Regulatory Toxicology and Pharmacology 92 (2018) 128–137

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Derivation of an oral reference dose (RfD) for di 2-ethylhexyl cyclohexan-1, 4-dicarboxylate (DEHCH), an alternative to phthalate plasticizers

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ARTICLE INFO

Keywords:
DEHCH
Reference dose
Phthalate alternative
Plasticizer

ABSTRACT

Di 2-ethylhexyl cyclohexane-1,4-dicarboxylate (DEHCH, CAS 84731-70-4) is an ester of polycarboxylic acid assessed in a variety of mammalian toxicity assays as a substitute for phthalate ester-type plasticizers. An OECD 422 combined systemic toxicity study with a reproductive/developmental toxicity screening test in SD rats found minimal effects on the liver, spleen, and thyroid and no indication that DEHCH is a developmental or reproductive toxicant. In a 90-day feeding study in SD rats, no toxicologically relevant effects were noted. Low genotoxic potential of DEHCH is indicated by the lack of mutagenicity or clastogenicity *in vitro*. No studies assessing mode of action were identified. Where data gaps exist for DEHCH, a read-across approach was used to assess other toxicological endpoints of interest. Di-ethylhexyl terephthalate (DEHT, CAS 6422-86-2) and 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH, CAS 474919-59-0) have higher tiered studies to supplant the data lacking for health-based standard setting. DEHT and DINCH were chosen as the source substances due to similar physical/chemical properties and thus anticipated metabolism and toxicological characteristics. An oral reference dose (RfD) for DEHCH was calculated using the human equivalent NOAEL from the OECD 422 study. A total uncertainty factor of 100 was comprised of interspecies (3x), intraspecies (10x), subchronic to chronic (1x), LOAEL to NOAEL uncertainty (1x) and database uncertainty (3x) factors, resulting in an RfD of 0.3 mg/kg-day.

1. Introduction

Di 2-ethylhexyl cyclohexane-1,4-dicarboxylate (DEHCH) is a plasticizer used in the production of polyvinyl chloride (PVC) polymers (Hanwha Chemical, 2016). DEHCH is produced by the hydrogenation of di(2-ethylhexyl)terephthalate (DEHT) in the presence of a catalyst. Plasticizers are used to increase the flexibility of plastics found in a variety of applications such as medical devices, food contact materials, water systems, toys, gloves, and construction materials. DEHCH is recommended for use as a chemical additive for PVC, plastic, rubber, ink, glue, paint and lubricants and in these applications may be used up to a maximum of 30%. In commercial applications DEHCH has a purity of > 99% and < 1% DEHT (Hanwha Chemical, 2016). DEHCH is a colorless, odorless, liquid with a low vapor pressure of < 1.5 mmHg 50 °C.

Occupational exposures may occur at the workplace when transferring chemicals between vessels/large containers, in processing during synthesis and formulation, or in handling articles where the substance is bound in the material. Consumer exposures may be indirect due to leaching from plastics used in water distribution systems or inclusion into or onto materials when employed as a binding agent in paints, coatings or adhesives (ECHA, 2017).

2. Data gaps and read-across justification

As an alternative approach to address data gaps for standard setting, read-across has been used in lieu of animal testing. The use of a read-across approach is not unique among regulatory agencies. Under REACH regulations, read-across approaches have been widely applied to group similar substances based on structural similarities to meet regulatory requirements (ECHA, 2015).

An adequate database to support the derivation of a high confidence RfD includes at least a 90-day repeat dose study in two species, a two-generation study, and developmental studies in two species. Due to the absence of a developmental study and a two-generation reproductive study for DEHCH, the substance DEHT is a surrogate for read across based on the following considerations: 1) the metabolism of the compound is similar to the predicted metabolites of DEHCH involving hydrolysis into the monoester and 2-ethylhexanol and 2) there are similar physical chemistry and toxicological properties to fill the necessary

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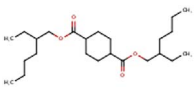
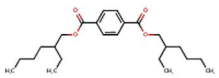
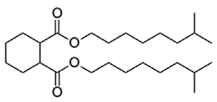
https://doi.org/10.1016/j.yrtph.2017.11.010
Received 24 August 2017; Received in revised form 14 November 2017; Accepted 16 November 2017
Available online 21 November 2017
0273-2300/

Table 1
Some Physical and Chemical Properties of Di 2-ethylhexyl cyclohexane-1,4-dicarboxylate (DEHCH), Di (2- ethylhexyl) terephthalate (DEHT), and Di-isononyl cyclohexane-1,2-carboxylate terephthalate (DINCH).

	DEHCH		DEHT		DINCH	
						
	Target Chemical		Source Chemical		Source Chemical	
Empirical Formula	C24H44O4	ChemIDplus, 2017	C24H38O4	ECHA, 2017	C26H48O4	BASF, 2014
CAS Number	84731-70-4	ChemIDplus, 2017	6422-86-2	ECHA, 2017	474919-59-0	BASF, 2014
Molecular Weight	396.6	ChemIDplus, 2017	390.6	ECHA, 2017	424.7	BASF, 2014
Appearance	Liquid	Hanwha Chemical, 2016	Liquid	ECHA, 2017	Liquid	BASF, 2014
Color	Colorless	Hanwha Chemical, 2016	Colorless	ECHA, 2017	Almost Odorless	BASF, 2014
Odor	Odorless	Hanwha Chemical, 2016	Slight	ECHA, 2017	Mild	BASF, 2014
Melting/Freezing Point	−40.7 °C	Hanwha Chemical, 2016	< -67.2 °C	ECHA, 2017	−54	BASF, 2014
Initial Boiling Point and Boiling Range	406.4 °C	Hanwha Chemical, 2016	375 °C	ECHA, 2017	394 °C	BASF, 2014
Flash Point	217 °C	Hanwha Chemical, 2016	212 °C	ECHA, 2017	224	BASF, 2014
Solubility	Insoluble in water	Hanwha Chemical, 2016	Insoluble in Water	ECHA, 2017	< 0.02 mg/L	BASF, 2014
Vapor Pressure	< 1.5 mmHg (50 °C)	Hanwha Chemical, 2016	< 0.001 Pa (25 °C)	ECHA, 2017	< 0.000001 hPa (20 °C)	BASF, 2014
Relative Density	0.954 (20 °C)	Hanwha Chemical, 2016	0.98 g/cm3 (20 °C)	ECHA, 2017	0.944-0.954 g/m3 @ 20 °C)	BASF, 2014
Partition Coefficient: n-octanol/water	logKow ≥ 6.2	Hanwha Chemical, 2016	LogKow ~8.39 (QSAR EPI Suite: KowWIN)	U.S. EPA, 2017	10	BASF, 2014
Viscosity	44 cP (20 °C)	Hanwha Chemical, 2016	65.8 mPa (25 °C)	ECHA, 2017	44-60 mPa.s.	BASF, 2014
Similarity Scores compared to DEHCH (Dice coefficient)			71%–79%	OECD Toolbox, 2017; ChemIDplus, 2017	41%	OECD Toolbox, 2017

data gaps. According to Gray et al. (2000) endocrine disruption in phthalates depends on the ortho-position of the ester side chains and a carbon length of four to six carbons. Therefore, terephthalate esters do not possess the same toxicological properties as the ortho-phthalate esters. DEHCH and DEHT lack key critical structural activity relationships and would lack reproductive/developmental effects attributed to these structural differences. Whether substituting the central aromatic ring with the cyclohexane impacts these endpoints is unclear due to the scarcity of data on experimental animals. Therefore DINCH, an ortho-cyclohexane-diacid, is another source molecule which shares this similarity with DEHCH. There are no other known substitutes with different length carbon side chains in the para position for comparison. Similarity scoring between DEHCH and DEHT was in the range of 71–79% and for DEHCH and DINCH was 41% (OECD Toolbox, 2017; ChemIDplus, 2017). The physical chemical properties of each substance are shown in Table 1.

3. Toxicokinetics

No studies designed to determine the toxicokinetics of DEHCH were found. Gastrointestinal absorption of the material can be expected due to the lipophilic nature of the substance. The log Pow is > 6.62 (Hanwha Chemical, 2016). Repeat dose studies reveal treatment-related effects on the liver at relatively high doses indicating that some absorption is occurring.

There is no empirical information on the distribution of DEHCH. Since DEHCH has a high octanol/water partition coefficient (log Pow = 6.2), once systemically absorbed it is expected to accumulate in fatty tissues.

An *in silico* approach was used to determine the possible metabolism of DEHCH. The predicted metabolites using QSAR (OECD QSAR Toolbox Version 3.4) was the monoester, 2-ethylhexyl cyclohexane-1,4-carboxylate, cyclohexan-1,4-dicarboxylate, 2-ethylhexanol, 2-ethylhexanal, and 3-ethylheptan-2-one.

There is no empirical evidence as to the excretion of DEHCH through the oral route.

3.1. Surrogate information

Barber et al. (1994) orally gavaged rats with a 100 mg/kg ester chain ^{14}C radiolabeled DEHT. Based on the amount of radioactivity recovered, the estimated amount absorbed from the gut was approximately 50%. At 144 h after exposure analysis revealed that the compound was found in all organs examined with the highest levels of radioactivity found in the liver and fat. Elimination via the gastrointestinal tract included 36.6% of the parent compound, 2.6% of the monoester, and glucuronide metabolites of the 2- ethylhexanol ester. Excretion in the urine accounted for 51% of the dose. Urinary metabolites include terephthalic acid, oxidized metabolites of 2-ethylhexanol, mono-2-ethylhexanol terephthalate and glucuronic and sulphuric acid conjugates. In a subacute study, rats were fed DEHT in the diet at 0, 3000, 6000, or 10000 ppm for 15 days (Battelle, 2007 as cited in Ball et al., 2012). On day 15, a 24-h urine collection was taken and analyzed revealing that terephthalic acid, 2-ethylhexanol and 2-ethylhexanoic acid were excreted at 4–10% of the daily dose.

Studies of the metabolism of DINCH were reviewed by Bhat et al. (2014). The bioavailability of DINCH was determined by dosing female and male Wistar rats with [^{14}C]-DINCH at 20 or 1000 mg/kg-day via a single oral gavage (BASF AG, 2005 as cited by Bhat et al., 2014). The systemic bioavailability of DINCH was 40–49% and 5–6% at doses of 20 and 1000 mg/kg-day, respectively, indicating that gastrointestinal absorption was saturated at high concentrations.