For final decision: TPE-D-0000002086-78-05/F Helsinki, 6 June 2012

**DECISION on a TESTING PROPOSAL SET OUT IN a registration pursuant to Article 40(3) of regulation (EC) no 1907/2006**

**For Sodium hydroxymethanesulphinate, CAS No. 149-44-0 (EC No. 205-739-4), registration number:** [redacted]

**Addressee:** [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined testing proposals set out in the registration dossier for Sodium hydroxymethanesulphinate, CAS No. 149-44-0 (EC No. 205-739-4), submitted by [redacted] (Registrant), latest submission number [redacted], for 1000 tonnes or more per year.

In accordance with Articles 10(a)(ix) and 12(1)(e) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the registration dossier to fulfil the information requirements set out in Annex IX:

- Annex IX, 8.6.2: Sub-chronic toxicity study (90-day) via the oral route in rodents, according to OECD Guideline 408;
- Annex IX, 8.7.2: Pre-natal developmental toxicity study, according to OECD Guideline 414:
- Annex IX, 9.1.5: Long-term toxicity testing on invertebrates, according to OECD Guideline 211 (Daphnia magna Reproduction Test); and
- Annex IX, 9.1.6: Long-term toxicity testing on fish, according to OECD Guideline 204 (Fish, prolonged toxicity test: 14-day study).

The examination of the testing proposals was initiated on 6 October 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 15 April until 30 May 2011. ECHA received information from third parties (see Section III below).

On 17 November 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

By 19 December 2011, the Registrant did not provide any comments on the draft decision.

On 20 January 2012 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 23 February 2012 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and has decided to amend the draft decision.

On 5 March ECHA referred the draft decision to the Member State Committee.

On 19 March 2012 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 24-27 April 2012, a unanimous agreement of the Member State Committee on the draft decision as amended by ECHA was reached on 25 April 2012 and ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the requirements of the REACH Regulation. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

II. Testing required

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant shall carry out the following proposed tests using the indicated test method:

a) Sub-chronic toxicity study in the rat via the oral route (Annex IX 8.6.2, test method: EU B.26/ OECD 408);

b) Pre-natal developmental toxicity study in the rat via the oral route (Annex IX, 8.7.2, test method: EU B.31/ OECD 414); and

c) Long-term toxicity testing on invertebrates (Annex IX, 9.1.5, test method: EU C.20/ OECD 211).

Pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant shall carry out the following additional test using the indicated test method:

d) Long-term toxicity testing on fish (Annex IX, 9.1.6., test method: OECD 210 (Fish, Early-life Stage Toxicity Test)

while the originally proposed long-term toxicity study on fish, test method: OECD Guideline 204 for provision of Annex IX 9.1.6 is rejected in accordance with Article 40(3)(d) of the

REACH Regulation.

Concerning all studies, the Registrant shall determine the appropriate order of the studies taking into account the possible outcomes and considering the possibilities for adaptations of the standard information requirements according to column 1 or 2 provisions of the relevant Annexes of the REACH Regulation. More specifically, prior to conducting the tests c) and d) above, the Registrant shall take into account the Guidance related to integrated testing strategy for aquatic toxicity testing to determine the sequence in which the tests are to be conducted.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **6 June 2014** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfil this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

At any time, the Registrant 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

The decision of ECHA is based on the examination of the testing proposals of the Registrant for the registered substance and scientific information submitted by third parties.

Examination of testing proposals

a) Sub-chronic toxicity

According to Section 8.6.2 of Annex IX of the REACH Regulation, a sub-chronic toxicity study (90-day) is required to fulfil the standard information requirements for substances registered in a tonnage band of 100 tonnes per year or more. As the proposed test for sub-chronic toxicity is not available for the registered substance but needs to be present in the technical dossier to meet the information requirement of Section 8.6.2 of Annex IX of the REACH Regulation, it is necessary to generate the data and to perform the test, according to EU test method B.26/ OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents).

For sodium hydroxymethanesulphinate (hydrate), inhalation and dermal routes are relevant for workers. According to Column *2* of section 8.6.2 of Annex IX, the inhalation route is regarded appropriate if exposure via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of inhalable size. The substance is in solid form, with the vapour pressure being in the mPascal range. Only a very small proportion of the particles of the substance has diameter lower than 10 µm. Therefore, inhalation exposure to the substance is not probable and, consequently, the inhalation route is not appropriate. The dermal route is not regarded appropriate, since the dermal absorption was estimated to be low because the substance is

a salt. In addition, in the acute dermal toxicity study no adverse effects were observed. In conclusion, the oral route is the most appropriate route to be used in the 90-day study.

b) Pre-natal developmental toxicity

Pre-natal developmental toxicity studies are part of the standard information requirements as laid down in Annexes IX and X, section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to generate the data for this endpoint. The Registrant did not specify the species and route to be used for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat as a first species to be used.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out with the registered substance the following test: Pre-natal developmental toxicity study in rats, oral route (test method: EU B.31/OECD Guideline 414).

When considering the need for a testing proposal for a pre-natal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed.

c) Long-term toxicity testing on invertebrates

Long-term toxicity testing on invertebrates is a standard information requirement as laid down in Annex IX, 9.1.5. of the REACH Regulation. Column 2 of Section 9.1. of Annex IX further indicates that this information requirement must be fulfilled unless the chemical safety assessment leads to the conclusion that the test is not needed. As the proposed test for long-term toxicity to aquatic invertebrates is not available for the registered substance but needs to be present in the technical dossier to meet the information requirement of Section 9.1.5. of Annex IX of the REACH Regulation, it is necessary to generate the data and to perform the test.

d) Long-term toxicity study on fish

Long-term toxicity testing on fish is a standard information requirement as laid down in Annex IX, 9.1.6. of the REACH Regulation. Column 2 of Section 9.1. of Annex IX further indicates that this information requirement must be fulfilled unless the chemical safety assessment leads to the conclusion that the test is not needed. As the proposed test for long-term toxicity to fish is not available for the registered substance but needs to be present in the technical dossier to meet the information requirement of Section 9.1.6. of Annex IX of the REACH Regulation, it is necessary to generate the data and to perform the test.

The Registrant questioned the reliability of the acute fish test and proposed further testing

according to the OECD Guideline 204 (Fish, prolonged toxicity test: 14-day study). However, ECHA notes that the proposed test cannot fill the information requirement as it is not mentioned in Annex IX 9.1.6 as one of the valid tests that can cover the specific information requirement. More specifically, the Annex IX, 9.1.6 mentions that the information shall be provided for one of the Sections 9.1.6.1 (OECD Guideline 210: Fish early-life stage (FELS) toxicity test), 9.1.6.2 (OECD Guideline 212: Fish short-term toxicity test on embryo and sac-fry stages) or 9.1.6.3 (OECD Guideline 215: Fish, juvenile growth test). Furthermore, the Guidance on Information requirements and Chemical Safety Assessment (R.7.8.4.1, page 25) states that "*only such studies can be regarded as long-term fish test, in which sensitive life-stages (juveniles, eggs, larvae) are exposed. Thus, tests performed according to OECD 204 (Fish, Prolonged Toxicity Test: 14-Day Study (OECD 1984)) or similar guidelines cannot be considered suitable long-term tests. They are, in effect, prolonged acute studies with fish mortality as the major endpoint examined*". Consequently, only one of the three tests mentioned above can generate data fulfilling the information requirement.

ECHA notes that the preferred test method is the OECD Guideline 210 (FELS) in accordance with Annex IX, 9.1.6.1. as this method is the one that can be applied for any substance type, it has a longer test duration (depending on the species but usually 28 days post-hatch compared to 14 days) and it thus accounts better for long-term environmental exposures. FELS is internationally considered to be the most sensitive method covering the most critical life-stages and events for fish (embryos, larvae and juveniles) and it is the preferred and most widely used method for predicting chronic toxicity to fish within different regulatory frameworks (OECD Workshop on a Fish Toxicity Testing Framework, 2010). Performing the long-term toxicity test according to the most sensitive test (OECD Guideline 210) is particularly relevant for the registered substance, as the Registrant has identified the need to refine the hazard assessment due to the poor quality of the acute fish toxicity data being outdated and not having been performed in accordance with good laboratory practice.

For these reasons, the Registrant is requested to perform the study according to OECD Guideline 210 (Fish, Early-life Stage Toxicity Test).

As laid down in the introductory paragraphs of Annexes VII to X of the REACH Regulation the Registrant should consult further guidance on testing strategies. Therefore, prior to conducting the long-term aquatic toxicity tests mentioned above, the Registrant shall consult the Guidance on information requirements and chemical safety assessment (Version 1.1, May 2008, Chapter R7b, Section R.7.8.5, page 31). More explicitly, the Registrant is requested to consider the testing strategy by taking into account the sequence in which the aquatic long-term toxicity tests are to be conducted according to figure R.7.8-4, p.53 of the Guidance document and the overall necessity to conduct long-term toxicity testing on vertebrate animals.

<u>Consideration of third party information</u>

ECHA has further examined the scientific information submitted by a third party following the public consultation in order to determine whether there is already scientifically valid information that addresses the relevant substance and hazard endpoint. The third party suggested that before an Oral Sub-chronic Toxicity Study (OECD Guideline 408), and a Prenatal Developmental Toxicity Study (OECD Guideline 414) is conducted, consideration should be given to the following alternative testing strategies:

1. Presence of the existing Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test (OECD Guideline 422), in vivo and in vitro genotoxicity test results and other toxicological data. Extrapolation from sub-acute to sub-chronic is foreseen by the REACH Guidance, with an assessment factor of 3. The developmental study should be waived, as it is known or suspected mutagen, thus one of the three waiving criteria is met.

2. Perform in vitro (pre-) validated tests for the evaluation of the embryotoxic and endocrine disruption potential and apply QSAR classification models for developmental toxicity. Use results to waive developmental toxicity study (Prenatal Developmental Toxicity Study, OECD Guideline 414).

3. Exposure considerations: use the TTC for repeated dose and reproduction toxicity end point.

ECHA notes the following:

1. Both Sub-chronic Toxicity and Prenatal Developmental Toxicity are information requirements under REACH. The combined Reproduction/ Developmental Toxicity Screening Test (OECD Guideline 422) constitutes neither an alternative to the proposed tests nor does it replace the information requirements covered by these tests. Due to test design (e.g. small number of animals, selectivity of the endpoints, and different dosing regime) of the screening test, negative results do not provide sufficient level of certainty with respect to developmental toxicity. Moreover, the study is requested under Annex VIII, 8.7.1. to the REACH Regulation, and it cannot be used to adapt the standard information requirement for developmental toxicity even though vice verse the screening test can be omitted pursuant to column 2 of Annex VIII, 8.7.1. if a pre-natal developmental toxicity study is available.

Concerning the proposal to apply an assessment factor of 3, there is neither such a specific rule for adaptation of the information requirement for a 90-day study under column 2 of Annex 8.6.2 nor a general rule under Annex XI of the REACH Regulation. Therefore, the third party proposal does not provide a sufficient basis on which to reject the proposed test.

The developmental study could be waived, if the substance is a known or suspected germ cell mutagen, which is not the case for the registered substance.

2. The third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis for rejecting the testing proposals.

Additionally, ECHA notes the following. Scientifically validated in vitro methods such as the embryonic stem cell test, the limb bud micromass culture and the whole embryo culture may provide additional information which can be assessed together with existing in vivo data in a weight of evidence approach. However, the mentioned in vitro tests only cover some of the reproductive toxicity endpoints, modes of action and mechanisms covered by the in vivo pre-natal developmental toxicity study and therefore they cannot be used on their own as replacement to testing according OECD Guideline 414. Furthermore, these alternative methods are not part of the information requirements laid down in Annex VII to X of REACH and can therefore not be requested by ECHA in the context of a testing proposal examination. ECHA notes that it is the Registrant's responsibility to establish the weight of

evidence justification which demonstrates that any data that may be obtained from the conduct of the proposed tests would be sufficient to meet the information requirements when submitting and/or updating its registration dossier.

Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the adaptation on the basis of QSAR models and in vitro methods set out in Annex XI, Section 1.3 and 1.4. Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

3. The Registrant has not proposed to adapt the information requirements on the basis of Annex XI, Section 3 of the REACH Regulation. Furthermore, the Registrant did not perform a quantitative exposure assessment or risk characterisation for human health. Therefore, it can not be assessed if exposure is negligible.

The argumentation provided by the third party does not allow an adaptation of the information requirement for a 90-day sub-chronic toxicity study or for a pre-natal developmental toxicity study using the specific rules under column 2 of Annex 8.6.2 or column 2 of Annex 8.7.2 of the REACH Regulation.

IV. Adequate identification of the composition of the tested material

The process of evaluation of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the generation of information is tailored to real information needs in order to prevent unnecessary testing. The information submitted in the registration dossier was sufficient to confirm the identity of the substance for the purpose of assessing the testing proposal. It is noted, however, that this information, or the information submitted by other registrants of the same substance, 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 proposed tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all the joint registrants of the same substance to agree with the tests proposed in the testing proposal (as applicable to their tonnage level) and to document the necessary information on its composition. The substance identity information of the registered substance and of the sample tested must enable ECHA to confirm the relevance of the testing for the substance actually registered by each joint registrant. Finally, the studies must be shared by the joint registrants concerned.

V. General requirements for the generation of information and 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.

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as

adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such 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://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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