



MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

SUBSTANCE EVALUATION
CONCLUSION DOCUMENT
as required by REACH Article 48
for
2-Ethylhexanoic acid
(2-EHA)

EC No 205-743-6

CAS No 149-57-5

Evaluating Member State(s): Spain

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2012

Before concluding the substance evaluation a Decision to request further information was issued on: 26 February 2014.

Please find (search for) further information on registered substances here:

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

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.

In order to ensure a harmonised approach, ECHA in cooperation with the Member States developed risk-based criteria for prioritising substances for substance evaluation. The list of substances subject to evaluation, the Community rolling action plan (CoRAP), is updated and published annually on the ECHA web site¹.

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 the Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. In this conclusion document, the evaluating Member State shall consider how the information on the substance can be used for the purposes of identification of substances of very high concern (SVHC), restriction and/or classification and labelling. With this Conclusion document the substance evaluation process is finished and the Commission, the registrants of the substance and the competent authorities of the other Member States are informed of the considerations of the evaluating Member State. Thus this conclusion document is not reflecting an official position of ECHA. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes.

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

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1. CONCERN(S) SUBJECT TO EVALUATION

2-Ethylhexanoic acid (2-EHA) was originally selected for substance evaluation in order to clarify suspected risks about:

- CMR (reproductive toxicity - fertility)
- Wide dispersive use
- Consumer use
- High (aggregated) tonnage
- High RCR

During the evaluation also other concern was identified. The additional concern was:

- Postnatal development, related to potential neurodevelopmental toxicity.

The evaluation of 2-ethylhexanoic acid was targeted at human health endpoints.

2. CONCLUSION OF SUBSTANCE EVALUATION

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

Conclusions	Tick box
Need for follow up regulatory action at EU level <i>[if a specific regulatory action is already identified then, please, select one or more of the specific follow up actions mentioned below]</i>	
<i>Need for Harmonised classification and labelling</i>	
<i>Need for Identification as SVHC (authorisation)</i>	
<i>Need for Restrictions</i>	
<i>Need for other Community-wide measures</i>	
No need for regulatory follow-up action	X

3. JUSTIFICATION FOR THE CONCLUSION ON THE NEED OF REGULATORY RISK MANAGEMENT

3.1. NEED FOR FOLLOW UP REGULATORY ACTION AT EU LEVEL

3.1.1. Need for harmonised classification and labelling

Not applicable.

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

Not applicable.

3.1.3. Need for restrictions*Not applicable.***3.1.4. Proposal for other Community-wide regulatory risk management measures***Not applicable.***3.2. NO FOLLOW-UP ACTION NEEDED**

The concern could be removed because	Tick box
<i>Hazard and /or exposure was verified to be not relevant and/or</i>	X
<i>Hazard and /or exposure was verified to be under appropriate control and/or</i>	
<i>The registrant modified the applied risk management measures.</i>	
<i>other: <Please specify></i>	

The following concerns have been concluded in the scope of substance evaluation:

CMR (reproductive toxicity - fertility) and potential neurodevelopmental toxicity

An extended one generation reproductive toxicity study (EOGRTS) was required via ECHA decision during the substance evaluation process of 2-EHA since concerns regarding fertility and neurodevelopmental toxicity had been identified. These concerns were based on the results of a one-generation reproductive toxicity study (Pennanen *et al.*, 1993) which was neither carried out in accordance with any internationally recognized test method nor in compliance with GLP. In this study, an apparent reduction in sperm motility and a delay in fertilization were observed in parental animals. In addition, delay in the development of the grip and cliff avoidance reflex observed in pups of the mid and high-doses was considered as a potential neurodevelopmental toxicity effect. Furthermore, 2-EHA is an analogue of the anticonvulsant drug valproic acid.

Following the substance evaluation decision, both an oral combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) and an extended one generation reproductive toxicity study (EOGRTS, OECD TG 443) were conducted according to GLP with 2-EHA in Wistar rats (unnamed reports, 2015; 2016). The EOGRTS design included the extension of Cohort 1B to mate the F1 animals to produce the F2 generation and cohorts 2 and 3 to assess developmental neurotoxicity (DNT) and immunotoxicity (DIT).

No fertility or reproductive effects were observed in male and female rats in the oral combined repeated dose toxicity study with the reproduction/developmental toxicity screening test. This study was performed as a dose-range finder for the planned OECD 443 study.

The results obtained in the EOGRTS performed in Wistar rats dosed at 0, 80, 250 and 800 mg/kg bw/d 2-EHA did not show any treatment-related effects in fertility and reproductive parameters at any dose levels both in F0 and F1 generations. Additionally, neither treatment-related effects regarding neurodevelopmental toxicity were reported for cohorts 2A and 2B nor neurodevelopmental effects associated with treatment with 2-EHA. As a result of this study, a NOAEL for parental effects was established at 250 mg/kg bw/d, based on the effects on body weights, food consumption, kidney and liver weights and

kidney pathology observed in animals of the highest dose. The NOAEL for fertility and reproductive effects, developmental neuro- and immunotoxicity effects was established at 800 mg/kg bw/d, due to the lack of effects.

This new information from good quality studies does not confirm any of the findings related to fertility and neurodevelopmental toxicity that were observed in the previous non-guideline and non-GLP studies. Neither treatment-related effects on epididymal and testicular sperm parameters nor on fertility and reproductive performance of animals of the F0 generation and of cohort 1B of the F1 generation have been reported. No alterations in the neurodevelopmental parameters have been observed. In addition, no immunotoxic effects were recorded in cohort 3.

To summarize, the new studies results provide sufficient and reliable information to conclude that 2-ethylhexanoic acid does not show a specific effect on fertility and neurodevelopmental toxicity. For this reason, the evaluating MSCA (eMSCA) considers that the concerns have been clarified and neither further information nor additional classification is required following this substance evaluation.

Exposure (wide dispersive use, consumer use, high RCR)

Exposure was included as an initial ground for concern in CoRAP. In a first instance, the registration dossiers from 2010 contained 26 exposure scenarios covering industrial, professional and consumer uses. Several of them were considered wide dispersive. However, registrant(s) reported afterwards that some of the identified uses included in the registration dossiers from 2010 did not correspond to real uses of the substance itself, but of their derivatives, mainly the salts or esters of 2-EHA. Furthermore, other identified uses (consumer use) of 2-EHA were inappropriately reported in the dossier due to a mistaken identity of the substance. Updated registrations dossiers were submitted by all registrants and assessed by eMSCA.

In the updated registration dossiers, nine exposure scenarios were described by the registrants. These exposure scenarios related to occupational exposure and involved industrial and professional uses. Consumer exposure to 2-EHA as such was not confirmed. A declaration of use advice against for consumers was included.

Therefore, consumer exposure to 2-EHA is not expected. The substance is readily biodegradable and it will rapidly disappear from water and soil via mineralisation. Furthermore, the low n-octanol/water partition coefficient (log Kow) implies that an exposure via the food is not likely. Indirect exposure through the environment is considered negligible.

The exposure scenarios identified in the registration dossiers for occupational exposure covered manufacture of 2-EHA or its use as an intermediate for the production of other substances, formulation of mixtures, industrial and professional use in laboratories and industrial and professional use as functional fluids.

External exposure by inhalation and dermal routes was assessed for all working activities in each exposure scenario.

Based on the available information, the evaluating MSCA could support the conclusion of the registrants. The registration dossiers reported modelling data derived by the application of Tier 1 ECETOC TRA v3 exposure model. The modelled exposure estimations calculated by the evaluating MSCA, using ECETOC TRA v3 and taking into account the conditions of use described in the registration dossiers, were in line with the values reported by the registrants in all exposure scenarios. The operational conditions and risk management measures described in the registration dossiers were sufficiently detailed in order to enable the recalculation of exposure estimates.

For quantitative risk characterization of 2-EHA, exposure data from inhalation and dermal exposure were compared with the derived long-term systemic inhalation and dermal DNELs, respectively.

The evaluating MSCA supports the conclusion of the registrants. For every activity described in each exposure scenario, all calculated RCR values were below 1 for the inhalation and dermal routes.

Consequently, the risks for human health were considered controlled for each route of exposure and the initial concerns were removed.

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

Not applicable.