Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

2-Ethylhexanoic acid and its salts, with the exception of those specified elsewhere in this Annex

EC Number: -
CAS Number: -

CLH-O-0000006817-63-01/F

Adopted

11 June 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-ETHYLHEXANOIC ACID AND ITS SALTS, WITH THE EXCEPTION OF THOSE SPECIFIED ELSEWHERE IN THIS ANNEX

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: 2-Ethylhexanoic acid and its salts, with the exception of those specified elsewhere in this Annex
EC number: -
CAS 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.				
Dossier Submitter's Response				
Thank you for your comments. The test material used for the reprotoxicity studies is 2-ethylhexanoic acid in its racemic form. We do not have any information concerning the toxicity for reproduction of any specific enantiomer of 2-EHA. Regarding the degree of purity of the different registered salts, specific values have not been included in Table 3 as this information is not publicly available.				
RAC's response				
Thank you, noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-ETHYLHEXANOIC ACID AND ITS SALTS, WITH THE EXCEPTION OF THOSE SPECIFIED ELSEWHERE IN THIS ANNEX

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

Dossier Submitter's Response

Thank you for this new information on a 2-ethylhexanoic acid salt. We note that, at the time of the preparation of the CLH dossier, the salt refered to in this comment was not registered under REACH Regulation. According to the ECHA dissemination web, the publication date of the registration data is May 2019, when the public consultation of the CLH started.

Regarding the negative results of the OECD TG 422 study cited in this comment, we note that the screening tests (OECD TG 421 or 422) are not meant to provide complete information on all aspects of reproduction and development. As it is stated in the OECD TG 422 "Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test" this test can be used to provide initial information on possible effects on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition, either at an early stage of assessing the toxicological properties of test chemicals, or on test chemicals of concern. Nevertheless, this test does not provide complete information on all aspects of reproduction and development. In particular, it offers only limited means of detecting postnatal manifestations of prenatal exposure, or effects that may be induced during postnatal exposure. Due (amongst other reasons) to the selectivity of the endpoints, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/developmental effects.

On the contrary, the prenatal developmental toxicity study (EU B.31, OECD TG 414) provides a focused evaluation of potential effects following prenatal exposure, although only effects that are manifested before birth can be detected. More specifically, this study is designed to provide information on substance-induced effects on growth and survival of the foetuses, and increased incidences in external, skeletal and soft tissue malformations and variations in foetuses.

Therefore, we cannot disregard the positive results of the prenatal developmental studies with 2-EHA on the basis of a negative result in a screening test.

RAC's response

Thank you for this new information.
RAC agrees with the DS that an OECD TG 422 compliant screening does not cover the whole range of endpoints investigated in an OECD TG 414 study. Read-across from 2-ethylhexanoic acid, for which full prenatal developmental toxicity and generational studies are available, is therefore still warranted. RAC further notes that the top dose of 300 mg/kg bw/d did not induce systemic toxicity in maternal animals while the OECD TG specifies that the top dose should be chosen with the aim to induce toxicity but not death or severe suffering.

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.				
Dossier Submitter's Response				
We acknowledge this comment. We have considered that according to the text of the proposed Note, i.e. *"The classification for the hazard class(es) in this entry is based only on the hazardous properties of the part of the substance which is common to all members in the entry. The hazardous properties of any member in the entry also depends on the properties of the part of the substance which is not common to all members of the group; they must be evaluated to assess whether (a) more severe classification(s) (e.g. a higher category) or (b) a broader scope of the classification (additional differentiation, target organs and/or hazard statements) might apply for the hazard class(es) in the entry"*, the classification for reprotoxicity should be applicable to this salt.				
RAC's response				
Noted.				

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).

Dossier Submitter's Response

Thank you very much for this comment.

Concerning the analogy between 2-EHA and valproic acid in relation to the effects on development, we note that during the 2-EHA substance evaluation process, the analogy with valproic acid was claimed only as a trigger to justify the need for the DNT cohort. In fact, the following paragraph was included in the ECHA SEv final decision at this respect: *"For DNT, results from the available one-generation reproductive toxicity study included as part of the registration showed that 2-EHA delayed the development of the grip and cliff avoidance reflexes of the pups. Furthermore, 2-EHA is an analogue of the anticonvulsant drug valproic acid. The anticonvulsant effect of 2-EHA has been reported as 40% of valproic acid (Löscher and Nau, 1985). The reported sedative/hypnotic side effects displayed by valproic acid and some analogues can not be excluded for 2-EHA. Considering this information together the performance of the DNT cohort is justified."*

Thus, in the SEv report (section 5.11.1.1) the relationship between 2-EHA and valproic acid was explained, always in relation to neurodevelopmental effects. At this respect, several references were included.

We would like to highlight that finally, the results of the EOGRTS study performed after substance evaluation, did not show any developmental neutotoxic effects in the cohort 2 animals (DNT cohort).

In relation to the publication by Ritter *et al.*, 1987 on the teratogenicity effect of Di(2-ethylhexyl) phthalate, 2-ethylhexanol, 2-EHA and valproic acid, and potentiation by caffeine, we did not consider appropriate to discuss it as part of the CLH proposal. The main reason was that, although the observed effects on development after valproic acid and 2-EHA administration were similar, what suggests the possibility of a similar teratogenic mechanism, valproic acid was approximately twice as potent a teratogen agent as 2-EHA. This might imply differences in the mode of actions of the two substances.

In addition, the study described in this paper did not follow any guidance. The test was performed in Wistar rats, with the administration of 2-EHA and valproic acid, amongst others substances, on day 12 of gestation.

Therefore, taking into account the whole available dataset from the reproductive toxicity studies with 2-EHA, we consider that it is justified the current classification with respect to developmental toxicity as Repr. 2 (H361d) in accordance with the criteria for classification as defined in Annex I, Regulation (EC) No. 1272/2008 (CLP). This

classification is appropriate as there is some evidence from experimental animals of adverse effects on development.

From our point of view, the current evidence is not sufficiently convincing to place the substance in the Category 1. As reported in the CLH proposal, even though clear developmental effects were observed in a non-GLP developmental toxicity study (Pennanen *et al.*, 1992), some of them were non-uniformly dose-dependent (skeletal variations such as wavy ribs) or were non-dose related (visceral malformation of pelvic dilation of the urinary tract). In another developmental toxicity study (Hendrickx *et al.,* 1993) most of the foetotoxic alterations were observed at doses which did cause maternal toxicity. Additionally, results obtained in the most recently performed OECD TG 422 and OECD TG 443 studies, did not showed any treatment-related developmental effects.

In response to your comment on the usefulness of including the results on the repeated dose toxicity on 2-EHA or its salts as supportive information on the reproductive toxicity assessment, we did not consider it necessary since the results of the EOGRTS and the combined repeated dose toxicity study with reproduction/developmental toxicity screening test are included and discussed in the CLH proposal for 2-EHA and its salts. Furthermore, any indications related to reproductive toxicity effects (eg. testicular atrophy) were obtained in any of the available repeated dose toxicity tests.

RAC's response

Thank you for your comments. Indeed, 2-ethylhexanoic is a structural analogue of valproic acid, an established human teratogen, and both substances showed a similar profile in rodent developmental studies (although valproic acid was more potent). In a weight of evidence assessment taking into account not only studies with 2-ethylhexanoic acid alone, but also animal and human data on valproic acid and comparative developmental toxicity studies with 2-ethylhexanoic acid and valproic acid (Ritter *et al.*, 1987; Narotsky *et al.*, 1994; Nau *et al.*, 1991), RAC concludes that 2-ethylhexanoic acid should be classified in Category 1B for development. For further details please see the RAC opinion and the background document.

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.

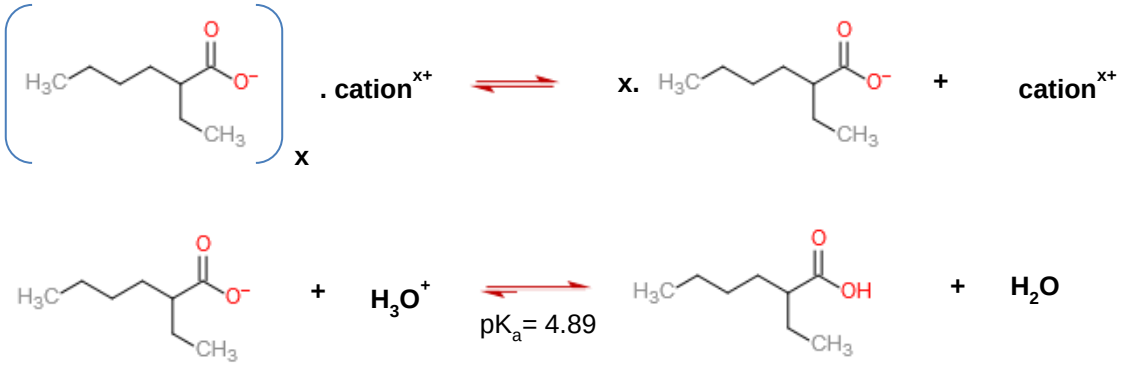
3) The Report relies heavily on a non-GLP study on 2-EHA from 1992 -- that is not compliant with current OECD guidelines -- to draw its conclusions on the developmental toxicity of 2-EHA. An out of date non-GLP study should not be used to read across to all the metal salts of 2-EHA for classification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

Dossier Submitter's Response

Thank you for your comments.

Regarding the read-across justification of 2-Ethylhexanoic acid and its salts, it should be kept in mind that the read-across hypothesis relies in the formation of 2-EHA from the salts. Consequently, the CLH proposal of 2-Ethylhexanoic acid and its salts is based on the existing data for 2-EHA as it represents the common (bio) transformation product. 2-Ethylhexanoic acid currently has its own Annex VI entry (index no. 607-230-00-6) with the classification as Repr. 2 (H361d). Different salts of 2-EHA only differ in the cation counterion. The possible hazardous properties of the respective cationic moiety are not considered for this CLH proposal. Therefore, reproductive toxicity of the cationic part and its contribution to the classification of the salt of 2-EHA needs to be always assessed separately.

From the available data, salts readily dissociate to the corresponding cation and 2-ethylhexanoate anion. Further protonation at acidic pH may allow bioavailability of 2-ethylhexanoic acid. The dissociation constants of the salts indicate that in the neutral pH range, the substances will be mainly dissociated. In addition, at the low pH of the stomach a complete dissociation and further protonation of the anion carboxylate is anticipated. As 2-EHA is a weak acid (pK_a= 4.89), the conjugate carboxylate anion can be regarded as a strong base. Therefore, while reducing the pH, hydronium (H_3O^+, pK_a= -1.74) concentration will increase and readily react with carboxylate anions to form 2-EHA. This decrease in the concentration of carboxylate anions will shift equilibrium to favor solubility of the corresponding metal salts following Le Chatelier's principle. Thus, high acidic conditions at the stomach are expected to form and allow bioavailability of 2-ethylhexanoic acid from their salts. This is represented in Figure 3 of the CLH proposal.



Carboxylic acid salts are ionic compounds usually soluble in water. Registration data from the registered salts but 2-ethylhexanoic acid, zirconium salt, show solubility in water in different degree, from the very soluble salts, i.e. sodium, potassium, calcium, manganese and barium, to the moderately/slightly soluble molybdenum salt. Water solubility data may indicate differences in bioavailability of the toxicant. However, concerning the Zr and Mo salts of 2-EHA, it is important to consider the fact that water solubility tests (OECD TG 105) for these salts have been carried out by measuring metal concentration and not 2-EHA formation. In this context, formation of low-solubility metal oxide species after dissolution of the mentioned salts is expected. Consequently, the moderate to low solubility in water observed for these salts could be explained by the formation of insoluble metal compounds after salt dissociation.

In summary, as all the group members but 2-EHA itself are salts of 2-EHA, they are expected to be a relevant source of this organic acid. Consequently, organism exposure to 2-EHA and to the different cations is foreseen. As possible hazardous properties of the respective cationic moiety are not considered in this CLH proposal, in all cases the biological targets are expected to be exposed to the acid and, thus, at minimum the same adverse effects on reproductive toxicity are reasonably foreseen for all salts.

Regarding the adverse effects taken into account as the basis for the proposed harmonized classification and labelling, not only developmental variations but mainly malformations have been used to classify 2-EHA for developmental toxicity.

2-EHA was found to cause developmental effects in a non-GLP developmental toxicity study (Pennanen *et al.*, 1992) in Wistar rats at doses of 100, 300 and 600 mg/kg bw/d 2-EHA as sodium salt via drinking water, during gestational days 6 to 19. Skeletal variations (wavy ribs, reduced ossification) and skeletal malformations (clubfoot) were observed at dose levels without maternal toxicity. 2-EHA affected normal development of foetuses at all dose levels. Dose-dependent increases in the number of foetuses with skeletal or visceral anomalies were observed at all dose levels. As regards to the malformations, clubfoot occurred in all treatment groups, being statistically significant at the two highest doses. Only few visceral malformations were found. The degree of dilation of brain ventricles, which is inversely related to the developmental stage of conceptus, was increased in the dose groups of 300 and 600 mg/kg bw/d, being statistically significant at 600 mg/kg bw/d.

In another prenatal developmental study with 2-ethylhexyl-2-ethylhexanoate where 2-EHA was used as the positive control substance (Anonymous, 1997), clear signs of selective developmental toxicity and teratogenicity related to external (adactyly, tail malformations) and skeletal malformations (vertebral column, sternum, ribs, femur) and skeletal and overall variations and retardations were reported.

In addition, in the one-generation reproductive toxicity study with 2-EHA in Wistar rats, the incidence of kinky tail was statistically significant at the mid- and high-dose groups (Pennanen *et al.*, 1993).

Finally, in relation to the quality of the study on 2-EHA from 1992, we considered that althought it is not compliant with GLP, the results are valid and relevant to establish the classification of the acid and its salts. Furthermore, these results were confirmed in a GLP sudy (Anonymous, 1997).

RAC's response

Thank you for your comments.

Read-across

RAC acknowledges that the proposed entry encompasses salts with different structures and physicochemical properties. Still, even metal salts of 2-ethylhexanoates that may have available coordination sites and form precipitates at a neutral pH, are expected to convert to the free acid at the low pH in the human stomach (for details see the RAC opinion). RAC concludes that even in the absence of (robust) experimental data to support the read-across, all elements of the RAAF have been fulfilled and the read-across is acceptable.

Wavy ribs and delayed ossification

RAC agrees that wavy ribs and delayed ossification on their own are normally not a reason for classification especially when occurring at maternally toxic doses. Nevertheless, GLP studies with 2-ethylhexanoic acid (Anonymous, 1997; Anonymous, 1988c) showed retarded ossification and reduced foetal weight even in the absence of maternal toxicity and additionally other anomalies. Furthermore, 2-ethylhexanoic acid showed a qualitatively similar developmental toxicity profile in rodents to that of its structural analogue valproic acid, a known human teratogen.

Study Pennanen *et al.* (1992)

The evaluation by RAC takes into account all available information in a weight of evidence assessment. Study Pennanen *et al.* (1992) has not been found completely unreliable, but at the same time does not play a major role in the justification of the RAC proposal of Repr. 1B; H360D.

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.

Dossier Submitter's Response

Thank you for your comment and for your support.

As previously stated in our response to comment no. 4, from our point of view, the current evidence is not sufficiently convincing to place the substance in the Category 1.

In relation to the prenatal developmental study with 2-ethylhexyl-2-ethylhexanoate where 2-EHA was used as the positive control substance (Anonymous, 1997), we note that this study was not included as part of the 2-EHA registration data by the Registrant. On the contrary, it was provided to us as evaluating MSCA by the Registrant during the substance evaluation process and therefore it is kept as confidential. Thus, apart form the paragraph mentioned in your comment, we also included more detailed information in the confidential Annex to the CLH proposal.

RAC's response

Thank you for your comment. Details of study Anonymous (1997) are provided in the RAC opinion.
RAC agreed on Repr. 1B; H360D based on a weight of evidence assessment taking into account not only studies with 2-ethylhexanoic acid alone, but also animal and human data on its structural analogue and a human teratogen valproic acid, which showed a qualitatively similar profile in the rodent developmental studies.

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