[b] Test solutions were not buffered.

[c] Carp were force-fed doses of 88, 109, 117 mg/kg·bw of 2-EHA.

[d] This study was designated as a chronic endpoint because the embryo phase of zebra fish, and particularly its early stages, are short-lived. Zebra fish embryos hatch in 3 to 4 days, with most organs being developed within the first day. Treatment was started at stage 14 (there are 23 stages identified, with the early stage lasting about 20 minutes and the late stages – stages 19 to 23 – occurring from 17 to 28 hours). The animals were scored for retardation of development on day 2 whenever the control group had reached stage 23.

[e] 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.

[f] EC_{50} – The concentration of a substance that is estimated to cause some effect on 50% of the test organisms.

These experimental results are relatively consistent amongst all organisms tested, and the majority of acute and chronic effect concentrations spanned less than two orders of magnitude (8.65–670 mg/L; with the exception of the effect at 1000 mg/L). The lowest effect concentration was reported for zebrafish embryos (Herrmann 1993) where 2-EHA exposure led to a concentration-dependent retardation of embryonic development and a maximum allowable toxicant concentation (MATC) of 8.65 mg/L. This chronic value was used to derive the predicted no-effects concentration (PNEC) as described later in this report.

Daphnia magna and rainbow trout were exposed to serial dilutions (100, 50, 25, 12.5, and 6.25% by volume) of a solution of 1700 mg/L 2-EHA (Horn et al. 2004). The LC_{50} was

determined after a 48-hour period for *D. magna* (120 mg/L) and a 96-hour period for rainbow trout (180 mg/L). In the same study, fathead minnows were exposed to serial dilutions (100, 50, 25, 12.5, and 6.25% by volume) of a solution of 86 mg/L 2-EHA. At a concentration of 23 mg/L, a 25% decline in body weight of fathead minnows was reported for the 7-day study.

The effect of 2-EHA alone or in combination with other carboxylic acids was investigated on *Xenopus laevis* embryo development (Dawson 1991). The single chemical and chemical mixtures were tested on three occasions in embryos from a different breeding pair for each of the three tests. Each treatment included five concentrations and a control, each with 25 embryos. The concentrations of 2-EHA tested were 0, 22, 44, 55, 66, and 88 mg/L. After an exposure period of 96 hours (with solution renewal every 24 hours), the embryos were fixed and the types of malformations were recorded. As found in previous investigations, the effect of carboxylic acids on total malformation induction was concentration-additive and the mixture of carboxylic acids (with 2-EHA) resulted in an EC_{50} value (5.7 mg/L) an order of magnitude lower than that obtained for 2-EHA tested alone (47.5 mg/L). At the highest concentration of 2-EHA tested (88 mg/L), malformations were observed in 80% of the embryos exposed, and microcephaly and abnormal gut coiling were the most commonly observed. The incidence of multiple defects was 42%.

Berking (1991) investigated the effects of 2-EHA (among other substances) on the developmental processes in hydroids, including the freshwater polyp *Hydra* and the marine hydroid *Hydractinia*. Results showed that 2-EHA interfered with embryogenesis and metamorphosis in *Hydractinia* and caused head regeneration in *Hydra*.

Nalli et al. (2002) reported the acute toxicity of this substance based on the 5 minute Microtox assay, which involves the short-term incubation of 2-EHA with the luminescent marine bacterium *Photobacterium phosphoreum*. A concentration of 43 mg/L caused a 50% decrease in light output.

Modelled predictions for aquatic toxicity were also performed for 2-EHA. ECOSAR (2008) results for neutral organics (predicted values were multiplied by a factor of 10 owing to the existence of an acid moiety in the structure) included: fish (96-hour LC_{50}), 159 mg/L; daphnid (48-hour LC_{50}), 103 mg/L; and green alga (96-h EC_{50}), 74 mg/L. Chronic toxicity values included: fish (30-day) 18 mg/L, daphnid 14 mg/L, and green algae 33 mg/L. TOPKAT results were deemed unreliable overall. Results from CPOPs (2008) included: *D. magna* (48-hour LC_{50}), ≤10.7 mg/L; and fathead minnow (BCF_{max} LC_{50}), ≤19.1 mg/L. The CPOPs model recognizes that reactive groups exist and that the substance may be more toxic than is the predicted baseline narcosis (i.e., the “less than value” is added to results). These predictions are consistent with the empirical data as discussed.

No ecological effects studies were found for 2-EHA in media other than water.

The majority of these results indicate that 2-EHA is moderately toxic to aquatic organisms (acute LC_{50}s or EC_{50}s > 1.0 mg/L and < 100 mg/L).

Ecological Exposure Assessment

Data concerning concentrations of 2-EHA in the Canadian environment and elsewhere have been identified (Table 6).

Table 6. Concentrations of 2-EHA in the environment

Medium	Location; year	Concentration	Reference
Water/Effluent (mg/L)			
Melted snow	Montreal, Québec; 2004	0.0067	Horn et al. 2004
River water	Montreal, Québec; 2004	0.0032	
Creek water	Montreal, Québec; 2004	0.0012	
Influent; wastewater treatment plants[a]	Montreal, Québec; 2005	0.036	Barnabé et al. 2008
	Quebec City, Québec; 2005	0.004	Barnabé et al. (unpublished data)
	Gatineau, Québec	0.068	
	Drummondville, Québec	0.014	
	Granby, Québec	0.013	
	Victoriaville, Québec	0.009	
	Thetford Mines, Québec	0.014	
Effluent; wastewater treatment plants[a]	Montreal, Québec; 2005	0.015	Barnabé et al. 2008
	Quebec City, Québec; 2005	0.039	Barnabé et al. (unpublished data)
	Gatineau, Québec	0.044	
	Drummondville, Québec	0.005	
	Granby, Québec	0.007	
	Victoriaville, Québec	Not detected	
	Thetford Mines, Québec	Not detected	
Sediment/Sludge (mg/kg)			
River sediment	Montreal, Québec; 2004	0.110	Horn et al. 2004
Homogenized sludge (or primary)	Montreal, Québec; 2005	20.7	Barnabé et al. 2008
Press-filtered sludge (or dewatered)	Montreal, Québec; 2005	14.6	
Primary sludge	Québec; 2005 (three WWTPs)[b]	20–228	Beauchesne et al. 2008
Secondary sludge	Québec; 2005 (four WWTPs)	5–65	Beauchesne et al. 2008
Thickened sludge	Québec; 2005 (three WWTPs)	11–19	Beauchesne et al. 2008
Digested sludge	Québec; 2005 (three WWTPs)	5–30	Beauchesne et al. 2008
Dewatered sludge	Québec; 2005 (five WWTPs)	2–64	Beauchesne et al. 2008

[a] Listed in decreasing order of population served.

[b] WWTP: wastewater treatment plant

2-EHA has been detected in precipitation, surface waters and river sediment in eastern Canada (Horn et al. 2004), along with common plasticizers such as di(2-ethylhexyl) adipate or DEHA. River sediments had the highest concentration of 2-EHA (0.110 mg/kg) but this substance was not observed in samples of a landfill leachate (which may be attributed to the anaerobic conditions of the landfill, as suggested by the authors). These authors suggest that the source of 2-EHA in these environmental samples is most likely from the biodegradation of the plasticizers DEHA and di(2-ethylhexyl) phthalate or DEHP.

In addition, 2-EHA has been measured in the influents, effluents and sludges of wastewater treatment plants (Barnabé et al. 2008; Barnabé et al. 2008 unpublished data; Beauchesne et al. 2008). Following primary and physico-chemical treatment at a sewage treatment plant in Montreal (Barnabé et al. 2008), about 43% of 2-EHA inputs were discharged in the effluent going into receiving surface waters (i.e., the St. Lawrence River), and about 5% was found in the dewatered sludge (which was subsequently incinerated). This substance was also found in the sludges from several WWTPs in Québec, in which measured concentrations ranged from 2–228 mg/kg in primary, secondary, digested, and dewatered sludges (Beauchesne et al. 2008).

Concentrations of 2-EHA were measured in the influent, effluent and sludge of six other WWTPs in Québec (Barnabé et al. unpublished data). The industrial contribution to influent was determined to be < 5% (for Québec City, Gatineau, and Victoriaville), 49% (Granby), and 60% (Drummondville). Concentrations ranged from 0.004 to 0.068 mg/L (influents), not detected to 0.044 mg/L (effluents), 0.005 to 0.019 mg/kg (untreated sludge; 4 plants), 0.005 to 0.03 mg/kg (digested sludge; 3 plants), and 0.002 to 0.064 mg/kg (dewatered sludge; 4 plants) (Barnabé et al., unpublished data; Beauchesne et al. 2008).

Industrial Release

The aquatic exposure of 2-EHA 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 with the equation

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

where:

$C_{water-ind}$ 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 the five industrial sites reporting the highest industrial use quantities of 2-EHA. These sites were identified from the 29 companies who responded to the CEPA section 71 survey (Environment Canada 2010a). The uses of this substance varied amongst these sites and included either use as a lubricant and lubricant additive, an intermediate in an anti-tack agent, a gelling agent, a metal-working lubricant, a metal carboxylate (salt), an antifreeze additive, a substance to control ash clog in incinerator boilers, a dryer to promote polymerization, or in paint formulations. These top five industrial users each reported an annual use quantity of 2-EHA in the range of 10 000 to 1 000 000 kg/year. The selection of these sites is based on a general assumption that the quantity released is proportional to the quantity used and that these sites would represent a realistic worst-case scenario in Canada.

In this site-specific exposure analysis (Environment Canada 2010c), each site includes one facility, one WWTP, and one receiving water body. The PEC in the receiving water was estimated based on the concentration in the wastewater treatment effluent and by applying a dilution factor of up to 10. The concentration in the wastewater treatment effluent was estimated based on a fraction of the substance lost from the facility to a local municipal wastewater treatment plant, a wastewater treatment plant removal rate, and its effluent flow. The loss fraction was conservatively estimated to be in the range of 2.3 to 5% resulting from the chemical container handling operations and the industrial processes relevant to the facilities under consideration. This range is expected to represent the upper bound of the losses to wastewater, and the release from an actual facility is expected to be below this upper bound. The removal rate by a local WWTP is assumed to be zero in the case of unknown treatment and estimated by a computer model (Simple Treat 1997) to be

4.4% for primary treatment and 77.4% for secondary treatment. The effluent flow of a local WWTP is proportional to the population served and is in the range of 32 000 to 2 000 000 m^3/day for the sites considered.

Based on the above assumptions, the PECs are estimated to be in the range of 0.23–16 µg/L for the top five industrial users of 2-EHA. An assumption for the frequency of release was also used in the estimation which is 250 days/year for the industrial users (small or medium sized facilities).

Consumer Release

As 2-EHA can be found in consumer and commercial products and is reported to be released to water, Mega Flush, Environment Canada's spreadsheet tool, was employed to estimate the substance concentration in multiple water bodies receiving sewage treatment plant effluents to which consumer and commercial products containing the substance may have been released (Environment Canada 2009). The spreadsheet tool provides these estimates for approximately 1000 release sites across Canada based on the following assumptions:

- loss to sewer at 100%,
- sewage treatment plant removal rate estimated at 77.4% (secondary treatment) and 4.4% (primary treatment)
- number of annual release days at 365 days/year
- receiving water dilution factor in the range of 1 to 10
- low (10th percentile) flow conditions in receiving waters

The PEC of 2-EHA in the receiving water bodies was estimated to be in the range of 0.018–0.11 mg/L. The estimate is based on the expectation that a total of ~29 000 kg/year of the substance is used by residential and commercial consumers (i.e., the total quantity related to use in a consumer or commercial product, which does not include quantities used as an intermediate based on the assumption that the substance is no longer available). The equation and inputs used to calculate the PEC are described in Environment Canada (2010d).

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 conservative risk quotient calculations, as well as information on persistence, bioaccumulation, toxicity, sources, and fate of the substance.

2-EHA is not expected to be persistent in air, water, soil or sediment. It is also expected to have a low bioaccumulation potential. The high importation volumes of 2-EHA into Canada, along with information on its uses and presence in wastewater effluents, indicate potential for widespread and continual release into the Canadian environment. Once released into the environment, it will be found mainly in water. It also has moderate potential for toxicity to aquatic organisms.

A predicted no-effect concentration (PNEC) was derived by dividing the chronic toxicity value of 8.65 mg/L (the most sensitive valid experimental value) for zebrafish embryos by an assessment factor of 100 (to account for interspecies and intraspecies variability in sensitivity, to estimate a long-term no-effects concentration, and to extrapolate from lab to field studies). The resulting PNEC value is 0.08 mg/L.

A risk quotient analysis, integrating conservative estimates of exposure in Canada with toxicity information (calculated as PEC/PNEC), was performed for the aquatic medium to determine whether there is potential for ecological harm in Canada. Measured concentrations of 2-EHA in river water, creek water, and snow near Montreal, Québec, compared with the PNEC, resulted in risk quotients of less than 0.1. PECs were calculated using the measured concentration of 2-EHA in effluents at a number of WWTPs in Québec, with a dilution factor of 10 applied to estimate the concentration in the receiving water (similar to the approach used in the site-specific industrial release scenarios). These analyses also resulted in risk quotients of much less than 1. The site-specific industrial scenarios presented (which considered the actual receiving water bodies) yielded PECs of 0.23–16 µg/L (Environment Canada 2010c). The resulting risk quotients for the five industrial sites evaluated ranged from 0.008 to 0.2. Therefore, harm to aquatic organisms is unlikely at these sites. Using a similar PEC/PNEC approach, the consumer release scenario tool predicted that PECs for 2-EHA would not exceed the PNEC in any water bodies receiving wastewater across Canada under low (10th percentile) flow conditions (Environment Canada 2010d).

This information suggests that 2-EHA is not causing harm to ecosystems in Canada.

Uncertainties in Evaluation of Ecological Risk

In assessing the persistence of this substance in the environment, some of the empirical data on primary aerobic biodegradation were contradictory, although complete details were not available to further evaluate these studies. The experimental data for ultimate aerobic and anaerobic biodegradation were however consistent and indicated the fast biodegradation of this substance by activated sludge. Model results were consistent and also predicted that this substance would biodegrade quickly in water.

The bioaccumulation assessment for 2-EHA is limited by the absence of experimental bioaccumulation data. This situation necessitated the use of models to generate predicted BCF and BAF values. Although all predictions have some degree of error, generally these

models are relatively accurate and the metabolism-corrected model outputs confirmed that 2-EHA can be expected to have a low bioaccumulative potential.

There is the potential for this substance to partition to a limited extent to sediments and wastewater sludge (and hence potentially end up being applied to soil as biosolids), as indicated by the concentration data available. However, the effects data available apply only to aquatic organisms, and it is not feasible to calculate a PNEC for soil or sediment based on equilibrium partitioning theory as this substance ionizes. In addition, it is important to note that this substance is acidic, and depending on the quantity added to soil and the buffering capacity of the soil, could influence the acidity of the soil under moist conditions.

Potential to Cause Harm to Human Health

Exposure Assessment

As 2-EHA is primarily an industrial intermediate (Bizzari et al. 2009), it is unlikely that measured concentrations of 2-EHA in environmental media and foods are due to uses of 2-EHA itself (CAS RN 149-57-5). 2-EHA is a breakdown product and/or metabolite of several high volume plasticizers, including DEHP and DEHA. For example, these plasticizers may undergo biodegradation to release 2-EHA in wastewater treatment plants. The substance is also released from products containing metal salts of 2-EHA.

Environmental Media and Foods

2-EHA was identified but not quantified in one ambient air study that collected five samples from three sites along the Niagara River (Hoff and Chan 1987). Based on the physical and chemical properties of 2-EHA and the release information reported under the section 71 survey, concentrations in air are not expected to be significant.

One report of 2-EHA measured in tap water in Montreal, Québec was identified; a single sample was collected and determined to contain 0.050 µg/L 2-EHA (Horn et al. 2004). The authors also reported concentrations of the substance in natural waters, snow and river sediment; the concentrations are presented in Table 6. A more recent publication from the group reports the concentration of 2-EHA in wastewater treatment plant influents (25.6–48.0 µg/L) and effluents (14.8 µg/L) (Barnabé et al. 2008). The tap water concentration was considered the most relevant value and was used to estimate intake of this substance by Canadians. Intake of 2-EHA is estimated to range from 0.0003 µg/kg-bw per day to 0.0053 µg/kg-bw per day for individual 12–19 years of age and formula-fed infants, respectively (see Appendix 1).

Reports of 2-EHA in terrestrial soil or house dust were not identified; one measurement of the substance in river sediment was identified (Table 6). This was not considered an appropriate surrogate because the low estimated Henry's Law constant suggests the

substance will have low volatility from moist soil while the moderate experimental vapour pressure suggests it will volatilize from dry soil.

No Canadian data on the presence of 2-EHA in foods were identified. There are two reports on levels of 2-EHA found in baby food and fruit juice packaged in glass jars sealed with metal lids on the European market (Elss et al. 2004; Ežerkis et al. 2007). The authors suggest that the substance migrates from the plastic seal, as 2-EHA salts are used as heat stabilizers in plastics. No association was observed between the concentration of 2-EHA measured and the composition (fat or water content) of the food product. An association between supplier and concentration was noted and the authors indicated that migration is most strongly influenced by technological processes such as thermal sterilization (Ežerkis et al. 2007). In 2004, the German Federal Institute for Risk Assessment (BfR) estimated the intake of 2-EHA by infants (weighing 7.5 kg) to range from 0.06 to 0.3 mg/kg-bw per day based on the results of Elss et al. (BfR 2004). In the Elss et al. (2004) report, 34 of 35 samples contained less than 0.6 mg/kg of 2-EHA, and one sample contained 3.2 mg/kg of 2-EHA in the food product. These values represent the intake range reported by BfR (2004); it is assumed that the entire 700 g/day diet contains these concentrations. In 2007, Ežerkis and coworkers reported measurements of 2-EHA in baby food from 13 European countries; in this study 53 of 63 samples (84%) contained <0.6 mg/kg of 2-EHA in the food product and the maximum concentration was 3.4 mg/kg (Ežerkis et al. 2007). Generally these results are consistent with that of Elss et al. (2004); the increased incidence of concentrations greater than 0.6 mg/kg of 2-EHA in food products was primarily associated with a single supplier. Based on these data, exposure estimates were developed with 0.6 and 3.4 mg/kg of 2-EHA in food products representing 89% of samples and the maximum concentration reported, respectively. The highest exposure group is non-formula-fed infants 0–6 months of age with an estimated intake ranging from 19 to 107 μg/kg-bw per day, followed by the 0.5–4-year and 20–59-year age groups at 3.5–20 and 1.5–8 μg/kg-bw per day, respectively (see Appendix 1). These estimates were derived assuming the substance was only present in foods likely packaged in glass jars sealed with metal lids (e.g., baby food, fruit juice, condiments, jam, etc.).

Confidence in the characterization of exposure to 2-EHA via environmental media (air, water and soil) is low because neither air nor soil concentrations were identified and although the substance was measured in river sediment, this was not considered an appropriate surrogate. One measurement of the substance in tap water was identified, and while the data were from Canada, only one sample was taken. Confidence in the exposure via food is low because no Canadian values were identified, and only two publications describing concentrations of 2-EHA in European baby foods were identified. Confidence is high that the numerical intake estimate of exposure for the highest exposure group, non-formula-fed infants 0–6 months old, is conservative because the upper end of the intake estimate is based on the maximum concentration reported.

Consumer Products

Release of 2-EHA from products containing salts, esters and 2-ethylhexanol-based plasticizers is considered to be a source of general population exposure.

In Europe, the Danish Ministry of the Environment has measured the release of 2-EHA from a number of consumer products. 2-EHA was extracted by saliva simulant from the surface of one wooden toy at a very low concentration, 3.2 µg of 2-EHA per gram surface material (Hansen and Pedersen 2005). It was also identified but not quantified in one brand of marker pen intended for children (Hansen et al. 2008). 2-EHA acid was reported to volatilize from several products containing polyvinyl chloride (PVC) such as clay when heated (Pors and Fuhlendorff 2002), household voltage converters (Malmgren-Hansen et al. 2003), artificial turf (Nilsson et al. 2008), and adult toys (Nilsson et al. 2006). Nilsson et al. (2006) reported that upper-bounding estimates of exposure for use of adult toys was up to 0.1 mg/kg-bw per day.

Consistent with these findings other groups have reported 2-EHA emissions from household products such as PVC-containing floor tiles and wall papers (Karpe et al. 1995; Kirchner and Karpe 1996), as well as lacquers and foils for furniture coating (Salthammer 1997). These studies did not provide sufficient information to form the basis of an exposure scenario.

Based on information submitted through the section 71 survey and on information in the literature, 2-EHA may be present in the following products available to the general public: alkyd paints, spray paints, paint driers, stains and antifreeze (HPD 2009a, 2009b; Environment Canada 2010a). Concentrations of 2-EHA were reported to range from 0.01% to <1% in liquid and spray paint products (Environment Canada 2010a). According to the Household Products Database (HPD) (2009a), 2-EHA concentrations ranged from <0.04% in a translucent stain (arts and crafts)to 1–5% in a paint drying product, and 1–8% in antifreeze.

Estimates of dermal and inhalation exposure to 2-EHA for adults (aged 20–59 years old) who used alkyd paint and spray paint were derived with the ConsExpo model (ConsExpo 2006) and are presented in Appendix 2. In addition to the use of ConsExpo (ConsExpo 2006), the U.S. Environmental Protection Agency's Wall Paint Exposure Model (WPEM) software (US EPA 2001) was used to model consumer exposure from use of alkyd paint. The WPEM results were consistently lower; therefore, the ConsExpo model outputs were considered to provide a more conservative estimate of exposure. A range of potential 2-EHA concentrations (from 0.01 to 1%) in paint was used to provide a lower and upper estimate of exposure. Modelled estimates of dermal exposure to 2-EHA from use of alkyd paint ranged from 0.005 to 0.5 mg/kg-bw per event for paint containing 0.01 and 1% 2-EHA, respectively. Modelled estimates of dermally applied doses of 2-EHA from the use of spray paint ranged from 0.002 to 0.2 mg/kg-bw per event for paint containing 0.01% and 1% 2-EHA respectively. Modelled air concentrations (mean event) ranged from 0.08 to 8.2 mg/m^3 from use of akyld paint, and from 0.03 to 3.4 mg/m^3 from use of spray paint. Estimates of exposures from use of paint dryers, stains, and antifreeze were not derived because of a lack of available model parameters; however, the estimates

presented for alkyd and spray paints are considered sufficient to account for acute exposures from these other potential consumer products.

According to the Cosmetic Notification System, 2-EHA is an ingredient in two temporary tattoos. The concentration of 2-EHA, mineral spirits, and 2-ethylhexanoate combined, ranged from 0.3 to 1% in one product and from 3 to 10% in the other (CNS 2010). Exposure estimates from the use of these products could not be derived because of the lack of 2-EHA specific concentration data in the products and the lack of model parameters.

Confidence in the modelled estimates is moderate as some data on specific Canadian products containing 2-EHA and the concentrations in the final products were identified; however, some scenarios could not be derived because of a lack of model parameters. Confidence is high that actual exposures from use of consumer products do not exceed the upper-bounding exposure estimates presented for paint products. Confidence is also high that exposure to 2-EHA from the use of CAS RN 149-57-5 in consumer products is low; however, confidence in the exposure to the 2-EHA moiety from sources such as 2-EHA salts is low as this assessment did not thoroughly investigate these substances. Several of these salts have been categorized as organic metal salts and will be assessed separately.

Health Effects Assessment

A summary of the available health effects information for 2-EHA is presented in Appendix 3. In view of the limited available database on 2-EHA, data on 2-ethylhexanol was also taken into consideration. Data on 2-ethylhexanol was considered relevant to the assessment of 2-EHA because 2-ethyhexanol is rapidly and extensively metabolized to 2-EHA via oxidation *in vivo* and subsequently undergoes biotransformation via the same metabolic pathway as 2-EHA (Albro 1975; Deisinger et al. 1994; BG Chemie 1999).

The European Commission has classified 2-EHA as Category 3 for developmental toxicity (causes concern for humans owing to possible developmental toxic effects) (European Commission 1995, 1996; ESIS c1995-2010). This classification was based on observed developmental effects, such as skeletal variations (wavy ribs, reduced ossification) and skeletal malformations (club foot) in rats following oral doses of 2-EHA given on days 6-19 of gestation. The studies are described below and are also presented in Appendix 3.

In an oral developmental toxicity study in which pregnant rats were exposed to 2-EHA at 0, 100, 300, or 600 mg/kg-bw per day via drinking water during days 6-19 of gestation, skeletal variations, such as wavy ribs and reduced cranial ossification, were observed in the absence of maternal toxicity at the lowest dose in fetuses. A dose-dependent increase in skeletal malformations (club foot) was also observed in fetuses (statistically significant at the highest and intermediate dose). The lowest-observed-adverse-effect level (LOAEL)

for maternal toxicity in this study was 600 mg/kg-bw per day based on decreased maternal body weight gain (Pennanen et al. 1992). In another study, pregnant rats were administered 2-EHA by gavage during days 6 to 15 of gestation and exhibited skeletal variations (reduced ossification) at 250 mg/kg-bw per day in fetuses. Maternal toxicity (lethargy, ataxia, respiratory distress, and increased absolute and relative liver weight) was noted at 500 mg/kg-bw per day. In the range-finding study in rats done by the same authors, a LOAEL of 500 mg/kg-bw per day was identified based on reduction in fetal body weight and significant decrease in the percentage of living fetuses, and a LOAEL for maternal toxicity of 1000 mg/kg-bw per day based on mortality of seven out of eight (7/8) rats between days 7 and 9 of gestation was observed (Bushy Run 1988a; Hendrickx et al. 1993). In pregnant rats exposed to high dose levels, fetal malformations and early fetal deaths were also observed at 900 mg/kg-bw per day and higher. Although no effects in the dams were noted in one study, maternal deaths were observed at 1200 mg/kg-bw per day in the second study (Ritter et al. 1987; Narotsky et al. 1994). Rabbits appear less sensitive to developmental effects of 2-EHA. When New Zealand white rabbits were exposed to 2-EHA by gavage to 0, 25, 125, or 250 mg/kg-bw per day during gestation days 6 to 18, no developmental effects in fetuses were observed. However, the treatment-related death of 1/15 dams and the abortion by 1/15 dams was observed at 125 mg/kg-bw per day. Death of 1/15 dams and clinical signs of toxicity in surviving dams (lethargy, ataxia, respiratory distress and significant reduced body weight gain) were observed at 250 mg/kg-bw per day. In the range-finding study in rabbits, maternal toxicity was noted at 500 mg/kg-bw per day and higher, based on high mortality (Bushy Run 1988b; Hendrickx et al. 1993).

In addition, when pregnant rats and mice were exposed to 2-ethylhexanol by the oral route, similar developmental effects were observed. However, developmental effects were only seen at levels causing maternal toxicity. In pregnant rats administered 0, 130, 650, and 1300 mg/kg-bw per day of 2-ethylhexanol by gavage during days 6 to 15 of gestation, skeletal malformations, variations and retardations were noted at the highest dose. Increases in the number of resorption and post-implantation losses and a reduction in fetal weights were also observed at that dose, as well as a reduction in body weight gain in dams (BASF AG 1991l). In a study in which pregnant mice were exposed by gavage to 2-ethylhexanol at 0 (control) or 1525 mg/kg-bw per day during days 7-14 of gestation, significant reductions in the number of live pups and in their weight compared with controls were observed in the presence of maternal toxicity (Hazleton 1983; Hardin et al. 1987).

In these studies, the lowest oral LOAEL for developmental toxicity was 100 mg/kg-bw per day in fetuses of pregnant Han Wistar rats exposed to 2-EHA via drinking water, based on skeletal variations (wavy ribs and reduced cranial ossification) and malformations (club foot) (Pennanen et al. 1992). The lowest LOAEL for maternal toxicity, identified in rabbits, was 125 mg/kg-bw per day based on treatment related death and abortion in dams (Bushy Run 1988b; Hendrickx et al. 1993).

No data on the potential developmental toxicity via inhalation exposure to 2-EHA was identified. However, developmental effects were not reported in an inhalation study in

which pregnant rats were exposed to 2-ethylhexanol at 850 mg/m^3 for 7 hours/day, on days 1 to 19 of gestation. A lowest-observed-effect concentration (LOEC) for maternal toxicity was identified at the same dose level based on significant reduction in feed consumption in dams (Nelson et al. 1988, 1989, 1990).

No dermal developmental toxicity studies conducted with 2-EHA were identified. Dermal application of its parent compound, 2-ethylhexanol, at doses up to 2520 mg/kg-bw per day during gestation days 6-15 did not cause developmental toxicity in rats, but maternal toxicity was observed at 1680 mg/kg-bw per day based on decreased body weight gain in the dams (Bushy Run 1989; Fisher et al. 1989; Tyl et al. 1992). However, it has been reported that 2-ethylhexanol may be absorbed through the skin to a lesser extent than 2-EHA (Deisinger et al. 1994).

Effects on the male reproductive system were observed in rats exposed orally to 2-EHA. The lowest LOEL for reproductive toxicity was 100 mg/kg-bw per day based on reduction in sperm motility in male Han Wistar rats exposed via drinking water to 0, 100, 300, or 600 mg/kg-bw per day for 10 weeks before mating and 3 weeks during mating with treated females (Pennanen et al. 1992). A parental LOEL of 600 mg/kg-bw per day was identified based on reversible decreased body weight gain in females.

In short-term and subchronic studies, 2-EHA causes liver toxicity following oral administration in experimental animals. In a study in which rats were exposed to 2-EHA in the diet for 15 days, a dose-dependent increase in liver weight was observed in both sexes at doses of 706-2276 mg/kg-bw per day. Histological changes in the liver (cellular atrophy and necrosis) were also reported at 1351 mg/kg-bw per day (Eastman Kodak 1987c). In a 3-month study in rats, a slight (but statistically significant) reduction in body-weight gain in conjunction with reduced feed consumption was observed at the highest dose during the treatment period (917 mg/kg-bw per day). Increased relative liver weight in males and females was also observed at 303 mg/kg-bw per day and higher. Again, this increase was accompanied by histological changes in the liver (hepatocyte hypertrophy) in males from 303 mg/kg-bw per day and in females at the highest dose tested only, i.e., 1068 mg/kg-bw per day (Eastman Kodak 1988; Juberg et al. 1998). In rats exposed orally to 2-ethylhexanol for short-term or subchronic duration, reduced body weight and liver and stomach effects were among the principal effects observed. When rats were administered 2-ethylhexanol by gavage nine times over a period of 12 days, dose-dependent effects such as local damage to the stomach, effects on the immune system, and effects on the haematopoietic system were observed in both sexes at 275 mg/kg-bw per day and above (Bushy Run 1988c). In a 90-day study, in which rats were given 2-ethylhexanol in the diet, reduced body weight gain was observed at 500 mg/kg-bw per day, the highest dose tested (BASF AG 1991g, 1991h; Astill et al. 1996a). In this study, other effects in rats such as hepatic peroxisome proliferation and increases in relative liver and stomach weight were also observed. The lowest LOAEL for repeated-dose oral exposure was 275 mg/kg-bw per day as 2-ethylhexanol, based on effects on the stomach, immune system, and the haematopoeietic system in male and female rats.

No repeated-dose inhalation studies have been identified for 2-EHA. Inhalation of 2-ethylhexanol was investigated in one study. No treatment-related adverse effects were observed in rats exposed for 6 hours/day, 5 days/week, for 90 days at concentrations up to 120 ppm (638 mg/m^3) (BASF AG 1992a).

Likewise, no short-term or subchronic dermal toxicity studies have been reported for 2-EHA. However, the LOAEL for dermal repeated-exposure to 2-ethylhexanol was 834 mg/kg-bw per day, the highest dose tested, based on lymphopenia, an increase in triglyceride levels, reduced spleen weight, and histopathological effects on the skin (exfoliation, acanthosis, hyperkeratosis, dermatitis, oedema, and eschar formation) in both sexes in rats (Bushy Run 1988c).

With regards to chronic toxicity studies (including carcinogenicity bioassays), no data are available for 2-EHA. In chronic lifetime studies in rats dosed by gavage with 2-ethylhexanol, no increased incidence of neoplastic lesions (liver adenomas, hepatocellular carcinomas) were noted at any tested concentrations (50, 150, or 500 mg/kg-bw per day). In a similar study in mice (dosed with 2-ethylhexanol by gavage at 50, 200, or 750 mg/kg-bw per day), a significant increase in hepatocellular carcinomas was observed in female mice at 750 mg/kg-bw per day when compared with the vehicle control group. However, the study investigators concluded that the tumours were spontaneous and not biologically relevant because the increase was not statistically significant when compared with the control group, historical controls, or relevant data from the literature, and no metastases were observed. No significant increase in incidence of hepatocellular carcinomas when compared with the control groups were observed in males (BASF AG 1991k, 1992b, 1992c, 1992d). In the published version of the same study (Astill et al. 1996b), the liver tumour findings in mice were reported slightly differently than those reported in the original study. Time-dependent and time-independent statistical analyses showed a weak adverse trend in the incidence of hepatocellular carcinomas in male and female mice at high dose levels. The time-adjusted incidence of hepatocellular carcinomas in male mice (18.8%) was within the historical normal range at the testing facility (0-22%), but that in female mice (13.1%) was outside the normal range (0.2%). It was concluded that 2-ethylhexanol was not carcinogenic in male mice and that a weak or equivocal carcinogenic response was observed in female mice. Non-cancer effects observed in rats included reduced body weight gain and isolated occurrences of mild clinical signs of toxicity in males and females at 150 mg/kg-bw per day, and increased mortality in females and reduced body weight gain, occurrence of clinical signs of toxicology, and significant increases in relative brain, stomach, kidney and liver weights occurred in both sexes at 500 mg/kg-bw per day (BASF AG 1992b, 1992c; Astill et al. 1996b). Non-neoplastic effects observed in mice included increased mortality, reduction in body weight gain, and effects on the blood count (slight increase in polynuclear neutrophils and a slight drop in lymphocytes) in both sexes at 750 mg/kg-bw per day. A significant change in some organ weights and foci in the liver and stomach were also noted after 13 months of exposure at that dose level (BASF AG 1991k, 1992d; Astill et al. 1996b). The LOAEL for non-neoplastic effects was 150 mg/kg-bw per day, based on increased mortality, reduced body weight gain, occurrence of clinical signs of toxicology, and a significant increase in some organ weights in rats.

In *in vitro* assays, 2-EHA was not mutagenic in bacterial mutation assays that used *Salmonella typhimurium* and *Escherichia coli*, with and without metabolic activation (Hoechst 1982; Warren et al. 1982; Zeiger et al. 1988; JETOC 2000). Similarly, an assay for chromosomal aberration in Chinese hamster ovary cells in the absence of metabolic activation showed a negative response. However, in this assay, a weak positive result was observed in the presence of metabolic activation (NTP 1986, 1991). Positive results were also reported in assays for DNA damage and unscheduled DNA synthesis in rat hepatocytes in absence of metabolic activation, and for sister chromatid exchange (SCE) in Chinese hamster ovary cells in the presence and absence of metabolic activation (NTP 1986, 1991; Plant et al. 1998). Also, a weak positive result for SCE was noted in human lymphocytes in the absence of metabolic activation (Sipi et al. 1992).

In vivo assays for 2-EHA have not been identified in the literature. However, 2-ethylhexanol was not found to be genotoxic in *in vivo* assays in experimental animals. 2-Ethylhexanol produced negative results in a dominant lethal assay in mice exposed orally and did not cause DNA binding in the liver of mice given 2-ethylhexanol by gavage (Rushbrook et al. 1982; von Däniken et al. 1984). Also, no increase in the number of polychromatic erythrocytes containing micronuclei was seen in mice exposed to 2-ethylhexanol via intraperitoneal injection and negative results were obtained in a chromosome aberration assay in bone marrow cells of rats dosed orally (Litton Bionetics, Inc. 1982; Putman et al. 1983).

Based on the collective evidence on genotoxicity, especially the negative *in vivo* results for 2-ethylhexanol, it is considered that 2-EHA is not mutagenic.

No epidemiological data and no standard carcinogenicity assays in experimental animals have been identified for 2-EHA, and oral carcinogenicity studies in rats and mice using 2-ethylhexanol have reported only a weak or equivocal carcinogenic response in female mice. However, although a thorough analysis of the mode of action of 2-EHA is beyond the scope of this screening assessment, it has been shown that the compound induces peroxisome proliferation in rats and mice treated orally (see Appendix 3), and that a range of other peroxisome proliferators have induced liver cancer in rodents following longer-term administration. It is well established that the peroxisome proliferator-activated receptor PPARα plays a role in peroxisome proliferation-induced liver cancer (Corton and Lapinskas 2005). The relevance of the induction of PPARα and peroxisome proliferation by 2-EHA in rodents to health effects in humans remains to be established, as does the role of PPARs in reproductive toxicity. However humans are, in general, much less susceptible than rodents to peroxisome proliferation, suggesting that the peroxisome proliferating effects of 2-EHA in rodents are unlikely to be relevant to a human risk assessment (Klaunig et al. 2003).

2-EHA was not irritating to eyes in a study in rabbits (Hoechst 1985). Other studies showed that 2-EHA is severely irritating to the eye and capable of causing injury to the cornea, based on the results of studies in which the clinical signs (clouding of the cornea, severe reddening and oedema formation, iritis, and ocular discharge) were not reversible

or not reversible in all animals within the 8- or 6-day observation periods (BASF AG 1953, 1967, 1978a, 1978b; BG Chemie 2000). Application of 2-EHA to the skin of rabbits resulted in severe irritation with erythema, oedema, and necrotic changes which were not reversible within the observation period or healed up only very slowly. Evaluation of skin irritancy by the various authors is extremely divergent, spanning all assessments from not irritating, mildly irritating, moderately irritating and severely irritating to corrosive (BASF AG 1953, 1967, 1978a, 1978b; Eastman Kodak 1955, 1986, 1987e; Mellon Institute 1972a, 1972b; Hoechst 1985; BG Chemie 2000).

Toxicokinetic studies on 2-EHA in rats showed that it is rapidly and extensively absorbed from the gastrointestinal tract. Following dermal exposure, absorption up to 50 % of the substance was observed 96 hours after application (English et al. 1998). 2-Ethylhexanol is equally rapidly and extensively absorbed after oral administration in rats, but only 5 to 6 % of the substance was absorbed 96 hours after dermal exposure (Deisinger et al. 1994). In the mouse and rat, 2-EHA exhibits preferential distribution in the kidneys, liver, and blood. In pregnant mice, 2-EHA is able to cross the placenta and can be detected in the embryos at concentrations similar to those in the dams (BG Chemie 2000). The toxicokinetics studies of 2-EHA also demonstrated that it is subjected to oxidative metabolism and glucuronidation. Metabolites are rapidly excreted, primarily in the urine. Also, evidence for incorporation of 2-EHA into normal cellular intermediary metabolism was obtained (English et al. 1998). Oxidative and conjugated metabolites of 2-EHA have also been identified in urine of humans exposed to 2-EHA from plasticizers (Walker and Mills 2001). Rapid elimination of 2-EHA after intraperitoneal administration to rats and mice and in workers exposed by the dermal and inhalation routes has been reported (Kröger et al. 1990; Pennanen and Manninen 1991). After intraperitoneal administration of ^{14}C-labelled 2-EHA to rats and mice, radioactivity detected within 1-2 hours in the blood, liver and kidney was cleared rapidly (Pennanen and Manninen 1991). After repeated administration, there is a decrease in total elimination of 2-EHA and its metabolites, compared with single-dose administration. It has been suggested that repeated dosing induces oxidation of 2-EHA and results in the compound being incorporated into normal cellular metabolism to a greater extent (Eastman Kodak 1987e; English et al. 1989).

The confidence in the health effects database for 2-EHA is considered to be low to moderate, as the data for this substance are supported by data on 2-ethylhexanol. Dermal and inhalation exposure studies (short-term, subchronic and chronic toxicity, carcinogenicity and genotoxicity, reproductive toxicity, and developmental toxicity) are limited.

Characterization of Risk to Human Health

Based on consideration of the weight-of-evidence-based classification of 2-EHA by the European Commission as Category 3 for developmental toxicity (European Commission 1995, 1996; ESIS c1995-2010) and consideration of available relevant data for the

substance as well as for 2-ethylhexanol, a critical effect for characterization of risk to human health for 2-EHA is developmental toxicity based on skeletal variations and malformations observed in rat fetuses. Accordingly, upper-bounding estimates of exposure (females) were compared with critical effect levels for developmental toxicity. In addition, effects including liver and stomach effects and reduced body weight gain were observed in experimental animals following repeated-dose exposures at higher dose levels of 2-EHA. Therefore, margins of exposure were also derived for the general population comparing upper-bounding estimates of exposures with the lowest effect levels for these non-developmental effects.

The main contributor to the estimate of total daily intake from environmental media and food for the general population of Canada (see Appendix 1) is the estimate of exposure from foods packaged in glass jars sealed with metal lids such as those used for baby food. Exposure from air, water, or soil is not considered significant because releases to air were very low, soil concentrations are expected to be low because 2-EHA is expected to volatilize from dry soil, and intake based on the one drinking water measurement was significantly lower than intake from food and beverages.

A comparison between the lowest oral LOAEL available for developmental toxicity in experimental animals (i.e., 100 mg/kg-bw per day) and the highest estimate of oral daily intake in females (20–59 years old; 8 µg/kg-bw per day) results in a margin of exposure of approximately 12 500. A comparison of the most conservative oral intake of 107 µg/kg-bw per day for non-formula-fed infants up to 0.5 years of age with the lowest LOAEL from a chronic oral study (i.e., 150 mg/kg-bw per day) results in a margin of exposure of approximately 1400. These margins are considered adequate to account for uncertainties in the health effects and exposure databases.

Estimates of exposure to 2-EHA for the general population of Canada from the use of consumer products such as alkyd paint may result in dermal and inhalation exposures. While inhalation or dermal developmental toxicity studies were not available for 2-EHA, there were developmental toxicity studies conducted via inhalation and dermal routes with the analogue 2-ethylhexanol which were considered appropriate for characterizing risk.

In a dermal developmental toxicity study conducted with 2-ethylhexanol, there was no evidence of toxicity to the developing young up to a maximum tested dose of 2520 mg/kg-bw per day (Bushy Run 1989; Fisher et al. 1989; Tyl et al. 1992). A comparison of the NOAEL (2520 mg/kg-bw per day) and the highest range of estimated dermal applied doses (0.005 to 0.5 mg/kg-bw per event for an acute exposure to 2-EHA while using alkyd paint) results in margins of exposure ranging from approximately 5000 to 500 000. There is uncertainty regarding the relative dermal absorption of 2-EHA and 2-ethylhexanol. However, these margins are considered adequate taking into consideration the exposure duration of the study relative to the exposure scenario for the general population and the absence of acute endpoints of concern in the animal database.

There is a possibility of acute inhalation exposure to 2-EHA when using paints. Given the lack of inhalation toxicity studies for 2-EHA, a developmental toxicity study with 2-ethylhexanol was used. In this study, no effects were observed in rat fetuses at the maximum tested dose of 850 mg/m^3 after exposure for 7 hours/day on days 1 to 19 of gestation (Nelson et al. 1988, 1989, 1990). Comparing this NOAEL with the highest estimated range of mean event air concentrations during the use of alkyd paint products (0.08 to 8.2 mg/m^3, an acute exposure event) results in margins of exposure ranging from 104 to 10 625. These margins are considered adequately protective of human health. As supporting information, a study of workers noted a maximum concentration of 0.7 mg/m^3 2-EHA in the breathing zone of employees treating wood with the sodium salt of this substance (Kröger et al. 1990). Since these workers were using products with a higher concentration (26% by weight) and their activities involved working in an oven (temperature 60°C) and still recorded relatively low breathing zone concentrations of 2-EHA, the acute inhalation exposure and risk characterization noted above is considered highly conservative.

Uncertainties in Evaluation of Risk to Human Health

This screening assessment does not take into account all possible intraspecies and interspecies variation. However, the liver effects related to peroxisome proliferation which have been observed in mice and rats are unlikely to be relevant in human health risk assessment. There is uncertainty with the carcinogenicity of 2-EHA owing to the lack of long-term studies, although the available information from genotoxicity tests and carcinogenicity studies available for 2-ethylhexanol does not indicate a concern. In addition, dermal and inhalation exposure studies (short-term, subchronic, and chronic toxicity, carcinogenicity and genotoxicity, reproductive toxicity, and developmental toxicity) were limited.

There is uncertainty regarding the estimation of population exposure because of the lack of data, including the lack of Canadian data, and because models were used. No quantitative information on concentrations of 2-EHA in air or soil were identified, and only one drinking water value was identified. Intake estimates for food were based on two publications reporting 2-EHA concentrations in baby foods and fruit juices, which are not representative of a typical non-infant diet. Also, the intake estimates for infants may be over-estimates as Health Canada recommends that infants be exclusively breastfed and solids not introduced until 6 months of age (Health Canada 2005; Health Canada 2007). There is some uncertainty related to actual exposures from the use of certain consumer products containing 2-EHA (e.g., paint dryers, stains, and antifreeze) since model parameters were not available for all potential scenarios. However, confidence is high that these exposures would be lower than the ones presented for alkyd paint and spray paint. There is also uncertainty regarding exposure from use of temporary tattoos. In addition, there is uncertainty related to the total exposure of the general population to the 2-EHA moiety from sources including salts, esters, and plasticizers.

Conclusion

Based on the information presented in this screening assessment, it is concluded that 2-EHA is not 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 or that constitute or may constitute a danger to the environment on which life depends. Additionally, 2-EHA does not meet the criteria for persistence and bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

On the basis of the adequacy of the margins between upper-bounding estimates of exposure to 2-EHA and critical effects levels, it is concluded that 2-EHA be considered to be a substance that is not 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 2-EHA does not meet any 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.

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Appendix 1. Upper-bounding estimates of daily intake of 2-EHA by the general population in Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of 2-EHA by various age groups							
	0–6 months[1, 2, 3]			0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	breast fed	formula fed	not formula fed					
Air[9]	N/A[10]			N/A	N/A	N/A	N/A	N/A
Drinking water[11]	N/A	0.0053	0.0013	0.0006	0.0006	0.0003	0.0003	0.0003
Food and beverages[12]	N/A	N/A	18.9–107.3	3.60–20.4	1.47–8.3	0.75–4.26	1.49–8.43	0.80–4.52
Soil[13]	N/A			N/A	N/A	N/A	N/A	N/A
Total intake	N/A	<0.01	18.9–107.3	3.60–20.4	1.47–8.3	0.75–4.26	1.49–8.43	0.80–4.52

1 No data describing concentrations of 2-EHA in breast milk were identified.

2 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 0.2 L/day (not formula fed) and ingest 30 mg of soil per day (Health Canada 1998).

3 For exclusively formula-fed infants, intake from water is synonymous with intake from food. The concentration of 2-EHA in water used to reconstitute formula was based on a tap water measurement in Montreal, Québec (Horn et al. 2004). No data describing concentrations of 2-EHA in formula were identified. Approximately 50% of infants not formula fed are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990, in Health Canada 1998).

4 Assumed to weigh 15.5 kg, breathe 9.3 m^3 of air per day, drink 0.2 L of water per day, and ingest 100 mg of soil per day (Health Canada 1998).

5 Assumed to weigh 31.0 kg, breathe 14.5 m^3 of air per day, drink 0.4 L of water per day, and to ingest 65 mg of soil per day (Health Canada 1998).

6 Assumed to weigh 59.4 kg, breathe 15.8 m^3 of air per day, drink 0.4 L of water per day, and ingest 30 mg of soil per day (Health Canada 1998).

7 Assumed to weigh 70.9 kg, breathe 16.2 m^3 of air per day, drink 0.4 L of water per day, and ingest 30 mg of soil per day (Health Canada 1998).

8 Assumed to weigh 72.0 kg, breathe 14.3 m^3 of air per day, drink 0.4 L of water per day, and ingest 30 mg of soil per day (Health Canada 1998).

9 2-EHA was identified but not quantified in one study that sampled along the Niagara River (Hoff and Chan 1987). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

10 N/A = not available

11 One report of 2-EHA in drinking water was identified; the publication reported 0.050µg/L from a single sample of Montreal, Québec tap water (Horn et al. 2004).

12 Estimates of intake from food are based upon concentrations in foods that are selected to represent the 12 food groups addressed in calculating intake (Health Canada 1998). Two reports describing concentrations of 2-EHA in baby food and fruit juices, products packaged in glass jars with metal lids, were identified (Elss et al. 2004; Ežerkis et al. 2007). The source of 2-EHA was determined to be the plastic gasket. Estimates of intake from food were based on food products considered to be packaged in glass jars sealed with metal lids: baby food, condiments, juice, beer, and sauces. The concentrations of 2-EHA in these products was estimated to range from 0.6–3.4 mg 2-EHA/kg food product, representing the >89% and the maximum concentration (Elss et al. 2004; Ežerkis et al. 2007). Amounts of foods consumed on a daily basis by each age group are described by Health Canada (Health Canada 1998).

13 No information reporting the concentration of 2-EHA in soil or house dust was identified.

Appendix 2. Estimates of exposures to 2-EHA from use of alkyd paint and spray paint

Consumer product scenario	Assumptions	Estimated exposure
Alkyd paint (use brush/roller painting, high solid paint scenario from RIVM 2007)	Concentration in paint product ranging from 0.01% to less than 1% (Environment Canada 2010a). One percent is used as an upper-bounding concentration. **Inhalation: evaporation from increasing area** Exposure duration of 132 minutes, application duration of 120 minutes, product amount of 1300 g, room volume of 20 m^3, ventilation rate of 0.6/hour, release area of 10 m^2, temperature of 20°C, Langmuir method for mass transfer rate, molecular weight matrix of 550 g/mol (RIVM 2007), vapour pressure of 4 Pa (refer to Table 2, footnote *) (US EPA 2010). **Dermal: constant rate** Contact rate of 30 mg/minute, release duration of 120 min (RIVM 2007) Adult body weight of 70.9 kg (Health Canada 1998), inhalation rate of 36.7 m^3/day (rate while doing light exercise a body weight of 70.9 kg) (RIVM 2007).	**Inhalation** – Mean event concentration 0.08 to 8.2 mg/m^3 **Dermal** – Acute applied dose 0.005 to 0.5 mg/kg-bw per event
Spray paint (use spraying paint with a spray can from RIVM 2007)	Concentration in paint product ranging from 0.01% to less than 1% (Environment Canada 2010a). One percent is used as an upper-bounding concentration. **Inhalation: spray model** Spray duration of 15 minutes, exposure duration of 20 minutes, room volume of 34 m^3, room height or 2.25 m, ventilation rate of 1.5/hour, mass generation rate of 0.33 g/second, airborne fraction of 1 g/g, total fraction of non-volatile compounds in products of 0.3, mass density of total non-volatile compounds of 1.5 g/cm^3, initial droplet distribution of 30 µm (coefficient of variance of 0.8), inhalation cut-off diameter of 15 µm (RIVM 2007), vapour pressure of 4 Pa (refer to Table 2, footnote *) (US EPA 2010). **Dermal: constant rate** Contact rate of 100 mg/minute, release duration of 15 minutes (RIVM 2007). Adult body weight of 70.9 kg (Health Canada 1998), inhalation rate of 36.7 m^3/day (rate while doing light exercise using a body weight of 70.9 kg) (RIVM 2007).	**Inhalation** – Mean event concentration 0.03 to 3.4 mg/m^3 **Dermal** – Acute applied dose 0.002 to 0.2 mg/kg-bw per event

Appendix 3. Summary of health effects information for 2-EHA

Endpoints	Lowest effect levels[a]/results
Acute toxicity (2-EHA)	**Lowest oral LD_{50}** (guinea pig) : >800-1600 mg/kg-bw (Eastman Kodak 1966, 1982) **Other oral LD_{50}s** : >1600-3640 mg/kg-bw from five studies (rat, guinea pig) (BG Chemie 2000) **Lowest inhalation LC_{50}** (rat, guinea pig; 6 hours): >2356 mg/m^3 (Eastman Kodak 1966, 1982). **Other inhalation LC_{50}** : No other studies identified **Lowest dermal LD_{50}** (rabbit): 1260 mg/kg-bw (Union Carbide 1971). **Other dermal LD_{50}** : Two studies (rat, guinea pig), > 2000-6300 mg/kg-bw (BG Chemie 2000)
Short-term repeated-dose toxicity (2-EHA)	**Lowest oral LOAEL:** 706 mg/kg-bw per day based on dose-dependent increase in liver weight in both sexes in F344 rat (five males and five females per dose) exposed in the diet to 0, 0.75, 1.5, or 3% (0, 706, 1351 or 2276 mg/kg-bw per day in males; 0, 756, 1411 or 2658 mg/kg-bw per day in females), for 15 days. This increase was accompanied with histological changes in liver (cellular atrophy and necrosis) at the highest and intermediate dose in both sexes (Eastman Kodak 1987c). **Oral LOEL:** 9 mg/kg-bw per day based on dose-related increase in carnitine acetyltransferase activity and inhibition of citrulline biosynthesis in liver mitochondria in Wistar rats (five males per dose) exposed via drinking water to 0, 0.1, 1, 5, or 10 g/L (equivalent to 0, 33, 130, or 200 mg per day or 0, 9, 95, 370, or 570 mg/kg-bw per day using a dose conversion from Health Canada 1994) for 20 days (Manninen et al. 1989). **Other oral LOAEL:** 800-1608 mg/kg-bw per day in mice or rat exposed for 15 days (Eastman Kodak 1987a, 1987d). **Other oral LOEL:** 200-1600 mg/kg-bw per day in rat or mice exposed for 15 days (Eastman Kodak 1987a, 1987b). Also, numerous studies in the rat and mouse have demonstrated that oral administration of 2-EHA in the diet or by gavage for 3 to 21 days at dose levels ranging from 150 to 5332 mg/kg bw/day results in hepatic peroxisome proliferation, characterized by an increase in relative liver weight and elevated levels of various peroxisomal enzyme activities (Moody and Reddy 1978, 1982; Lundgren et al. 1987 a, 1987b, 1988 a, 1988b; Keith et al. 1988, 1992; Sunberg et al. 1994; Hamdoune et al. 1995). No inhalation and dermal studies were identified.

Endpoints	Lowest effect levels[a]/results
Short-term repeated-dose toxicity (2-ethylhexanol)	**Lowest oral LOAEL:** 275 mg/kg-bw per day based on dose-dependent effects such as local damage to the stomach, effects on the immune system and effects on the haematopoietic system in both sexes in F344 rats (10 males and 10 females per dose) dosed by gavage with 0, 0.1, 0.33, 1.0, and 1.5 mL/kg-bw (equivalent to 0, 83, 275, 834, and 1250 mg/kg-bw per day), 9 times over 12 days (Bushy Run 1988c). **Other oral LOAEL:** 330 mg/kg-bw per day in rats exposed for 11, 17 and 22 days or mice exposed for 11 days (Schmidt et al. 1973; BASF 1991 a, 1991b, 1991c, 1991d, 1991e, 1991f) **Oral LOEL:** 320-2857 mg/kg-bw per day in rats or mice exposed in the diet or by gavage for 7 to 21 days; hepatic peroxisome proliferation (increase in absolute and relative liver weight, increased activity of different liver enzymes) was observed (Lake et al. 1974, 1975; Moody et al. 1976; Moody and Reddy 1978, 1982; Hammock and Ota 1983; Keith et al. 1985, 1992; Hodgson 1987). **Lowest dermal LOAEL:** 834 mg/kg-bw per day based on lymphopenia, reduced spleen weights and histopathological effects on the skin (exfoliation, acanthosis, hyperkeratosis, dermatitis, edema, and eschar formation) in both sexes in rats (10 males and 10 females per dose) exposed to 0, 0.5, or 1.0 mL (equivalent to 0, 417 or 834 mg) 2-ethylhexanol/kg-bw per day through dermal route for 9 times within 12 days. Other effects include increased triglyceride levels in both doses groups (Bushy Run 1988c). **Other dermal LOAEL:** 1670 mg/kg-bw per day based on significant reductions in body weight, decreases in the relative and absolute thymus weight and histological effects on the liver, lungs, kidneys, heart, testes, thymus, and adrenal glands in rats (10 per group) exposed to 0 or 1670 mg/kg-bw per day through dermal route once daily, 5 days/week for 12 treatment days (Schmidt et al. 1973). No inhalation studies were identified.
Subchronic toxicity (2-EHA)	**Lowest oral LOAEL:** 917 mg/kg-bw per day based on reduced body weight gain (slight but statistically significant) in conjunction with reduced feed consumption in male and female F344 rats (10 males and 10 females per dose) exposed in the diet to 0, 0.1, 0.5, or 1.5% (0, 61, 303, or 917 mg/kg-bw per day in males; 0, 71, 360, or 1068 mg/kg-bw per day in females), for 91-93 days. A LOEL of 303 mg/kg-bw per day based on increased relative liver weight in both sexes accompanied with histological changes in liver (hepatocyte hypertrophy) at the highest and intermediate dose in males and in the highest dose only in females was also determined in this study (Eastman Kodak 1988; Juberg et al. 1998). **Other oral LOAEL:** 1040 mg/kg-bw per day based on reduced body weight gain at the highest and intermediate dose in female and at the highest dose only in male B6C3F1 mice (10 males and 10 females per dose) exposed in the diet to 0, 0.1, 0.5, or 1.5% (0, 180, 885, or 2728 mg/kg-bw per day in males; 0, 205, 1038, or 3139 mg/kg-bw per day in females), for 91-93 days. A LOEL of 885 mg/kg-bw per day based on increased relative liver weight and histological changes in liver (hepatocyte hypertrophy and increased eosinophilia) in males and females was also determined. Changes in the epithelial cells of the proximal convoluted renal tubules in males and females kidneys and forestomach lesions in males at the highest dose were also observed (Eastman Kodak 1988; Juberg et al. 1998). No inhalation and dermal studies were identified.

Endpoints	Lowest effect levels[a]/results
Subchronic toxicity (2-ethylhexanol)	**Lowest oral LOAEL:** 500 mg/kg-bw per day based on reduced body weight gain in males and females F344 rats (10 males and 10 females per dose) given 0, 25, 125, 250 or 500 mg 2-ethylhexanol/kg-bw per day by gavage 5 days/week for 3 months. At this dose level, hepatic peroxisome proliferation was determined by measuring the increase in activity of hepatic cyanide-insensitive palmitoyl Coenzyme A in livers. Also, macroscopic examination revealed a slight increase in the number of individual and multiple foci in the mucosa of the forestomach. In addition, a small number of rats showed fatty infiltration at the margins of the liver lobes. At 250 mg/kg-bw per day, an increase in relative liver weight in males and females and increased relative stomach weight in females only was observed. Diminution in alkaline phosphatase activity and blood sugar in males and decrease in alanine aminotransferase activity in females was noted also at that dose level (BASF AG 1991g, 1991h; Astill et al. 1996a). **Other oral LOAEL:** 833 mg/kg-bw per day based on increased absolute and relative liver weight and signs of liver and kidney damage (hyperaemic and/or swollen livers in females and degenerative effects in males' kidneys) in DW rats (10 males and females per dose) exposed to 2-ethylhexanol in the diet to 0, 100, 500, 2500 or 12 500 ppm (equivalent to 0, 7, 33, 167, or 833 mg/kg-bw per day) for 90 days (Mellon Institute 1961a, 1961b). **Oral LOEL:** 250 mg/kg-bw per day based on non-dose-dependent increased in relative stomach weight in males only in B6C3F1 mice (10 males and 10 females per dose) given 0, 25, 125, 250, or 500 mg 2-ethylhexanol/kg-bw per day by gavage 5 days/week for 3 months. At the highest dose, histological examination revealed mild focal or multi-focal acanthosis of the forestomach mucosa in two males and one female. No hepatic peroxisome proliferation was observed at all dose tested (BASF AG 1991i, 1991j; Astill et al. 1996a). **Inhalation NOAEL:** 638 mg/m^3 based on no treatment related toxic effects in both sexes in rats (10 males and 10 females per groups) exposed to 0, 15, 40, or 120 ppm (equivalent to 0, 80, 212, or 638 mg/m^3), 6 hours/day, 5 days/week, for 90 days (BASF AG 1992a). No other inhalation studies. No dermal studies were identified.
Chronic toxicity/ carcinogenicity (2-EHA)	No chronic study identified.
Chronic toxicity/ carcinogenicity (2-EHA)	**Oral study in rats:** Groups of 50 F344 rats per sex were administered 0, 50, 150 or 500 mg 2-ethylhexanol/kg-bw per day in Cremophor EL by gavage 5 days/week for 24 months. At the top dose level, the sum of all primary benign and malignant tumours (liver adenomas, hepatocellular carcinomas) was clearly lower than that in either control group. Thus, no neoplastic lesions were attributed to exposure to 2-ethylhexanol in both male and female rats. **Non-neoplastic LOAEL:** 150 mg/kg-bw per day based on reduced body weight gain in males and females and isolated occurrences of mild clinical signs of toxicity. Other non-neoplastic effects included increased mortality in females and reduced body weight gain and occurrence of clinical signs of toxicology in both sexes at 500 mg/kg-bw per day. Significant increase in relative brain, stomach, kidneys, and liver weights were also observed at the highest dose after 18 months (BASF AG 1992b, 1992c; Astill et al. 1996b).

Endpoints	Lowest effect levels[a]/results
	Other oral studies: Groups of 50 B6C3F1 mice per sex were administered 0, 50, 200 or 750 mg 2-ethylhexanol/kg-bw per day in Cremophor EL by gavage 5 days/week for 18 months. No treatment-related differences from controls were observed in the incidence of liver adenomas in males and females but a significant increase in hepatocellular carcinomas (10% incidence) was observed in female mice at 750 mg/kg-bw per day compared with the vehicle control group. However, this increase was not statistically significant when compared with the water controls, the historical controls or the relevant data from the literature. As no metastases were observed either, the hepatocellular carcinomas were judged by the authors of the study to be spontaneous and biologically irrelevant. No significant increase in incidence of hepatocellular carcinomas (18% incidence) when compared with the control groups were observed in males. In the published version of the study by Astill et al. (1996b), the findings on the liver tumours in mice were reported slightly differently than those reported in the original study. Time-dependent and time-independent statistical analyses showed a weak adverse trend in the incidence of hepatocellular carcinomas in male and female mice at high dose levels. The time-adjusted incidence of hepatocellular carcinomas in male mice (18.8%) was within the historical normal range at the testing facility (0-22%), but that in female (13.1%) lay outside the normal range (0.2%). It was concluded that 2 ethylhexanol was nononcogenic in male mice and that a weak or equivocal oncogenic response was observed in female mice. **Non-neoplastic LOAEL:** 750 mg/kg-bw per day based on increased mortality, reduction in body weight gain and effects on the blood count (slight increase in polynuclear neutrophils and a slight drop in lymphocytes) in both sexes. A significant change in some organ weight and foci in the liver and stomach were also noted after 13 months of exposure (BASF AG 1991k, 1992d; Astill et al. 1996b). No inhalation or dermal studies were identified.
Reproductive toxicity (2-EHA)	**Lowest LOEL for reproductive toxicity:** 100 mg/kg-bw per day based on reduction in sperm motility in male Han Wistar rats exposed via drinking water to 0, 100, 300 or 600 mg/kg-bw per day for 10 weeks before mating and 3 weeks during mating with females treated 2 weeks before mating, 3 weeks during mating, and for a further 3 weeks postpartum during the entire gestation and lactation period. An increase in sperm abnormality was observed at the highest and intermediate doses, although it was non-significant. A slight but dose-dependent decrease in fertility was also observed in females, but no information is given on the extent to which the effect on fertility was statistically significant. LOEL for systemic toxicity = 600 mg/kg-bw per day based on reversible decreased body weight gain in females (Pennanen et al. 1992). **Other study:** No other oral studies No inhalation or dermal studies were identified.

Endpoints	Lowest effect levels[a]/results
Developmental toxicity (2-EHA)	**Lowest oral LOAEL:** 100 mg/kg-bw per day based on skeletal variations (wavy ribs and reduced cranial ossification) and increase in skeletal malformations (club foot) in fetuses of pregnant Han Wistar rats (20-21 females per group) exposed via drinking water to 0, 100, 300, or 600 mg/kg-bw per day during days 6-19 of gestation. The increase in club foot was dose-dependent and statistically significant at the highest and intermediate dose. Slight but significantly reduced foetal body weight was noted at 300 mg/kg-bw per day and higher**.** A maternal toxicity LOAEL of 600 mg/kg-bw per day based on decreased maternal body weight gain was identified (Pennanen et al. 1992). **Other oral study:** A study in pregnant F344 rats (25 females per groups) dosed by gavage during gestation days 6 to 15 to 0, 100, 250, or 500 mg/kg-bw per day resulted in a LOEL of 250 mg/kg-bw per day based on skeletal variations (reduced ossification) in fetuses. **LOAEL for maternal toxicity:** 500 mg/kg-bw per day based on maternal lethargy, ataxia, respiratory distress, and increased liver weight (absolute and relative to corrected body weight). The range-finding study in rats conducted by the same authors find a LOAEL of 500 mg/kg-bw per day based on reduction in fetal body weight and significant decrease in the percentage of living fetuses. A maternal toxicity LOAEL of 1000 mg/kg-bw per day based on mortality of seven out of eight (7/8) animals between days 7 and 9 of gestation was identified (Bushy Run 1988a; Hendrickx et al. 1993). In a study in pregnant New Zealand white rabbits (15 females per groups) exposed by gavage during gestation days 6 to 18 to 0, 25, 125, or 250 mg/kg-bw per day, no treatment-related effects on developmental parameters were observed, although the **LOAEL for maternal toxicity** = 125 mg/kg-bw per day, based on the treatment-related death of 1/15 dams and the abortion by 1/15 dams. Death of 1/15 dams and clinical signs of toxicity in surviving dams (lethargy, ataxia, respiratory distress and significant reduced body weight gain) were observed at 250 mg/kg-bw per day. In the range-finding study in rabbits done by the same authors, there was no clear indication of developmental toxicity in the offspring. A maternal toxicity LOAEL of 500 mg/kg-bw per day based on high mortality (7 or 8/8 animals died) was identified (Bushy Run 1988b; Hendrickx et al. 1993). In a study in Wistar rat (7-10 per groups) exposed by gavage on day 12 of gestation to 0, 900, and 1800 mg/kg-bw per day, fetal malformations and early fetal deaths at 900 mg/kg-bw per day and above was observed. No data on maternal toxicity was reported (Ritter et al. 1987). In a study in Sprague-Dawley rat (15-20 per groups) exposed by gavage on days 6-15 of gestation to 0, 900, and 1200 mg/kg-bw per day, fetal malformations and early fetal deaths at 900 mg/kg-bw per day and above was observed. Maternal deaths were also observed at the highest dose (Narotsky et al. 1994). No inhalation or dermal studies were identified.

Endpoints	Lowest effect levels[a]/results
Developmental toxicity (2-ethylhexanol)	**Lowest oral LOAEL:** 1300 mg/kg-bw per day based on skeletal malformations, variations, and retardations in fetuses of pregnant Wistar rats (10 females per group) dosed by gavage during gestation days 6 to 15 to 0, 130, 650, and 1300 mg 2-ethylhexanol/kg-bw per day. Increases in the number of resorption and post-implantation losses and reduction in fetal weights were also observed at 1300 mg/kg-bw per day. **LOAEL for maternal toxicity** = 1300 mg/kg-bw per day based on decreased body weight gain in the dams during the second half of the treatment period (BASF AG 1991l). **Other oral studies:** A study in pregnant CD-1 mice (50 females per group) dosed by gavage during days 7-14 of gestation to 0 (control) or 1525 mg 2-ethylhexanol/kg-bw per day resulted in a LOAEL of 1525 mg/kg-bw per day based on significant reductions in the number of live pups and in their weight compared with the controls. **LOAEL for maternal toxicity** = 1525 mg/kg-bw per day based on deaths (of the 50 mice treated, 18 died during the study and the investigators attributed the deaths of 17 of these animals to 2-ethylhexanol), reduced body weight, reduced movement, ataxia, hypothermia, unkempts coats and blood in the urine (Hazleton 1983; Hardin et al. 1987). **Inhalation NOAEL:** 850 mg/m^3. 2-Ethylhexanol was neither teratogenic nor embryotoxic in fetuses of pregnant Sprague-Dawley rats (15 females per group) exposed by inhalation to 0 or 200 ppm (equivalent to 850 mg/m^3, according to the investigators), 7 hours/day, on days 1 to 19 of gestation. **LOEL for maternal toxicity** = 850 mg/m^3 based on significant reduction in feed consumption (Nelson et al. 1988, 1989, 1990). No other inhalation studies were identified. **Dermal NOAEL:** 2520 mg/kg-bw per day based on no treatment-related increases in external, visceral, or skeletal malformations or variations in pregnant F344rats (25 females per group) exposed to 0, 252, 420, 840, 1680, or 2520 mg 2-ethylhexanol/kg-bw per day through dermal route during gestation days 6-15. **LOAEL for maternal toxicity** = 1680 mg/kg-bw per day based on decreased body weight gain in the dams (Bushy Run 1989; Fisher et al. 1989; Tyl et al. 1992). No other dermal studies were identified.
Genotoxicity and related endpoints: *in vivo* (2-ethylhexanol)	**Micronuclei** **Negative:** polychromatic erythrocytes; B6C3F1 male and female mice; intraperitoneal (0 or 436 mg/kg-bw, once or twice within 24 hours) (Litton Bionetics Inc. 1982). **Dominant lethal assay** **Negative:** Male ICR/SIM mice; oral (0, 250, 500 or 1000 mg 2-ethylhexanol/kg-bw per day, on five consecutive days) (Rushbrook et al. 1982). **DNA binding** **Negative:** No activity attributable to covalent binding to DNA was detected in the liver in mice given 110 or 120 mg ^{14}C-labelled ethylhexanol/kg-bw per day by gavage or in the liver in rats given 51 or 52 mg ^{14}C-labelled ethylhexanol/kg-bw per day by gavage after a pre-treatment for 4 weeks with 1 % di(2-ethylhexyl) phthalate in the diet (von Däniken et al. 1984). **Chromosome aberration assay** **Negative:** Bone marrow cells; male and female F344 rats; oral (0.02, 0.07, or 0.2 mL 2-ethylhexanol (equivalent to 16.7, 58.9 and 167 mg/kg-bw per day) for 5 days) (Putman et al. 1983).

Endpoints	Lowest effect levels[a]/results
Genotoxicity and related endpoints: *in vitro* (2-EHA)	**Mutagenicity in bacteria** **Negative:** *Salmonella typhimurium*, strains TA97, TA98, TA100, and TA1535, with and without activation (Zeiger et al. 1988). **Negative:** *S. typhimurium*, strains TA98, TA100, TA1535, and TA1537, with and without metabolic activation (JETOC 2000). **Negative:** *S. typhimurium*, strains TA98 and TA100, with and without metabolic activation (Warren et al. 1982). **Negative:** *S. typhimurium*, strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation (Hoechst 1982). **Negative:** *Escherichia coli*, strain WP2uvrA/pKM101, with and without metabolic activation (JETOC 2000). **Negative:** *E. coli*, strain WP2uvrA, with and without activation (Hoechst 1982). **DNA damage** **Positive:** Rat hepatocytes, in absence of metabolic activation (Plant et al. 1998). **Positive:** Unscheduled DNA synthesis in rat hepatocytes, in absence of metabolic activation (Plant et al. 1998). **Chromosome aberration assay** **Negative:** Chinese hamster ovary cells in absence of metabolic activation (NTP 1986, 1991). **Weak positive:** Chinese hamster ovary cells in presence of metabolic activation (NTP 1986, 1991). **Sister chromatid exchanges (SCE) assay** **Positive:** Chinese hamster ovary cells in presence and absence of metabolic activation (NTP 1986, 1991). **Weak positive:** Human lymphocytes in absence of metabolic activation (Sipi et al. 1992).
Sensitization	No evidence that 2-EHA has sensitizing potential (Hoechst 1986; BASF AG 1997).
Irritation	**Skin irritation** Application of 2-EHA to the skin of rabbits resulted in severe irritation with erythema, edema, and necrotic changes which were not reversible within the observation period or healed up only very slowly. Evaluation of skin irritancy by the various authors is extremely divergent, spanning all assessments from not irritating, mildly irritating, moderately irritating, and severely irritating to corrosive (BASF AG 1953, 1967, 1978a, 1987b; Eastman Kodak 1955, 1986, 1987e; Mellon Institute 1972a, 1972b; Hoechst 1985; BG Chemie 2000).
	Eye irritation 2-EHA was not irritating to eye in a study in rabbit (Hoechst 1985). Other studies showed that 2-EHA is severely irritating to the eye and capable of causing injury to the cornea, based on the results of studies in which the clinical signs (clouding of the cornea, severe reddening and oedema formation, iritis and ocular discharge) were not reversible or not reversible in all animals within the 8- or 6-day observation periods (BASF AG 1953, 1967, 1978a, 1987b; BG Chemie 2000).
Human studies	No relevant human studies were identified.

[a] Definitions; LD_{50}: median lethal dose; LOEL/LOEC: lowest-observed-effect level/concentration; LOAEL/LOAEC: lowest-observed-adverse-effect level/concentration; NOAEL/NOAEC: no-observed-adverse-effect level/concentration.