COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

ECHA accepts no responsibility or liability for the content of this table.

Last data extracted on 31.07.2019

Substance name: 2-Ethylhexanoic acid and its salts, with the exception of those specified elsewhere in this Annex
CAS number: -
EC number: -
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
26.07.2019	France		MemberState	1
Comment received				
Please precise whether this classification proposal is related to the racemic form or to a specific enantiomer salts of 2-EHA (2-Ethylhexanoic acid)? In the section Substance characterization, it is specified that: "The substances characterization, including the impurity profiles has been clearly provided for the registered group members in the corresponding registration dossiers. In all the cases, they are registered as mono-constituent substances with a high degree of purity (see Table 3). The evidence for similarity between the source (2-EHA) and the target substances (its salts) purities is considered sufficient." However, Table 3 does not contain any indication of the purity of the different salts of 2-EHA. Please update this section accordingly.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2019	Italy	<confidential>	Company-Manufacturer	2
Comment received				
New data is available from a study carried out according to the OECD guideline 422 for a 2-ethylhexanoic acid salt. The results of the study indicate the absence of any fertility and reproductive effects. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Public Consultation - Data from OECD 422 for a 2-ethylhexanoic acid salt.zip				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2019	Germany		MemberState	3
Comment received				
In Table 2 registered substances that fall under the description "2-Ethylhexanoic acid and its salts" are listed. One of these substances "1-(2-hydroxypropyl)-1,4-diazabicyclo[2.2.2]octan-1-ium 2-ethylhexanoate" has a harmonised classification as Eye Irrit. 2 and Skin Sens. 1 (Index number 613-184-00-8) but not as Repr. 2. The proposed				

entry is named "2-Ethylhexanoic acid and its salts, with the exception of those specified elsewhere in this Annex". Please check wether the proposed classification should also apply to this substance although it is specified elsewhere in the annex.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
26.07.2019	France		MemberState	4
Comment received				
Although 2-EHA is a structural analog of valproic acid, this analogy is not discussed in this CLP proposal. Valproic acid is self-classified (H360 - Repro 1A or 1B) and is known to impact human fetal development (see Tomson et al., 2015 and 2019). This analogy with a developmental toxicant should have been discussed and considered in this CLP proposal. Indeed, some of the effects observed with 2-EHA are common with those of valproic acid. The results obtained in the experimental reproductive toxicity studies with 2-EHA should have been put into perspectives with valproic acid results. Results of Ritter et al., 1987 on teratogenicity effect of 2-EHA and valproic acid should have been discussed. The embryo-fetal toxicity and malformations observed with 2-EHA deem a classification Repro 1B - H360 instead of Repr. 2 - H361d. Indeed, it should be noted that valproic acid or sodium valproate provoke embryofoetoxicity and teratogenicity effects in rats, mice and rabbits such as: - severe toxicity for the offspring during the period of organogenesis in the rat and the mouse (resorptions, reduction of the fetal weight), - embryotoxicity and teratogenicity in rats at 100 mg/kg bw/day, mice at 200-400 mg/kg bw/day, rabbits at 350 mg/kg bw/day and monkeys at 20 mg/kg bw/day. The most commonly observed abnormalities were in the vertebrae, ribs and kidneys. In the monkey, craniofacial and skeletal abnormalities were mainly observed (Mast et al., 1988, Hendricks et al., 1988) as well as ear malformation (Mast et al., 1988). In mice, cleft palates and exencephalia were also observed. - Lastly malformations such as ectrodactylie (Vorhees, 1987a and Ong et al., 1983) and tail malformation (Vorhees, 1987a and Ritter et al., 1987). Some of the embryo-fetal toxicity and malformations induced by sodium valproate were also observed with 2-EHA, the growing evidence on human developmental toxicity of valproic acid / sodium valproate would need to reconsider the actual classification of 2-EHA as Repr. 2 - H361d to Repro 1B - H360. This CLP proposal on reproductive toxicity should have also been considered the repeated dose toxicity results available on 2-EHA or on its salts since such studies may bring useful information on reproductive toxicity assessment (eg. testicular atrophy).				

Date	Country	Organisation	Type of Organisation	Comment number
25.07.2019	United States	<confidential>	Company-Downstream user	5
Comment received				
1) The April 16, 2019 CLH Report's (aka 'the report') read across justification is not sufficiently robust to group all the metal salts with the same classification as 2-EHA for reproductive toxicity:				

a. The report provides zero anchoring or bridging studies around toxicokinetic, reproductive, and developmental toxicity endpoints for any of the metal salts to justify their hypothesis for the category approach. One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism, and elimination of substances in the category. The CLH report only presents TK data for 2-EHA and relies on theoretical considerations for the metal salts. Without TK data on any of the metal salts one cannot assess the qualitative and quantitative internal systemic exposure to metal salts nor can one determine whether the substances have the same systemic toxicity profiles as 2-EHA.
b. The report states "although bioavailability studies are not available for any salt of 2-EHA, the dissociation constants of the salts indicate that in the neutral pH range, the substances will be mainly dissociated". It is important to note that the GI tract does not have a neutral pH along its length (i.e., pH ranges from 1 to 7.5 along GI), and there are very different retention times. The CLH report's reliance on theoretical considerations of dissociation in the GI tract without comparative studies in the metal salts does not support the read across.
c. Physical form would most certainly impact activity and bioavailability of the metal salts, many of which are not liquids like 2-EHA but rather powders, crystalline, pasty, lumpy, highly viscous, and waxy. In addition, the metal salts as placed on the market may contain mineral oil or other stabilizers that would impact the rate and extent of dissociation in the GI tract if ingested. No experimental studies have shown that salts of 2-EHA will be completely dissociated to pure 2-EHA in gastrointestinal tract. Even if 2-EHA salts are dissociated, not all 2-EHA might be released, which means that only lower dosage of 2-EHA will be available for absorption.
d. The CLH report groups 2-EHA and its metal salts with very broad physical chemical properties: e.g., from water solubility values that are insoluble to those above 2000 grams per liter; e.g., from logKow values of 1.3 to >5.7. These ranges are very broad, and many structurally very different chemicals fall in these ranges. Such broad ranges indicate likely differences in the hazard properties and do not support the proposed grouping without further experimental anchoring studies.
e. The report provides zero anchoring or bridging studies around the impact of metal basicity, which would certainly impact the stability of the salt. Numerous metals have been grouped together with 2-EHA including Na, K, Ba, Ca, Mn, Zn, Mo, Zr, Sn, and Co, and the report provides no experimental data on the similarity or dissimilarity of the important variable of metal basicity.
f. The Report concedes that for the majority of human health endpoints the data matrix "cannot be built since there is scarce information on the target substances themselves". This is an unacceptable foundation for read across that is inconsistent with ECHA's RAAF guidance.
g. One of the concepts in read-across approach is to determine if the target organ is same between target and source substances. Since there are no repeat dose toxicity studies available with any of the 2-EHA salts, it is impossible to determine if the salts of 2-EHA and 2-EHA will have the same mechanism of action and target organ toxicity.
h. In the ECHA Guidance (QSARS and grouping of chemicals, ECHA May 2008) the applicability domain of the category must be described by a "set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members. Clearly indicates the borders of the category and for which chemicals the category does not hold". The CLH Report on 2-EHA does not formally discuss or define the applicability domain, nor justify with experimental data why the apparent dissimilarities between 2-EHA and the metal salts do not compromise the grouping.

2) The Report appears to simply treat developmental variations (e.g., page 21 "wavy ribs, reduced ossification) observed in some of the toxicity studies on 2-EHA as necessarily

adverse, which is not justified and should not be used in isolation to classify for developmental toxicity
a. Developmental variations are defined as those alterations in anatomic structure that are considered to have no significant biological effect on animal health or body conformity and/or occur at high incidence, representing slight deviations from normal.
b. Delayed or incomplete ossification of developing bones and wavy/bent ribs are the two most commonly observed skeletal variations noted in regulatory guideline developmental toxicity studies (Carney, EW and Kimmel CA. Interpretation of Skeletal Variations for Human Risk Assessment: Delayed Ossification and Wavy Ribs. Birth Defects Research (Part B) 80: 473–496 2007). Reduced maternal food consumption, and reduced gestational body weight gain, have previously been shown to cause fetal weight reductions and reduced ossification (Khera KS. Common fetal aberrations and their teratologic significance: a review. Fundamental and Applied Toxicology 1:13-18 1981). Furthermore, it has been demonstrated that maternal malnutrition can result in reduced placental blood flow which can induce fetal growth retardation (Ahokas RA, Anderson GD, Lipshitz J. Effect of dietary restriction, during the last week only or throughout gestation, on cardiac output and uteroplacental blood flow in pregnant rats. Journal of Nutrition 113(9) :1766-1776 1983). Since skeletal ossification is highly dependent upon maternal physiological factors, such as nutritional status and blood flow, it is not unexpected that fetal ossification rates can be altered by maternal toxicity.
c. It is widely accepted that delays in ossification and wavy/bent ribs are resolved during postnatal skeletal remodelling and are not mechanistically linked to malformations (Carney et al. 2007). These developmental variations are considered to have no significant biological effect on animal health or body conformity and in isolation should therefore not be sufficient to classify metal salts of 2-EHA as developmental toxicants without further scientific justification. Furthermore, it is our opinion that such findings should not have been considered sufficient to justify assigning a harmonised classification as a developmental toxicant to 2-EHA and should certainly not be the sole criterion by which metal salts of 2-EHA are classified as a developmental toxicant.

3) The Report relies heavily on a non-GLP study on 2-EHA from 1992 -- that is not compliant with current OECD guidelines -- to draw its conclusions on the developmental toxicity of 2-EHA. An out of date non-GLP study should not be used to read across to all the metal salts of 2-EHA for classification and labelling, without further scientific justification (which is not included in the CLH report).

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2019	Germany		MemberState	6

Comment received

Classification for reproductive toxicity of 2-ethylhexanoic acid (2-EHA) was harmonized under the former Dangerous Substance Directive (DSD) and was included in the CLP Annex VI with Repr. 2 (H361d***). The classification of 2-EHA as toxic for reproduction was based on skeletal variations and malformations observed in a non-GLP developmental toxicity study in Wistar rats (Pennanen et al., 1992).

From the point of view of the German CA classification as Repr. 1B (H360D) should be considered by RAC.

In the non-GLP developmental toxicity study in Wistar rats (Pennanen et al., 1992) a statistically significant increase of foetuses with clubfoot (malformation) was observed without maternal toxicity. In addition, in the non-GLP one-generation reproductive

toxicity study in Wistar rats, in the absence of maternal toxicity the number of pups with kinky tail (malformation) was statistically significant increased. Furthermore, delayed physical development of pups and delayed development of the grip and cliff avoidance reflexes was also observed (Pennanen et al., 1993). It has to be noted that in both studies (Pennanen et al. 1992 und 1993) 2-EHA was administered as a sodium salt.

The DS mentioned that the results of Pennanen et al. (1992) fit well to the findings of external (adactyly, tail malformations) and skeletal malformations (vertebral column, sternum, ribs, femur) in another prenatal developmental study with 2-ethylhexyl-2-ethylhexanoate where 2-EHA was used as the positive control substance (Anonymous, 1997). We ask the DS to provide further details of this study.

With respect to the different results observed in the other developmental study (Hendrickx et al., 1993) and the EOGRTS (Anonymus, 2016) it should be noted that different strains and different administration forms of the substance were applied. In the view of the German CA this does not reduce the concern regarding the observed effects on development.

The proposal to have one Annex VI entry for 2-EHA and its salts is supported.

CONFIDENTIAL ATTACHMENTS
1. Public Consultation - Data from OECD 422 for a 2-ethylhexanoic acid salt.zip [Please refer to comment No. 2]