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**DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF
REGULATION (EC) NO 1907/2006****For 2-Ethylhexanoic acid, CAS No 149-57-5 (EC No 205-743-6)****Addressees: Registrants of 2-Ethylhexanoic acid (concerned registrants)**

This decision is addressed to all Registrants of the above substance with active registrations on the date on which the draft for the decision was first sent, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided in Annex 2 to this decision.

Registrants meeting the following criteria are *not* addressees of this decision: i) Registrants who exclusively use the above substance as an on-site isolated intermediate and under strictly controlled conditions and ii) Registrants who have ceased manufacture/import of the above substance in accordance with Article 50(3) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by the Ministry of Health, Social Services and Equality as the Competent Authority of Spain (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision does not take into account any updates of the registrations of the concerned registrants after 5 September 2013, the date upon which the draft decision was circulated to the other Competent Authorities of the Member States and ECHA pursuant to Article 52(1) of the REACH Regulation.

This decision does not imply that the information provided by the concerned registrants in the registrations is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossiers of the concerned registrants at a later stage, nor does it prevent a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of Spain has initiated substance evaluation for 2-Ethylhexanoic acid, CAS No 149-57-5 (EC No 205-743-6) based on registration dossiers submitted by the concerned registrants and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to suspected toxicity on fertility as well as wide dispersive use, potential consumer use, high aggregated tonnage and risk characterisation ratios close to 1 for

human health, 2-Ethylhexanoic acid was included in the Community rolling action plan (CoRAP) for substance evaluation pursuant to Article 44(2) of the REACH Regulation to be evaluated in 2012. The CoRAP was published on the ECHA website on 29 February 2012. The Competent Authority of Spain was appointed to carry out the evaluation. In the course of the evaluation, the evaluating MSCA noted additional concerns regarding postnatal development related to potential neurodevelopmental toxicity.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 28 February 2013.

On 4 April 2013 ECHA sent the draft decision to the concerned registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

By 6 May 2013 ECHA received comments from concerned registrant(s) of which it informed the evaluating MSCA without delay.

The MSCA considered the registrants' comments received and did not amend Section II of the draft decision. The comments were reflected in Section III of the draft decision (Statement of Reasons).

In accordance with Article 52(1) of the REACH Regulation, on 5 September 2013 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days.

Subsequently, MSCAs submitted proposals for amendment to the draft decision.

On 11 October 2013 ECHA notified the concerned registrants of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA has reviewed the MSCAs' proposals for amendment and amended the draft decision accordingly.

On 21 October 2013 ECHA referred the draft decision to the Member State Committee.

By 11 November 2013 the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 10-13 December 2013, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 12 December 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the concerned registrants shall submit the following information using the indicated test method and the registered substance subject to the present decision:

Extended one-generation reproductive toxicity study in rats, oral route (test method: OECD 443) including the Cohorts 2 and 3 to assess developmental neurotoxicity (DNT) and immunotoxicity (DIT). The need for the extension of Cohort 1B to mate the F1 animals to produce the F2 generation, which shall be kept until weaning, shall be considered in accordance with the conditions outlined in Section III.

Pursuant to Article 46(2) of the REACH Regulation, the concerned registrants shall submit to ECHA by 26 May 2016 an update of the registration dossiers containing the information required by this decision.

At any time, the concerned registrants shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

1. Extended one-generation reproductive toxicity study

Based on the evaluation of all relevant information submitted on 2-Ethylhexanoic acid (2-EHA) and other relevant and available information and taking into account the comments of the concerned registrants, proposals for amendment submitted by Member State Competent Authorities/ECHA and the deliberations of the Member State Committee, ECHA concludes that further information is required in order to enable the evaluating MSCA to complete the evaluation of whether the substance constitutes a risk to human health.

Initial grounds for concern relating to suspected toxicity on fertility were confirmed by the assessment of the available information. Concern on postnatal development, related to potential neurodevelopmental toxicity, was also revealed during the evaluation.

The registration dossiers contain information on a one-generation reproductive toxicity study published in the literature (Pennanen *et al.*, 1993). This study was neither carried out in accordance with any internationally recognised test method nor in compliance with GLP requirements. However, results showed that 2-EHA caused an apparent reduction in sperm motility and a delay in fertilisation. Delayed postnatal development was also evidenced in the reflex and physical parameters evaluated. The observed delay in the development of the grip and cliff avoidance reflex may suggest a potential neurodevelopmental toxic effect of this substance. Despite the questionable quality of this study and the inconsistency of some of its results, it provides indications of a reproductive toxic potential which justifies further testing.

In the comments submitted in the 30-day period, the Registrants judge that the quality of the available one-generation reproductive toxicity study is sufficient for evaluation and that the results of this study provide no hint for significantly impaired fertility up to doses that cause developmental toxicity and teratogenicity. The Registrants emphasise that the avoidance of unnecessary testing and duplication of tests is a general aim of the REACH Regulation (Article 25). However, it is noted that the mentioned study, only available as published literature, showed altered parameters related to fertility and effects on postnatal development at doses that are not overtly toxic. The biological significance of the reported findings can not be elucidated with the available information. Therefore, the requested EOGRTS study is regarded as necessary to clarify this issue. Furthermore, it should not be considered a duplication of tests since the available study does not fulfil the information requirement specified in Annex IX/X, 8.7.3 of the REACH Regulation. Therefore, the draft decision has not been amended.

In the initial DD sent to the Registrants on 4 April 2013, a reference to the potential effects on implantation was made according to the results of a separate pilot study (Pennanen *et al.*, 1993). The Registrants provide scientific argumentation as to why effects on implantation of 2-EHA are unlikely. The considerations are based on the poor quality of the separate pilot study and on available information that the Registrants present only now. After considering the new information, the reference to this effect in the draft decision has been omitted.

It is noteworthy that the substance has an EU harmonised classification as toxic for reproduction, category 2 (H361d: suspected of damaging the unborn child) on the basis of observed developmental effects in prenatal developmental studies in rats, such as skeletal variations and malformations. Moreover, 2-EHA is an intermediate in the metabolism of bis(2-ethylhexyl) phthalate (DEHP) classified as a category 1B (H360FD: may damage fertility and the unborn child) reproductive toxicant for both fertility and developmental effects (Annex VI to Regulation (EC) No 1272/2008 (CLP Regulation)). This fact would further support the need to clarify the potential effect of the evaluated substance on fertility.

In their comments to the initial draft decision, the Registrants relate the potential effects of 2-EHA more with di(2-ethylhexyl)terephthalate (DEHT) than with DEHP based on metabolic considerations. They refer to a scientific publication that shows the absence of adverse effects through a two-generation study with DEHT. After considered these arguments, it has been concluded that the same pattern of toxicity for DEHT and 2-EHA should not be assumed taking into account that 2-EHA is a classified developmental toxicant but effects on development were not observed in a prenatal developmental toxicity study with DEHT (Faber *et al.*, 2007). It is also noted that even recognising that the metabolite of DEHP (MEHP) is considered responsible of the testicular toxicity, the role of other metabolites in the DEHP reproductive toxicity cannot be excluded. Therefore, the draft decision has not been amended.

On the other hand, the available one-generation reproductive toxicity study does not fulfil the requirements of information on reproductive toxicity as described in Annex IX/X, 8.7.3 of the REACH Regulation. The Registrants justify the adaptation to the standard information requirements by stating that *"There is no hint for significantly impaired fertility up to teratogenic doses and that it is unlikely that the NOAEL observed in a 2-gen. reproductive toxicity study would be lower than the NOAEL from the developmental toxicity study. The observed NOAEL from a 2-gen. study would most probably not contribute to the overall risk assessment. From a scientifically point of view (including animal welfare reasons) and in consideration of the uses (no consumer uses), it is not justified to conduct a 2-gen. reproductive toxicity study"* (CSR section 5.9.1).

The justification provided by the Registrants does not meet the conditions for adaptation of column 2 of Annex IX/X, section 8.7. Consequently, there is an information gap for reproductive toxicity. Furthermore, the doubts raised by the effects observed in the available study justify the request for further studies in the scope of substance evaluation.

The requested information is thus needed to establish whether the suspected concern may be realised or not. Without this information it will not be possible to verify whether there remains an uncontrolled risk with the substance that should be subject to further risk management measures.

The Registrants indicate in their comments that it is unlikely that a new NOAEL would contribute to the overall risk assessment. However, it is considered that it is important for RMM to identify the effect even if quantitative dose-response relationship is similar. This

identification is also a request of Annex IX or X, 8.7 of REACH Regulation. Therefore, the draft decision has not been amended.

The OECD test guideline for an extended one-generation reproductive toxicity study (EOGRTS, OECD TG 443), adopted by the OECD Council on 28 July 2011, is an internationally accepted test that can be applied to generate information on intrinsic properties of a substance according to Article 13(3) of the REACH Regulation. Testing according to OECD TG 443 includes extensive endpoint determinations and relevant data on reproductive toxicity, endocrine parameters and on developmental neuro and immunotoxicity aspects.

The study design of OECD TG 443 consists of a reproductive cohort with a single generation that may be extended to include a second generation, a DNT cohort and a DIT cohort. In accordance with the test guideline, decisions on whether to assess the second generation and/or to omit the DNT and/or DIT cohorts should reflect existing knowledge for the chemical being evaluated, as well as the needs of various regulatory authorities.

In this particular case, taking into account the unclear results obtained in the available one generation reproductive toxicity study, the eMSCA reminds the Registrants that the extension of the Cohort 1B to produce the second generation shall be considered where the results obtained during the study do not allow drawing a clear conclusion on this endpoint. This includes the consideration of whether the available information obtained during the requested test, i.e. before it is decided to terminate the relevant F1 Cohort 1B animals, already indicate the possibility to conclude on the fulfilment of the classification criteria for developmental toxicity and fertility. Whether to produce the F2 generation should be based on scientific considerations.

ECHA also notes that no exposure to 2-EHA as such has been confirmed for consumers. However, there is a relevant source of exposure to the substance from contact with products containing its metal salts. These 2-EHA derivatives are described in the literature to be used in many different industrial applications, for example as PVC stabilizers, lubricants, drying additives for paints, inks, varnishes, lacquers and wood preservatives. Some of these products might be available to the general public. Effects of these salts are anticipated to be due primarily to the 2-EHA moiety. Therefore, metal salts of 2-EHA constitute a secondary, but still important, source of exposure to 2-EHA for the population.

In relation to the DNT and DIT cohorts, there is no scientific reason to omit these cohorts on the basis of the available information on 2-EHA, as outlined below.

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.

The Registrants discussed in their comments the need for the DNT cohort. They considered that developmental neurotoxicity testing (DNT) is triggered by neurotoxic effects in adult animals and that there is no indication of neurotoxicity neither in adult animals nor in their offspring. These arguments are rejected and it is considered that, in this case, specific substance information supports the need of DNT cohort. Therefore, the draft decision has not been amended.

With regard to immunotoxicity, no conclusions can be drawn from a limited *in vitro* immunotoxicity study on human polymorphonuclear leukocytes (PMNL) included in the registration dossiers (Pennanen *et al.*, 2000). 2-EHA is a biotransformation product of bis(2-ethylhexyl) phthalate (DEHP). This substance has been suggested to have immunomodulatory properties (Larsen and Nielsen, 2007; Larsen *et al.*, 2001; Jaakkola and Knight, 2008). In addition, a recent study has shown a relatively higher sensitivity of the developing immune system in juvenile versus adult rats exposed to DEHP (Tonk *et al.*, 2012). Overall, without further testing, a concern for the developmental immunotoxicity of 2-EHA still remains. In addition, the performance of this cohort will complete the knowledge about the postnatal developmental effects profile of this substance.

In their comments to the initial draft decision, the Registrants argue that the available studies gave no hints for any immunotoxic effect of 2-EHA, and that the modulatory effect seen in the mentioned *in vitro* study by Pennanen *et al.* (2000) is observed at high concentrations unlikely to be reached in blood of workers exposed to 2-EHA. After considering these comments, it has been concluded that the Registrants have not provided substance specific information permitting to exclude a developmental immunotoxic effect. Therefore, the draft decision has not been amended.

Further to the first draft decision and following the PfA period, the Registrants provided some comments on the proposals for amendment. They agreed with one of the PfAs that suggests that the requirement for Cohorts 2A and 2B for DNT and Cohort 3 for DIT should be waived. The arguments used by the registrants were not different from those previously raised during the commenting period and they were not based in new information. The eMSCA had already considered these comments and provided reactions to them above. Therefore, the Registrants' comments on the PfAs did not lead to an amendment of the draft decision.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the concerned Registrants are required to carry out the following study using the registered substance subject to this decision: Extended one-generation reproductive toxicity study in rats, oral route including the Cohorts 2 and 3 to assess developmental neurotoxicity (DNT) and immunotoxicity (DIT); (test method: OECD 443). The need for the extension of Cohort 1B to mate the F1 animals to produce the F2 generation, which shall be kept until weaning, shall be considered in accordance with the conditions outlined above.

2. Deadline

In the draft decision communicated to the Registrants the time indicated to provide the requested information was 27 months from the date of the adoption of the decision. In their comments on the draft decision of 6 May 2013 the Registrants indicated their concern about the limited laboratory capacity to carry out the test, and indicated that additional time may be needed to perform the test. However, the Registrants did not at this stage request a modification of the deadline and did not substantiate their claim regarding potential delays. Therefore, the deadline of the decision has not been modified.

IV. Adequate identification of the composition of the tested material

The substance identity information submitted in the registration dossiers has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the required test, the sample of substance used for the new study shall have a composition that is within the specifications of the substance composition that are given by

all concerned registrants. It is the responsibility of all the concerned registrants to agree on the tested materials to be subjected to the test subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the study must be shared by the concerned registrants.

V. Avoidance of unnecessary testing by data- and cost- sharing

Avoidance of unnecessary testing and the duplication of tests is a general aim of the REACH Regulation (Article 25). The legal text foresees the sharing of information between registrants. Since several registrants of the same substance are required to provide the same information, they are obliged to make every effort to reach an agreement for every endpoint as to who is to carry out the test on behalf of the other concerned registrants and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation.

If ECHA is not informed of such agreement within 90 days, it shall designate one of the concerned registrants to perform the tests on behalf of all of them. If a registrant performs a test on behalf of other registrants, they shall share the cost of that study equally and the registrant performing the test shall provide each of the others concerned with copies of the full study reports.

This information should be submitted to ECHA using the following form stating the decision number above at:

https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/datasharing_en.asp.

VI. General requirements regarding Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

VII. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at <http://www.echa.europa.eu/regulations/appeals>. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.



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Annexes:

1. References
2. List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

Annex 1: References

Faber WD, Deyo JA, Stump DG, Navarro L, Ruble K, Knapp J (2007). Developmental toxicity and uterotrophic studies with di-2-ethylhexyl terephthalate. *Birth Defects Research: Part B, Developmental and Reproductive Toxicology* **80**, 396-405.

Jaakkola JJ, Knight TL (2008). The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. *Environmental Health Perspectives* **116**, 845-853.

Larsen ST, Lund RM, Nielsen GD, Thygesen P, Poulsen OM (2001). Di-(2-ethylhexyl) phthalate possesses an adjuvant effect in a subcutaneous injection model with BALB/c mice. *Toxicology Letters* **125**, 11-18.

Larsen ST, Nielsen GD (2007). The adjuvant effect of di-(2-ethylhexyl) phthalate is mediated through a PPARalpha-independent mechanism. *Toxicology Letters* **170**, 223-228.

Löscher W, Nau H (1985). Pharmacological evaluation of various metabolites and analogues of valproic acid. Anticonvulsant and toxic potencies in mice. *Neuropharmacology* **24**, 427-435.

Pennanen S, Tuovinen K, Huuskonen H, Kosma V, Komulainen H (1993). Effects of 2-ethylhexanoic acid on reproduction and postnatal development in Wistar rats. *Fundamental and Applied Toxicology* **21**, 204-212.

Pennanen SMA, Heiskanen KM, Savolainen KM, Komulainen H (2000). Effects of 2-ethylhexanoic acid on the production of reactive oxygen species in human polymorphonuclear leucocytes *in vitro*. *Toxicology Letters* **117**, 79-84.

Tonk ECM, Verhoef A, Gremmer ER, van Loveren H, Piersma AH (2012). Relative sensitivity of developmental and immune parameters in juvenile versus adult male rats after exposure to di(2-ethylhexyl) phthalate. *Toxicology and Applied Pharmacology* **260**, 48-57.