EUROPEAN CHEMICALS AGENCY

Helsinki, 27 May 2020

Addressees
Registrants of Hydroxyethanesulphonate_sodium listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
10/04/2015

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Sodium 2-hydroxyethanesulphonate
EC number: 216-343-6
CAS number: 1562-00-1

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***6 March 2023***.

A. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rabbit), oral route with the Substance.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, with the Substance, specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier. You have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendices state the reasons for the requests for information to fulfil the requirements set out in Annexe X of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference

documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix A: Reasons for the requests to comply with Annex X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage abve 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

You have provided a key study by [redacted] (2009), according to OECD TG 414 corresponding to a Pre-natal developmental toxicity study conducted in rats with the Substance.

For the information on a PNDT in a second species, you argue that *"Article 18(d) of Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 20 November on cosmetic products (Cosmetic regulation) prohibits testing of cosmetic ingredients (raw materials) on animals. This general testing ban includes testing for reproductive toxicity. As the registered substance is exclusively used for cosmetic purposes, testing for developmental toxicity / teratogenicity is legally only permitted in order to ensure the protection of workers coming in contact with the substance during manufacturing processes. It can be assumed that workers are trained in handling chemicals and according to general occupational health regulations an exposure of pregnant workers to Sodium 2-hydroxyethanesulphonate at the production site is excluded. Therefore, the testing of Sodium 2-hydroxyethanesulphonate for developmental toxicity in rat is considered to be sufficient to cover all criteria required for occupational health and safety measures"*.

To benefit from the exemption provided by Art 18(d) of the Cosmetic Regulation, a registrant must demonstrate that the Substance is handled under strictly controlled conditions during all stages of the life-cycle, other than the use as a cosmetic product (i.e. manufacture, formulation and/or packaging stage). In all circumstances, the registrant must provide a reasoned justification for requesting the exemption.[2]

However in your technical dossier, you indicated PROC 4 (Chemical production where opportunity for exposure arises), 8a (Transfer of substance or mixture (charging and discharging) at non-dedicated facilities), 8b (Transfer of substance or mixture (charging and discharging) at dedicated facilities), and 14 (Tabletting, compression, extrusion, pelletisation, granulation).

All of the process categories described above imply workers' exposure. Therefore, the information contained in your dossier contradicts your assertion that "*exposure of pregnant workers* [...] *at production site is excluded*". Moreover, in the absence of information actually demonstrating strictly controlled conditions during handling of the Substance at all stages of its life-cycle, the registration dossier cannot meet the conditions for an exemption of the information requirement.

ECHA's factsheet[3] on the interface between REACH and Cosmetics Regulations, provides that registrants of substances that are exclusively used in cosmetics may not perform animal

[2] For more information on this exemption, see the ECHA Factsheet on *Interface between REACH and the Cosmetic Regulations* at https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf; as well as the Q&A on REACH and Cosmetics at https://echa.europa.eu/support/qas-support/browse.

[3] https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf

testing to meet the information requirements of the REACH human health endpoints. The exception is any testing required to assess the risks from exposure to workers in the absence of strictly controlled conditions.

In your comments to the draft decision you consider that you can justify the request for the exemption of animal testing on the basis of strictly controlled conditions provided by Art 18(d) of the Cosmetic Regulation read in conjunction with Article 2(4)(b) of the REACH Regulation. You indicate that the Substance is intended to be used only in cosmetic products. You also provide information on the description of the stages of manufacturing of the Substance and formulation of cosmetic products taking place in the EU, and on the measures taken to achieve strictly controlled conditions. You also expressed your intention to update the dossier with this information "*to demonstrate that the measures described [...] are met and/or that the controls and processes that are in place across the life cycle of the Substance are such that any exposure to workers, if any, is minimised to the point of being negligible*".

ECHA acknowledges your intention to update the dossier with the above information to demonstrate that the Substance is handled only under strictly controlled conditions and that worker exposure can be excluded.

However, currently in your dossier there is no indication that during the manufacture, formulation and/or packaging stages the Substance is handled under strictly controlled conditions (e.g. there are PROCs 5, 8a, 8b and 14 reported in the dossier). Therefore, potential worker exposure may exist, and testing for human health endpoints is justified to assess the hazards for workers. Such testing would not trigger the testing and marketing bans under the Cosmetics Regulation as the testing is to be performed for the purposes of meeting the requirements of the REACH Regulation.[4]

In this respect, the requests in this decision are based on the information provided in your current dossier, including the information relating to exposure of workers.

You have also invoked Article 25(1) of REACH related to animal welfare considerations, as a justification not to perform the test required. However, the avoidance of duplication of animal testing is without prejudice to the primary objective of ensuring a high degree of protection of human health and the environment. This objective is notably achieved by the obligation of the manufacturers or importers of a substance to submit the information on the intrinsic properties set out in the Annexes VII to X of the Regulation, including a test on pre-natal developmental toxicity in a second species. Therefore this test is both required by the provisions of the Regulation and justified to achieve its objectives.

Besides this claim, you have also adapted the information requirement for a PNDT study on a second species by using weight of evidence with reference to Annex XI, Section 1.2.

In support of your adaptation, you have provided the following sources of information:
i. OECD 414 pre-natal developmental study with Substance in rats
ii. A subchronic toxicity OECD 408 study with Substance in rats.

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on the 2nd species developmental toxicity because "*It can therefore be concluded with sufficient certainty that due to the above described toxicological profile of the Sodium 2-hydroxyethanesulphonate (LD50 oral > 5000 mg/kg bw, no irritating or sensitizing properties, non-genotoxic, no severe effects observed in a 90 days repeated*

[4] see Commission Communication of 11 March 2013 on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics (COM(2013)135))

dose toxicity study, no developmental toxic effects in rats) Sodium 2-hydroxyethanesulphonate will not cause developmental toxicity when tested in mammalian species other than rats and therefore, testing for developmental toxicity in a second species is not scientifically necessary." In addition you argue that the Substance "*is neither genotoxic, irritant nor sensitizing*". However, you do not provide a source of information which can be taken into account in your weight of evidence.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory information requirement. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous/hazardous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

However, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property. In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

In order to allow concluding on prenatal developmental toxicity in two species for the Substance in a weight of evidence adaptation, the information provided must cover the key parameters foreseen to be investigated in an OECD TG 414 study in two species. The key parameters of this test guideline include external, skeletal and soft tissue alterations (variations and malformations) in developing animals of a second species.

ECHA has assessed to what extent the information submitted enables a conclusion of this property as investigated in the information requirement proposed to be adapted and identified the following deficiencies:

The OECD TG 408 study (ii) does not provide information in developing animals and these studies are therefore not relevant for the weight of evidence on pre-natal developmental toxicity.

While the OECD TG 414 study (i) brings information on external, skeletal and soft tissue alterations (variations and malformations) in developing animals, it only concerns animals of a first species (rats). Therefore, this study is not relevant for developmental toxicity on a second species.

Your weight of evidence adaptation does not include any relevant sources of information to conclude on the property of prenatal developmental toxicity on a second species.
Therefore, your adaptation is rejected and information requirement is not fulfilled.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have adapted this the information requirement by using weight of evidence according to Annex XI, Section 1.2. In your justification for the weight of eivdence adaptation the following sources of information are presented:

i. Results from Pre-natal developmental toxicity study in rats (OECD TG 414) with the Substance
ii. Results from Repeat dose toxicity study in rats (OECD TG 408) with the Substance

In addition you argue that because the Substance does not have to be classified as skin sensitizing or as skin or eye irritating, this indicates its very low tendency to interact with living cells and tissue. However, you do not provide a source of information which can be taken into account in your weight of evidence.

Based on these sources of information you argue that *"It can therefore be concluded with sufficient certainty that Sodium 2-hydroxyethansulphonate will not cause toxicity to reproduction and that testing is not scientifically necessary."*

As explained in the previous section, Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/ conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

In order to allow concluding on toxicity to reproduction for the Substance in a weight of evidence adaptation, the justification must cover the key parameters foreseen to be investigated in an EOGRT study with the appropriate study design. The key parameters include sexual function and fertility, as well as toxicity to offspring.

1) ECHA has assed to what extent the information submitted enables a conclusion of hazardous properties for reproduction and identified the following deficiencies: *Sexual function and fertility*

A PNDT study has limited relevance because does it does not cover all the life stages foreseen to be investigated in OECD TG 443, i.e. does not provide information on effects that may occur as a result of pre- and postnatal chemical exposure (e.g. during premating and mating, parturition and lactation).

An OECD 408 has relevance only in detecting toxicity to gonads of adult animals. However, it does not provide any functional information i.e. impact on the sexual function and fertility.

2) Toxicity to offspring

A PNDT study is relevant for the toxicity to offspring as it can detect malformations upon exposure during gestation (*in utero*). However, as specified above the life stages investigated in OECD 443 go beyond in utero exposure and therefore, this property cannot be assessed similarly as in an OECD 443.

As explained above, none of the provided studies cover alone or together all relevant life stages required in OECD TG 443; OECD 414 covers only part of pregnancy and OECD 408 only adulthood and endpoints required by OECD TG 443 such as effects on mating, fertility, pregnancy, lactation and postnatal development of the fully exposed F1 generation up to the adulthood are not investigated.

In conclusion, none of the pieces of information alone or together allows to conclude whether the Substance has or has not hazardous properties related to sexual function and fertility or toxicity to offspring.

Therefore, your adaptation is rejected and the information requirement is not fulfilled.

In your comments on the draft decision you consider that you can "*justify the request for the exemption [of animal testing on the basis of strictly controlled conditions] provided by Art 18(d) of the Cosmetic Regulation read in conjunction with Article 2(4)(b) of the REACH Regulation.*" However, as explained under Section A.1. above, based on the information provided in your current dossier, the animal testing is required for the purposes of REACH Regulation and in accordance with its provisions.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.

Therefore, the requested premating exposure duration is ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection must be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and must be included.

Species and route selection

The study must be performed in rats with oral[5] administration.

[5] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[6].

In your comments on the draft decision you consider that you can *"justify the request for the exemption [of animal testing on the basis of strictly controlled conditions] provided by Art 18(d) of the Cosmetic Regulation read in conjunction with Article 2(4)(b) of the REACH Regulation."* However, as explained under Section A.1. above, based on the information provided in your current dossier, the animal testing is required for the purposes of REACH Regulation and in accordance with its provisions.

[6] ECHA Guidance R.7a, Section R.7.6.

Appendix B: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 12 April 2019.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA took into account your comments and did not amend the requests.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix C: Observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[7].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[9]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[10]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[11]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[11] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.