BUREAU FOR CHEMICAL SUBSTANCES

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Substance name: 2-ethylhexan-1-ol

EC No 203-234-3

CAS No 104-76-7

Evaluating Member State(s): Poland

Dated: 25 March 2015

Evaluating Member State Competent Authority

MSCA name: Bureau for Chemical Substances

Dowborczykow 30/34 Str.
90 – 019 Lodz,
Tel: + 48 42 25 38 440
Fax: + 48 42 25 38 440
Email: evaluation@chemikalia.gov.pl

Year of evaluation in CoRAP: 2014

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

2-Ethylhexan-1-ol was originally selected for substance evaluation in order to clarify suspected risks about:

- CMR properties, in particular developmental toxicity
- wide dispersive use,
- consumer use,
- high RCR,
- aggregated tonnage.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

No completed/ongoing processes.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action	X

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

Not applicable.

4.1.1. Harmonised Classification and Labelling

The substance is self-classified by the Registrants. In the view of the eMSCA there is no priority for harmonised classification.

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4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure*	X
Actions by the registrants to ensure safety, as reflected in the registration dossiers** (e.g. change in supported uses, applied risk management measures, etc.)	
*This conclusion can be reached e.g. if the outcome of a test on hazardous properties clarified that substance is not hazardous, the exposure data shows no risk. This can be due to the fact that the data was originally available in the registration dossiers or was obtained due to a substance evaluation decision. **This conclusion can be reached if registrants changed their registrations e.g. the supported uses, applied risk management measures, reduction of the aggregated tonnage, cease of manufacture etc.	

One of the reasons for the selection of 2-EH was health hazard concern. It was noted that the developmental effects were observed in the pre-natal developmental toxicity studies. This concern could be removed because outcome of a full evaluation of the available information shows that doses of 2-EH are not toxic or are only slightly toxic to maternal animals and no developmental toxicity warranting classification is observed.

Another reason for the selection of 2-EH was exposure concern. This concern could be removed because the exposure data shows no risk after updating the registration dossier by the Lead Registrant.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

2-Ethylhexan-1-ol was originally selected for substance evaluation in order to clarify suspected risks about:

- CMR properties, in particular developmental toxicity
- wide dispersive use,
- consumer use,
- high RCR,
- aggregated tonnage.

Table 4

EVALUATED ENDPOINTS **Endpoint evaluated**	**Outcome/conclusion**
Identity of the substance	2-Ethylhexan-1-ol is an racemic mixture and should be considered as a multi-constituent substance.
Human health hazard assessment • Toxicity for reproduction	Evaluation of the available information does not warrant classification of 2-EH for the developmental toxicity.
Exposure assessment (and related risk characterisation)	Evaluation of the updated, available information shows that RCRs for all scenarios are below 1 and the risks are adequadely managed for all scenarios (on the basis of the updated registration dossier and chemical safety report submitted by the Lead Registrant).

7.2. Procedure

The evaluation was performed on the basis of the registration dossier (IUCLID file) and Chemical Safety Report (CSR) submitted by the lead registrant (8 April 2014) as well as on other additional information available from scientific databases and publications.

All the available information was assessed regarding adequacy for evaluation of the main grounds of concern of 2-ethylhexan-1-ol on humans. The particular emphasis was placed on the possible developmental effects of 2-EH. A full evaluation of the available

information was conducted in order to assess whether the observed developmental effects are the result of maternal toxicity.

The assessment of exposure was performed to determine whether the conditions required to achieve an RCR < 1 would be met during uses.

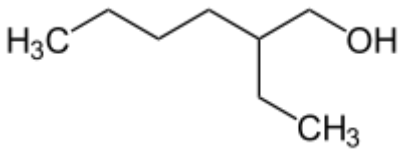
The results of the evaluation are documented in this report.

7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	2-ethylhexan-1-ol
EC number:	203-234-3
CAS number:	104-76-7
Index number in Annex VI of the CLP Regulation:	Not applicable
Molecular formula:	C8H18O
Molecular weight range:	130.2279
Synonyms:	1-Hexanol, 2-ethyl

Structural formula:



Multiconstituent substance

2-Ethylhexan -1-ol has an one chiral centre and it can exist as a mixture of enentiomers. The result of optical activity measurement shows that the optical rotation for 2-ethylhexan-1-ol was negligibly small and the values were within the range of measurement error.

Based on this result it could be considered that the 2-ethylhexan-1-ol exists as equimolar mixture of enantiomers (racemat). According to *Guidance for identification and naming of substances under REACH and CLP* (Version:1.3 February 2014) racemates are considered as multi-constituent substances. Therefore, in the eMSCA opinion, 2-ethylhexan-1-ol should be treated as multi-constituent substance.

7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	93 Pa at 20 °C
Water solubility	0.9 g/L at 20 °C and pH = 5.8
Partition coefficient n-octanol/water (Log Kow)	log Pow = 2.9 at 25 °C
Autoflammability /self-ignition temperature	280 °C at 1013 hPa
Explosive properties	Non explosive
Oxidising properties	The substance does not possess oxidising properties
Granulometry	Substance is marketed or used in a non solid or granular form
Stability in organic solvents and identity of relevant degradation products	Stable in organic solvents
Dissociation constant	pKa 15.75; no dissociation at pH 4-9.
Melting / freezing point	Melting point: -89 °C
Boiling point	185 °C at 1013 hPa
Relative density	The density of the test item is 0.8325 g/cm³ at 20 °C.
Surface tension	47 mN/m at 20 °C (concentration 0.81 g/L)
Viscosity	9.8 mPa s (dynamic) at 20 °C

7.5. Manufacture and uses

7.5.1. Quantities

Aggregated tonnage (per year): 100,000 - 1,000,000 tonnes

7.5.2. Overview of uses

Table 9

USES	
	Use(s)
Formulation	distribution formulation use in laboratories
Uses at industrial sites	manufacture distribution

	formulation in coatings in laboratories in functional fluids in oil and gas field drilling in cleaning products as intermediate under non strictly controlled conditions
Uses by professional workers	in coatings dilution of a concentrate in functional fluids in cleaning products co-formulants in plant protection products
Consumer Uses	dilution of a concentrate
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

There is no harmonised classification of 2-ethylhexan-1-ol.

7.6.2. Self-classification

The substance is self-classified by registrants as follows:

Table 10

Classification		*Labelling*	
Hazard Classes and Category Codes	**Hazard Statement Codes**	**Hazard Statement Codes**	**Pictograms, Signal Word Code**
Acute Tox 4 *Skin Irrit. 2* *Eye Irrit. 2* *STOT SE 3*	H332: Harmful if inhaled H315: Causes skin irritation H319: Causes serious eye irritation H335: May cause respiratory irritation	H332: Harmful if inhaled H315: Causes skin irritation H319: Causes serious eye irritation H335: May cause respiratory irritation	GHS07 Wng

Self classification notifications for 2-ethylhexan-1-ol (EC Number: 203-234-3) are available in the C&L Inventory (http://echa.europa.eu/pl/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/66567). An overview (status of March 2015) for 2-ethylhexan-1-ol is given in the table below:

Table 11

Classification		Labelling	
Hazard Classes and Category Codes	**Hazard Statement Codes**	**Hazard Statement Codes**	**Pictograms, Signal Word Code**
Acute Tox 4 *Skin Irrit. 2* *Eye Irrit. 2* *STOT SE 3*	H332: Harmful if inhaled H315: Causes skin irritation H319: Causes serious eye irritation H335: May cause respiratory irritation	H332: Harmful if inhaled H315: Causes skin irritation H319: Causes serious eye irritation H335: May cause respiratory irritation	GHS07 Wng
Skin Irrit. 2 *Eye Irrit. 2*	H315: Causes skin irritation H319: Causes serious eye irritation	H315: Causes skin irritation H319: Causes serious eye irritation	GHS07 Wng
Eye Irrit. 2	H319: Causes serious eye irritation	H319: Causes serious eye irritation	GHS07 Wng

7.7. Environmental fate properties

Not relevant for evaluation.

7.8. Environmental hazard assessment

Not relevant for evaluation.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

The data submitted in CSR is sufficient for evaluation of toxicokinetics of 2-ethylhexan-1-ol.

7.9.2. Acute toxicity and Corrosion/Irritation

Not relevant for evaluation.

7.9.3. Sensitisation

Not relevant for evaluation.

7.9.4. Repeated dose toxicity

Not relevant for evaluation.

7.9.5. Mutagenicity

Not relevant for evaluation.

7.9.6. Carcinogenicity

Not relevant for evaluation.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

One of the reasons for the selection of 2-EH was health hazard concern. It was noted in the screening that developmental effects were observed in the pre-natal developmental toxicity studies. Therefore, a full evaluation of the available information was required in order to assess whether the observed developmental effects are the result of maternal toxicity. This part of the document reviews the available study reports in order to assess reproductive toxicity of 2-EH, and assess whether a proposal of harmonised C&L is needed for this endpoint.

Fertility

There is no study aimed at assessment of effect of 2-EH on fertility and sexual function on animal. Also observations on humans are not available.

However, taking into account that di (2 -ethylhexyl) terephthalate (DEHT) is metabolised to 2 -ethylhexan-1-ol (2-EH) and terephthalic acid, the 2- generation reproduction toxicity study of Faber et al. (2007) with DEHT provide some information on effect of 2-EH on fertility and sexual function. The 2 -ethylhexan-1 -ol and terephthalic acid are thus available in the body after di (2 -ethylhexyl) terephthalate (DEHT) application. Terephthalic acid has been shown to not affect fertility and sexual function (study report, 2003). Lack of effects of DEHT on fertility and sexual function found in the study of Faber et al. (2007) confirms findings of study report study (2003) and gives no indication that 2-EH would affect fertility and sexual function.

This conclusion is further supported by the results of repeated dose toxicity studies. The results of 90-day oral gavage study (Astil et al. , 1996) indicate that 2-EH at dose 250 and 500 mg/kg/day, thus comparable to the doses of 2-EH estimated in Faber et al. study (2007), does not affect morphology of testes or ovaries in rats and in mice. The relative weight of testes at a dose of 500 mg/kg/day was increased and that of ovaries decreased in rats only at dose 250 mg/kg /day, but not at a dose of 500 mg/kg. The relative weight of the testes (related to body weight) of 500 mg/kg/day group was slightly increased (5.5 % compared to control group). However, neither the absolute testes weight nor the relative weight of the testes related to brain weight did show any significant changes. Thus, the weight changes in testes can be attributed to the decreased body weight in males of high dose group (93 % of control value) and were not considered as adverse. There was decreased body weight gain in male and female rats at 500 mg/kg amounting to weight losses of 7% in males and 6% in females by Week 13. Due to low intensity, lack of dose response relationship and due to lack of histopathological changes in testes and ovaries, the changes in the weight of testes and ovaries alone are not regarded as adverse and do not warrant classification for fertility and sexual function. The weight of these reproductive organs were not affected in mice administered 2-EH by gavage at doses 250 and 500mg mg/kg, day for 13 weeks (Astil, 1996).

The effects of 2-EH on the testis are of interest because of the testicular atrophy and Sertoli cell damage produced in rats by high doses of DEHP, of which 2-EH is a metabolite (Gray and Gangolli, 1986). Sjoberg et al. (1986) showed that 350 mg of 2EH/kg/day administered to Sprague-Dawley (SD) rats by oral gavage for 5 days had no effect on testis weight and produced no effects on the seminiferous tubule. Similarly, concentrations of 0.2 mM of 2-EH were without effect on Sertoli cells from SD rats in primary culture studies (Gray and Beamond 1984). In the 13-week study in rats (Astil et al., 1996) there was a slight increase in relative testis weight at 500 mg/kg, not correlated with any morphological changes, and there were no gross or microscopic changes in testes of mice at 500 mg/kg. Therefore it is thus unlikely that the effects of DEHP on the testis are attributable to 2-EH.

The available data does not raise concern that 2-EH would affect fertility and sexual function.

Developmental toxicity

There are several studies to evaluate developmental toxicity of 2-EH: two studies in mice (study report 1991; Hardin et al. 1987) and four studies in rats (Hellwig and Jäckh, 1997; Ritter et al. 1987, Tyl et al. 1992, Nelson et al. 1989).

Mice

The first one, GLP and OECD TG 414 compliant study (study report 1991 reported also as NTP, 1991) provided evidence that 2-EH in doses 17, 59, and 191 mg/kg bw/day does not induce embryo or fetal toxicity in mice.

In the second mice study (Hardin et al. 1987) in which mice were given 1525 mg/kg on day 6 till day 13 of gestation the following developmental effects were observed: decreased number of viable litters and pups per liter, decreased birth weight and weight gain for pups. However these effects should be considered as a secondary non-specific consequence of other toxic effects in dams, because 2-EH at a dose applied in this study caused 34% mortality in the exposed mice. In addition, short term toxicity study in mice using similar dose of 1500 mg/kg/d for (study report, 1992b) provided evidence that 2-EH at this repeated dose level causes damage of several organs (stomach, liver, kidney) which may affect intrauterine and early postnatal development of pups.

Rats

There were two oral studies (Hellwig and Jäckh, 1997; Ritter et al. 1987), one dermal study (Tyl et al. 1992) and one inhalation study (Neslon et al. 1989) of developmental toxicity of 2-EH in rats.

In the Hellwig and Jäckh oral study (1997) performed in accordance with GLP and OECD TG 414 (except that 10 animals instead of 20 was used per group) 2-EH at dose of 1300 mg/kg/d caused intrauterine deaths of embryos and pups, reduced foetal weight, increased incidence of internal and skeletal malformations as well as of skeletal variations and retardation. However, 2-EH at the dose of 1300 mg/kg/d was also very toxic to dams; 6 out of 10 treated dams were found dead before the end of the study. Therefore high maternal toxicity was most probably responsible for some effects such as increased intrauterine deaths or reduced foetal weight, as well as for some of the internal and skeletal malformations observed in that group, although their incidence was very low. 2-EH did not induced developmental toxicity at a dose of 130 mg/kg/d, while at a dose of 650 mg/kg/d the foetal weight slightly reduced, but still within historical control level. Therefore it may be concluded that in this study 2-EH did not exert developmental toxicity in doses not lethal to dams.

The oral study of Ritter et al. (1987) has limited reliability because the study design was not similar to that required by OECD TG 414 or method B.31 (Council Regulation (EC) No 440/2008). In addition, the observed results were not consistent with those observed in other studies. In spite of high doses used (800 and 1600 mg/kg/d) the study did not provide any information on maternal toxicity and no embryo or pup mortality was observed. Malformations in fetuses following single treatment with 2-EH at a dose approximately 1600 mg/kg included hydronephrosis (7.8% of live fetuses), tail defects (4.9% of live fetuses), limb defects (9.7% of live fetuses). Such defects were not observed after 2-EH treatment in studies of Hellwig and Jäckh (1997) and study report (1991) or in other studies. Taking into account a purpose of the study focused on clarification of developmental toxicity of di(2-ethylhexyl) phthalate (DEHP, use of only 7 females in a group, application of 2-EH only as a single dose at 12 day of gestation, lack of compliance of study design with OECD TG 414, lack of consistency of effects observed

with other studies, it is doubtful whether study of Ritter et al. (1987) should be taken as a reliable source of information on developmental toxicity of 2-ethylhexanol.

The embryonic or fetal development of rats was not affected in the dermal developmental toxicity study (Tyl et al., 1992) conducted under GLP and with a design compliant with OECD TG 414 in which 2-EH was administered at doses 252, 840, and 2520 mg/kg bw/day, although the systemic maternal toxicity was observed at the highest dose.

No developmental toxicity was noted in an inhalation study (Nelson et al., 1989), in which female rats were exposed 2-EH at 850 mg/m³ during days 0-19 of gestation. At this exposure level 2-EH was moderately toxic to dams as can be judged based on reduction of feed consumption and body weight gain during gestation.

Based on the existing body of evidence it is concluded that at doses not lethal to mothers, in studies performed in compliance with methodological requirements, 2-EH does not induce developmental toxicity in mice and rats. Only at high doses, which were lethal to dams 2-EH increases intrauterine lethality of embryos and pups and leads to retardation of development. Even at these lethal doses the increase of fetal malformations is very low and no dose-response relationship is seen.

It is concluded that these developmental effects at doses highly toxic to dams are secondary non-specific consequence of other toxic effects in dams, and they do not justify classification of 2-EH for developmental toxicity. Several studies (study report 1991 reported also as NTP, 1991; Hellwig and Jäckh, 1997; Tyl et al., 1992 and Nelson et al., 1989) provided evidence that 2-EH is not a developmental toxicant in rats and mice.

2-ethylhexanoic acid (2-EHA)

The substance evaluation for 2-EHA is currently ongoing and the conclusions of this evaluation will be published on ECHA website once the evaluation is concluded.

2-ethylhexanoic acid (2-EHA) (EC No205-743-6, CAS No 149-57-5)), which is major urinary metabolite of 2-ethyl-1-hexanol in rats (Albro, 1975; Deisinger et al. 1993;1994) has harmonised classification as Repr. Cat. 3; R63 Possible risk of harm to the unborn child, which has been transposed to Repr. 2 H361d *** in Table 3.1 List of harmonised classification and labelling of hazardous substances of Annex VI of the Regulation 1272/2008. In the study by Deisinger et al. (1994), the main metabolites in urine of orally treated rats were 2-ethylhexanoic acid, 5-hydroxy-2-ethylhexanoic acid, 6-hydroxy-2-ethylhexanoic acid and 2-ethyl-1,6-hexane diacid. Together, they represented 37 - 45% of the administered dose. Minor metabolites were 5-hydroxy-2-ethylhexanoic acid as well as lactones of 5-hydroxy-2-ethylhexanoic acid and 2-ethyl-5-hexanoneacid. They represented 3 - 5% of the administered dose. About 1% of the administered dose was recovered as 2-ethylhexanol. All these compounds were predominantly excreted as glucuronides (Deisinger et al.,1994). Albro (1975) reported the formation of about 50% 2-ethylhexanoic acid following a single oral exposure of rats to 275 mg/kg.

1. The range-finding study in Fischer 344 rats showed significant maternal toxicity (death in seven of eight dams) and statistically significant reduction of maternal weight gain at 1000 mg/kg for GD 6-9. Indications of maternal toxicity were also observed at 500 mg/kg, including not statistically significant weight gain reduction and clinical sings of toxicity.

In the main developmental toxicity study, groups of 25 pregnant Fischer 344 rats per dose level received daily doses of 0, 100, 250 and 500 mg/kg 2-EHA (nominal in corn oil) by oral gavage from gestational day 6 to 15 (study report, 1988c; 1988d; study report, 1993) the clinical signs of maternal toxicity were only observed at the high-dose level (500 mg/kg) and included hypoactivity, ataxia, audible respiration, ocular discharge and

periocular encrustations. No mortality and no effects on body weight were observed. Liver weight (absolute and relative) was significantly increased in the high-dose group.

Foetal effects: There were no changes in the incidence of resorptions and dead foetuses or in the percentage of viable foetuses. Foetal body weights (males and females) per litter were significantly reduced at 500 mg/kg, but these findings may be confounded by the slightly larger mean litter size. No significant differences in the incidence of external, skeletal or visceral malformations were observed among all groups.

There was a reduction in ossification of the axial and appendicular skeletons at 500 mg/kg. An increase in the number of foetuses with unossified anterior arch of the atlas and proximal phalanges of the forelimb and hindlimb was also observed at 250 mg/kg.

NOAEL of 250 mg/kg for maternal toxicity of 2-EHA was obtained, based on clinical signs of toxicity and increased liver weights. For developmental toxicity, a NOAEL of 100 mg/kg was established, based on reduced skeletal ossification at a dose of 250mg/kg/d. (study report, 1988c; 1988d; study report, 1993). However, minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity, do not necessarily warrant classification as developmental toxicant (point 3.7.2.4.3. of the CLP Regulation).

2. The range-finding study in pregnant rabbits treated with 500 and 1000 mg/kg 2-EHA showed high toxicity. Mortality was observed at the high and mid doses. No changes in resorptions, deaths or malformed foetuses occurred. No external malformations were observed in foetuses at any of the treated groups (study report, 1988c; 1988d; study report, 1993).

In the definitive study, groups of 15 pregnant rabbits per dose level were administered, by gavage, daily doses of 0, 25, 125 and 250 mg/kg 2-EHA in corn oil on gestational days 6 to 18. In this study, mortality was recorded at 125 and 250 mg/kg (one female each) on days 15 and 16 of gestation, respectively. One abortion was observed on gestational day 27 at 125 mg/kg. A significant reduction in body weight gain and food consumption was observed in the high-dose group during the post-treatment period (gestational days 18 to 29). At necropsy, no gross pathology, no changes in corrected body or gestational weights or in absolute and relative liver weights were observed.

Foetal effects: There was no increase of resorptions and dead foetuses or changes in the percentage of viable foetuses. No effects on foetal body weights and sex ratios were observed and no differences in malformations or variations were seen either.

3. In addition, a non-GLP developmental toxicity study, equivalent or similar to OECD 414, has been reported in the IUCLID dataset and considered as the supporting study (Pennanen *et al*., 1992). Groups of 20 or 21 female Wistar rats per dose level received daily doses of 100, 300 and 600 mg/kg 2-EHA as sodium salt via drinking water, during gestational days 6 to 19. Control animals received deionized water.

Body weight of dams suffered a slight decrease at the high-dose level from day 13 onward. At termination, statistically significant reductions in mean body weight and corrected maternal body weight gain were observed. In the same dose group, a decrease of 20% in the consumption of drinking water containing 2-EHA was seen from day 6, compared to the control group. No differences in food consumption were observed at any dose level. No maternal toxicity was noted at the low- and mid-dose groups.

In the mid- and high-dose groups the placental weight was also statistically significant reduced. No changes in gravid uterus weight were observed. At necropsy, no gross pathological changes in the organs of the dams occurred.

Foetal effects: The number of implantations, living foetuses or resorptions were not affected by treatment with 2-EHA . No dead foetuses were seen either in treated or control groups. Significant decreases in mean foetal body weight per litter were observed

at 600 mg/kg. At 300 mg/kg, the mean body weight of female foetuses was also decreased.

Dose-dependent increases in the number of foetuses with skeletal or visceral anomalies were observed at all dose levels, compared to controls. It has to be pointed out that the number of litters affected by these alterations has not been indicated. Clubfoot (congenital deformity of the foot, which is twisted out of shape or position) was the most severe skeletal malformation, occurred in all treatment groups, being only statistically significant at the two highest doses.

Those results justified the EU harmonised classification of 2-ethylhexanoic acid as Repr. 2 H361d: Suspected of damaging the unborn child based on the observed developmental effects in animals, such as fetotoxicity and skeletal malformations (clubfoot) in rat following oral doses given on days 6-19 of gestation.

The analysis of data on of 2-EHA indicate that potency of its developmental toxicity in rats is rather low, while it does not exert developmental toxicity in rabbits, since no embryonal or foetal effects were observed in rabbits given 2-EHA et doses of 25, 125, 250, 500 and 1000 mg/kg (study report, 1993). In rats the developmental toxicity is shown as retardation in ossification of skeletal system in fetuses of rats exposed at doses of 250 and 500 mg/kg/d. (study report (1993)) or as a decreased foetal body weight, and increases incidence skeletal or visceral anomalies and of clubfoot in foetuses of females rats exposed to EHA at 300 and 600 mg/kg.

Assuming that in the worst case 50 % of orally given 2-EH is metabolised to 2-EHA in order to reach developmental toxicity the doses of 2-EH would have to be at the level of 600 – 1200 mg/kg, which are known to be rather highly toxic to adult rats (Hellwig and Jäckh, 1997; study report, 1991). Therefore the data showing developmental toxicity of 2-EHA do not provide sufficient evidence of developmental toxicity of the parent substance.

7.9.8. Hazard assessment of physico-chemical properties

Not relevant for evaluation.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The eMSCA agrees with the registrant's selection of critical studies and the DNEL derivation.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

The existing data do not warrant classification of 2-EH to category Repr. 1B, H360D May damage the unborn child or to category Repr. 2 with hazard statement H361d Suspected of damaging the unborn child based on the results of animal studies.

The results of animals studies provide evidence of an adverse effect of 2-EH on development at very high doses causing strong toxic effects in dams, therefore they can be considered as a secondary non-specific consequence of other toxic effects. Evaluation of the available information shows that no maternal toxicity or slight maternal toxicty was observed with in animal studies and no developmental toxicity warranting classification is observed.

7.10. Assessment of endocrine disrupting (ED) properties

Not relevant for evaluation.

7.11. PBT and VPVB assessment

Not relevant for evaluation.

7.12. Exposure assessment

7.12.1. Human health

The Polish CA checked whether all identified uses reported in the registration dossier were considered in the Chemical Safety Assessment as well as in exposure scenarios.

7.12.2. Environment

Not relevant for evaluation.

7.13. Risk characterisation

The exposure scenarios as provided in the updated Chemical Safety Report were carefully reviewed. In summary, there are no inconsistencies and no missing information has been identified.

The combined RCRs (inhalation + dermal) calculated by the registrant for workers and concumers for all contributing exposure scenarios are below 1.

With the proposed operational conditions and risk management measures the risks to workers and consumers are under control for the identified uses of 2-Ethylhexan-1-ol.

7.14. References

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7.15. Abbreviations

2-EHA	2-ethylhexanoic acid
2-EH	2-Ethylhexan-1-ol
CoRAP	Community Rolling Action Plan
CSR	Chemical Safety Report
DEHT	di (2-ethylhexyl) terephthalate
DNEL	Derived No Effect Level
ECHA	The European Chemicals Agency
ED	Endocrine Disruption/Disrupting
GLP	Good Laboratory Practice
eMSCA	The Evaluating Member State Competent Authority
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level

NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
RCR	Risk Characterisation Ratio
RMS	Rapporteur Member State
SVHC	Substance of Very High Concern
US EPA	The United States Environmental Protection Agency