EUROPEAN CHEMICALS AGENCY

Helsinki, 17 December 2018

**Addressees: The Lead Registrants of all substances covered by the category "Stilbene Fluorescent Whitening Agents" (SFWA)**

(The identity of the addressees of the decision and the substances concerned are specified in Appendix 4 of the present decision)

## DECISION ON A COMPLIANCE CHECK

The substances subject to this decision are the members of the category "Stilbene Fluorescent Whitening Agents" (SFWA). The registrants of all substances covered by the SFWA category referred to the same adaptations according to Annex XI, Section 1.5 (grouping and read-across) in order to fulfil their respective information requirements. These registrants have grouped the substances into subcategories on the basis of their structural variations. The underlying hypothesis for predictions is based on structural similarity, similar toxicity profiles, similar metabolic pathways, low uptake and no or low toxicity.

The compliance of the dossiers of the substances covered by the SFWA category with the applicable information requirements depends on the validity of the adaptations invoked collectively by the registrants of these substances. The adaptations are in the form of a comprehensive category of several substances. In order to enable the consolidation of the adaptations so that it becomes acceptable, the present decision assesses the validity of the SFWA category as a whole and addresses together all of the substances it covers.

The approach followed by the present decision is part of a pilot project initiated by ECHA on category adaptations that are deemed plausible, but still not conclusive yet. More specifically, this project aims to determine the workability of regulatory measures designed to consolidate such category adaptations, rather than adopting measures identifying the deficiencies of such adaptations, rejecting them and requesting the missing information on every substance covered. Accordingly, the approach followed by ECHA in the present decision shall not prejudge the way the Agency interacts or will interact with registrants in other cases.

The introductory sections below describe the steps ECHA performed to come to the current decision and explains how the requests are structured.

For some information requirements ECHA accepts the proposed adaptation. These are therefore not addressed in the present decision. In contrast, for other information requirements ECHA found a number of flaws in the arguments of the adaptations and contradictions in the experimental data provided by the registrants. However, ECHA's basic assumption is that the proposed adaptations may meet the provisions in Annex XI, Section 1.5 following the submission of the information requested in the present decision. A prerequisite is that sufficient experimental source studies are available which cover the structural variations of the SFWA member substances and that there is sufficient bridging information for those substances that do not have experimental data.

In any case, ECHA emphasises that any final determination on the validity of the category adaptation would be premature at this point in time. The eventual validity of the adaptation will therefore be reassessed once the requested information is submitted. ECHA reserves the rights at this point to request any further information necessary to bring the dossiers of the substances covered by the SFWA category into compliance.

***ECHA Analysis***

Studies addressing information requirements in the REACH Annexes VII – X must be adequate and reliable for the substance registered and also when used as source studies for predictions based on grouping and read-across. ECHA analysed the provided information for all substance dossiers and in the document which provides reasoning of the registrants for the adaptations (hereafter, the "justification document").

The outcome was that for some properties (acute toxicity, skin and eye irritation, skin sensitisation) sufficient information is present to conclude that the predictions to fill remaining data gaps for these properties meet the provisions of Annex XI, Section 1.5. Therefore, no further requests for experimental data are made for these properties in this decision.

For properties related to genotoxicity the information requirements are often met by the provided information. Furthermore, most of the proposed adaptations meet the provisions of Annex XI, Section 1.5. Nevertheless, some requests for additional experimental data for genotoxicity are made in this decision.

For higher tier toxicological properties (repeated dose toxicity, pre-natal developmental toxicity, and reproductive toxicity) and for environmental properties (toxicity to algae, short-term toxicity to fish, short- and long-term toxicity to aquatic invertebrates) many studies provided were found to be not adequate and/or reliable or absent (e.g. long-term toxicity to fish). As a result, the data matrices for these properties contain only little experimental information which is useful for supporting adaptations. Also, the presented evidence for similar metabolic pathways and low or no toxicity was weak or contradictory. For these properties, ECHA concluded that the adaptations proposed for the substances without experimental data currently need to be rejected. ECHA considers, however, that the justification shall be improved by further experimental data.

***Studies and Information requested in order to consolidate the SFWA category***

ECHA has identified all substances with data gaps, which must be addressed either with new experimental studies or with adaptations.

ECHA considers that new experimental data is not needed to address all of the information requirements for each substance. Instead, the data availability must be improved to a level that the chemical structures present in the subcategories are addressed by reliable experimental data. For some substances the information requirement will be addressed by the standard test (e.g. 90 day repeat dose toxicity study; pre-natal developmental toxicity studies in two species) conducted on the substance itself and such studies will also provide the additional source data for use by grouping and read-across for other substances of the category. Furthermore, appropriate studies are requested, which not only address standard information requirements, but will also deliver bridging information and may confirm similar toxicity profiles for the other substances in the category/subcategories.

For the human health hazard assessment, studies conducted according to OECD TG 422, not only meet standard information requirements, but will also serve as bridging studies for those substances for which a confirmation is needed in order to establish that the proposed adaptations meet the provisions of Annex XI, Section 1.5. This type of screening study provides information for repeated dose toxicity as well as for pre-natal developmental toxicity and reproductive toxicity in the rat. Therefore, the results of these studies should be able to confirm the proposed adaptations for these information requirements.

For the environmental hazard assessment, ECHA considers that toxicity studies on algae and long-term testing on *Daphnia* need to be conducted not only to meet standard information requirements for the substances tested, but they will also serve as bridging studies to allow predictions for the property long-term testing on fish. Furthermore, in the absence of any long-term toxicity data on fish, studies on some of the substances need to

be conducted to fulfil the standard information requirements for those substances and to obtain the necessary source studies for the other SWFA category members.

The source studies and the bridging studies have to be provided by the deadline set in the present decision. On the basis of the results obtained from these studies, the registrants are further requested to update by the same deadline their technical dossier and the justification document and conclude on the possibility to adapt the information requirements based on Annex XI, Section 1.5 for their substance without experimental information on each property.

ECHA will review all the provided information. If the information obtained does not confirm that the proposed adaptations meet the provisions in the REACH Regulation for some or all substances, further experimental data will be requested to fill the remaining data gaps. If this is the case a decision will be taken according to Article 42(1).

ECHA determined the design of the EOGRTS studies on the basis of the current knowledge. This design may need to be changed after all other information requested in the present decision is known. The registrants may only commence the extended one-generation reproductive toxicity studies after ECHA has reviewed this information. Details are specified in this decision.

ECHA
EUROPEAN CHEMICALS AGENCY

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**Requests**

The substances in the SFWA category are identified with name, EC number and CAS number in Appendix 4. The substances for which information is requested in this request section are identified by acronyms which contain the CAS numbers (see below). Further explanation of the acronyms is provided in II.B.

1-MSA#42355-78-2
1-DSA#41098-56-0
2-A#16090-02-1
2-MSA#28950-61-0
2-DSA#52301-70-9
3a-A(free acid)#4404-43-7
3a-A(NaK)#70942-01-7
3a-A(Na)#4193-55-9
3a-MSA#16470-24-9
3a-DSA#68971-49-3
3b-A#13863-31-5
3c-A#17958-73-5 *
3c-MSA#16324-27-9
4-MSA#67786-25-8
5-A#27344-06-5

* Concerning substance 3c-A#17958-73-5 (registration n° 01-2119540143-52-0000; EC number 241-883-4; CAS number 17958-73-5), ECHA notes that an intention to cease manufacture was notified to ECHA on 6 November 2018, after the unanimous agreement of the Member State Committee, but before the notification of this decision to the Registrant concerned. In accordance with Article 50(3) of the REACH Regulation, this cease of manufacture leads to a termination of the compliance check procedure for that registration and the Registrant concerned is not required to provide the information contained in the decision. The cease manufacture has no impact on the requests for the other substances addressed in the decision.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3. Appendix 4 lists the addressees of this decision and the substances concerned. Information and tables which aid understanding the decision are provided in Appendix 5.

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests the registrants to which the corresponding information requirement applies to submit the following:

**Information to be provided in order to consolidate the SFWA category**

**In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14./ OECD TG 471);**

For the reasons explained in Appendix 1, III.A.4, the registrant of the following substance shall conduct an experimental study with the substance to fulfil this information requirement:

(request 1) 4-MSA#67786-25-8

**In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487);**

For the reasons explained in Appendix 1, III.B.4.1, the registrants of the following substances shall conduct an experimental study with their respective substance to fulfil this information requirement:

(request 2) 3a-DSA#68971-49-3

(request 3) 3c-A#17958-73-5 [1]

(request 4) 4-MSA#67786-25-8

(request 5) 5-A#27344-06-5

For the reasons explained in Appendix 1, III.B.4.2, the registrant of the following substance, invoking an adaptation according to Annex XI, Section 1.5, shall submit the robust study summaries of the experimental studies mentioned above. He shall also submit an updated justification explaining whether, why and how this information requirement can be adapted, taking into account the newly generated information obtained in the SFWA category:

(request 6) 3c-MSA#16324-27-9

**In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) ;**

For the reasons explained in Appendix 1, III.C.4.1, the registrant of the following substance shall conduct an experimental study with the substance to fulfil this information requirement:

(request 7) 3c-A#17958-73-5 [2] provided that the study for this substance requested under Annex VIII, 8.4.2 has negative results

For the reasons explained in Appendix 1, III.C.4.2, the registrant of the following substance, invoking an adaptation according to Annex XI, Section 1.5, shall submit the robust study summary of the experimental study mentioned above. He shall also submit an updated

[1] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

[2] *Idem*.

justification explaining whether, why and how this information requirement can be adapted, taking into account the newly generated information obtained in the SFWA category:

(request 8) 3c-MSA#16324-27-9

**Toxicokinetic information: inclusion of measurements in blood, plasma, bile and/or urine in the conduct of repeated dose toxicity studies; see III.D**

While toxicokinetic information is not a formal information requirement imposed by the REACH Regulation, ECHA expects that the SFWA category may be further consolidated by such information, as also proposed by the registrants. The registrants may therefore submit results obtained by toxicokinetic investigations on blood, serum and urine included in the studies requested in the present decision. ECHA notes that the structural variations in the category need to be covered in order to deliver useful information for the interpretation of the study results. In the same line, ECHA considers that bile excretion and the impact of the administration route and of the vehicle on the availability for oral absorption should require the attention of the registrants.

It is at the registrants' discretion to define the substances for which toxicokinetic measurements are included in the studies requested below.

**Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats;**

For the reasons explained in Appendix 1, III.E.4.1, the registrants of the following substances shall conduct an experimental study with their respective substance to fulfil this information requirement:

(request 9) 1-MSA#42355-78-2

(request 10) 3a-MSA#16470-24-9

(request 11) 5-A#27344-06-5

For the reasons explained in Appendix 1, III.E.4.2, the registrant of the following substance shall submit a robust study summary to fulfil this information requirement for the substance:

(request 12) 1-DSA#41098-56-0 (Short term (17-days) and Sub-chronic (90-days) toxicity studies with [redacted] in Rats with Cover Letter dated 100992, [redacted] OTS 0571834 for the substance)

For the reasons explained in Appendix 1, III.E.4.4, the registrants of the following substances, invoking an adaptation according to Annex XI, Section 1.5, or an adaptation according to Annex IX, Section 8.6.2 Column 2, shall submit the robust study summaries of experimental studies mentioned above. They shall also submit an updated justification explaining whether, why and how this information requirement can be adapted, taking into account the newly generated information obtained in the SFWA category:

(request 13) 3a-A(Na)#4193-55-9

(request 14) 3a-A(NaK)#70942-01-7

(request 15) 3a-DSA#68971-49-3

(request 16) 3c-A#17958-73-5 [3]

(request 17) 4-MSA#67786-25-8

**Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 422 in rats, oral route (gavage) with the registered substances;**

For the reasons explained in Appendix 1, III.E.4.3, the registrants of the following substances shall conduct an experimental study with their respective substance to fulfil this information requirement:

(request 18) 2-DSA#52301-70-9

(request 19) 3a-A(Na)#4193-55-9

(request 20) 3a-DSA#68971-49-3

(request 21) 3b-A#13863-31-5

(request 22) 3c-A#17958-73-5 [4]

(request 23) 4-MSA#67786-25-8

For the reasons explained in Appendix 1, III.E.4.4, the registrants of the following substances, invoking an adaptation according to Annex XI, Section 1.5, or an adaptation according to Annex IX, Section 8.6.2 Column 2, shall submit the robust study summaries of experimental studies mentioned above. They shall also submit an updated justification explaining whether, why and how this information requirement can be adapted taking into account the newly generated information obtained in the SFWA category:

(request 24) 3a-A(NaK)#70942-01-7

(request 25) 3c-MSA#16324-27-9

**Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat), oral gavage;**

For the reasons explained in Appendix 1, III.F.4.1, the registrants of the following substances shall conduct an experimental study with their respective substance to fulfil this information requirement:

(request 26) 1-MSA#42355-78-2

(request 27) 2-A#16090-02-1

(request 28) 5-A#27344-06-5

[3] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

[4] *Idem*.

For the reasons explained in Appendix 1, III.F.4.2, the registrants of the following substances, invoking an adaptation according to Annex XI, Section 1.5, shall submit the robust study summaries of the experimental studies mentioned above. They shall also submit an updated justification explaining whether, why and how this information requirement can be adapted, taking into account the newly generated information obtained in the SFWA category:

(request 29) 1-DSA#41098-56-0

(request 30) 3a-A(Na)#4193-55-9

(request 31) 3a-A(NaK)#70942-01-7

(request 32) 3a-DSA#68971-49-3

(request 33) 3c-A#17958-73-5 [5]

(request 34) 4-MSA#67786-25-8

**Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbit), oral gavage;**

For the reasons explained in Appendix 1, III.G.4.1, the registrants of the following substances shall conduct an experimental study with their respective substance to fulfil this information requirement:

(request 35) 2-A#16090-02-1

(request 36) 4-MSA#67786-25-8

For the reasons explained in Appendix 1, III.G.4.2, the registrants of the following substances, invoking an adaptation according to Annex XI, Section 1.5, shall submit the robust study summaries of the experimental studies mentioned above. They shall also submit an updated justification explaining whether, why and how this information requirement can be adapted, taking into account the newly generated information obtained in the SFWA category:

(request 37) 3a-A(Na)#4193-55-9

(request 38) 3a-DSA#68971-49-3

**Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: OECD TG 443) in rats, oral gavage route specified as follows;**

For the reasons explained in Appendix 1, III.H.4.1, the registrant of the following substance shall conduct an experimental study with their respective substance to fulfil this information requirement:

(request 39) 1-DSA#41098-56-0

[5] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

- 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) with extension to mate the Cohort 1B animals to produce the F2 generation.

**Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral gavage route specified as follows;**

For the reasons explained in Appendix 1, III.H.4.1, the registrant of the following substance shall conduct an experimental study with the substance to fulfil this information requirement:

(request 40) 2-A#16090-02-1
- 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.

For the reasons explained in Appendix 1, III.H.4.2, the registrants of the following substances, invoking an adaptation according to Annex XI, Section 1.5, shall submit the robust study summaries of the experimental studies mentioned above. They shall also submit an updated justification explaining whether, why and how this information requirement can be adapted, taking into account the newly generated information obtained in the SFWA category:

(request 41) 3a-A(Na)#4193-55-9

(request 42) 3a-DSA#68971-49-3

(request 43) 4-MSA#67786-25-8

**Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201);**

For the reasons explained in Appendix 1, III.I.4.1, the registrants of the following substances shall conduct an experimental study with their respective substance to fulfil this information requirement:

(request 44) 1-MSA#42355-78-2

(request 45) 2-A#16090-02-1

(request 46) 2-DSA#52301-70-9

(request 47) 3a-A(Na)#4193-55-9

(request 48) 3a-DSA#68971-49-3

(request 49) 3b-A#13863-31-5

(request 50) 3c-A#17958-73-5 [6]

For the reasons explained in Appendix 1, III.I.4.2, the registrants of the following substances, invoking an adaptation according to Annex XI, Section 1.5, shall submit the robust study summaries of the experimental studies mentioned above. They shall also submit an updated justification explaining whether, why and how this information requirement can be adapted, taking into account the newly generated information obtained in the SFWA category:

(request 51) 1-DSA#41098-56-0

(request 52) 3a-A(NaK)#70942-01-7

(request 53) 3a-MSA#16470-24-9

(request 54) 3c-MSA#16324-27-9

**Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211);**

For the reasons explained in Appendix 1, III.J.4.1, the registrants of the following substances shall conduct an experimental study with their respective substance to fulfil this information requirement:

(request 55) 1-MSA#42355-78-2

(request 56) 2-A#16090-02-1

(request 57) 3a-A(Na)#4193-55-9

(request 58) 3a-DSA#68971-49-3

(request 59) 3c-A#17958-73-5 [7]

(request 60) 4-MSA#67786-25-8

(request 61) 5-A#27344-06-5

For the reasons explained in Appendix 1, III.J.4.2, the registrants of the following substances, invoking an adaptation according to Annex XI, Section 1.5, shall submit the robust study summaries of the experimental studies mentioned above. They shall also submit an updated justification explaining whether, why and how this information requirement can be adapted, taking into account the newly generated information obtained in the SFWA category:

(request 62) 1-DSA#41098-56-0

(request 63) 3a-A(NaK)#70942-01-7

[6] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.
[7] *Idem*.

**Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210);**

For the reasons explained in Appendix 1, III.K.4.1, the registrants of the following substances shall conduct an experimental study with their respective substance to fulfil this information requirement:

(request 64) 1-MSA#42355-78-2

(request 65) 2-A#16090-02-1

(request 66) 3a-A(Na)#4193-55-9

(request 67) 5-A#27344-06-5

For the reasons explained in Appendix 1, III.K.4.2, the registrants of the following substances, invoking an adaptation according to Annex XI, Section 1.5, shall submit the robust study summaries of the experimental studies mentioned above. They shall also submit an updated justification explaining whether, why and how this information requirement can be adapted, taking into account the newly generated information obtained in the SFWA category:

(request 68) 1-DSA#41098-56-0

(request 69) 3a-A(NaK)#70942-01-7

(request 70) 3a-MSA#16470-24-9

(request 71) 3a-DSA#68971-49-3

(request 72) 3c-A#17958-73-5 [8]

(request 73) 4-MSA#67786-25-8

**Specific considerations for the analytical determination of the test material**

The registered substances have physico-chemical properties, which trigger specific considerations and measures regarding the analytical control of the substances used for testing. These are provided in Appendix 3.

**Deadlines**

The registrants have to submit the requested information listed above, except the extended one-generation reproductive toxicity studies, by **4 January 2021**. The registrants also have to update the technical dossier, the chemical safety report, and the justification document, where relevant.

[8] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

After that deadline the information newly submitted will be reviewed by ECHA according to Article 42 of the REACH Regulation. If the proposed adaptations do not meet the provisions of Annex XI, Section 1.5, additional experimental studies may be needed. In that case, ECHA will initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to request additional experimental studies necessary to bring the dossiers of the substances concerned by the present decision in compliance with the applicable information requirements.

The registrants may only commence the extended one-generation reproductive toxicity studies (requests 39 and 40) only after **24 June 2021**, unless an indication to the contrary is communicated to the registrants by ECHA before that date.

The registrants have to submit the requested information listed for requests 39 – 43 by ***26 June 2023***.

ECHA has taken into account all the information currently available in the dossiers, including the experimental studies, the adaptations proposed based on Annex XI, Section 1.5, the adaptations proposed based on Column 2 provisions for some information requirements and the testing strategy. ECHA therefore considers that the adaptation possibilities are already integrated in this decision with the aim to achieve an adequate level of information and compliant dossiers for all substances, which are members of the category.

**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.

Authorised[9] by Ofelia Bercaru, Head of Unit, Evaluation E3

[9] 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 1: Reasons

### I. Toxicological and ecotoxicological information

Substances addressed in this decision are registered at above 1000, at 100 to 1000, at 10 to 100, or at 1 to 10 tonnes per year. Therefore, the information requirements for the registrations of individual substances vary from Annex VII only to Annexes VII-X. The applicable tonnage bands for each substance concerned by the present decision are specified in the Appendix 4.

In accordance with Articles 10(a) and 12(1) of the REACH Regulation,

- a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation,
- a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation
- a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII to the REACH Regulation.
- a technical dossier registered at 1 to 10 tonnes per year must contain, as a minimum, the information specified in Annex VII to the REACH Regulation.

The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The registration dossiers of all the substances covered by the SFWA category contain a justification document describing the "[redacted]" and a document "[redacted]" (hereafter the "[redacted]"). Both documents were updated on 10 August 2017 and were submitted to ECHA in response to a discussion between ECHA and the Registrants on the potential for improving the category justification. These documents are also considered in addition to the specific information contained in the registration dossiers for the individual substances.

Adaptation arguments in the form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH Regulation are used for multiple (eco)toxicological properties for multiple members of the category.

ECHA has assessed first the scientific and regulatory validity of the registrants' grouping and read-across approach in general before the specific information requirements were considered.

ECHA considers that the proposed category approach merits integrated evaluation of the information on all substances, which the registrants identified as members of the category. ECHA therefore assesses the category and the justification for using grouping and read-across for filling data gaps in this decision by considering the individual information requirements across the category member substances.

## II. Grouping and read-across approach for (eco)toxicological information

### II.A General considerations

The registrants have sought to adapt the information requirements listed above by applying a read-across approach in accordance with Annex XI, Section 1.5. According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physico-chemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and the consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physico-chemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as lead to transformation products that may be hazardous, bioaccumulative and/or persistent. Thus, physico-chemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physico-chemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

### II.B Description of the grouping and read-across approach proposed by the registrants

#### *II.B.1 Grouping*

The registered substances belong to the category of the Stilbene Fluorescent Whitening Agents (SFWA). "*The main applications fields are as fluorescent brighteners in paper,*

*textiles and household detergents. The stilbene central "body" is chemically identical for all substances (...) and has the following properties:*
*• chromophore that allows absorbance of light in the ultraviolet region and re-emission of light in the blue Region"*
*• and chemical stability granted by resonance / delocalisation."*

The category comprises of 15 substances (CAS numbers): 4193-55-9, 4404-43-7, 13863-31-5, 16090-02-1, 16324-27-9, 16470-24-9, 17958-73-5, 27344-06-5, 28950-61-0, 41098-56-0, 42355-78-2, 52301-70-9, 67786-25-8, 68971-49-3, and 70942-01-7. Appendix 4 to this decision, shows the Lead Registrants, the EC numbers, CAS numbers and substance names; and figures 1 and 2 of Appendix 5 show the chemical structures.

The substance CAS 52301-70-9 was registered in April 2017. It is listed as a category member and is included in the data matrices of the justification document as not registered, and substance specific justification for adaptions according to Annex XI, Section 1.5 are not provided in the justification document. Such justifications, however, are provided in the endpoint study summaries of the IUCLID dossier of CAS 52301-70-9. The reasoning refers to the SFWA category and uses similar arguments to those used in the justification document of the SFWA category which is attached to the IUCLID dossier of CAS 52301-70-9. ECHA therefore included CAS 52301-70-9 in the analysis of the SFWA category and in this decision.

The substance CAS 4404-43-7 is registered as an on-site isolated intermediate. With regard to the requests in this decision to meet REACH information requirements, this substance is not further considered in this decision. However, it is considered as a source substance for repeated dose toxicity information.

In the justification document the category is described: "*The category of Stilbene Fluorescent Whitening Agents is defined as a* structurally *related group of substances that are derivatives of 4,4'-bis(1,3,5-triazinyl-2-yl)amino)stilbene-2,2'-disulphonic acid, each with one aniline and one alkylderivative amino moiety at the triazine ring".*

The structural variations of the main constituents of the substances in the category are defined by two principle organic substituents. There are two R1 and two R2 moieties due to the symmetric nature of the main constituents.

R1 (amino aniline moiety): The aniline moiety may be just an aniline attached to an amino group or a mono- or a disulphonated aniline. Since all substances contain main constituents with two sulphonic acid groups on the core structure, the additional sulphonic acid groups at the amino aniline moiety bring the total number of sulphonic acid groups to 4 or 6. The total number of sulphonic acid groups in the substance defines also the number of counter ions: 2, 4 or 6 sodium ions, while CAS 70942-01-7 also has mixed sodium/potassium counter ions.

R2 (amino alkylderivative moiety): morpholino, methyl (2-hydroxyethyl)amino, 2-hydroxyethylamino, bis(2-hydroxyethyl)amino, diethylamino, (2-carbamoylethyl)(2-hydroxyethyl)amino, or bis(2-hydroxypropyl)amino.

The registrants used the combination of the different possible R1 and R2 substituents on the main constituents to group the substances into subcategories according to the R2 moieties and within those subcategories to order the substances according to the number of sulphonic acid moieties (see Appendix 5, figure 2). Additionally, hypothetical metabolic considerations were used by the registrants to claim relationships between the subcategories.

In order to develop a decision text which is more readily understandable with regard to the substances discussed, ECHA used acronyms for the substances, which combined the designation of the R2-subcategory (1, 2, 3a, 3b, 3c, 4, 5), with an acronym for the R1 moiety (A: amino aniline, MSA: amino monosulphonated aniline, DSA: amino disulphonated aniline), followed by a #sign and the CAS number, as follows:

1-MSA#42355-78-2
1-DSA#41098-56-0
2-A#16090-02-1
2-MSA#28950-61-0
2-DSA#52301-70-9
3a-A(free acid)#4404-43-7
3a-A(NaK)#70942-01-7
3a-A(Na)#4193-55-9
3a-MSA#16470-24-9
3a-DSA#68971-49-3
3b-A#13863-31-5
3c-A#17958-73-5 [10]
3c-MSA#16324-27-9
4-MSA#67786-25-8
5-A#27344-06-5
To describe the subcategories, the registrants use the term "group", but ECHA has used "subcategory" (abbreviated as SC in this decision) to avoid the generic term 'group'.

Based on R2 substituents, the registrants grouped the substances into the subcategories explained below and also shown in Appendix 5. Within the subcategories the registrants ordered the substances according to the R1 substituents (increasing number of sulphonic acid functions).

Subcategory 1 (SC1): Diethyl amino derivatives
- 1-MSA#42355-78-2 (tetrasulphonated, sodium salt)
- 1-DSA#41098-56-0 (hexasulphonated, sodium salt)

Subcategory 2 (SC2): Morpholino derivatives
- 2-A#16090-02-1 (disulphonated, sodium salt)
- 2-MSA#28950-61-0 (tetrasulphonated, sodium salt)
- 2-DSA#52301-70-9 (hexasulphonated, sodium salt)

Subcategory 3 (SC3): 2-hydroxyethyl amino derivatives

SC3a: bis (2-hydroxyethyl) amino derivatives
- 3a-A(free acid)#4404-43-7 (disulphonated, free acid form)
- 3a-A(NaK)#70942-01-7 (disulphonated, sodium and potassium salt salt)
- 3a-A(Na)#4193-55-9 (disulphonated, sodium salt)
- 3a-MSA#16470-24-9 (tetrasulphonated, sodium salt)
- 3a-DSA#68971-49-3 (hexasulphonated, sodium salt)

SC3b: methyl, 2-hydroxyethyl amino derivative
- 3b-A#13863-31-5 (disulphonated, sodium salt)

[10] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

SC3c: 2-hydroxyethyl amino derivative
- 3c-A#17958-73-5 (disulphonated, sodium salt) [11]
- 3c-MSA#16324-27-9 (tetrasulphonated, sodium salt)

Subcategory 4 (SC4) bis(2-hydroxy isopropyl) amino
- 4-MSA#67786-25-8 (tetrasulphonated, sodium salt)

Subcategory 5 (SC5) (2-carbamoylethyl)(2-hydroxyethyl)amino
- 5-A#27344-06-5 (disulphonated, sodium salt).

To support the structural similarity for the grouping and subgrouping, the registrants provided relative Tanimoto distances for the main constituents.

### *II.B.2 Predictions*

As support for the proposed predictions within the category, the registrants provided:

- Results obtained with the QSAR toolbox to model various properties such as protein binding, skin/eye irritation, mutagenicity, aquatic toxicity, bioaccumulation, carcinogenicity, DNA (binding) alerts, oestrogen receptor binding, oncologic primary classification; similar results were obtained for all members of the category
- Metabolism patterns predicted by the OECD toolbox, focused on R2 function groups (rat S9 metabolism simulator); similar patterns were obtained for R2 groups within the category subgroups
- Lipinski parameters to assess permeability and solubility; the parameters consistently indicated low bioavailability
- Calculations of dermal absorption by Dermwin; the calculations consistently indicated low dermal absorption
- Substance identities, structural formulas and impurity profiles
- For some impurities results obtained with the rat S9 metabolism simulator are presented
- For some impurities the OECD QSAR toolbox was used to model various properties; identical results to the main constituents were obtained.

Furthermore, experimental results for physico-chemical parameters, mammalian toxicity, environmental fate and environmental toxicity were presented in data matrices.

With regard to R1 the registrants claim that the order from less sulphonated to higher sulphonated constituents would be predictive for toxicity since sulphonation is regarded as a detoxifying mechanism leading to better excretion in the urine and the registrants relate this statement to the action of sulphotransferases. Furthermore, the registrants provide the example of amino stilbene derivatives, for which carcinogenicity was demonstrated. However, when the sulphonated derivative (4,4'-diaminostilbene-2,2' –disulphonic acid) was administered, carcinogenic activity was not detected. The registrants take this as evidence of the detoxifying effect of the sulphonic acid function.

The registrants also state in their category justification document that "*R1 variability would influence bioavailability and it is also known that an increase of sulphonated groups within an organic molecule will lower the general toxicity of a substance (Parkinson T.M., 1981)*". The registrants do not explain nor provide supportive evidence for these arguments.

With regard to R2 the registrants claim that the alkyl moiety of constituents in SC1 substances has the lowest biological reactivity, that the morpholino group of constituents of

[11] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

SC2 substances undergo ring opening, that all main constituents of SC3 substances have in common the mono(2-hydroxyethyl) moiety, that the bis(2-hydroxy isopropyl) amino moiety in the main constituent of the SC4 substance has a lower reactivity compared to SC3 substances due to the secondary alcohol function and that the carbamoylethyl moiety in the main constituent of the SC5 substance modifies the reactivity of the 2-hydroxyethyl group.

According to the registrants' justification document, the results of the OECD QSAR toolbox indicate that all main constituents have the same patterns of alerts/no alerts and the metabolism predictions for rat liver S9 show a common metabolism pattern with no small metabolites and no breakdown products.

For physico-chemical parameters, the registrants state that all the substances of the category have a high molecular weight (ranging from 873 to 1369), have a high thermal stability, have a negative log Pow, and a high to very high water solubility. The registrants also state that the water solubility is strongly influenced by the salt content present in the aqueous solution. Therefore, the water solubility for the morpholino derivative 2-A#16090-02-1 decreases by three orders of magnitude with increasing ionic strength in the solution.

To demonstrate the similarity of the substances with regard to mammalian toxicity, the registrants have provided matrices of the data which confirm that all SFWA substances tested are not irritating to skin or eyes, are not acutely toxic, and are not sensitizing. For these properties, remaining data gaps for substances without experimental data were addressed by read-across. The predictions for these substances were further supported by results obtained with the OECD QSAR toolbox. Detailed justifications were provided for these predictions, focussing on the fact that the main constituent of the source substances for the predictions had the same R2 function as the main constituent of target substance and that the main constituents of source and target substances only differed in respect of R1. To establish that the difference in R1 does not change the property under consideration, supporting results from substances in another subcategory but with the same R1 function were used. The data matrices for other mammalian toxicity properties are analysed in Section III of the decision.

For repeated dose toxicity, pre-natal developmental toxicity and reproductive toxicity the registrants claim that sufficient information is available to cover the structural variations of the SFWA substances, that the tested SFWA substances are basically not absorbed, behave similarly from a metabolic point of view and that the tested substances present the most conservative case and are without relevant toxic effects.

For ecotoxicological information the registrants intend to demonstrate that the available studies indicate that the category members are of low toxicity to aquatic organisms, based on acute tests with freshwater species of three trophic levels (algae, *Daphnia*, fish) and a long-term test (*Daphnia*) which are available for representative substances. The registrants consider that one disregarded long-term toxicity test on CAS 16090-02-1 may indicate a risk. However, they consider that it presents a number of inconsistencies and thus disregard the study. The registrants have fulfilled the remaining data gaps by read-across and provided property-specific and substance-specific reasoning.
Based on the presented evidence the registrants conclude that "*there is no convincing evidence that any one of the substances within the category/subcategories might lie out of the overall profile of this category or subcategory, respectively.*"

ECHA understands that on the basis of

- *"common use -optical brightener agents with similar application field and chemistry*
- *Similar structural features (have a common central core)*
- *Similar metabolic pathways*
- *Similar physicochemical properties (highly soluble, log Kow <-2)"*
- *Common properties for environmental fate, toxicological and eco-toxicological profile within the category"*

the registrants applied a read-across approach for which test results obtained with selected members of the category were used to predict the results for untested members of the category.

ECHA understands that as an integral part of these predictions, the registrants propose that the source and target substances have similar properties for the information requirements under consideration. ECHA considers this as the read-across hypothesis.

In the justification document the registrants report on performed exposure calculations and they state that based on the obtained results the RCR are < 0.01 and no relevant exposure occurs. Further, they describe that the SFWA substances were widely used in the last 60 years and that they show generally low toxicity. In view of these observations the registrants refrain from proposing further *in vivo* testing, because of concerns for animal welfare. These arguments are repeated in their testing strategy.

However, the registrants also state in their testing strategy that in the case ECHA concludes that the provided information is still not sufficient, they agree to increase the amount of data and to consolidate the category approach. In the testing strategy the registrants propose a stepwise approach, comprising of steps 1 to 3 for toxicological properties. They describe that the criteria for moving from step 1 to step 2 and then further to step 3 are the assessment of the relationship within each subgroup for the sulphonation degree and the verification of the reliability of the existing feeding studies. The registrants did not describe how outcomes of the studies in the proposed steps trigger which studies in the next steps and why. In the discussion on the individual properties ECHA has discussed their proposed strategy in more detail.

For environmental endpoints, the registrants state in their testing strategy that although no concern has been indicated by the current studies, they agree that there are some issues with the reliability of the available information. Therefore, the registrants propose to perform further studies on algae toxicity, short-term toxicity on invertebrates and fish and long-term studies on invertebrates. After that they propose to calculate PNECs and revise the risk characterisation in order to determine the need for long-term fish studies.

## II.C ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

### *II.C.1 Grouping*

ECHA considers that the structural diversity of the category members, mainly related to the R1 and R2 substituents for the main constituents, was sufficiently explained by the registrants. The formation of the subcategories 1 to 5 (see figure 2 in Appendix 5) based on these structural differences is regarded as plausible.

However, besides the structures of the main constituents, also the other constituents present in the registered substances have to be considered in a read-across approach.

All substances in the SFWA category, (except 1-DSA#41098-56-0, 3b-A#13863-31-5, 5-A#27344-06-5, see below) are mono-constituent substances. The percentage of the main constituent in the mono-constituent substances is at 80 % (w/w) or higher. The registrants explain that these substances show very similar patterns of by-products. Indeed, the main impurities are related to incomplete reactions in the production of the main constituents, leading to different substitution patterns on R2 or missing sulphonic acid groups. Other impurities above 1 % may be water, sodium chloride, and/or sodium carbonate. All substances have non-specified impurities, ranging from 2 % to < 12 %.

The highest non-specified impurities for the mono-constituent substances are identified for 4-MSA#67786-25-8 with < 12 % and 3a-MSA#16470-24-9 with < 7 %.

For 1-DSA#41098-56-0, the main constituent concentration range is >[redacted]% and the following impurities are identified: one aniline ring substituted with only one sulphonic acid instead of two (<7%), only one side chain on the stilbene moiety, the side of the stilbene has one sulphonic acid and a NH2 function (<3%), sodium chloride and sulphate (<22%), and water (<7 %).

For 3b-A#13863-31-5 the main constituent concentration range is ca. [redacted]% and the following impurities are identified: sodium chloride (<30 %), water (<5 %), non-specified impurities (<3 %), and sodium sulphate (<0.2 %).

For 5-A#27344-06-5, the typical concentration of the main constituent is about [redacted] % and the following impurities are identified: for one R2 the carbamoylethyl moiety is lacking (<25 %), the carbamoylethyl moiety is replaced with a propionic acid moiety (<7 %), both R2 lacking the carbamoyl ethyl moiety (<5%), the amine hydrogen atoms of the carbamoylethyl replaced by hydroxyethyl and carbamoylethyl, (<3 %), a dimeric stilbene structure (<3%), water (<8 %), sodium chloride (<5%), and non-specified impurities (<8%, each of which <1%).

ECHA considers that the description of the constituents of the SFWA member substances allow the assessment of the grouping and read-across approach.

The structural similarities between the SFWA member substances were explained (see above); ECHA considers that the applicability domain is clear and the members of the present category are defined. The subcategories as defined by the registrants are appropriate and facilitates the justification and analysis of the category.

### *II.C.2 Predictions*

The experimental study results obtained for the substances in the SFWA category need to sufficiently cover the structural differences of the substances with regard to R1 and R2. This is needed to present a robust justification which meets the requirements of Annex XI, Section 1.5. that human health effects or environmental effects or environmental fate may be predicted from data for reference substance(s) within the group. ECHA therefore has assessed whether the experimental studies were adequate and reliable and in how far the variations in R1 and R2 are covered by experimental results and what justifications are provided for the predictions for substances without experimental results.

The results of this assessment for the individual information requirements for which ECHA has identified shortcomings in the available experimental studies or in the justification for the predictions are presented in section III below. Here, ECHA's general observations are provided.

Assessment of the experimental information provided

Adaptations based on grouping and read-across to address information requirements need to have adequate and reliable source studies.

Annex XI, Section 1.5 provides with regard to the reliability and adequacy of the source studies that in all cases the results of the read-across should:

- *be adequate for the purpose of classification and labelling and/or risk assessment,*
- *have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),*
- *cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and*
- *adequate and reliable documentation of the applied method shall be provided.*

Studies which do not meet these criteria or are conducted with a test material not representative of the registered substance are not considered as adequate or reliable and cannot serve as source studies for the properties under consideration. Such studies may be used as a source of information for a weight of evidence approach. A prerequisite for such use is that the tested substance is clearly identified, the methods and scope of the investigation are clearly described and the results are described in such sufficient detail that an independent assessment of the conclusion is possible.

Assessment of the justifications for the predictions
From its assessment, ECHA concludes that the predictions for the mammalian toxicity properties of skin and eye irritation, acute toxicity and skin sensitisation meet the conditions of Annex XI, section 1.5. In particular, the structural variations in R1 and R2 are sufficiently covered with experimental data, the predictions are justified and supported.

For other information requirements ECHA has identified shortcomings.

ECHA considers that the substances have rather unique features in terms of technical applications. Their chemical structure backbone, the *trans*-stilbene group, ensures the whitening effect, the absorption of ultraviolet light and emission of the absorbed energy as blue fluorescent light. They are used in the textile, detergent and paper industries. In order to have the desired whitening effect they must remain intact and attached to the substrates during the production/ application process. For instance, they get attached to cotton, regenerated cellulosic and polyamides fibres, as well as to paper. The so called "fastness" towards the substrates depends on the modifications of the core structure. The anionic properties of these substances, a result of the presence of sulphonic groups, are the driving parameter for the affinity with the substrates. The number of sulphonic groups and the affinity with the substrate are assumed to be proportional. The substituents can vary the chromophore optical properties, depending on their position and also have a role on the application property and substantivity (Siegrist AE, Eckhardt C, Kaschig J, Schmidt E. Optical Brighteners. Ullmann's. Encyclopaedia of Industrial Chemistry, 2012, 427 ff.).
The registered substances have a *trans*-conformation. However, as stated in the category justification document, under environmental conditions in aqueous solutions and in presence of sunlight, the stilbene moiety undergoes photo-isomerisation, and the *cis*- and *trans*-forms are in equilibrium within a few minutes. Also, photo-degradation of the cis- and trans-forms may occur in the surface layers of rivers and lakes as the registrants explain in the category justification document. The registrants suggest that the first reaction is an oxidative cleavage forming an aldehyde and the half-life determined in the lake Greifensee was found to be 4.6 ±0.5 hours. Further photo-degradation reactions lead to numerous degradation products that were not identified in detail. The registrants also reported relatively high adsorptivity for the substances. ECHA notes that these technical features pose the question how the substances behave during (eco)toxicity testing and what role the technical features play in the interaction with biological molecules. With regard to the administration of test substances specific care should therefore be taken to ensure that the intended concentrations/doses are actually applied. Strict analytical control is needed, both on concentration determination of the parent substances, their transformation products and the degree of *cis-trans* speciation. It is doubtful that studies which did not have such controls in place are adequate and reliable, since the actually applied concentrations/doses may be overestimated. For the future testing requested in this decision specific precautions have to be taken to ensure sufficient information on the actual tested substance. This results in a specific requirement for the analytical control of the test substances as described in Appendix 3.

The registrants' claims for repeated dose toxicity, pre-natal developmental toxicity and reproductive toxicity (i.e. sufficient information, no uptake, no relevant toxicity) are

analysed in Section III in the corresponding sections. Their claims regarding metabolism of the R2 moieties are analysed in Section III.D. In summary, ECHA does not consider the provided information as being sufficient to cover the structural variations and there are contradictions to their claims in the experimental data. Although their proposed metabolic fate for R2 moieties has some plausibility, other possibilities have not and cannot be excluded and there is no experimental evidence provided in this regard.

The registrants' arguments on the sulphonation degree have to be viewed in light of the technical properties. Whereas in principle the observation on the detoxifying mechanisms based on the action of sulphotransferases is correct, this argument is misleading with regard to the SFWA substances. The sulphonic acid functions are present in the parent constituent and are not transferred to hydroxyl or amino groups in a phase II reaction for detoxifying the parent compound for the main constituents of the SFWA substances. The registrants currently do not present evidence on how the different number of sulphonic acid functions in different positions of the amino aniline moiety of the SFWA substances may directly or indirectly influence the interaction(s) with biological structures in investigations of systemic toxicity. The example on amino stilbene provided by the registrants is not sufficient to conclude that sulphonic acid functions at the amino aniline substituents of the SFWA constituents are reducing systemic toxicity (see also III.E).

The registrants' arguments for low toxicity to aquatic organisms are also analysed in Section III in the corresponding sections. In summary, ECHA does not consider the provided information as being sufficient to cover the structural variations and there are contradictions to the claims in the experimental data. In particular, ECHA notes that indeed most, but not all, of the current short-term toxicity data does not indicate toxicity in acute exposures, but the reliable data across the category is too scarce to draw firm conclusions. Furthermore, the registrants intend to use one existing reliable long-term toxicity study on daphnids to conclude absence of risk for all the SFWA substances. ECHA notes that the effects in the two existing long-term toxicity studies with daphnids (see III.J) indicate some level of toxicity, and lethal or sub-lethal effects after long-term exposure to fish cannot be ruled out in view of the complete absence of experimental data.

ECHA notes that currently there are no data to support the prediction for all structural variations in the category, which is currently solely based on results obtained with one substance. The registrants currently do not present evidence on how the different number of sulphonic acid functions in different positions of the amino aniline may influence the bioavailability for SFWA substances directly or indirectly, the bioaccumulation potential or the interaction with biological structures in investigations on toxicity to aquatic organisms. Further, there is no evidence to support predictions between the subcategories considering the structural variety in R2 moieties. The registrants also do not provide evidence on how the photo-isomerisation or photo-transformation may or may not change the eco-toxicological properties, apart from two acute studies with 'photo-degraded' substance without analytical determination of the degradation products. In the absence of such explanations and supporting evidence, the influence of the sulphonation degree, R2 moieties and photo-isomerisation or photo-transformation on (long-term) aquatic toxicity remains unclear.

Despite the scarcity of reliable short-term toxicity data to cover the structural variations across the category, ECHA considers that no further short-term toxicity testing is needed for fish and invertebrates. Instead, ECHA considers that long-term aquatic testing for fish and invertebrates is of a greater value considering the properties of the SFWA substances, for the purpose of consolidating the category for properties indicating a more relevant concern. Ultimately, when reliable long-term toxicity information will be available for the SFWA substances (either by experimental studies or by updated adaptations), the information

requirements for short-term toxicity endpoints can be fulfilled as per column two of sections 9.1.1 of Annex VII and 9.1.3 of Annex VIII.

With regard to the exposure calculations and the RCRs, ECHA notes that the hazard identification for toxicological properties in the REACH regulation is not dependent on the exposure, unless Annex XI, section 3 (exposure driven testing) applies or the specific conditions in Column 2 of the Annexes VIII to X are met. Furthermore, the DNEL derivations rely on incomplete datasets.

Similarly, in the risk characterisation for the aquatic compartment, ECHA notes that the derived PNECs and RCRs are currently based on incomplete datasets and consist of data that are largely unreliable. The registrants currently propose to use the risk characterisation as a basis to adapt the information requirement on long-term toxicity to fish. ECHA notes that several conditions need to be fulfilled which are further clarified in the section III.K below.

ECHA acknowledges that the registrants propose a testing strategy to increase the data coverage for the structural variations of the main constituents in the SFWA substances and strengthen the power of the category approach, in the case that ECHA finds that the current approach is not sufficient.

### *II.C.3 Registrants' general comments to the draft decision and ECHA's responses*

ECHA has addressed your general comments here. Comments related to specific information requirements are addressed in the appropriate sections.

Claim of low toxicity and reference to Section XI 1.3 of the REACH Regulation

You use the general low toxicity of the category members and the wide dispersive use in textile and paper industry as well as household detergents over the last 60 years to dismiss concerns. Therefore you would like to refrain from proposing additional in vivo testing. You also point at the provisions of Annex XI, Section 3 of the REACH Regulation on substance-tailored exposure-driven testing. You indicate that you consider exposure to workers or consumers as not relevant and that the risk management measures currently applied are sufficient to manage even a hypothetical risk.

ECHA has explained in the decision that low toxicity of the substances included in this category is not established for repeated dose toxicity, reproductive toxicity or developmental toxicity. Furthermore, long experience with the use of a substance is not a valid adaptation according to the REACH Annexes VIII to XI for the information requirements.

With regard to substance-tailored exposure-driven testing according to Annex XI, Section 3, ECHA notes that currently you do not justify any adaptation with reference to this provision in the registration dossiers of the SFWA member substances. ECHA further considers that your considerations on risk management measures are based on an incomplete and contradictory hazard data set and that based on the uses reported in the dossiers for these substances, it cannot be concluded that there is "absence of or no significant exposure" to the substances.

Stepwise Approach

You agree to re-evaluate your proposed stepwise testing strategy only, if the outcome from the competent authorities is that the provided hazard data is still not sufficient to assess the repeated dose toxicity and reproductive/developmental toxicity hazards of the SFWA category.

ECHA points out that the decision-making process set out in Article 51 of the REACH regulation enables each competent authorities to propose any amendments to the draft decision they would deem necessary.

You stress the importance of your stepwise approach. The aims for this approach are

- to clarify the value of the feeding studies,
- to support your claim that tests with less sulphonated substances within a subgroup will cover also more sulphonated substances, and
- that results of some studies may lead to classification and subsequent risk management measures, which would allow adaptations of other studies based on the provisions in Column 2 of the appropriate Annexes.

ECHA considers that the information requested in this decision is designed to take into account these aims.

Requests for information on environmental toxicity
You have provided no specific comments on the draft decision with regard to environmental toxicity requests.

Risk characterisation
Regarding risk characterisation, you agree that there is uncertainty related to the derivation of DNELs and PNECs. However, you claim that all RCRs for the environment are <0.01 (based also on monitoring data), only for one PROC worker the RCR value is [redacted] and for the consumer RCR is < 0.001. ECHA notes that you have not explained in your comments how these statements on risk characterisation are related to the information requested in section III. The deficiencies in DNELs, PNECs and risk characterisations are already addressed in section II.C.2 and III.K in this decision.

### *II.C.4 ECHA's conclusions on the registrants' category approach*

ECHA has identified the shortcomings of the registrants' argumentation as pointed out above and in section III below. In particular, although there are plausible elements in their arguments, there is insufficient supporting experimental evidence for their assumptions for some of the information requirements.

Based on the information currently submitted, ECHA considers that the approach the registrants have proposed is plausible for the information requirements analysed in Section III, but it still needs to be consolidated in order to be eventually accepted. Under these conditions and in order to facilitate that the missing information is generated, whenever possible, through the use of alternative methods to testing on vertebrate animals, the present decision aims at requesting from the registrants concerned by the category only the information necessary to consolidate the adaptations and category justification.

For the acceptance of such adaptations according to Annex XI, Section 1.5 a prerequisite will be that:

1. the structural variations of the SFWA substances are sufficiently addressed by definitive data;
2. the proposed grouping and read-across for substances without such definitive data will be confirmed by supporting data; and that
3. the justifications for the proposed adaptations will be improved taking into account the new information obtained.

The eventual validity of the category approach will be reassessed after the submission of the information requested in this decision.

## III. Specific considerations on the information requirements

### III.A *In vitro* gene mutation study in bacteria (Annex VII 8.4.1)

An "*in vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation.

Adequate information on this endpoint needs to be present in the technical dossier for all registered SFWA substances to meet this information requirement.

#### *III.A.1 The registrants' hypothesis to address this information requirement in the category*

The registrants have provided results obtained in experimental studies for some of the substances. Using the results obtained in these studies the registrants have sought to adapt this information requirement for substances without experimental data. The adaptation is based on Annex XI, Section 1.5 of the REACH Regulation in a category approach as explained under II.B.

In addition to the general arguments explained in II.B, the registrants have provided specific arguments for this information requirement to justify their category approach. These arguments are focused on structural similarity and that the variations of the R1 and R2 moieties are covered for the substances in the SFWA category. For 3a-A(NaK)#70942-01-7, the registrants state that the Na/K salt does not influence the Ames test results in comparison to the Na salt. Furthermore the registrants have provided results of the OECD QSAR toolbox, which predict that the SFWA substances are not mutagenic.

#### *III.A.2 Available information to justify the category approach*

In table 21 of the justification document the registrants summarised the information for *in vitro* gene mutation in bacteria in the dossiers submitted for the SFWA substances. In addition, the endpoint summaries in the dossiers report the information.

##### *III.A.2.1 Experimental information considered as adequate and reliable by ECHA*

Studies according to OECD TG 471 are available for
SC1: 1-MSA#42355-78-2 (GLP, 2014), 1-DSA#41098-56-0 (GLP, 1989, without 5$^{th}$ strain)
SC2: 2-A#16090-02-1 (GLP, 1991 and 2015), 2-MSA#28950-61-0 (GLP, 2008)
SC3a: 3a-A(Na)#4193-55-9 (GLP, 1998), 3a-MSA#16470-24-9 (1987, separate study from 1982 on E.coli strain WP2 uvrA)
SC3b: 3b-A#13863-31-5 (GLP 2015 E.coli only)
SC3c: 3c-A#17958-73-5 (GLP, 2014) [12]
SC5: 5-A#27344-06-5 (1980)
The mutation frequency in bacteria was not increased in the available experimental studies with SFWA member substances.

##### *III.A.2.2 Experimental information considered as not adequate and/or reliable by ECHA*

SC3b: two studies with a Klimisch reliability 4 (publications 1975, 1976), indicated to be used as weight of evidence; purity of test substance not clear,
SC3c: the study with 3c-MSA#16324-27-9 (1979) is regarded as not adequate, since the test material is not representative for the registered substance.

[12] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

*III.A.2.3 Other supporting information*
The registrants have provided results of the OECD QSAR toolbox, which predict that the SFWA substances are not mutagenic.

### *III.A.3 ECHA's Assessment*
For five substances no or no adequate and/or reliable experimental information is available. These are 2-DSA#52301-70-9, 3a-A(NaK)#70942-01-7, 3a-DSA#68971-49-3, 3c-MSA#16324-27-9 and 4-MSA#67786-25-8. In addition, for 3b-A#13863-31-5 a reliable result with E. coli with one (5th) test strain is available.

ECHA considers that the structural variation of R1 is addressed by the test results obtained. Also, the variation in R2 is covered by experimental results for SC1, SC2, SC3a, SC3c and SC5.

Therefore, ECHA considers that the prediction "*does not increase the mutation frequency in bacteria*" for 2-DSA#52301-70-9, 3a-A(NaK)#70942-01-7, 3a-DSA#68971-49-3, and 3c-MSA#16324-27-9 meets the requirements of Annex XI, section 1.5., that human health effects may be predicted from data for reference substance(s) within the group.

For 3b-A#13863-31-5, a weight of evidence approach is proposed in the corresponding Registration dossier, which uses the older studies with the registered substance on four strains, the new study from 2015 on the 5$^{th}$ strain, and the information from the other substances within the category as independent lines of evidence to conclude that the substance is not increasing the mutation frequency in bacteria. ECHA considers that this conclusion meets the criteria of Annex XI, Section 1.2.

For 4-MSA#67786-25-8 the registrants argue that a prediction can be based on the results of 3a-MSA#16470-24-9, a substance with the same number of sulphonic acid moieties in R1. However, the R2 substituents are bis(2-hydroxy ethyl) amino groups in 3a-MSA#16470-24-9 versus bis (2-hydroxy propyl) amino groups in 4-MSA#67786-25-8, which are not addressed by experimental results within the category. Furthermore 4-MSA#67786-25-8 has the highest percentage of unspecified impurities (<12%) of all SFWA member substances. The impact of these impurities on the experimental results is currently not known. ECHA therefore rejects the adaptation based on Annex XI, Section 1.5. for 4-MSA#67786-25-8.

In your comments to the draft decision, you express your concerns with ECHA's request for a new study on 4-MSA#67786-25-8. You indicate that you consider that sufficient evidence exists throughout the category for genotoxicity and that no alerts are detected from QSAR predictions based on the structures of the category members. You also claim that the information requirement of Annex VII, 8.4.1 for an *in vitro* gene mutation in bacteria is adequately covered by available information from an *in vitro* gene mutation study and by data from the also requested *in vitro* chromosomal aberration test on 4-MSA#67786-25-8.

However, ECHA observes that you have not commented on the potential impact of the structural differences in R2 substituents between 3a-MSA#16470-24-9 and 4-MSA#67786-25-8 and on the role of the rather high percentage of unspecified impurities reported in the composition of 4-MSA#67786-25-8 which were raised in the draft decision.
ECHA further stresses that the existence of information from an *in vitro* gene mutation study and/or of an *in vitro* chromosomal aberration test do not constitute valid adaptations for the information requirement of Annex VII, 8.4.1 for an *in vitro* gene mutation in bacteria.

### *III.A.4 ECHA requests to consolidate the registrants' category*

For the reasons presented above, ECHA concludes that the information provided for the registered substance 4-MSA#67786-25-8 does not meet the information requirement.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrant of the substance indicated below is requested to submit the following information derived with its substance:

(request 1) 4-MSA#67786-25-8

Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471)

See table 1 in Appendix 5 for an overview of ECHA's assessment on genotoxicity.

## III.B *In vitro* cytogenetic study in mammalian cells or *in vitro* micronucleus study (Annex VIII 8.4.2.)

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation.

Adequate information on this endpoint needs to be present in the technical dossier for all registered SFWA substances (except for 2-MSA#28950-61-0; registered at 1 to 10 tonnes per year) to meet this information requirement.

For 3c-MSA#16324-27-9 the registrants apply Annex VII information requirements in the justification document, but in fact Annex VIII information requirements are applicable on the basis of the registered tonnage. Therefore, the information requirement concerning chromosomal aberration properties is also applicable for this substance.

### *III.B.1 The registrants' hypothesis to address this information requirement in the category*

The registrants have provided results obtained in experimental studies for some of the substances. Using the results obtained in these studies they have sought to adapt this information requirement for the substances without experimental data. The adaptation is based on Annex XI, Section 1.5. of the REACH Regulation in a category approach as explained under II.B.

In addition to the general arguments explained in II.B, the registrants have provided endpoint specific arguments to justify their category approach. These arguments are focused on structural similarity and that the variations of the R1 and R2 moieties are covered for the substances in the SFWA category. For 3a-A(NaK)#70942-01-7, the registrants state that the Na/K salt does not influence the test results in comparison to the Na salt. For 3c-A#17958-73-5[13] the registrants argue that the substance is covered by test results obtained with 3a-A(Na)#4193-55-9 with an additional hydroxyethyl function as remaining difference for R2. Further they claim that the substances with di-hydroxyethyl function as R2 (SC3a) are metabolically converted to mono hydroxyethyl substances

[13] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

(SC3c). For some substances, the registrants propose to adapt the information requirement based on results obtained from *in vivo* studies.

***III.B.2 Available information to justify the category approach***

In table 22 of the justification document the registrants summarised the available information on the *in vitro* cytogenetic studies in mammalian cells or *in vitro* micronucleus studies. Furthermore, the endpoint study summaries in the dossiers report the information provided in the justification document.

*III.B.2.1 Experimental information considered as adequate and reliable by ECHA*

The following study results according to appropriate guidelines are available:
SC1: 1-MSA#42355-78-2 (OECD TG 487, GLP, 2014)
SC2: 2-A#16090-02-1 (OECD TG 473, GLP 1991)
SC3a: 3a-MSA#16470-24-9 (OECD TG 473, GLP 1991; OECD TG 474, GLP 1991 *in vivo* micronucleus assay)
The available experimental study results with SFWA member substances did not report an increase in the frequencies of chromosomal aberrations.

*III.B.2.2 Experimental information considered as not adequate and/or reliable by ECHA*

SC2: 2-A#16090-02-1 (OECD TG 478, GLP, 1995 *in vivo* dominant lethal assay)
SC3a: 3a-A(Na)#4193-55-9 (similar to OECD TG 478, 1973 *in vivo* dominant lethal assay)
SC3a: 3a-MSA#16470-24-9 (OECD TG 478, GLP 1995, *in vivo* dominant lethal assay)
SC3b: 3b-A#13863-31-5 (similar to OECD TG 478 *in vivo* dominant lethal assay, 1974)
SC4: 4-MSA#67786-25-8 (similar to OECD TG 478 *in vivo* dominant lethal assay, 1977)
SC5: 5-A#27344-06-5 (473, GLP, 1989, not adequate since the test material had a purity of 25 % and therefore is not representative for the registered substance)
The available *in vivo* studies did not report increases in the frequencies of embryonic or foetal death.

For 2-A#16090-02-1 and 3a-MSA#16470-24-9 there are dominant lethal studies according to OECD TG 478 and GLP. For these substances adequate and reliable in vitro studies are also available. Therefore, the dominant lethal studies results are not needed to cover this information requirement.

The registrants argue that for 3a-A(Na)#4193-55-9 (SC3a), 3b-A#13863-31-5 (SC3b), and 4-MSA#67786-25-8 (SC4) the property "chromosomal aberration *in vitro*" is covered by *in vivo* study results. For these substances there are studies claimed to be similar to OECD TG 478 (Genetic Toxicology: Rodent Dominant Lethal Test, DLT) from 1973, 1974 and 1977 in mice or hamsters. Dominant lethal effects are most probably due to structural and numerical chromosome aberrations, but, as stated in paragraph 6 of OECD TG 478 (2016), gene mutations cannot be excluded. However, ECHA does not consider the rodent dominant lethal test as an adequate *in vivo* cytogenicity assay: since the investigated parameters are not the chromosomes (aberrations in their number or structure) but embryonic or foetal death, the absence of effects in this assay does not indicate absence of chromosomal damage in somatic cells. ECHA thus considers that the provisions of column 2, 8.4.2, Annex VIII of REACH do not apply.

Moreover, OECD TG 478 states that "[para.1] *this assay is not intended for use as a primary method, but rather as a supplemental test method which can only be used when there is no alternative for regulatory requirements*" and "[para.4] *the sensitivity of the assay for detection of small increases in the mutation frequency is limited*". Finally, ECHA reminds the registrants that a negative DLT result does not warrant that a chemical is not classified for

the mutagenicity hazard class, as a chemical can be classified category Muta 2 (mutagen to somatic cells) even if the substance is negative in the DLT.

Moreover, the studies conducted in 1973, 1974, or 1977 were not conducted according to any test guideline, as the original test guideline 478 was only adopted in 1984. The test substances were administered orally in single doses (5000 mg/kg bw/day). However, the registrants claim that the substances of the SFWA category are not absorbed after oral administration or that the absorption is low (see Section III.D). If this is true, the germ cells as the target were not reached and the registrants cannot rely on such *in vivo* studies to demonstrate absence of effects with regard to chromosomal aberrations. In Section III.D, absorption after oral administration is discussed in detail. Due to these considerations, ECHA regards the dominant lethal study results as not adequate to adapt the Annex VIII, Section 8.4.2 information requirement.

*III.B.2.4 Other supporting information*

The registrants have provided results of the OECD QSAR toolbox, which predict that the SFWA substances are not mutagenic.

### *III.B.3. ECHA's Assessment*

For the substances 1-DSA#41098-56-0, 2-DSA#52301-70-9, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-DSA#68971-49-3, 3b-A#13863-31-5, 3c-A#17958-73-5 [14], 3c-MSA#16324-27-9, 4-MSA#67786-25-8, and 5-A#27344-06-5 registered at a tonnage band of 10 to 100 tonnes per year or higher no experimental information is available.

The structural variations for R2 in SC1, SC2, and SC3a are addressed by the test results and the R1 variations amino aniline and amino monosulphonated aniline are also addressed by the available study results. ECHA considers that the prediction "the frequency of chromosomal aberrations is not increased" for 1-DSA#41098-56-0, 2-DSA#52301-70-9, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-DSA#68971-49-3, meets the requirements of Annex XI, section 1.5., that human health effects may be predicted from data for reference substance(s) within the group.

For 3a-DSA#68971-49-3, the R2 moiety is covered with experimental results, but there is no experimental result available for the amino disulphonated aniline in R1 in any subcategory. The proposed prediction for 3a-DSA#68971-49-3 based on Annex XI, Section 1.5 is therefore rejected.

For 3b-A#13863-31-5 ECHA considers that that the additional methyl group instead of a hydroxyethyl group in SC3a substances is covered by the test result with 1-MSA#42355-78-2 (containing ethyl groups) and by the test result with 3a-MSA#16470-24-9 (containing hydroxyethyl groups in R2). The result with amino aniline obtained with 2-A#16090-02-1 covers the R1 group also present in 3b-A#13863-31-5. The prediction "the frequency of chromosomal aberrations is not increased" is meeting the requirements of Annex XI, section 1.5., that human health effects may be predicted from data for reference substance(s) within the group.

For 3c-A#17958-73-5 ECHA notes that the lacking hydroxyethyl function creates for R2 a NH function in the substances of SC3c, which is not present in other subcategories of the

[14] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

SFWA substances. ECHA further notes that the registrants' claim that the substances with bis(2-hydroxyethyl) function as R2 are metabolically converted to mono 2-hydroxyethyl substances is not proven by experimental data and is also not relevant in view of the test guideline requesting also a test module using no metabolic activation. The proposed prediction for 3c-A#17958-73-5 based on Annex XI, Section 1.5 is therefore rejected.[15]

For 4-MSA#67786-25-8 there is no adequate and reliable information and the substance has bis (2-hydroxy propyl) amino groups, which are not addressed by experimental results within the category. Furthermore 4-MSA#67786-25-8 has the highest percentage of unspecified impurities (<12%) of all SFWA member substances. The impact of these impurities on the experimental results is currently not known.

For substance 5-A#27344-06-5 there is no adequate and reliable experimental information. The main constituent of the substance is present at a typical concentration of about ■ % and has a carbamoylethyl function at R2 which is not present in any of the other SFWA member substances. The proposed prediction for 5-A#27344-06-5 based on Annex XI, Section 1.5 is therefore rejected.

In your comments to the draft decision you express your agreement with ECHA's conclusions on the inadequacy of the information obtained in vivo Rodent Dominant Lethal Tests (DLT) to fulfil the information requirement of Annex VIII, 8.4.2 (requests 2, 3, 4, 5) for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study. However, you stress that you still consider that this information may be used as part of a weight of evidence approach together with QSAR predictions.

ECHA acknowledges your agreement on the inadequacy of the information from DLT tests to fulfil the information requirement of Annex VIII, 8.4.2.

You claim that the results from the DLTs may be relevant in a weight of evidence approach. You do not provide details on the different independent sources of information, which would allow to conclude/assume whether the substances under consideration have or have not cytogenic properties. Therefore, ECHA considers that you have not submitted and documented a weight of evidence approach as required by Annex XI, Section 1.2.

### *III.B.4 ECHA requests to consolidate the registrants' category*

For the reasons presented above, ECHA concludes that the information provided on this endpoint for the registered substances 3a-DSA#68971-49-3, 3c-A#17958-73-5 [16], 3c-MSA#16324-27-9, 4-MSA#67786-25-8, and 5-A#27344-06-5 does not meet the information requirement.

Therefore, the registrants of the above-mentioned substances are requested to provide the studies and further justifications mentioned below (see also II.C.4). ECHA will reassess the eventual validity of the registrants' category approach after submission of this information.

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[15] *Idem*.

[16] The Registrant of substance 3c-A#17958-73-5 has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

*III.B.4.1 Experimental studies requested to fulfil the information requirement and to provide source studies for future adaptations*

ECHA considers that both substances in SC3c do not need to be tested [17]. To decide which substance of SC3c should be tested ECHA considered the following: With regard to sulphonic acid groups there are two GLP studies on chromosomal aberration available for substances, for which the main constituent contains 4 sulphonic acid groups. There is currently only one GLP study on chromosomal aberration for a substance containing a main constituent with 2 sulphonic acid groups. The registrants must consider the opportunity to test the substance 3c-A#17958-73-5 in order to obtain results for the amino hydroxyethyl moiety and strengthen the data base for substances containing constituents with amino aniline as R1 (= two sulphonic acid moieties in total for the main constituent).

As explained above the registered substances 3a-DSA#68971-49-3, 4-MSA#67786-25-8 and 5-A#27344-06-5 need to be tested.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrants of the substances indicated below are requested to submit the following information derived with their respective substance:

(request 2) 3a-DSA#68971-49-3

(request 3) 3c-A#17958-73-5 [18]

(request 4) 4-MSA#67786-25-8

(request 5) 5-A#27344-06-5

*In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

*III.B.4.2 Updated justifications requested to adapt the information requirement*

Subject to the consideration of the registrants to perform the requested studies on substance 3c-A#17958-73-5 [19], the future result obtained with this substance may be used to predict the outcome of the study with 3c-MSA#16324-27-9. ECHA points out the explanations provided in the Read-Across Assessment Framework [20] on the elements assessed in justifications on grouping and read-across approaches.
Therefore, ECHA requests the registrant of the following substance to submit updated justifications explaining whether, why and how this information requirement can be adapted according to Annex XI, Section 1.5 for the substance listed below, taking into account the

[17] *Idem*.
[18] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.
[19] *Idem*.
[20] RAAF, https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

newly generated information obtained in the SFWA category, including the experimental studies requested above:

(requests 6) 3c-MSA#16324-27-9

See table 1 in Appendix 5 for an overview of ECHA's assessment of genotoxicity.

**III.C *In vitro* gene mutation study in mammalian cells (Annex VIII 8.4.3).**

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation.

Adequate information on this endpoint needs to be present in the technical dossier for all registered SFWA substances (except for 2-MSA#28950-61-0; registered at 1 to 10 tonnes per year) to meet this information requirement, if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained.

The following paragraphs analyse for which substances the information requirement applies.

For 3c-MSA#16324-27-9 the registrants apply Annex VII information requirements in the justification document, but in fact the Annex VIII information requirements are applicable on the basis of the registered tonnage. Therefore, the information requirement for a gene mutation study in mammalian cells is also applicable for this substance, provided the results of the other *in vitro* studies were negative.

The results of the already available studies performed to meet Annex VII Section 8.4.1 were negative or were predicted to be negative for all SFWA substances. The predictions are accepted as valid by ECHA in this decision (see above). The results of the study with 4-MSA#67786-25-8 is not yet known, but for this substance an *in vitro* gene mutation study in mammalian cells is already available.

The results of the already available studies performed to meet Annex VIII Section 8.4.2 were negative or were predicted to be negative for most SFWA substances. The predictions are accepted as valid by ECHA in this decision (see above). Therefore, for 1-MSA#42355-78-2, 1-DSA#41098-56-0, 2-A#16090-02-1, 2-DSA#52301-70-9, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-MSA#16470-24-9, and 3b-A#13863-31-5, the information requirement applies. The results of the study with 3a-DSA#68971-49-3, 4-MSA#67786-25-8 and 5-A#27344-06-5 are not yet known, but for these substances *in vitro* gene mutation studies in mammalian cells are already available.

For 3c-A#17958-73-5 the results of study to meet Annex VIII 8.4.2 is not yet known (see above). For 3c-MSA#16324-27-9, the prediction to meet Annex VIII 8.4.2 is dependent on the outcome of the study with 3c-A#17958-73-5. The *in vitro* gene mutation study in mammalian cells is therefore only required, if the outcome of the study with 3c-A#17958-73-5 to meet Annex VIII 8.4.2 is negative.[21]

***III.C.1 The registrants' hypothesis to address this information requirement in the category***

The registrants have provided results obtained in experimental studies for some of the substances. Using the results obtained in these studies they have sought to adapt this

[21] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

information requirement for the substances without experimental data. The adaptation is based on Annex XI, Section 1.5. of the REACH Regulation in a category approach as explained under II.B.

In addition to the general arguments explained in II.B the registrants have provided endpoint specific arguments to justify their category approach. The registrants explained how they have selected the substances to be tested for *in vitro* mammalian gene mutation studies. The aim was to have experimental information for the R1 and R 2 variations and therefore also for the least and most soluble of the SFWA member substances. For 3c-A#17958-73-5 the registrants argue that 3a-DSA#68971-49-3 covers all substances in SC3 in terms of R2[22].

### *III.C.2 Available information to justify the category approach*

In table 23 of the justification document the registrants summarised the available information obtained in mammalian gene mutation studies. The endpoint study summaries in the dossiers report the information provided in the justification document.

*III.C.2.1 Experimental information considered as adequate and reliable by ECHA*

Results from GLP studies conducted according to appropriate Guidelines are available for
SC1: 1-MSA#42355-78-2 (2015)
SC2: 2-A#16090-02-1 (2014),
SC3a: 3a-DSA#68971-49-3 (2014),
SC4: 4-MSA#67786-25-8 (2014)
SC5: 5-A#27344-06-5 (2015).
The available experimental studies with SFWA member substances did not increase the frequencies of gene mutations in mammalian cells.

*III.C.2.4 Other supporting information*

The registrants have provided results of the OECD QSAR toolbox, which predict that the SFWA substances are not mutagenic.

### *III.C.3 ECHA's Assessment*

For eight substances registered at 10 – 100 tonnes per year or higher no or no adequate and reliable experimental information is available. These are 1-DSA#41098-56-0, 2-DSA#52301-70-9, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-MSA#16470-24-9, 3b-MSA#13863-31-5, 3c-A#17958-73-5[23] and 3c-MSA#16324-27-9.

In terms of R2 variations the SC1, SC2, SC3a, SC4 and SC5 substances are addressed with experimental data. In terms of R1 variations, moieties with 2, 4 and 6 sulphonic groups are addressed with experimental data. ECHA considers that the prediction "the frequency of gene mutation in mammalian cells is not increased" for 1-DSA#41098-56-0, 2-DSA#52301-70-9, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-MSA#16470-24-9, and 3b-A#13863-31-5 does meet the requirements of Annex XI, section 1.5., that human health effects may be predicted from data for reference substance(s) within the group.

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[22] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

[23] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

For 3b-A#13863-31-5 ECHA considers that the additional methyl group instead of a hydroxyethyl group is covered by the test result with 1-MSA#42355-78-2 (containing ethyl groups) and by the test result with 3a-DSA#68971-49-3 (containing hydroxyethyl groups), since the R1 variations (containing 2 sulphonic acid groups) did not lead to different outcomes for SC2 or SC5 substances.

For 3c-A#17958-73-5 the registrants argue that 3a-DSA#68971-49-3 covers all substances in SC3 in terms of R2. ECHA notes that for SC3c substances the lacking hydroxyethyl function creates for R2 a NH function, which is not present in other subcategories of the SFWA substances and ECHA further notes that their generic claim that substances with a di-hydroxyethyl function as R2 are metabolically converted to mono-hydroxyethyl substances in R2 is not proven and is also not relevant in view of the test guideline which requests also a test module using no metabolic activation. The proposed prediction based on Annex XI, Section 1.5 is therefore rejected[24].

In your comments on the draft decision you agree with ECHA's request for a new study on 3c-A#17958-73-5.[25]

### *III.C.4 ECHA requests to consolidate the registrants' category*

For the reasons presented above, ECHA concludes that the information provided on this endpoint for the registered substances 3c-A#17958-73-5[26] and 3c-MSA#16324-27-9 does not meet the information requirement.

Therefore, the registrants are requested to provide the study and further justifications mentioned below (see also II.C.4). ECHA will reassess the eventual validity of their category approach after submission of this information.

#### *III.C.4.1 Experimental studies requested to fulfil the information requirement and to provide source studies for future adaptations*

ECHA considers that both substances in SC3c do not need to be tested. To decide which substance of SC3c should be tested ECHA considered the following: With regard to sulphonic acid groups there are two GLP studies on *in vitro* gene mutation in mammalian cells available for substances, for which the main constituent contains 4 sulphonic acid groups, and two GLP studies for which the main constituent contains 2 sulphonic acid groups. Since this does not allow a conclusion to be drawn on which substance is to be tested in SC3c, ECHA decided that the substance registered at the higher Annex should be tested. Therefore 3c-A#17958-73-5 should be tested for an *in vitro* gene mutation in mammalian cells to obtain results for the amino hydroxyethyl moiety[27].

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

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[24] *Idem.*
[25] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.
[26] *Idem.*
[27] *Idem.*

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrant of the substance indicated below is requested to submit the following information derived with its substance:

(request 7) 3c-A#17958-73-5[28]

*in vitro* mammalian cell gene mutation test (test method: OECD TG 476 or OECD TG 490) provided that the study requested for Annex VIII 8.4.2. has negative results.

*III.C.4.2 Updated justifications requested to adapt the information requirement*
Subject to the consideration of the registrants of the opportunity of performing the requested studies on substance 3c-A#17958-73-5[29], the future result obtained with this substance may be used to predict the outcome of the study with 3c-MSA#16324-27-9. ECHA points out there are explanations provided in the Read Across Assessment[20] Framework on the elements assessed in justifications on grouping and read-across approaches.

Therefore, ECHA requests the registrant of the following substance to submit an updated justification explaining whether, why and how this information requirement can be adapted according to Annex XI, Section 1.5 for the substance listed below, taking into account the newly generated information obtained in the SFWA category, including the experimental studies requested above:

(request 8) 3c-MSA#16324-27-9.

See table 1 in Appendix 5 for an overview of ECHA's assessment.

## III.D Toxicokinetics

An assessment of the toxicokinetic behaviour to the extent that can be derived from the relevant available information is a standard information requirement as laid down in Annex VIII, Section 8.8.1 of the REACH Regulation.

Adequate information on this property needs to be present in the technical dossier for all registered SFWA substances (except for 2-MSA#28950-61-0; registered at 1 to 10 tonnes per year) to meet this information requirement.

Toxicokinetic information is in particular relevant for adaptations based on Annex XI, Section 1.5. Therefore, ECHA has discussed the provided information in detail below.

### *III.D.1 The registrants' hypothesis to address this information requirement in the category*

In their justification document the registrants state that the SFWA substances are organic salts with high molecular weight, low Kow and high to very high water solubility. The substances are claimed to have a generally low systemic absorption, and claimed to be not metabolised and mainly excreted in the faeces in a few hours. The registrants have used the OECD QSAR toolbox to simulate potential metabolites and the results indicate various possibilities. They conclude from these simulations that N-alkyl R2 functions are de-alkylated.

[28] *Idem.*
[29] *Idem*

***III.D.2. Available information to justify the category approach***

The registrants have provided a table (table 5 of the justification document) showing the parameters used to predict permeability and solubility according to the "Lipinski rule of five", which was developed to broadly categorise the oral bioavailability for drugs. They state that all substances have similar characteristics in this regard and that they are all expected to have a very low bioavailability on this basis. As supporting information, they claim that the study results available did not show toxicity and they conclude that the substances are not systemically absorbed after oral administration. Furthermore, the registrants provide results obtained in toxicokinetic studies with two substances 2-A#16090-02-1 and 3b-A#13863-31-5. They claim that -in comparison with the other SFWA member substances- these substances have the highest log Kow, the lowest molecular weight and the lowest solubility and therefore are potentially the most bioavailable. Furthermore, Dermwin calculations for dermal uptake are provided, indicating very low dermal absorption.

*III.D.2.1 Experimental information considered as adequate and reliable by ECHA*

The percutaneous absorption was investigated for 3b-A#13863-31-5 [redacted]_1975_[redacted]) in rabbits according to a method similar to OECD TG 427 (1975, skin absorption *in vivo*) using a 14C radioactive labelled test substance in water. Twenty micrograms of the test material were applied/cm2. The application material, the subcutaneous tissue, urine and faeces were analysed. The test substance is not absorbed by rabbits after topical application as tested in this study. There is also a similar study on guinea pigs [redacted]_1975_[redacted]), which is rated with a Klimisch score of 3 (not reliable) by the registrants.

In [redacted]_1972_[redacted] (1972)/[redacted] (1975), 2-A#16090-02-1 was radiolabelled at the triazine ring with 14C. Rats were dosed with about 6 mg/kg bw/day via oral gavage with water as vehicle, and faeces, urine and CO2 were monitored. After 96 hours animals were sacrificed and tissues analysed. The faeces proved to be practically the only route of elimination for the applied radioactive material. About 90 % of the applied radioactivity was eliminated in faeces within 24 hours of dosing, indicating, according to you, in combination with the short half-life times, that no significant amounts of test substance were absorbed from the gastro-intestinal tract. Radioactivity found in urine was at the limit of detection (0.02 % of applied dose). No radioactivity was found in the expired air (< 0.01 %). No sex differences were observed. A calculation of the excretion half-life using the net rate coefficient of drug elimination (24 hours excretion value) revealed that 50% of the dose had been excreted within 7-13 hours after dosing. The radioactive material in the faeces was extractable with methanol. Thin layer chromatography revealed the presence of two compounds which behaved like the cis- and trans-forms of the main constituent of the substance. No radioactive residues were found in tissues 96 hours after dosing. Under the assumption that the trans-isomer conformation was exclusively present in the test material (as this is the default conformation of SFWA main constituents), the possible identification of the cis-isomer of the test substance in faeces indicates that the trans-isomer of the test substance may have isomerised to the cis-isomer during the conduct of the test.

In the same study 3b-A#13863-31-5 was radiolabelled at the triazine ring with 14C. Rats were dosed with about 5 mg/kg bw/day via oral gavage with water as vehicle, and faeces, urine and CO2 were monitored. After 96 hours animals were sacrificed and tissues analysed. More than 90% of the administered radioactivity was excreted within 48 hours of dosing. The faeces being the main, and practically only route of elimination. Little or no radioactivity was found in the urine and expired air. The faeces were lyophilized, ground to a fine powder, and exhaustively extracted in a Soxhlet apparatus, firstly with methanol and then with water. Practically no radioactivity was extracted with these solvents. The authors state that the results indicate that test substance is not absorbed from the gut of the rat and probably passes through the gut tightly bound to cellulose in the gut contents. The rate of

excretion would be probably only dependent on the rate at which the gut contents pass through the gastro-intestinal tract.

In [redacted] (1977), 2-A#16090-02-1 was radiolabelled with tritium at the aniline moiety. Rats were treated via oral, dermal, intraperitoneal and subcutaneous administration, either in water or in aqueous detergent.

The administered amount was quantified by specific activity of the radiolabelled substance and is indicated as 78 micrograms in detergent or 79 micrograms in water (137 microCi/mg) for the oral administration. The rats were fed pelleted diet ad libitum and were placed in metabolic cages to collect urine and faeces daily for four days. After four days the rats were sacrificed and the tissues analysed for radioactivity. The results indicated excretion in the faeces (about 72 micrograms, detergent as vehicle, and 78 micrograms, water as vehicle), mainly in the first 24 hours. Urinary excretion amounted to about 0.05 micrograms, with detergent as vehicle increasing the amount of radioactivity excreted in urine.

After intraperitoneal injection of 35 microgram radiolabelled substance the main excretion route (32 micrograms) is via the faeces, about 0.25 micrograms via urine. The excretion was complete after 2 days with the major part excreted within the first day.
After subcutaneous injection of 57 microgram radiolabelled substance the main excretion route is via the faeces (56 micrograms), about 0.5 micrograms via urine. The excretion took two days with 31 micrograms in the faeces on the first day and 22 micrograms in the faeces on the second day.

After topical application of 60 micrograms radiolabelled substance in aqueous detergent about 0.2 micrograms was excreted in faeces and about 0.23 micrograms in urine.
The tissues investigated did in general not show elevated levels of radioactivity. However, the livers and kidneys from animals administered the radioactive labelled substance via intraperitoneal or subcutaneous injection showed elevated levels of radioactivity after 24 hours, which decrease to about zero in the livers after 96 hours but remained elevated in the kidneys.

*III.D.2.2 Experimental information considered as not adequate and/or not reliable by ECHA*

A study reported on toxicokinetics (Lyman *et al.* 1975) for 2-A#16090-02-1 and 3b-A#13863-31-5 investigated residual substance levels in tissues of rats and dogs after two years of daily feed with the substance. The reporting does not allow ECHA to conclude on the results and further it appears that the study was conducted at [redacted] and is not regarded as reliable by ECHA unless formally audited by a regulatory authority (OECD, Manual for investigation of HPV Chemicals, Chapter 3: Data Evaluation, 2005). There is no indication that the study results were audited.

Another study reported for toxicokinetics ([redacted] 1976) on 2-A#16090-02-1 investigating skin absorption appears to be a study on the feasibility of the method and does not provide useful information.

The registrants claim that the metabolism of morpholino derivatives have been deeply studied by Abdul *et al.,* 2007. This publication is not reporting on the stilbene substances but on (S)-N-[1-(3-morpholin-4-ylphenyl)ethyl]-3-phenyl acrylamide and its difluoro analogue. The results show that the metabolism is dependent on the configuration of the molecules investigated and it is not clear to ECHA what credible conclusions are possible regarding the morpholino derivatives in the SFWA category.

*III.D.2.3 Other supporting information*

Rat liver S-9 simulations with the OECD toolbox were conducted for representative structures of main constituents and resulted in a number of possible metabolic pathways. Oxidative N-dealkylation is one of them and forming also small metabolites like glycolic acid derivatives, formaldehyde and acetic acid depending on the R2 substituents.

In Table 19 of their justification document the registrants provide DERMWIN estimations, indicating that the dermal permeability coefficient Kp is below 4e-10 cm/h for the main constituents.

*III.D.2.4. Additional testing proposed by the registrants to consolidate the category approach*

In the testing strategy the registrants propose to include measurements in blood, urine and serum if studies with repeated dose administration are requested by ECHA. Their aim is to obtain information on toxicokinetics and excretion of the substance. They did not specify what would be the analytical target of such measurements: the main constituent, other constituents, metabolites of the main constituent, or small metabolites.

***III.D.3 ECHA's Assessment***

Absorption

The possibility for dermal absorption appears to be low. According to a study using 3b-A#13863-31-5 and radiolabelled material in rabbits the uptake via skin as measured by excretion in urine and faeces appears to be < 2%. [redacted] confirmed low uptake for 2-A#16090-02-1. Experimental data are not available for the other substances. Low dermal absorption would be also expected in view of the molecular weight, the polarity, and the DERMWIN estimation. Whether this low absorption is of concern cannot be assessed due to lacking toxicodynamic information (see III.E)

The results by [redacted] (1975) on 3b-A#13863-31-5 investigated after oral administration were interpreted by the author as proof for a tight association of the test substance to cellulose which could not be extracted from the faeces. ECHA notes that there is no experimental information clarifying, which percentage of a test substance of the individual SFWA substances would not be available for uptake when administered in combination with rat diet. The registrants argue in the justification document that the observed differences between 3a-A#13863-31-5 and 2-A#16090-02-1 cannot be explained with the difference in fastness towards cellulose, but they provide no experimental data. Further they argue about the digestive system of rats, which would digest the cellulose and make the test substances bioavailable. No experimental proof is provided.

The potential for absorption after oral administration therefore appears to be unclear. ECHA notes that the doses in the toxicokinetic studies with oral administration were rather small. Furthermore, rats had access to diet pellets prior to, and after, the oral administration. Rat diet contains cellulose fibres and therefore the test substance might attach to them. Due to this possible binding to the feed ingredients it is therefore unclear what amount of radioactive labelled substance was available for systemic uptake.

On one hand the physico-chemical characteristics of the substances indeed would indicate low oral absorption. On the other hand, the results of available studies indicate systemic toxicity (see below at III.E), which can only be observed when absorption has taken place. In a 90-day feeding study conducted with 1-DSA#41098-56-0 kidney, liver, testes and blood were identified as target organs. Also for 3a-MSA#16470-24-9, in the 28-day gavage study, toxicity for livers, kidneys, testes and blood was observed. The rabbit gavage PNDT study for 3a-MSA#16470-24-9 indicated systemic toxicity. The 2-generation study revealed substance-related effects on the kidney and liver. In the 2-year feeding studies on 2-

A#16090-02-1 and 3a-A(free acid)#4404-43-7 treatment-related effects on liver and kidneys were reported, but not regarded as adverse. If the absorption is indeed very low, the observed toxicity would indicate a high potency of the absorbed percentage of the test substance to induce toxicity. It remains unclear how the structural differences between the substances of the SFWA category influence the absorption and/or the toxicity potential.

Metabolism

The metabolic breakdown products *in vivo* are not known for any of the substances according to the information provided. This is true for possible breakdown products during the passage through the gastrointestinal tract and for possible metabolites formed when the substances are taken up. The predictions on potential small molecules included in the justification document are indicated by the OECD QSAR toolbox but are not confirmed by *in vitro* or *in vivo* data.

With regard to metabolism therefore it is not possible to come to sound conclusion on the basis of the presented information. The toxicokinetic studies conducted in the nineteen-seventies did not investigate metabolism and the presented rat liver S9-simulations result in a number of possibilities for the fate of R2, with a two-step oxidative N-dealkylation as one possibility. ECHA notes that N-oxidation and N-dealkylation are two of a number of potential metabolic reactions.

No information is available on the toxicity of the formed possible intermediates. Since there is no *in vivo* information, the contribution of possibly formed small metabolites to the toxicity profiles cannot be assessed. It is claimed that substances that potentially form glycolic acid derivatives represent a worst case for the category members in a conservative approach. However, such a claim ignores the potential toxicity of the main chemical structures with ample functional groups and the technical properties of the substances which may also be relevant for the interaction with biological macromolecules. Furthermore, the potential formation of the cis-isomer and its consequences on metabolic pathways are not taken into account.

Excretion

The studies by [redacted] (1975) and [redacted] (1977) provide indications that the core structure 2-A#16090-02-1 is excreted unchanged in the faeces. However, it is not clear whether this finding applies only to the substance, which remains in the gastro-intestinal tract, or also to any of the substance, which is absorbed and potentially subject to metabolism and subsequent bile excretion. Sound analytical proof is not available.

As explained above, the results by [redacted] (1975) further may indicate that the cis-isomer is formed during testing of the substance. The registrants do currently not take this into account in their theoretical considerations on potential metabolism-pathways and potential differences in toxicity.

ECHA concludes that the main excretion is via faeces after all administration routes tested. It is however not clear whether the substances tested were excreted attached to rat feed. In addition, it is not clear whether the measured radioactivity is due to the intact substance or metabolites.

ECHA notes that excretion of the substance via the faeces was also observed after intraperitoneal and subcutaneous injection. This indicates that the substance crosses membranes and is excreted via bile. Therefore, the faeces excretion after oral administration cannot be taken as indication of no uptake, but bile appears to be the main excretion pathway, if the investigated substance is absorbed. This is in some contradiction to the result of repeated dose toxicity studies identifying kidney as target tissue.

Further toxicokinetic studies

ECHA considers toxicokinetic studies as appropriate to investigate whether and how the structures of the SFWA substances change the absorption after oral administration. The availability for absorption when the substances are mixed with rat diet is another question discussed in this decision. The metabolic fate may be investigated first *in vitro* and then by appropriate analytical methods *in vivo*. The excretion after absorption appears to be via bile according to the available toxicokinetic information, but kidney was a target tissue in available studies using repeated exposure.

Since clarification of all of these issues will aid in understanding potential similarities or differences in toxicity profiles across the category members, it is difficult to define in the absence of sufficient toxicodynamic data what studies of toxicokinetics may deliver most benefit.

In your comments on the draft decision you state: "*In the stepwise testing strategy, the Registrants committed to including measurements in blood, urine, and serum in studies with repeated dose administration. Their aim is to obtain information on toxicokinetics and excretion of the substances, such as the level of adhesion to intestinal substates, the rate of substance uptake or the influence of the degree of sulphonation on the route and timing of excretion. The analytical target of such measurements will be the main constituent and potential metabolites of the main constituent. The feasibility of such measurements will be analysed and implemented in the first step repeated dose toxicity studies*".

ECHA understands that you intend to conduct toxicokinetic investigations for the studies on repeated dose toxicity included in step 1 of your testing strategy: OECD TG 408 studies conducted with on 1-MSA#42355-78-2 and 5-A#27344-06-5 and the OECD TG 422 studies conducted with 3a-A#4193-55-9 and 4-MSA#67786-25-8.

ECHA notes that your proposal does not address the toxicokinetics of substances with six sulphonic acid groups and also not all subcategories.

***III.D.4. Information needs to consolidate the registrants' category***

ECHA reaches the conclusion that systemic exposure after oral administration (gavage) in principle is likely to occur for all substances, however the extent is unknown. The extent of absorption may be modified by the different R1 and R2 substituents. It may also be different for known impurities and not specified impurities. It is unclear which substance structure influences the absorption and in which way. Furthermore, the absorption may be influenced by the method of administration (feed vs. gavage) and the chosen vehicle. The registrants appear to agree to this conclusion: "*...solubility is dependent on pH but also strongly dependent on the saline environment (presence of Ca++ ions, Na+ ions, etc.) not to take into considerations possible impurities. As a consequence, the possibility of little absorption cannot be excluded*" (p. 68 Justification document).

With regard to *in vivo* metabolism it is not possible to come to sound conclusions on the basis of the presented information.

ECHA considers additional toxicokinetic measurements which can be included in repeated dose toxicity studies may be an appropriate tool to better define the internal doses, and to characterise the metabolism and the excretion. Such data may be very helpful to explain potential similarities or differences in observed effects across the SFWA member substances. Therefore, any such measurements would be needed for several representative structures to cover the structural variations in the category. In addition, measurements of the extent of association of the test substances to the diet of experimental animals would be useful. The SFWA category will likely be further consolidated by such information.

It is at the registrants' own discretion to include toxicokinetic investigations on blood, serum and urine in the studies requested to investigate repeated dose toxicity. ECHA in addition considers that bile excretion and the impact the administration route and the vehicle on the availability for oral absorption needs attention.

### III.E Repeated dose toxicity (Annex VIII 8.6.1, 8.7.1, and Annex IX 8.6.2)

A "short-term repeated dose toxicity study (28 days)" is a standard information requirement as laid down in Annex VIII, Section 8.6.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for substances registered at Annex VIII to meet this information requirement.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossiers for SFWA substances. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the substances registered at Annex VIII or IX to meet this information requirement.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

Since the SFWA substances are registered at different tonnage bands all three of these standard information requirements are considered in an integrated manner in this section.

2-A#16090-02-1, 3a-A(Na)#4193-55-9, 3a-MSA#16470-24-9, 3a-DSA#68971-49-3 and 4-MSA#67786-25-8 are registered above 1000 tonnes.

1-MSA#42355-78-2, 1-DSA#41098-56-0, 3a-A(NaK)#70942-01-7, 3c-A#17958-73-5 [30] and 5-A#27344-06-5 are registered at 100 to 1000 tonnes per year.

2-DSA#52301-70-9 and 3b-A#13863-31-5 are registered at 10 to 100 tonnes per year. For 3c-MSA#16324-27-9 the registrants have applied Annex VII information requirements in their justification document, however, the substance is registered at a tonnage level of 10 to 100 tonnes per year.

2-MSA#28950-61-0 is registered at 1 to 10 tonnes per year.

The corresponding information requirements of Annexes VII to X apply.

#### *III.E.1 The registrants' hypothesis to address these information requirements in the category*

The registrants have provided results obtained in experimental studies for some substances. Using the results obtained in these studies they have sought to adapt this information requirement for the substances without experimental data. The adaptation is based either

[30] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

on Annex XI, Section 1.5. in a category approach as explained under II.B. or on Annex IX, Section 8.6.2, Column 2 of the REACH Regulation.
In addition to the general arguments explained in II.B the registrants have provided endpoint specific arguments to justify their category approach. They propose to cover SC1, SC4 and SC5 substances by results obtained with SC3a substances. The reasons provided are structural similarity, generally lower reactivity of the substances in these subcategories versus the bis(hydroxyethyl)amino derivatives, and the lack of critical metabolites as modelled with the OECD QSAR toolbox. The registrants assume that all substances in SC3a, SC3b and SC3c are covered by the available information, since they claim that these substances are related to SC3a substances via metabolism of the R2 groups to amines.

### *III.E.2. Available information to justify the category approach*

In table 25 of the justification document the registrants summarised the available information on the repeated dose toxicity studies. Furthermore, the endpoint study summaries in the dossiers report some, but not all of the information provided in the justification document.

*III.E.2.1 Experimental information considered as adequate and reliable by ECHA*

The registrants did not provide any experimental information for SC1 substances for repeated dose toxicity. ECHA, however, identified in the National Technical Reports Library a report on a 90-day study conducted with 1-DSA#41098-56-0, which was conducted 1969 by TNO and submitted in 1992 to the US authorities under TSCA 8(e) (Microfiche number OTS 0571834). The test substance is identified as [redacted] (CAS 41098-56-0), no details on purity are provided. The substance was mixed with the diet and administered to Wistar rats at 0, 0.2 %, 1 % and 5 %. Dose calculations were not provided in the report but food consumption data and body weights are reported. Using this information ECHA calculated for week 12 of the study for the male 0.2 % group 115 mg/kg bw/day and for the female 0.2 % group 120 mg/kg bw/day[31]. For the 1 % group the dose was for males 723 mg/kg bw/day and for females 754 mg/kg bw/day. The 5 % group animals did not survive past week 9 of the study. The body weight in the 1 % groups was significantly reduced and at 0.2 % slightly lower. Relative liver and kidney weights were increased at 1 % in both sexes. Also, the relative brain weight was increased. Testicle weight was decreased in the 1 % group. The serum enzyme levels for glutamic-oxaloacetic transaminase (SGOT) and alkaline phosphatase (SAP) were increased at 1 %. For the differential blood cell counts the percentage of neutrophils was significantly increased and the percentage of lymphocytes was significantly decreased in males at 1 %. Gross and microscopic examinations revealed severe toxic tubular nephrosis in both sexes and testicular atrophy in all males at 1 %. A number of seminiferous tubules only contained sertoli cells and occasional spermatogonia which contained irregular vacuolated cytoplasm. Partial inhibition of spermatogenesis occurred in other tubules. No pathological changes occurred at 0.2 %. The NOAEL was identified at 0.2 % (about 120 mg/kg bw and day). The identification of the target organs liver, kidney, testes and blood appears to be reliable. These target organs were also identified in a 28-day GLP study with 3a-MSA#16470-24-9 (see below). The 90-day study with 1-DSA#41098-56-0 is a feeding study and it is unclear what percentage of test substance was available for uptake due to possible association of test substance to components of the diet. Therefore, the NOAEL may be not reliable, but also since the purity of the substance is not reported.

[31] The calculations used the w/w percentage of test material in food, the average body weights at week 12 and the average food consumption at week 12 as provided in the report. For example: for male rats at week 12: 0.2 % of 17 g food/rat/day = 34 (mg/rat/day) /294 (g bw)*1000 = 115.65 mg/kg bw/day; for female rats at week 12: 0.2 % of 10.9 g food/rat/day = 21.8 (mg/rat/day) /180.7 (g bw)*1000 = 120.64 mg/kg bw/day

For 2-A#16090-02-1 there is a GLP study according to OECD TG 407 using oral gavage administration with water as vehicle ([redacted]_1991). No effects were observed and a NOAEL of 825 mg/kg bw/day (highest dose tested, 825 mg/kg bw/day; based on the active substance content of 82.5%)) is reported.
For 3a-MSA#16470-24-9 results obtained in a GLP study according to OECD TG 407 is available using oral gavage administration of the test substance with 88.1 % purity in CMC (carboxymethyl cellulose 4% in water) as vehicle ([redacted]_1987_[redacted]). Administered doses were 0, 50, 200 and 1000 mg/kg bw/day. Several haematology parameters were decreased either only in high dose or in the mid and high dose groups of one or both sexes, such as the erythrocyte count, the haemoglobin concentration, the haematocrit value, a mean corpuscular volume, and the mean corpuscular haemoglobin concentration. The registrants interpret that these findings primarily reflect a slight haemolytic anaemia for rats of group dosed at 1000 mg/kg bw whereas the changes noted in the lower dose groups were not considered toxicologically significant. Significant differences in absolute and/or relative liver, kidney and testes weights were observed in animals dosed at 200 and 1000 mg/kg bw/day, respectively. Clinical chemistry data showed treatment-related effects for rats dosed at 200 and 1000 mg/kg bw/day. According to the registrants, these findings primarily reflect changes of an adaptive nature due to an increased functional load on the liver; however, slight injury to liver tissue was detected for the high dose group as indicated by the moderate increase in enzyme activity (ASAT 47 % increase and ALP 73 % increase) and hepatic fatty changes for males of group dosed at 1000 mg/kg bw. In the kidney of the high dose group minimal to slight renal tubular epithelial degeneration and necrosis was identified. It is not reported whether the testes weight changes were accompanied by adverse histopathology changes.
ECHA considers these results as indicative of systemic toxicity with liver, kidney, blood and testes as target tissues. The reported effects appeared to be dose dependent in severity and a NOAEL of 50 mg/kg bw/day may be more appropriate than the 200 mg/kg bw/day identified by the registrants.
ECHA notes that the effects on testes weight decrease reported in this study were not leading to reproductive effects as investigated in the reproductive toxicity study (see III.H).

*III.E.2.2 Experimental information considered as useful for a weight of evidence*

For 2-A#16090-02-1, the information requirement for a 90-day study is adapted according to Annex IX, Section 8.6.2, Column 2 (reliable chronic study) using information from a 2-year study ([redacted]1978_[redacted]). The study was conducted with the 2-A#16090-02-1 at a purity of 92 %. The test substance was mixed with the diet at 0, 100, 1000, and 10000 ppm corresponding to 0, 4.93, 51.35 and 523.88 mg/kg bw/day for male animals and 0, 7.48, 77.48 and 790.59 mg/kg bw/day in female animals. Fifty animals were used per dose and sex. The registrants reported no effects. However, the OECD SIAR conclusions (OECD SIAM 21, 18-20 October 2005) reported that the NOEL in this study was 1000 ppm based on increased kidney weights at the highest dose. In the report it was stated that in the absence of histo-pathological kidney changes and in the absence of accompanying haematological or biochemical changes, the effects on kidney weights are considered treatment-related but not toxicologically relevant. Therefore, 10 000 ppm (corresponding to 524 and 791 mg/kg bw/day for males and females, respectively) were established as a NOAEL for the 2-year study in the OECD report.

For 3a-A(free acid)#4404-43-7 a 2-year study was conducted [redacted]_1987), a substance covered in the category, but registered as an on-site isolated intermediate. It is the free acid form of the registered substances 3a-A(Na)#4193-55-9 and 3a-A(NaK)#70942-01-7. The registrants propose to read-across the results obtained in this study to the registered substance containing Na+ or Na+/K+ ions, according to Annex XI, Section 1.5, to meet then the information requirement for the 90-day repeated dose toxicity study by an adaptation according to Annex IX, Section 8.6.2 Column 2. The test material was 89 % pure

3a-A(free acid)#4404-43-7, the test material was mixed with rat diet prior to administration and was administered via the diet. The study was conducted similar to OECD TG 453. The kidney weights of female animals at mid- and high-dose groups increased with respect to the control group. No evidence of a carcinogenic effect was identified. The registrants reported no other effects and identified the NOAEL as 779 mg/kg bw/day (female) and 542 mg/kg bw/day (male), which were the highest doses tested. The extent of the attachment of the SFWA constituents in the test substance to components of the rat diet cannot be assessed on the basis of the current information. ECHA therefore considers that, due to the uncertainty on the available doses for absorption, the 2-year studies with feeding administration have currently unclear value, but can in principle be used in a weight of evidence approach. A prerequisite for this use is that the outcome of other studies confirms the findings in the 2-year feeding studies.

For 4-MSA#67786-25-8 there is a sub-chronic study of 13 weeks duration performed in 1972 in rats with groups of 15 males and 15 females ([redacted]_1972_[redacted]). The substance 4-MSA#67786-25-8 was administered by oral gavage with 0, 30, 100 and 300 mg/kg bw/day in 83.25 % purity (calculated on the free acid) in polyethylene glycol. The doses were not analytically verified. The thyroid, heart, lungs, liver, spleen, kidneys, adrenals, testes and ovaries were macroscopically evaluated and weighed. No effects were reported and a NOAEL of 300 mg/kg bw/day was determined. The study was not conducted according to the modern OECD TG 408 and the reporting of the results is lacking details. Many parameters investigated in a current guideline study were not assessed. The list of investigated tissues does not correspond to those currently listed in the test guideline, no histopathology was performed and no functional behavioural observation battery was included in the test. ECHA considers this study alone as questionable to prove absence of effects, however, it may be used in a weight of evidence approach, if confirming results are available for this substance.

*III.E.2.3 Experimental information considered as not adequate and/or not reliable by ECHA*

A 90-day study for 2-A#16090-02-1 ([redacted]_1969) cannot be evaluated since the basis for reporting is a summary only and the Klimisch score 4 is assigned. Therefore, the identity of the test material and the used methods remain unclear for this study and it cannot be used to assess the toxicity of 2-A#16090-02-1.

For substance 3a-A(Na)#4193-55-9 there is a 28-day study (1962), a 1-year drinking water study and a 1-year study with subcutaneous administration recorded in the data matrix table of the justification document. None of these studies are reported in the registration dossier. The registrants state that the study reports are not available. In the endpoint summary of the dossier they further reported that there is a 2-year feeding study ([redacted] 1974), but the study results are not included as endpoint entries nor are the study results available to them. Since for all these studies it remains unclear what substance was tested, what the applied methods were, and whether the outcomes are reported correctly, ECHA considers all of these studies results as not adequate and not reliable.

There is a 2-year feeding study ([redacted]1978_[redacted]) conducted with 3a-MSA#16470-24-9 at 81 % purity conducted similar to OECD TG 453. The diet was mixed with the test substance prior to administration. Analytical verification was not performed. The doses were 0, 100, 1000, and 10000 ppm (nominal) in diet, which were calculated in mg/kg bw/day for males to be 0, 5.23, 52.24, 520.78 and for females 0, 7.02, 69.33, and 709.25. Fifty males and 50 females were in each dose group. Slight liver and kidney effects were noted, but were regarded as not toxicologically relevant. No evidence of a carcinogenic effect was identified. NOAELs were identified at the highest dose tested which for males was 520

mg/kg bw/day and for females 709 mg/kg bw/day. ECHA notes that the results obtained in the 28-day study ([redacted]1987_[redacted]) with oral gavage of 3a-MSA#16470-24-9 demonstrate systemic toxicity and contradict the results of the 2-year feeding study for this substance. Also, the PNDT study in the rabbit and the 2-generation study in rats (both via oral gavage) on 3a-MSA#16470-24-9 do not support the findings in the 2-year feeding study. The extent of the attachment of the SFWA constituents in the test substance to components of the rat diet cannot be assessed on the basis of the current information. ECHA therefore considers that, due to the uncertainty on the amount of ingested substance available for absorption, the 2-year study with feeding administration of 3a-MSA#16470-24-9 is not adequate to assess the toxicity of the substance.

There are results obtained in another repeated dose toxicity study conducted with 3a-MSA#16470-24-9 ([redacted]_1967), in which 0, 30, 60, 120, 250 or 500 mg of the test substance/kg as a solution in oil were administered by gavage for 10 weeks (5 doses/week) to 6 males and 6 females per dose group. The tested substance is identified with the trade name, chemical name and CAS number, but no further information on purity is provided. No effects were reported, the NOAEL was defined as 500 mg/kg bw/day. The repeated dose toxicity study ([redacted]_1967) does not cover the parameters of a current guideline study according to OECD TG 408. The duration and the number of animals is not appropriate, the test material is not characterised in terms of purity, the list of tissues examined (liver, kidneys, adrenals, thyroid, spleen, ovary, testis, lung) does not correspond to the list currently required according to the test guideline, histopathology was not performed and no functional behavioural test battery was investigated. ECHA does not consider the results of this study as adequate and reliable.

For 3b-A#13863-31-5 a 90-day rat study and a 90-day dog study are mentioned in the justification document. These studies are specified in the endpoint summary and were identified to be conducted by [redacted] in 1973 and are not regarded as reliable by ECHA unless formally audited by a regulatory authority (OECD, Manual for investigation of HPV Chemicals, Chapter 3: Data Evaluation, 2005). There is no indication of such audit. Furthermore, a chronic toxicity study is mentioned. Also, two dermal studies in the mouse are listed with 40 weeks exposure. These studies are not described in the registration dossier for 3b-A#13863-31-5. Therefore, ECHA cannot confirm which substance was tested, what methods were used and whether the outcome is reliable. ECHA considers all of these studies and the results as being not adequate and not reliable.

There are two more studies for 3b-A#13863-31-5 reported in the registration dossier and the justification document ([redacted]1956). Both studies have a duration of 5 days and do not deliver useful information which can be used to address the information requirement.

*III.E.2.4 Other supporting information*

ECHA found, in addition to the results reported in the dossiers, results for 3a-MSA#16470-24-9 in the EPA iCSS ToxCast Database. The substance was tested in a battery of *in vitro* tests. There is a warning included in the database on the analytics: "Caution, very low concentration < [redacted] % of expected value. Biological activity unreliable." Despite this low concentration, the test battery identified a number of interactions with nuclear receptors in a human liver cell line HepG2 (human nuclear receptor subfamily 1), human kidney cell line HEK 293 (human cytochrome P450, peroxisome proliferator activated receptor delta), human cervix cell line HeLa (activating transcription factor 6), human intestinal cell line HCT116 (human tumour protein p53) and others. The ToxCast screening battery is difficult to interpret due to the included analytical warning. At face value the results indicate that for 3a-MSA#16470-24-9 under the conditions of the studies, interactions with biological macromolecules are possible and that receptor activities may be modulated via this interaction.

In your comments on the draft decision, you point out that you have changed your previous strategy to study substances in the SFWA category in the Toxcast testing battery, because of the general low expertise and toxicological experience in interpreting potential results. Further you state "*in case this data have been taken into account by ECHA in their decision to request an OECD 408 study with CAS 16470-24-9,*" you comment that "*that the use of ToxCast Evaluations cannot be considered as reliable information to be used as the driving decisional key factor*".

ECHA states that the Toxcast data on 3aMSA#16470-24-9 is regarded as supporting information. The results are difficult to interpret. However, this statement is not related to general issues with Toxcast data, but with the specific circumstances of the test substance analytics. ECHA did not use the Toxcast data to justify the request 10 for 3aMSA#16470-24-9.

*III.E.2.5 Additional information to consolidate the category approach proposed by the registrants*

In their testing strategy the registrants state that they would like to refrain from proposing additional *in vivo* testing to improve the toxicological assessment of the category. However, in the case that ECHA concludes that the current information is not sufficient to assess the toxicity of the SFWA category substances, they propose in step 1 of their testing strategy an OECD TG 408 study with 5-A#27344-06-5 and OECD TG 422 studies with 3a-A(Na)#4193-55-9 and 4-MSA#67786-25-8.

Furthermore, the registrants propose in step 2 of their testing strategy an OECD TG 408 with 1-MSA#42355-78-2 and OECD TG 422 studies with 3b-A#13863-31-5 and 3c-A#17958-73-5.[32]

In their testing strategy the registrants state that for SC1 there are no experimental data and that the justification for predictions based on read-across is weak. The registrants acknowledge the contradiction in the results for 3a-MSA#16470-24-9. They do not define how the outcome of the studies in step 1 would address the contradiction in results for 3a-MSA#16470-24-9 and how it would influence further testing.

ECHA understands that the registrants propose with this testing strategy to provide more information for some substances obtained in OECD TG 408 studies to cover more structural variations in the category with definitive data for this information requirements. For other substances the registrants propose to conduct screening studies according to OECD TG 422 to support the proposed predictions for substances without experimental data.

### *III.E.3 ECHA's Assessment*

ECHA's general assessment of the registrants' adaptations based on grouping and read-across is provided in section II.C of this decision. The considerations on toxicokinetics are presented in III.D of this decision.

The information requirements for SC1 substances are proposed to be covered by reading across data from substances from SC3a, i.e. from 3a-A(Na)#4193-55-9 and CAS 3a-MSA#16470-24-9 (2-year studies). ECHA considers that with this proposed prediction a worst case approach is proposed since the registrants claim that the general reactivity of the alkyl terminal moiety is lower than the hydroxyethyl moiety.

[32] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

ECHA considers that no information substantiating this claim is provided in the dossier. Without sound *in vitro /in vivo* information the metabolic pathways and their consequences on toxicity remain unclear. Metabolism pathways modelled with the OECD QSAR Toolbox are not regarded as sufficient in this regard, in particular since there is no evidence that the modelled metabolites exist *in vivo*, what other metabolites are potentially formed in *in vivo* and there is no knowledge which toxicity these metabolites might have, whether alone or in combination(s). Furthermore, the 90-day study conducted with 1-DSA#41098-56-0 contradicts the assumption of no or low toxicity for SC1 substances. The identification of the target organs to be liver, kidney, testes and blood appears to be reliable. There is a need to clarify the repeated dose toxicity for SC1 substances and the proposed adaptation based on read-across from 3a-A(Na)#4193-55-9 and 3a-MSA#16470-24-9 is rejected.

The study conducted with 1-DSA#41098-56-0 (Microfiche number OTS 0571834) is currently not reported in the dossier. ECHA regards these study results as being very relevant for the assessment of the SFWA category and its results need to be reported in the dossier and discussed in the justification document.

ECHA considers that, due to the uncertainty on the available doses for absorption, the 2-year studies with feeding administration have currently unclear value, but can in principle be used in a weight of evidence approach. A prerequisite for this use is that the outcome of other high quality studies with oral gavage administration confirms the findings in the 2-year feeding studies. For 2-A#16090-02-1 such confirmation is available, for 3a-A(free acid)#4404-43-7 (used for 3a-A(Na)#4193-55-9 and 3a-A(NaK)#70942-01-7) such confirmation is not yet available, and for 3a-MSA#16470-24-9 the available information contradicts the findings in the 2-year study.

Therefore, ECHA currently accepts the adaptation according to Column 2 of Annex IX, section 8.6.2 for 2-A#16090-02-1, whereas for 3a-MSA#16470-24-9 this adaptation is rejected. For 3a-A(Na)#4193-55-9 and 3a-A(NaK)#70942-01-7 the acceptance depends on the outcome of a study still to be conducted.

For 2-DSA#52301-70-9, no specific argument to justify the proposed read-cross to 2-A#16090-02-1 was provided. ECHA understands therefore that the registrants' general assumption is used that more sulphonate functions lead to less toxicity. Currently there is no proof for this assumption and the proposed adaption is rejected.

For 3b-A#13863-31-5, 3c-A#17958-73-5[33] and 3c-MSA#16324-27-9 ECHA did not detect a specific argument to justify the proposed read-cross to the available two-year studies in SC3a. ECHA therefore assumed that the general arguments on similarity of metabolism and similar intermediates as described under II.B are applicable and have to be assessed. As explained under III.D there is no experimental proof that the main constituents in the substances of SC3b, SC3c and SC3a are related via metabolism of the R2 groups to amines. The registrants' assumption is based on a simulator prediction and not experimentally proven, and even if correct, such metabolism would not be rapid, intermediates would be formed, other metabolic steps are likely at other moieties of the substances, and the parent compounds are expected to be systemically available for a considerable time. The R2-functions in SC3b and SC3c therefore are not covered by experimental data obtained with other substances in the SFWA category. Therefore, the proposed read-across for 3b-A#13863-31-5, 3c-A#17958-73-5 and 3c-MSA#16324-27-9 is currently rejected and a

[33] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

confirmation is needed that the toxicity of the proposed analogue substances are indeed similar to SC3b and SC3c substances.[34]

For 4-MSA#67786-25-8 the registrants propose to cover the information requirement by the study [redacted]_1972_[redacted] and by an adaptation based on read-across to the chronic feeding studies obtained with SC3a substances. As explained above, [redacted]_1972_[redacted] alone is not considered as adequate, but needs confirmation. ECHA does not consider the claim of a generally lower reactivity to be a sufficient explanation why read-across is possible from a bis(2hydroxy ethyl) amine to a bis(2-hydroxyl propyl) amine. There is no supporting evidence for this claim. The secondary hydroxyl function may be oxidised to a keto function. No other constituent in the SFWA member substances has the potential to form such a functional group. Furthermore, 4-MSA#67786-25-8 shows the highest percentage of not identified impurities (< 12 %). The adaptation based on read-across is therefore currently rejected and a confirmation is needed that the toxicity of the proposed analogue substances is indeed similar to 4-MSA#67786-25-8 substances.

For 5-A#27344-06-5 the registrants propose to cover the information requirement by read-across to the chronic feeding studies obtained with SC3a substances. ECHA does not consider the claim of a generally lower reactivity to be a sufficient explanation why read-across is possible from SC3a substances to the 5-A#27344-06-5 with a carbamoyl function in R2. There is no supporting evidence for this claim. Furthermore, the substance 5-A#27344-06-5 consists only to about [redacted] % (typical concentration) of the main constituent. The other constituents are described in II.C.2. The current adaptation arguments do not consider this composition. The adaptation based on read-across is therefore rejected.

A sound comparison of the repeated dose toxicity between the members of the SFWA category is currently not possible, since the data density of adequate and reliable studies across the category is not sufficient and studies which may be used in a weight of evidence approach need confirmation.

ECHA considered the stepwise approach proposed by the registrants in the testing strategy. ECHA understands that they want to consolidate their category approach by covering more structural variations in the category with definitive data. The proposed two step approach, however, relies on studies with unclear value, lacks a convincing relationship with the regulatory requirements for the substances, has unclear triggers for moving from one step to the next and lacks a fixed time schedule to achieve an adequate level of information and compliant dossiers for all substances. Therefore, ECHA considered in combination all the studies proposed by the registrants in the two steps to determine which structural variations are covered by their proposal and which additional information is considered as necessary by ECHA.

ECHA agrees to the studies proposed by the registrants in their testing strategy to consolidate the category approach with additional experimental information. ECHA considers also that in addition to the studies they have proposed, further studies need to be conducted to consolidate their category approach. ECHA does not agree to their proposed two-step process for this information requirement. For an efficient regulatory process, it is necessary to have sufficient information on all structural variations of the SFWA substances for this information requirement available. This allows ECHA to decide then on the proposed adaptations for substances without experimental information on this information

[34] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

requirement and to determine whether more testing is needed, if the adaptations fail to meet the provisions in the REACH Regulation.

ECHA has structured your comments on the draft decision into general comments, specific comments on the requests for studies according to OECD TG 408, and specific comments on the requests for studies according to OECD TG 422.

General comments on repeated dose toxicity

a) Claim of sufficient data and low toxicity
You state that 6 out of 15 members of the category were assessed with experimental studies for repeated dose toxicity and that only three of these report systemic toxicity. However, you do not dispute the detailed assessment made by ECHA with regard to adequacy and reliability of the study results provided in the registration dossiers. Furthermore you do not reflect in your comments on the impact of the results obtained from the study conducted with 1-DSA#41098-56-0, which reports severe toxic tubular nephrosis and testicular atrophy. Your present conclusion is still, that the substances are non-toxic upon repeated exposure.

As explained in the decision, your conclusion that the substances are non-toxic is currently contradicted by data. The relevance and limitations of the available toxicokinetic data are assessed in III.D.

b) Feeding study results versus gavage study results
You state that you accept ECHA's arguments on adequacy and reliability of studies, but you are "*...still of the opinion that further tests including higher doses may not reflect any differences to our present conclusion that the substances are non-toxic upon repeated exposure. This is based on the findings that either the substances adsorb to biomass within the gut and therefore not bioavailable or that the substances are rapid and completely excreted within a few hours as demonstrated by toxicokinetic studies in vivo*".

You further state: "*The Registrants confirm that a reactivity is expected as well as an interaction with biological macromolecules in a computational or in-vitro system. The substances of the category have been built in fact to be reactive towards a natural substrate, like the textile fibres for example.*"

ECHA acknowledges the confirmation of the concerns expressed in this decision on potential interactions of the SFWA substances with biological macromolecules due to their properties expressed in their technical applications. ECHA considers that such properties of the SFWA substances may also lead to interactions with macromolecules *in vivo*.

Furthermore, you confirm with these comments, that ECHA's concern on the value of the feeding studies is justified. In feeding studies, in which the test material was mixed with the rat diet prior to the administration, the test material may be not or only to an unknown degree be available for absorption. As explained in the decision, results obtained in feeding studies therefore are only acceptable, if confirmed by consistent results obtained in gavage studies.

On the basis of these comments ECHA emphasises the importance of an appropriate method and timing of administration of the test material to minimise interference with the diet in all the tests to be conducted via the oral route. To minimise the impact of diet constituents on the amount of test material available for absorption at gavage administration the access to diet has to be restricted.

This is specified in Appendix 3 point 5. Appropriate cross references to Appendix 3 are added in the appropriate sections.

Specific comments regarding requests for OECD TG 408 studies (see III.E.4.1 below):

a) Your consent
You agree with ECHA's request to conduct new studies with
- 1-MSA#42355-78-2 and
- 5-A#27344-06-5.

You state that ECHA regards the reliability of the 90-day repeated dose toxicity study conducted with 1-DSA#41098-56-0 as low. You expect that in line with your claim of decreasing toxicity with increasing number of sulphonic acid groups, the results from the study with 1-MSA#42355-78-2 either will show a similar or higher toxicity than those obtained with 1-DSA#41098-56-0. If the future result would show lower toxicity for 1-MSA#42355-78-2, then you conclude that the results obtained with 1-DSA#41098-56-0 have to be questioned.

However, ECHA does not regard the reliability of the 90-day repeated dose toxicity study conducted with 1-DSA#41098-56-0 as low. Since it is a feeding study ECHA considers that the dose of test material which was effectively available for systemic absorption is unknown, therefore ECHA regards the NOAEL as not reliable (i.e. as possibly too high), but considers the identification of the target organs as reliable.

With regard to your hypothetical comparison of future results, ECHA notes that you consider results which fit to your claim as valid, but if the results do not fit to your claim, you intend to question the study results obtained in the 90-day repeated dose toxicity study conducted with 1-DSA#41098-56-0.

b) Your concerns
You disagree with ECHA's request to conduct a new study with
- 3a-MSA#16470-24-9

You stress that the systemic effects detected in the 28-day oral gavage study, the 2-generation reproductive toxicity study and the developmental toxicity study in rabbits conducted with 3a-MSA#16470-24-9 were the only tests which reported systemic effects and interpret that these effects were detected at high doses only. Furthermore, you consider the existing studies as sufficiently reliable to cover the repeated dose endpoint for 3a-MSA#16470-24-9. You consider that the requested study can result in an unjustified overload of animal testing, if results of other studies would confirm the validity of the existing data.

However, with regard to 3a-MSA#16470-24-9 ECHA has stated its interpretation of the available studies in the decision and you did not dispute this interpretation. Furthermore, you did not dispute that there is a contradiction between the results obtained in the two year feeding study with 3a-MSA#16470-24-9 and other adequate and reliable studies with this substance administered via oral gavage. Firstly, the observation of systemic effects invalidates your general claim that the SFWA substances are not absorbed, and secondly, ECHA considers that the contradiction between the results from different studies on 3a-MSA#16470-24-9 needs to be investigated by additional experimental information with this substance. Data from other substances are not sufficient to address this contradiction. Furthermore it needs to be established whether a longer exposure duration results in a higher toxicity than observed in the 28-day study. This is of particular relevance, since 3a-MSA#16470-24-9 is currently the only substance in the

SFWA category with an almost complete data set and is proposed as source substance for several other substances.

c) New study identified
For 3a-A(Na)#4193-55-9 you report that you found the original report of a 2-year feeding study from [redacted] performed in 1976 in rats. A NOEL of 1000 ppm and a NOAEL of 10000 ppm (app. 500 – 1000 mg/kg bw /day) were identified for male and female rats.

ECHA considers the robust study summary is not yet in the dossiers and that an evaluation of the adequacy and reliability of this information can currently not be made. However, the current assessment of the SFWA category is not likely to be changed by the results of this newly identified study as reported in your comments, because there is already a feeding study reported with the free acid 3a-A(free acid)#4404-43-7. The uncertainty regarding the bioavailability of the test material administered via the diet also applies to the [redacted], 1976 study. The OECD TG 422 study requested on 3a-A(Na)#4193-55-9 will provide clarification on the value of these feeding studies.

Specific comments regarding requests for OECD TG 422 studies (see III.E.4.3 below)

a) Your consent
You agree with ECHA's request to conduct new studies with
- 3a-A(Na)#4193-55-9, and
- 4-MSA#67786-25-8.

You consider the study with 3a-A(Na)#4193-55-9 as key study to demonstrate both the consistency and the validity of the feeding studies and the relationship between the less and more sulphonated analogues.

ECHA agrees that the study requested for 3a-A(Na)#4193-55-9 is relevant for establishing the value of feeding studies conducted with 3a-A(Na)#4193-55-9 and 3a-A(free acid)#4404-43-7. However, in terms of your claim of decreasing toxicity with increasing number of sulphonic acid groups, this study alone will not be sufficient to establish such a trend. Results obtained in studies with 6 sulphonic acid groups in subcategory 2 and 3a are needed to confirm such claim.

b) Your consent, but proposal for postponement
You propose to postpone the conduct of new studies requested with
- 3b-A#13863-31-5
- 3c-A#17958-73-5[35]

to step 2 of your testing strategy to verify the best testing conditions and analytical parameters in the first set of testing in order to gather the best set and highest number of useful information in the second step.

ECHA considers that the studies with 3b-A#13863-31-5 and 3c-A#17958-73-5 will provide information on subcategory 3b and subcategory 3c, which is needed to confirm predictions for these subcategories. Furthermore, these studies can be conducted after the results of a first set of studies are known, if you consider this as appropriate. However, the results for studies with 3b-A#13863-31-5 and 3c-A#17958-73-5 - subject to the consideration of the

[35] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

registrants of the opportunity of performing the requested studies on this substance - [36] have to be submitted at the deadline set in the decision. The deadline set in the decision for submission of these studies allows for sequential testing.

c) Your concerns

You disagree with ECHA's request to conduct new studies with

- 2-DSA#52301-70-9, and
- 3a-DSA#68971-49-3.

You consider the request for the study with 2-DSA#52301-70-9 as questionable. You claim that the other requested information need to be assessed first to ascertain whether interpolation of data from other category members can fill the data gaps for 2-DSA#52301-70-9. Furthermore, you consider that the study can result in an unjustified overload of animal testing, if results of other studies would confirm the validity of the existing data. In addition, you regard this study as not needed in a first step, in case a trend within a subcategory towards more sulphonated analogues will be demonstrated. The same argument is made for 3a-DSA#68971-49-3.

However, ECHA considers that for 2-DSA#52301-70-9, there is currently no information for repeated dose toxicity or screening for developmental and reproductive effects. Therefore, there are no data available which could be used to support predictions for this substance. For subcategory 2, there is also no other substance data, which could confirm that predictions based on results obtained with 2-A#16090-02-1 are valid for 2-DSA#52301-70-9. Furthermore, the 90-day study for the substance with 6 sulphonic acid functions in subcategory 1 showed such effects that the extended one-generation reproductive toxicity study is triggered for this substance registered at Annex IX. This appears to be in contradiction to your claim that an increasing number of sulphonic acid groups result in lower toxicity. ECHA considers that this claim needs to be investigated for each subcategory. ECHA therefore regards the study with 2-DSA#52301-70-9 as essential to consolidate the category approach.

The same arguments apply to the study with 3a-DSA#68971-49-3. Currently there is no information for repeated dose toxicity, pre-natal developmental toxicity, or extended one-generation reproductive toxicity study for this substance registered at Annex X. There are no data available which could be used to support predictions. The OECD TG 422 is therefore essential to confirm that predictions for this substance based on results obtained with analogue substances from subcategory 3 are valid. Without such supporting evidence, there is no proof for the claimed trend whereby more sulphonated substances result in lower toxicity compared to less sulphonated substances in subcategory 3. Furthermore, the OECD TG 422 study results also will provide supporting information on the validity of predictions for pre-natal developmental toxicity or extended one-generation reproductive toxicity study for this substance. ECHA therefore regards the study with 3a-DSA#68971-49-3 as essential to consolidate the category approach.

***III.E.4 ECHA requests to consolidate the registrants' category***

For the reasons presented above, ECHA concludes that the information provided on this endpoint for the registered substances 1-MSA#42355-78-2, 2-DSA#52301-70-9 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-MSA#16470-24-9, 3a-DSA#68971-49-3,

[36] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

3b-A#13863-31-5, 3c-A#17958-73-5 [37], 3c-MSA#16324-27-9, 4-MSA#67786-25-8, and 5-A#27344-06-5 does not meet the information requirement.

Therefore, the registrants of the above-mentioned substances subject to the information requirements are requested to provide the definitive studies, supporting studies and further justifications mentioned below (see also II.C.4). ECHA will reassess the eventual validity of their category approach after submission of this information.

*III.E.4.1 Experimental studies requested to fulfil the information requirement and to provide source studies for future adaptations*

ECHA agrees with the registrants' testing strategy that an OECD TG 408 study by oral gavage in the rat is needed to be conducted with 1-MSA#42355-78-2. The study results will clarify whether the target organ toxicity observed for 1-DSA#41098-56-0 is also relevant for 1-MSA#42355-78-2. Furthermore, it will provide for SC1 substances a more reliable NOAEL, if the toxicity profiles are indeed similar.

As explained above, ECHA considers that in addition to the studies proposed in the registrants' testing strategy an OECD TG 408 study needs to be conducted with 3a-MSA#16470-24-9 in order to provide a reliable study according to the current guideline via oral gavage to meet this information requirement for this substance and at the same time provide a reliable potential source study for other substances in SC 3a, 3b, and 3c.

ECHA agrees with the registrants' testing strategy that an OECD TG 408 study by oral gavage in the rat needs to be conducted with 5-A#27344-06-5 to provide another reliable source study for the SFWA category. The study covers the carbamoyl moiety in R2, not present in other constituents of the SFWA category substances. In addition, the amino aniline function in R1 is covered. The main constituent of the substance is present typically at a concentration of about [redacted]%. The study may therefore also provide information on the consequences of combined exposure of constituents.

Experimental studies according to OECD TG 408 are conducted as default with rats. ECHA considers this species as adequate also for the studies requested here.

ECHA has evaluated the most appropriate route of administration for the studies on repeated dose toxicity requested below. The substances are solids and inhalation exposure is not indicated. Hence, the test shall be performed in the rat by the oral route using the test methods as indicated below. Due to the discussed possibility of the substances to associate to food components, the testing should be done via oral gavage.
Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrants of the substances indicated below are requested to submit the following information derived with their respective substance:

(request 9) 1-MSA#42355-78-2

(request 10) 3a-MSA#16470-24-9 and

(request 11) 5-A#27344-06-5

Repeated dose 90-day oral (gavage) toxicity study (test method: OECD TG 408) in rats.

[37] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

To minimise contact of the test material with the diet, the schedule described in Appendix 3 point 5 must be followed.

As pointed out in Section III.D it is at the registrants' own discretion to define the substances for which toxicokinetic measurements are included in the test protocols of the studies to be conducted.

*Notes for your consideration,*

ECHA notes that a revised version of OECD TG 408 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

*III.E.4.2 Robust study summary to fulfil the information requirement at Annex IX*

The publicly available report of the 90-day repeated dose toxicity study with 1-DSA#41098-56-0 is currently not in the dossier of the substance and is also not discussed in the registrants' justification document. Therefore, they need to provide a robust study summary for this study and discuss the results in the update of the justification document.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrant of the substance indicated below is requested to submit the following information concerning its substance:

(request 12) 1-DSA#41098-56-0

Robust study summary of the Short term (17-days) and Sub-chronic (90-days) toxicity studies with [redacted] in Rats with Cover Letter dated 100992, TNO, [redacted], OTS 0571834.

*III.E.4.3 Experimental studies to support the proposed adaptations*

ECHA currently agrees with the registrants, that not for all substances, for which the information requirement applies, there is a need to conduct a repeated dose toxicity study. For some substances, adaptations according to Annex XI, Section 1.5 may be justified in the future.

For other substances, adaptations according to Annex IX, Section 8.6.2, Column 2 may be justified. A prerequisite will be, that the structural variations of the SFWA substances will be sufficiently addressed by definitive data (i.e. results obtained in OECD TG 408 studies) and that the proposed grouping and read-across for substances without such definitive data will be confirmed by supporting data. Such supporting data are results that may be obtained in OECD TG 422 studies.

ECHA considers that in addition to the studies proposed in the registrants' testing strategy an OECD TG 422 study needs to be conducted for 2-DSA#52301-70-9 to meet the information requirement for this substance and to consolidate the category. The results also will clarify their assumption that a higher number of sulphonic groups does not increase but rather decrease the toxicity for SC2 substances.

ECHA agrees with the registrant's testing strategy that an OECD TG 422 study needs to be conducted with 3a-A(Na)#4193-55-9. The results of this study would be applicable also to 3a-A(NaK)#70942-01-7 and provide data on the least sulphonated members of SC3a.

ECHA considers that in addition to the studies proposed in their testing strategy an OECD TG 422 study needs to be conducted with 3a-DSA#68971-49-3 to get also information for the most sulphonated member of SC3a substances.

Taken together, the two studies according to OECD TG 422 on SC3a substances will provide evidence on the toxicity profiles across this SC and will allow comparison of the results with the OECD TG 408 study conducted with 3a-MSA#16470-24-9. The results may also support their assumption that a higher number of sulphonic groups does not increase but rather decrease the toxicity for SC3a substances.

ECHA agrees with the registrants' testing strategy that an OECD TG 422 study needs to be conducted with 3b-A#13863-31-5. This test provides data to establish whether the toxicity profiles of SC3b and SC3a substances are indeed similar.

ECHA agrees with the registrants' testing strategy that an OECD TG 422 study by oral gavage needs to be conducted with 3c-A#17958-73-5 to establish whether the toxicity profile of SC3c and SC3a substances indeed are similar.[38]

ECHA agrees with the registrants' testing strategy that an OECD TG 422 study by oral gavage in the rat needs to be conducted with 4-MSA#67786-25-8 to establish whether the toxicity profile of SC4 and SC3a substances indeed are similar with regard to repeated dose toxicity.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrants of the substances indicated below are requested to submit the following information derived with their respective substance:

(request 18) 2-DSA#52301-70-9

(request 19) 3a-A(Na)#4193-55-9

(request 20) 3a-DSA#68971-49-3

(request 21) 3b-A#13863-31-5

(request 22) 3c-A#17958-73-5 [39]

(request 23) 4-MSA#67786-25-8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral (gavage) route.

To minimise contact of the test material with the diet, the schedule described in Appendix 3 point 5 must be followed.

As pointed out in Section III.D it is at the registrants' own discretion to define the substances for which toxicokinetic measurements are included in the test protocols of the studies to be conducted.

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[38] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

[39] *Idem.*

The studies conducted according to OECD TG 422 also will provide evidence on possible reproductive toxicity at the screening level in the rat, including the investigation of parameters sensitive to endocrine disruption (see III.F, III.H). In addition, a behavioural functional test battery is included in the test design thereby providing this element of the repeated dose toxicity testing.

*III.E.4.4 Updated justifications requested to adapt the information requirement*

The OECD TG 408 studies requested (see III.E.4.1) and the already existing studies on repeated dose toxicity will provide information on this information requirement to cover the structural variations of the substances in the SFWA category. For SC1, SC2, SC3a, and SC5 there will be reliable information on the variation in R2. Furthermore, there will be information on the R1 function for amino aniline, and amino monosulphonated aniline from OECD TG 408 studies and for the amino disulphonated aniline from two OECD TG 422 studies.

Therefore, for the other substances of the SFWA category, for which the standard information of a repeated dose toxicity applies according to their registered tonnage, but no experimental study exists, there will be information available from studies conducted according to OECD TG 408 studies, and OECD TG 422 studies. Results from these studies will allow the assessment of whether the toxicity profiles (including type and strength of effects) observed for substances in the category with definitive source studies (OECD TG 408 in the rat) are indeed similar to the target substances or will confirm that the 2-year feeding studies can be used to adapt the information requirement. In that respect, ECHA considers that the following criteria are decisive for the actual determination of similarity in toxicity:

- No adverse effects are observed in any organ or tissue for the both source and target substances when tested up to the limit dose; or
- Comparable effects (i.e. in terms of type of effect, severity and incidence) are observed in the same organ(s) tissue(s) or parameters at similar dose level for both source and target substances.

Verifying that these criteria are met is an essential condition for the valid justification of the similarity of toxicity for the substances covered by the category and, hence, for meeting the provisions in Annex XI, Section 1.5 to adapt the information requirement.

In addition, ECHA points out there are explanations provided in the Read-Across Assessment Framework[3] on the elements assessed in justifications on grouping and read-across approaches.

Updated justifications need to be developed by the registrants to confirm that the existing and new studies to be generated on repeated dose toxicity can be used to predict the outcome of such studies for substances without experimental data.
ECHA requests the registrants of the substances indicated below to submit updated justifications explaining whether, why and how the information requirement Annex IX, Section 8.6.2 can be adapted according to Annex XI, Section 1.5 or according to Annex IX, Section 8.6.2 Column 2, taking into account the newly generated information obtained in the SFWA category, including the experimental studies requested above:

(request 13) 3a-A(Na)#4193-55-9

(request 14) 3a-A(NaK)#70942-01-7

(request 15) 3a-DSA#68971-49-3

(request 16) 3c-A#17958-73-5 [40]

(request 17) 4-MSA#67786-25-8.

Furthermore, ECHA requests updated justifications explaining whether, why and how the information requirement Annex VIII, Section 8.7.1 can be adapted according to Annex XI, Section 1.5, of the substances listed below, taking into account the newly generated information obtained in the SFWA category:

(request 24) 3a-A(NaK)#70942-01-7

(request 25) 3c-MSA#16324-27-9.

See table 2 in Appendix 5 for an overview of ECHA's conclusions on repeated dose toxicity

As pointed out in Section III.D it is at the registrants' discretion to define the substances for which toxicokinetic measurements are included in the test protocols of the studies to be conducted.

*Note to the Registrants*

Independent of the outcome of the future studies, further testing for repeated dose toxicity is not needed for substances registered at 10 to 100 tonnes per year, for which an OECD TG 422 study was conducted. Guidance R.7a (Version 6.0 July 2017) specifies that if "a 28-day study (EU B.7, OECD TG 407) is not already available, the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to the reproduction/developmental toxicity screening test (OECD TG 421). This approach offers the possibility to avoid carrying out a 28-day study, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.7.1 and that of REACH Annex VIII, 8.6.1."

### III.F Pre-natal developmental toxicity study on a first species (Annex IX, Section 8.7.2)

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substances to meet this information requirement.

The SFWA substances 1-MSA#42355-78-2, 1-DSA#41098-56-0, 2-A#16090-02-1, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-MSA#16470-24-9, 3A-DSA#68971-49-3, 3c-A#17958-73-5 [41], 4-MSA#67786-25-8 and 5-A#27344-06-5 are registered at tonnages 100 to 1000 tonnes per year or above 1000 tonnes per year. The information requirement applies for these substances.

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[40] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

[41] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

### *III.F.1 The registrants' hypothesis to address this information requirement in the category*

The registrants have provided results obtained in experimental studies for some of the substances. Using the results obtained in these studies they have sought to adapt this information requirement for the substances without experimental data. The adaptation is based on Annex XI, Section 1.5. of the REACH Regulation in a category approach as explained under II.B.

In addition to the general arguments explained in II.B the registrants have provided endpoint specific arguments to justify their category approach. They consider that SC2, SC3, and SC4 substances are covered by the experimental studies. For SC1 and SC5 substances, the registrants propose to use the results obtained with 3a-MSA#16470-24-9. The reasons provided in the justification document concern structural similarity, similar solubility, and a claimed lower reactivity of the substances in SC1 and SC5 compared to the substances in SC3a, and the lack of critical metabolites as modelled with the OECD QSAR toolbox.

### *III.F.2 Available information to justify the category approach*

In table 26 of the justification document the registrants summarised the available information on the prenatal developmental toxicity studies (PNDT) on a first species. Furthermore, the endpoint study summaries in the dossiers report some, but not all of the information provided in the justification document.

*III.F.2.1* Experimental information considered as adequate and reliable by ECHA

Results obtained in an oral gavage study in the rat according to EPA OPPTS 870.3700 (considered to be equivalent to OECD TG 414) and GLP and conducted with 3a-MSA#16470-24-9 (purity not reported, indicated to be the registered substance) are available (1999, [redacted]). The doses were administered at 0, 100, 440 and 1000 mg/kg bw/day in 0.5 % CMC (carboxymethyl cellulose). It was reported that no effects were observed for the maternal animals or the foetuses. The NOAELs for maternal toxicity and pre-natal developmental toxicity were determined to be higher than 1000 mg/kg bw/day.

*III.F.2.2 Experimental information considered as not adequate and/or not reliable by ECHA*

Results obtained in a pilot developmental oral gavage study in the rat conducted with a substance which is not listed as a member of the SFWA category and identified as free acid form of 2-A#16090-02-1 (CAS#32466-46-9, [redacted]_1998b(rat)). Purity profiles are not reported. No details on methods and results are reported. The doses are reported as 30, 300 and 1000 mg/kg bw/day, teratogenic investigations were not performed and no effects were observed. ECHA considers the study results as not adequate and reliable, since neither the identity of the test substance is clear, nor the methods, nor the scope of the investigations.

Another study is mentioned in the registration dossier on 2-A#16090-02-1. The study was conducted in 1972 by [redacted] and is not regarded as reliable by ECHA unless formally audited by a regulatory authority (OECD, Manual for investigation of HPV Chemicals, Chapter 3: Data Evaluation, 2005). There is no indication that the study was audited.

A study is mentioned in the justification document conducted with a substance which is not included as a member in the SFWA category ([redacted], 1975). The substance is claimed to be similar to 3b-A#13863-31-5. In the registration dossier of 3b-A#13863-31-5 this study is not included as endpoint study summary, therefore there is no clear substance

identity and purity profile, and also the methods and results are not reported. ECHA does not consider the results of this study as adequate or reliable.

*III.F.*2.3 Additional testing proposed by the registrants to consolidate the category approach

In their testing strategy the registrants state that they would like to refrain from proposing additional *in vivo* testing to improve the toxicological assessment of the category. However, in the case that ECHA concludes that the current information is not sufficient to assess the toxicity of the SFWA category substances they propose in step 1 of their testing strategy to conduct a study according to OECD TG 414 with 5-A#27344-06-5 by oral gavage in the rat and a OECD TG 422 study for 3a-A(Na)#4193-55-9 and for 4-MSA#67786-25-8, both via oral gavage in the rat.

Furthermore, the registrants propose in step 2 of their testing strategy an OECD TG 414 study with 1-MSA#42355-78-2 and with 2-A#16090-02-1 by oral gavage in the rat and an OECD TG 422 via oral gavage for 3c-A#17958-73-5 [42] and 3b-A#13863-31-5 in the rat.

The criteria to move from step 1 to step 2 of their testing strategy are not clearly defined.

ECHA understands that the registrants propose with this testing strategy to provide more information for some substances obtained in OECD TG 414 studies to cover more of the structural variations in the category with definitive data for this information requirement. For other substances the registrants propose to conduct screening studies according to OECD TG 422 to support the proposed predictions for substances without experimental data.

***III.F.3 ECHA's Assessment***

Except for 3a-MSA#16470-24-9, adequate and reliable information for pre-natal toxicity in a first species is not available for the SFWA substances. ECHA considers that this result alone does not cover the structural variation of R1 and R2 in the SFWA category.
The claim that substances in SC2, SC3 and SC4 are covered by experimental data is therefore not verified by ECHA.

ECHA's general assessment of the registrants' adaptations based on grouping and read-across is provided in section II.C of this decision. ECHA does not accept the reasons with regard to their specific justification explained above for SC1 and SC5 substances. The registrants have provided no evidence that the substances in SC1 or SC5 have a lower reactivity towards the developing foetus compared to SC3a substances. Sound conclusions on metabolism are not possible (see III.D), and the identification of critical metabolites would need information on the relation between effects for the developing foetus and potential metabolites. Such information is not available. The proposed adaptations for SC1 and SC5 substances are therefore rejected.

A comparison of the pre-natal developmental toxicity between the members of the SFWA category is not possible, since only one adequate and reliable study is available and no further supporting information is provided. ECHA therefore cannot verify the predictions proposed by the registrants.

ECHA agrees to the studies they propose in their testing strategy to consolidate the category approach with additional experimental information. However, ECHA does not agree

[42] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

to the two-step process proposed by the registrants for this information requirement. For an efficient regulatory process, it is necessary to have sufficient information available on all structural variations of the SFWA substances for this information requirement. This allows ECHA to decide then on the proposed adaptations for substances without experimental information on this information requirement and to determine whether more testing is needed, if the adaptations fail to meet the provisions in the REACH Regulation.

In your comments to the draft decision you agree with ECHA's requests for new studies conducted with 1-MSA#42355-78-2, 2-A#16090-02-1, and 5-A#27344-06-5.

***III.F.4 ECHA requests to consolidate the registrants' category***

ECHA concludes that the information provided on this endpoint for the registered substances 1-MSA#42355-78-2, 1-DSA#41098-56-0, 2-A#16090-02-1, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3A-DSA#68971-49-3, 3c-A#17958-73-5 [43], 4-MSA#67786-25-8 and 5-A#27344-06-5 does not meet the information requirement.

Therefore, the registrants of the above-mentioned substances are requested to provide the definitive studies, supporting studies and further justifications mentioned below (see also II.C.4). ECHA will reassess the eventual validity of the category approach after submission of this information.

*III.F.4.1 Experimental studies requested to fulfil* the information requirement and to provide source studies for future adaptations

ECHA agrees with the registrants' testing strategy that an OECD TG 414 study needs to be conducted with 1-MSA#42355-78-2, which has an amino diethyl function not otherwise present in constituents of the other subcategories.

ECHA agrees with the registrants' testing strategy that an OECD TG 414 study needs to be conducted with 2-A#16090-02-1, which has a morpholino function not otherwise present in constituents of the other subcategories.
ECHA agrees with the registrants' testing strategy that an OECD TG 414 study needs to be conducted with 5-A#27344-06-5, which has a carbamoyl function in the main constituent which is not covered by other members of the SFWA category and in addition has a large percentage of other constituents. Also, the consequences of combined exposure to these constituents is currently not known.

The registrants propose to test these substances via oral gavage and in the rat. ECHA considers this as appropriate.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. In order to obtain data on the rat for the consolidation of the category, ECHA considers testing should be performed with rats as first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substances to be tested are solids, ECHA concludes that testing should be performed by the oral route. Due

[43] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

to the discussed possibility of the substances to associate to food components, the testing should be done via oral gavage.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrants of the substances indicated below are requested to submit the following information derived with their respective substance:

(request 26) 1-MSA#42355-78-2

(request 27) 2-A#16090-02-1

(request 28) 5-A#27344-06-5

Pre-natal developmental toxicity study (test method: OECD TG 414) in the rat by the oral (gavage) route.

To minimise contact of the test material with the diet, the schedule described in Appendix 3 point 5 must be followed.

*Note for your consideration*

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

This note also applies to requests 37 and 38 (for pre-natal developmental toxicity study in second species), of the present decision.

*III.F.4.2 Updated justifications requested to adapt the information requirement*

The OECD TG 414 studies requested and the already existing OECD TG 414 study will provide information on this information requirement to cover the structural variations of the substances in SFWA category. In particular, the impact of the R2 variations will be investigated at least for one substance in each SC by an OECD TG 414 study (except SC4). Furthermore, there will be information on the R1 function for amino aniline, and amino monosulphonated aniline from OECD TG 414 studies and for the amino disulphonated aniline from two OECD TG 422 studies.

Supporting data for the information requirement pre-natal developmental toxicity in a first species will be obtained in OECD TG 422 studies and were already requested under III.E. They will provide supporting information for the proposed adaptations for repeated dose toxicity but also for pre-natal developmental toxicity.

Therefore, for the other substances of the SFWA category, for which the standard information of a pre-natal developmental toxicity study in a first species applies but no experimental study exists, there will be information available from studies conducted according to OECD TG 408 studies, and OECD TG 422 studies. Results from these studies will allow the assessment of whether the toxicity profiles (= type and strength of effects) observed for substances in the category with definitive source studies (OECD TG 414 in the rat) are indeed similar to the target substances. In that respect, ECHA considers that the following criteria are decisive for the actual determination of similarity in toxicity, for both parental animals and foetuses:

- No adverse effects are observed in any organ or tissue for the both source and target substances when tested up to the limit dose; or

- Comparable effects (i.e. in terms of type of effect, severity and incidence) are observed in the same organ(s) tissue(s) or parameters at similar dose level for both source and target substances.

Verifying that these criteria are met is an essential condition for the valid justification of the similarity of toxicity for the substances covered by the category and, hence, for meeting the provisions in Annex XI, Section 1.5 to adapt the information requirement.

In addition, ECHA points out there are explanations provided in the Read-Across Assessment Framework[3] on the elements assessed in justifications on grouping and read-across approaches.

Updated justifications need to be developed by the registrants to confirm that the existing and new studies to be generated on pre-natal developmental toxicity in the rat as first species can be used to predict the outcome of such studies for substances without experimental data.

Therefore, ECHA requests the registrants of the following substances to submit updated justifications explaining whether, why and how this information requirement can be adapted according to Annex XI, Section 1.5, taking into account the newly generated information obtained in the SFWA category, including the experimental studies requested above:

(request 29) 1-DSA#41098-56-0

(request 30) 3a-A(Na)#4193-55-9

(request 31) 3a-A(NaK)#70942-01-7

(request 32) 3a-DSA#68971-49-3

(request 33) 3c-A#17958-73-5 [44]

(request 34) 4-MSA#67786-25-8.

See *table 3* in *Appendix 5* for an overview of ECHA's conclusions on reproductive toxicity.

### III.G Pre-natal developmental toxicity study on a second species (Annex X, Section 8.7.2)

Pre-natal developmental toxicity studies (test method OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

[44] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

The SFWA substances 2-A#1609-02-1, 3a-A(Na)#4193-55-9, 3a-MSA#16470-24-9, 3a-DSA#68971-49-3, and 4-MSA#67786-25-8 are registered above 1000 tonnes per year and the information requirement applies for these substances.

### *III.G.1 The registrants hypothesis to address this information requirement in the category*

The registrants have provided results obtained in experimental studies for some of the substances. Using the results obtained in these studies they have sought to adapt this information requirement for the substances without experimental data. The adaptation is based on Annex XI, Section 1.5. of the REACH Regulation in a category approach as explained under II.B.

In addition to the general arguments explained in II.B the registrants did not provide endpoint specific arguments for the rabbit to justify their category approach.

### *III.G.2. Available information to justify the category approach*

In table 26 of the justification document the registrants summarised the available information on the prenatal developmental toxicity studies (PNDT) on a second species. Furthermore, the endpoint study summaries in the dossiers report the information provided in the justification document.

*III.G.2.1* Experimental information considered as adequate and reliable by ECHA

For 3a-MSA#16470-24-9 results obtained in a rabbit study are reported (1999, [redacted]_1999_[redacted] The study was conducted according to EPA OPPTS 870.3700 (considered to be equivalent to OECD TG 414) and GLP (purity of the test substance is not reported, but is indicated to be the registered substance). The test substance was administered via oral gavage with 0.5 % CMC (carboxymethyl cellulose) in water. The doses were 0, 100, 400, and 800 mg/kg bw/day in 3 treatment groups of 25 females and 1 vehicle control group.

The registrants reported an excessive mortality and maternal toxicity at 800 mg/kg/day. As a result, this group was terminated. A total of 8 does in this group were found dead and an additional doe was euthanized in extremis. Treatment-related mortality (except gavage error) was not observed in the control group or the other dose groups. Treatment-related clinical signs observed in the 800 mg/kg/day group included convulsions, decreased defecation soft stool, discoloured faeces and reddish fluid in the refuse pan. Seven does from the 800 mg/kg/day group aborted during the study, and these abortions were considered to be treatment-related.

Two does from the 400 mg/kg/day group delivered early and this was considered to be related to treatment. Slight increases in soft stool and discoloured faeces were also noted in the 400-mg/kg/day group when compared with the vehicle control group, and since these signs were also observed at 800 mg/kg/day, the findings were considered to be related to test article administration.

No effects on uterine parameters were noted at 100 or 400 mg/kg/day. Foetal body weights were statistically lower at 400 mg/kg/day when compared with the vehicle control group. There were no treatment-related increases in the incidence of visceral variations or malformations in this study. No treatment-related increases in skeletal variations or malformations were noted at 100 or 400 mg/kg/day when compared with the vehicle control group.
Based on treatment-related clinical observations and necropsy findings seen in does at 400 mg/kg/day, the NOAEL for maternal effects in this study was 100 mg/kg/day, the lowest dose tested. There were statistically significant decreases in foetal body weight at 400

mg/kg/day. These changes are interpreted as secondary to the maternal toxicity observed at this dose and were not considered to be an indication of developmental toxicity. However, slight, but not statistically significant, increases in several skeletal malformations were noted at the top dose of 400 mg/kg/day when compared with the vehicle control group, which are not regarded as being treatment-related.

*III.G.2.2* Experimental information considered as not adequate and/or not reliable by ECHA

For 2-A#16090-02-1 results obtained in a rabbit study is reported as a pilot developmental oral gavage study conducted with a substance not listed as a member of the SFWA category and identified as free acid form of 2-A#16090—02-1 (CAS#32466-46-9, [redacted]_1998a (rabbit)). Purity profiles are not reported. No details on methods and results are reported. The doses are reported as 30, 300 and 1000 mg/kg bw/day, teratogenic investigations were not performed. No effects were reported. ECHA considers the study results as not adequate and reliable, since neither the identity of the test substance is clear, nor the methods, nor the scope of the investigations.

*III.G.2.3* Additional testing proposed by the registrants to consolidate the category approach

In their testing strategy the registrants state that they would like to refrain from proposing additional *in vivo* testing to improve the toxicological assessment of the category. However, in the case that ECHA concludes that the current information is not sufficient to assess the toxicity of the SFWA category substances they propose to test 2-A#16090-02-1 in an OECD TG 414 via oral gavage in the rabbit at step 3 of their testing strategy. It is not explained which conditions would trigger the conduct of this study.

ECHA understands that the registrants propose with this testing strategy to provide more information for one substance to cover more of the structural variations in the category with definitive data for this information requirement.

***III.G.3 Assessment***

Except for 3a-MSA#16470-24-9, adequate and reliable information for pre-natal toxicity in a second species is not available for the SFWA substances. ECHA considers that this result alone does not cover the structural variations for R1 and R2 in the SFWA category.

ECHA's general assessment of the registrants' adaptations based on grouping and read-across is provided in section II.C of this decision. They have provided no evidence that the pre-natal developmental toxicity in the rabbit can be predicted for substances in SC2, SC3 or SC4 based on the results obtained in a study with 3a-MSA#16470-24-9. The proposed adaptations are therefore rejected.

In the study conducted with 3a-MSA#16470-24-9, test substance related mortality was observed in the rabbits at 800 mg/kg bw/day. This mortality is not explained and results from necropsies are not reported. The registrants argue in the justification document that the mortality could be stress-related. ECHA has to assume that the mortality could also be due to systemic toxicity of the administered substance which is observed at the high dose and to a lower degree at the mid dose. Except for a lower foetal body weight at the mid-dose, this study did not reveal statistically significant adverse effects on the foetuses.

ECHA agrees to the study proposed by the registrants in their testing strategy to consolidate the category approach with additional experimental information. ECHA considers that in addition to the study the registrants have proposed, further experimental information is needed. ECHA does not agree to the two-step process they proposed for this information requirement. For an efficient regulatory process, it is necessary to have sufficient

information on all structural variations of the SFWA substances for this information requirement available. This allows ECHA to decide then on the proposed adaptations for substances without experimental information on this information requirement and to determine whether more testing is needed, if the adaptations fail to meet the provisions in the REACH Regulation.

In your comments on the draft decision, you disagree with ECHA's requests to conduct new studies with 2-A#16090-02-1 and 4-MSA#67786-25-8. You state that the studies should be considered in a second step, after the information from the pre-natal developmental toxicity studies conducted in the first species would be available. You state that clarifications on the validity of a feeding study conducted with 2-A#16090-02-1 and the outcome of the requested OECD TG 422 with 4-MSA#67786-25-8 should be assessed first. If the provisions of Annex X, 8.7, column 2 relating to classification as toxic for reproduction 1A or 1B apply there would be no need to test the substances in a second species.

ECHA points out that the information requirement of Annex X, 8.7.2 for a developmental toxicity study in a second species is a standard information requirement for substances registered under REACH in the tonnage band of more than a 1000 tons per annum.

As indicated in your comments, Annex X, 8.7. Column 2 indicates that "*If a substance is known to cause developmental toxicity, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary*". Therefore ECHA acknowledges that the results from the requested pre-natal developmental toxicity studies in rats and the available relevant information on this endpoint from other category members should be taken into account prior to conducting the developmental toxicity study in rabbits. ECHA stresses that the timelines set in the decision allow for such sequential testing. Therefore, ECHA considers that your proposal of a stepwise approach is already taken into account.

In order to clarify this, ECHA has included a note to the Registrants at the end of section III.G

### *III.G.4 ECHA requests to consolidate the registrants category*

ECHA concludes that the information provided on this endpoint for the registered substances 2-A#16090-02-1, 3a-A(Na)#4193-55-9, 3a-DSA#68971-49-3, and 4-MSA#67786-25-8 does not meet the information requirement.

Therefore, the registrants of the above-mentioned substances are requested to provide the definitive studies, supporting studies and further justifications mentioned below (see also II.C.4). ECHA will reassess the eventual validity of their category approach after submission of this information.

#### *III.G.4.1* Experimental studies requested to fulfil the information requirement and to provide source studies for future adaptations

ECHA currently agrees with the registrants, that not for all substances, for which the information requirement applies, there is a need to conduct a pre-natal developmental toxicity study on a second species. For some substances, adaptations according to Annex XI, Section 1.5 or Annex XI, Section 1.2 may be justified in the future. A prerequisite will be, that the structural variations of the SFWA substances will be sufficiently addressed by definitive data (i.e. results obtained in OECD TG 414 studies). Supporting data in the species rabbit are currently not available and cannot be easily obtained. Therefore, proposed adaptations for substances without definitive data on a pre-natal developmental

toxicity study on a second species need to rely on the overall assessment of the available information, when the results of the still to be conducted studies are submitted.

ECHA notes that the available study in rabbits indicates a higher toxicity of the test substance in rabbits in comparison with rats. This may be taken as further evidence that the SFWA substances are taken up when orally administered via gavage. However, pre-natal developmental toxicity studies are not designed to investigate species dependent toxicity for adult animals. ECHA notes that the study results did not indicate concern for the rabbit pre-natal developmental toxicity.

ECHA agrees to the testing strategy of the registrants that an OECD TG 414 study in the rabbit needs to be conducted with 2-A#16090-02-1, which has a morpholino function in R2 not otherwise present in constituents of the SFWA substances. This study will fulfil this information requirement for this substance.

In addition, ECHA considers that an OECD TG 414 study in the rabbit needs to be conducted with 4-MSA#67786-25-8 which has a 2-hydroxypropyl amino function in R2 not otherwise present in the constituents of the SFWA substances. Furthermore, 4-MSA#67786-25-8 has the highest content of non-specified impurities, which need to be taken into account as well when deciding on the substances to be tested.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits as a second species, since rats are either tested or will be tested as first species in the pre-natal developmental toxicity study.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route. Due to the discussed possibility of the substances to associate to food components, the testing should be done via oral gavage.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrants of the substances indicated below are requested to submit the following information derived with their respective substance:

(request 35) 2-A#16090-02-1

(request 36) 4-MSA#67786-25-8

Pre-natal developmental toxicity study (test method: OECD TG 414) in a second species (rabbit) by the oral route (oral gavage).

To minimise contact of the test material with the diet, the schedule described in Appendix 3 point 5 must be followed.

*III.G.4.2 Updated justifications requested to adapt the information requirement*

The requested OECD TG 414 studies in the rabbit requested will provide information on this property to cover the 2-A#16090-02-1 and 4-MSA#67786-25-8. For 3a-MSA#16470-24-9 an adequate and reliable study is available.

Therefore, for the other substances of the SFWA category, 3a-A(Na)#4193-55-9, and 3a-DSA#68971-49-3 for which the standard information of a pre-natal developmental toxicity

study in a second species applies but no experimental study exists, there will be information available from studies conducted with other substances according to OECD TG 422 studies in the rat. Results from these studies will allow the assessment of whether the toxicity profiles in the rat observed for substances in the category with are indeed similar to the target substances and the additional studies in the rabbit will demonstrate how likely differences of such toxicity profile are between rat and rabbit. In that respect, ECHA considers that the following criteria are decisive for the actual determination of similarity in toxicity, for both parental animals and foetuses:

- No adverse effects are observed in any organ or tissue for the both source and target substances when tested up to the limit dose; or

- Comparable effects (i.e. in terms of type of effect, severity and incidence) are observed in the same organ(s) tissue(s) or parameters at similar dose level for both source and target substances.

Verifying that these criteria are met is an essential condition for the valid justification of the similarity of toxicity for the substances covered by the category and, hence, for meeting the provisions in Annex XI, Section 1.5 to adapt the information requirement.

In addition, ECHA points out there are explanations provided in the Read-Across Assessment Framework[3] on the elements assessed in justifications on grouping and read-across approaches.

Updated justifications need to be developed by the registrants to confirm that the existing and new studies to be generated on pre-natal developmental toxicity in rabbit can be used to predict the outcome of such studies for substances without experimental data.

Therefore, ECHA requests the registrants of the following substances to submit updated justifications explaining whether, why and how this information requirement can be adapted according to Annex XI, Section 1.5, taking into account the newly generated information obtained in the SFWA category, including the experimental studies requested above:

(request 37) 3a-A(Na)#4193-55-9

(request 38) 3a-DSA#68971-49-3.

See *table 3* in *Appendix 5* for an overview of ECHA's conclusions on reproductive toxicity.

*Notes for your consideration*

You are reminded that before performing a pre-natal developmental toxicity study in the rabbit you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2. In the context of this decision, a possible adaptation may be available after the conduct of the pre-natal developmental toxicity study with the rat, i.e. the results meet the criteria for classification as toxic to reproduction category 1A or 1B and the available data are adequate to support a robust risk assessment. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

## III.H Extended one-generation reproductive toxicity study (Annex IX and X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X.

As laid down in column 1 of 8.7.3., Annex IX of the REACH Regulation, test method OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3 is a standard information requirement, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.

If the conditions described in column 2 of Annex IX or X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017).
Substances registered above 1000 tonnes per year are 2-A#1609-02-1, 3a-A(Na)#4193-55-9, 3a-MSA#16470-24-9, 3a-DSA#68971-49-3, and 4-MSA#67786-25-8 and the extended one-generation reproductive toxicity study information requirement applies to these substances.

For 1-DSA#41098-56-0 registered at 100 to 1000 tonnes per year, the available 90-day study reported testicular atrophy in rats (see III.E). These adverse effects on reproductive tissues meet the provision for substances registered at Annex IX and trigger the need to conduct an extended one-generation reproductive toxicity study.

### *III.H.1 The registrants' hypothesis to address this information requirement in the category*

The registrants have provided results obtained in experimental studies for some of the substances. Using the results obtained in these studies they have sought to adapt this information requirement for the substances without experimental data. The adaptation is based on Annex XI, Section 1.5. of the REACH Regulation in a category approach as explained under II.B.
In addition to the general arguments explained in II.B the registrants have provided endpoint specific arguments to justify their category approach. They consider that SC2, SC3, and SC4 are covered with their experimental data. The reasons they provided in the justification document concern the arguments described for repeated dose toxicity studies in the rat.

### *III.H.2 Available information to justify the category approach*

In table 26 of the justification document the registrants summarised the available information on the reproductive toxicity. Furthermore, the endpoint study summaries in the dossiers report the information provided in the justification document.

#### *III.H.2.1 Experimental information considered as adequate and reliable by ECHA*

Results obtained in a two-generation reproductive toxicity study in rats with 3a-MSA#16470-24-9 according to EPA OPPTS 870.3800 (considered to be equivalent to an OECD TG 416 study) and GLP are described (2001, [redacted]_2001_[redacted]). The test substance had a purity of was 88.3 % and was administered via oral gavage in 0.5 % aqueous carboxymethyl cellulose. Doses were 0, 100, 300 and 1000 mg/kg bw/day Analytical verification of dosing solution was performed.

P0-generation
A test substance-related statistically significant increases in absolute and relative (to brain and body weight) kidney weight in P0-females at 1000 mg/kg/day was noted when compared with control values. Since similar changes in kidney weight were noted in F1 parents at 1000 mg/kg/day, the change in kidney weight was considered to be test substance related.

Statistically significant decreases in absolute and relative (to brain weight) epididymis weight were noted at 300 and 1000 mg/kg/day when compared with controls. These changes were not correlated with any microscopic changes in the epididymis and there was no evidence of test article-related change in epididymal sperm concentrations. Since there was no microscopic correlation or a dose-related change in epididymal sperm concentrations, the decreases in epididymis weights were not considered to be test article related.

Also noted were statistically significant increases in absolute and relative (to brain weight) pituitary weight in P0-females at 1000 mg/kg/day when compared with control values. Microscopic evaluation of the pituitary did not reveal any changes, and consequently, these increases were not considered to be test article related.

There were no test substance-related effects on reproductive performance noted during the P0 generation. Slight, though statistically significant, decreases in the majority of sperm evaluation parameters were noted at 300 mg/kg/day when compared with controls. Since similar decreases were not noted at 1000 mg/kg/day, these changes were not considered to be toxicologically meaningful.

F1
The registrants reported statistically significant increases in absolute and relative kidney weight in both males-and females at 1000 mg/kg/day as well as relative kidney (to body weight) in females at 300 mg/kg/day. No microscopic evidence of kidney changes was noted. However, there was a clear change noted in both males and females at 1000 mg/kg/day, and this was considered to be test substance-related. The statistical change in 300 mg/kg/day females was considered to be spurious since no changes in absolute weight or the kidney weight relative to brain weight were observed, and similar decreases were not seen in 300 mg/kg/day males.

Absolute liver weight was statistically lower in males at 300 and 1000 mg/kg/day when compared with controls. Relative (to brain and body) liver weight was statistically lower than controls in males at 300 mg/kg/day, but this was not noted in males at 1000 mg/kg/day.

No changes in liver weight were noted in the females. Also noted were statistically significant increases in absolute and relative adrenal weight in females, but not males, at 1000 mg/kg/day. There were no corresponding macroscopic changes noted in these organs, and, consequently, the changes in the adrenal and liver weights were considered to be sporadic and unrelated to test article administration.

No test article-related changes in F1 parental reproductive performance were noted. Slight decreases in male and female mating and fertility indices were noted at 1000 mg/kg/day, but comparison with the historical controls indicate that the finding was not considered to be toxicologically relevant or test substance-related. No other test-substance related effects were reported.

No test substance-related changes in litter parameters were noted for the F1 litters and no other effects on F1 animals were reported.

F2
No test substance-related changes were reported for parturition, offspring survival, clinical observations, and offspring growth were noted in F2 pups during lactation.
No test substance-related changes in brain, spleen or thymus weights were noted in the treatment groups when compared with controls. It is not reported whether effects on kidneys were investigated.

The NOAEL for parental toxicity identified as 300 mg/kg/day and for parental reproductive performance, the NOAEL was 1000 mg/kg/day. For offspring growth and development, the NOAEL was also identified as 1000 mg/kg/day.

This study was conducted according to EPA-guideline EPA OPPTS 870.3800 which is considered as equivalent to the OECD TG 416. According to Annex X, Section 8.7.3, Column 2, two generation reproductive toxicity studies according to OECD TG 416 that were initiated before 13 March 2015 shall be considered appropriate to address the standard information requirement for an OECD TG 443 study. Therefore, adequate and reliable information for reproductive toxicity is available for 3a-MSA#16470-24-9.

*III.H.2.2* Experimental information considered as not adequate and/or not reliable by ECHA

There are two studies claimed to have investigated the effects of 3b-A#13863-31-5 and 2-A#16090-02-1 in three generations of rats. Both studies were conducted by [redacted] and are not regarded as reliable by ECHA unless formally audited by a regulatory authority (OECD, Manual for investigation of HPV Chemicals, Chapter 3: Data Evaluation, 2005). There is no indication that the studies were audited. In contrast to the position of the registrants, ECHA does not regard it possible to use results from non-reliable studies as lines of evidence in a weight of evidence approach.

The registrants also indicated the results of 5 dominant lethal studies in mice conducted according to, or similar to, OECD TG 478 in table 26: for 2-A#1609-02-1 (GLP, 1995, [redacted]_1995_[redacted]), 3a-A(Na)#4193-55-9 (1973, [redacted]1973_[redacted] 3a-MSA#16470-24-9 (GLP, 1995, [redacted]_1995_[redacted]), 3b-A#13863-31-5 (1974, [redacted]_1974), and 4-MSA#67786-25-8 1977, [redacted]_1977_[redacted]).
The animals were treated by oral gavage with a single dose. All studies reported no effects at 5000 mg/kg bw/day, the highest dose tested. It is not explained in the justification document or in the registration dossier why and how the results of these studies would contribute to the assessment of reproductive toxicity as investigated in an EOGRTS study. ECHA considers that the purpose of the dominant lethal test is to investigate whether chemicals produce mutations resulting from chromosomal aberrations in germ cells. Incidentally, data on some parameters relevant to embryotoxicity and reproduction are investigated: number of corpora lutea, implantations, alive and dead embryo, and foetus weight. The focus of this study type is however very limited in scope and ECHA considers that results of this study type have very limited value in assessing reproductive toxicity under conditions of repeated dose exposure as would be investigated in guideline reproductive toxicity studies.

*III.H.2.3 Additional testing proposed by the registrants to consolidate the category approach*

In their testing strategy the registrants state that they would like to refrain from proposing additional *in vivo* testing to improve the toxicological assessment of the category. However,

in the case that ECHA concludes that the current information is not sufficient to assess the toxicity of the SFWA category substances they propose to test 2-A#16090-02-1 in an OECD TG 443 via oral gavage in the rat at step 3 of their testing strategy. It is however not clear under which circumstances the conduct of this study would be triggered. The registrants did not describe the design of this study.

***III.H.3 ECHA's Assessment***

Except for 3a-MSA#16470-24-9, adequate and reliable information for reproductive toxicity is not available for the SFWA substances. ECHA considers that this result alone does not cover the structural variations for R1 and R2 in the SFWA category. The claim that substances in SC2, SC3 and SC4 are covered by experimental data is therefore not verified by ECHA.

ECHA's general assessment of the registrants' adaptations based on grouping and read-across is provided in section II.C of this decision. They have provided no evidence that the substances in SC2, SC3 and SC4 have a similar toxicity profile with regard to fertility and peri-and post-natal toxicity in comparison to 3a-MSA#16470-24-9. The registrant's justification, i.e. structural similarity and S9-metabolism simulation, are repeated as used for the justification for predictions for repeated dose toxicity. ECHA considers that this approach does not cover the structural variations for R1 and R2 in the SFWA category for the property reproductive toxicity and does not consider the specific aspects of fertility and peri- and postnatal toxicity. ECHA therefore rejects this adaptation on the basis of the information currently available.

For 1-DSA#41098-56-0 the registrants did not include the results of the 90-day study (Microfiche number OTS 0571834) in the dossier (see III.E.) nor did they discuss the severe effects on the reproductive male organs in their justification dossier. Therefore, the registrants also did not discuss the consequences of these findings for further testing. According to Annex IX, Section 8.7.3, Column 1, adverse effects on reproductive organs lead to the need to conduct an EOGRTS study.

ECHA agrees to the study proposed by the registrants in their testing strategy to consolidate the category approach with additional experimental information. ECHA considers that in addition to the study they have proposed, further experimental information is needed. ECHA does not agree to the three-step process proposed by the registrants for this information requirement.

In your comments to the draft decision, you did not disagree with ECHA's requests for new studies conducted with 1-DSA#41098-56-0 and 2-A#16090-02-1.

You stressed that the design of the requested extended one-generation reproductive toxicity studies should be confirmed or amended on the basis of the results from other studies requested in this decision.

ECHA notes, that such considerations are foreseen and are explained in the section on deadlines and in the *"Notes for the registrants' consideration"* below.

A Member State Competent Authority (MSCA) proposed to amend the outcome of ECHA's assessment. Whilst the MSCA agreed with ECHA on the need to conduct an EOGRTS on 1-DSA#41098-56-0 as a result of the findings on male reproductive organs in a 90-day repeated dose toxicity study, the MSCA considered it unnecessary to conduct an EOGRTS on 2-A#16090-02-1. The MSCA is of the opinion that based on the information available 1-DSA#41098-56-0 can be seen as a worst-case for the whole category. The MSCA considered that the combination of the information obtained from an EOGRTS on 1-

DSA#41098-56-0 and the results of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) conducted on 2-DSA#52301-70-9 should be considered before requesting an EOGRTS on 2-A#16090-02-1. The registrants indicated in their comments on the proposal for amendment that they considered that one EOGRTS may be sufficient to address reproductive toxicity properties of the category members but did not specify which category member should be tested in that study. They questioned the reliability of the 90-day study conducted with 1-DSA#41098-56-0 and its adequacy for triggering an EOGRTS. The registrant also proposed to remove all requests for EOGRTSs from the decision and to assess the need to conduct any such studies once the data from all other studies requested in this decision is available.

ECHA has taken the proposal for amendment and the registrant's comments into account and did not modify the draft decision. ECHA maintained is opinion expressed above that the 90-day study on 1-DSA#41098-56-0 is valid and that the findings reported from that study constitute a reliable basis for triggering an EOGRTS on 1-DSA#41098-56-0. ECHA stressed that there is currently no experimental data supporting the identification of 1-DSA#41098-56-0 as a worst-case substance across the category as suggested by the MSCA in their proposal for amendment. ECHA reiterated that in order to consolidate the category, the impact of the structural differences between the substances included in the category needs to be investigated and warrants further testing for reproductive toxicity with members of subcategory 2, i.e. 2-A#16090-02-1. ECHA is of the opinion, that the extent of the information obtained from the combination of an EOGRTS on 1-DSA#41098-56-0 and of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) conducted on 2-DSA#52301-70-9 alone, will not adequately inform on the impact of the structural differences between the substances included in the category on reproductive toxicity.

### *III.H.4 ECHA requests to consolidate the registrants' category*

ECHA concludes that the information provided on this endpoint for the registered substances 1-DSA#41098-56-0, 2-A#16090-02-1, 3a-A(Na)#4193-55-9, 3a-DSA#68971-49-3, and 4-MSA#67786-25-8 does not meet the information requirement.

Therefore, the registrants of the above-mentioned substances are requested to provide the definitive studies, supporting studies and further justifications mentioned below (see also II.C.4). ECHA will reassess the eventual validity of their category approach after submission of this information.

#### *III.H.4.1 Experimental studies requested to fulfil the information requirement and to provide source studies for future adaptations*

ECHA agrees with the testing strategy proposed by the registrants that for 2-A#16090-02-1 an extended one-generation reproductive toxicity study (EOGRTS) according to OECD TG 443 needs to be conducted to fulfil the information requirement, which has a morpholino function not otherwise present in the constituents of the substances in the SFWA category.

In addition to their proposed study, there is concern for reproductive toxicity for 1-DSA#41098-56-0 and an extended one-generation reproductive toxicity study needs to be conducted to fulfil the information requirement for this substance.

The following refers to the specifications of the required studies.

*Information from studies to be conducted before the extended one-generation reproductive toxicity study*

The results obtained in the studies still to be conducted (i.e. before the extended one-generation reproductive toxicity study) shall be used, among other relevant information, to

decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). The sub-chronic toxicity studies, the screening studies or the PNDT studies conducted with member substances of the SFWA category may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

*Premating exposure duration and dose-level setting*

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should 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 because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017

The highest dose level shall aim to induce systemic toxicity (c.f. OECD TG 443 paragraph 21) to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

*Extension of Cohort 1B*

If the column 2 conditions of 8.7.3., Annex IX are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

According to the dossier submitted the use of substance 1-DSA#41098-56-0 is leading to significant exposure of consumers because it is released from paper and treated textiles (ERC 11a).

Furthermore, there are indications for endocrine-disrupting modes of action because in a repeated dose (90-day) study conducted with 1-DSA#41098-56-0 testicular atrophy was observed.

Therefore, ECHA concludes that for 1-DSA#41098-56-0 Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the

registered substance are leading to significant exposure of consumers and observations in an available study indicate endocrine-disruption modes of action for the registered substance.

*Species and route selection*

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route. Due to the discussed possibility of the substances to associate to food components, the testing should be done via oral gavage.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrants of the substances indicated below are requested to submit the following information derived with their respective substance:

(request 39) 1-DSA#41098-56-0

(request 40) 2-A#16090-02-1

Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral gavage route, according to the following study-design specifications:
- 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 for 2-A#16090-02-1; and with extension to mate the Cohort 1B animals to produce the F2 generation for 1-DSA#41098-56-0.

To minimise contact of the test material with the diet, the schedule described in Appendix 3 point 5 must be followed.

While the specifications for the study design are given above, the registrants shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Currently, the extension of Cohort 1B is only requested for 1-DSA#41098-56-0 and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested.

However, the other studies requested on member substances of the SFWA category in this decision and/or any other relevant information may trigger changes in the study design. Therefore, these studies are to be conducted first and the study results submitted to ECHA in a dossier update by the 24-month deadline indicated in this decision. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform the registrants concerned within six months after expiry of the 24-month deadline and initiate a new decision making procedure under Articles 41, 50 and

51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If the registrants do not receive a communication from ECHA by the expiry of the six months following the 24-month deadline for providing the results of the studies requested in this decision, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and the registrants may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision.

*III.H.4.2 Updated justifications requested to adapt the information requirement*

ECHA currently agrees with the registrants, that not for all substances, for which the information requirement apply, there is a need to conduct an extended one-generation reproductive toxicity study. For some substances, adaptations according to Annex XI, Section 1.5 may be justified in the future. A prerequisite will be, that the structural variations of the SFWA substances will be sufficiently addressed by definitive data (i.e. results obtained in OECD TG 443/416 studies) and that the proposed grouping and read-across for substances without such definitive data will be confirmed by supporting data. Such supporting data are results obtained in OECD TG 422 studies.

The OECD TG 443 studies requested and the already available study (method similar to 416) will provide information on this property to address the SC1, SC2 and SC3 variations for at least one substance per SC. Furthermore, there will be information on all R1 functions in the SFWA category from these studies

The supporting data will be obtained in OECD TG 422 studies conducted with 3a-A(Na)#4193-55-9, 3a-DSA#68971-49-3, and 4-MSA#67786-25-8 and were already requested under III.E. They will provide supporting information for the proposed adaptations for repeated dose toxicity but also for reproductive toxicity.

Therefore, for the other substances of the SFWA category, for which the standard information of an EOGRTS study applies but no experimental study exists, there will be information available from studies conducted according to OECD TG 422 studies. Results from these studies will allow the assessment of whether the toxicity profiles (= type and strength of effects) observed for substances in the category with definitive source studies (OECD TG 443 in the rat) are indeed similar to the target substances. In that respect, ECHA considers that the following criteria are decisive for the actual determination of similarity in toxicity, for both parental animals and pups:

- No adverse effects are observed in any organ or tissue for the both source and target substances when tested up to the limit dose; or
- Comparable effects (i.e. in terms of type of effect, severity and incidence) are observed in the same organ(s) tissue(s) or parameters at similar dose level for both source and target substances.

Verifying that these criteria are met is an essential condition for the valid justification of the similarity of toxicity for the substances covered by the category and, hence, for meeting the provisions in Annex XI, Section 1.5 to adapt the information requirement.

In addition, ECHA points out there are explanations provided in the Read-Across Assessment Framework[3] on the elements assessed in justifications on grouping and read-across approaches.

Updated justifications need to be developed by the registrants to confirm that the existing and new studies to be generated for reproductive toxicity can be used to predict the outcome of such studies for substances without experimental data.

Therefore, ECHA requests the registrants of the following substances to submit updated justifications explaining whether, why and how this information requirement can be adapted according to Annex XI, Section 1.5, taking into account the newly generated information obtained in the SFWA category, including the experimental studies requested above:

(request 41) 3a-A(Na)#4193-55-9

(request 42) 3a-DSA#68971-49-3

(request 43) 4-MSA#67786-25-8.

*Notes for the registrants' consideration*

When submitting the study results of the studies requested in this decision the registrants are invited to also include in the registration update their considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017)*).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, the registrants may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/ triggers must be documented.

## III. I Growth inhibition study of aquatic plants (Annex VII, 9.1.2)

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for all registered SFWA substances to meet this information requirement.

### *III.I.1. The registrants' hypothesis to address this information requirement in the category*

The registrants have provided experimental information for some substances and they have sought to adapt this information requirement for the substances without experimental data according to Annex XI, Section 1.5. of the REACH Regulation in a category approach as explained under II.B.

In addition to the general arguments explained in II.B the registrants have provided endpoint specific arguments to justify their category approach. They consider that SC1, SC2, SC3a, SC3c, SC4 and SC5 substances are covered by the experimental studies, and for substances with no reliable experimental information in these SCs they propose predictions within the SC. The registrants provide reasons for these predictions in the justification document that concern water solubility which is higher for the source substance(s) and thus the bioavailability of the source substance(s) is also higher. The registrants argue that for this reason the predictions of ecotoxicity can be considered as a conservative approach. For the SC3b substance, they propose to use the results obtained with SC3a substances. They justify this prediction also by arguments on water solubility, but

also state that the substances have same metabolic and degradation pathways and similar biological reactivity.

In Table 33 of their justification document, the registrants have also provided "*ECOSAR predictions for algae*" which lists toxicity values (Green Algae, 96-hr EC50 and a chronic value) for triazines, aromatic-acid and melamines -acid.

When the data for 3a-A(NaK)#70942-01-7 is proposed for prediction, the registrants state that *"The presence of potassium ion has no relevant toxicological influence for the endpoint".*

### *III.I.2. Available information to justify the category approach*

In table 32 of the justification document the registrants summarised the available information on the growth inhibition on aquatic algae.

*III.I.2.1 Experimental information considered as adequate and reliable by ECHA*

A study according to OECD Guideline 201 (Alga, Growth Inhibition Test) is available for 2-MSA#28950-61-0 ("[redacted] *TE Toxicity to Pseudokirchneriella subcapitata (formerly Selenastrum capricornutum) in a 72-hour algal growth inhibition test"*, 2008). This study provides a 72-h EC50 of >100 mg/L (growth rate, nominal) and 72-h NOEC of 22 mg/L (growth rate, nominal). The following nominal concentrations of the test item were tested: 4.6, 10, 22, 46 and 100 mg/l. While the registrants base the effect values in nominal concentrations, they also indicate in the details on test conditions that for measurement of the actual concentrations of the test item, duplicate samples were taken from the test media at the start of the test (without algae) and at the end of the test (containing algae). The registrants report that the measured concentrations of the test item in the test media were between 95 and 104 % of the nominal values at the start and the end of the test. They do not report the details on the analytical methods. ECHA considers this a sufficiently valid study, despite the deficiencies in reporting.

A study according to OECD Guideline 201 (Alga, Growth Inhibition Test) is available for 4-MSA#67786-25-8 ("[redacted] *alga, Growth Inhibition Test with Pseudokirchneriella subcapitata, 72 hours*", 2015). This is a GLP limit study (nominal: 100 mg/l) and provides a 72-h EC50 of >34.9 mg/L and NOEC of 34.9 mg/L (growth rate, measured). The measured concentration of the test item at the start of the exposure (0 h) and at the end of the exposure (72 h) was in range of 116 to 10.5 % of the nominal values. Effect values provided are based on the geometric mean of the measured concentrations. The registrants report that the test outcomes can be considered as partial, because the measured concentrations were determined analysing only one of the two isomers present in the tested solutions. They do not report which isomer has been measured. ECHA considers this a sufficiently valid study.

Study according to OECD Guideline 201 (Alga, Growth Inhibition Test) is available for 5-A#27344-06-5 ("*OB230 alga, Growth Inhibition Test with Pseudokirchneriella subcapitata, 72 hours*", 2015). Based on this GLP study the registrants report a 72-h EC50 of >111 mg/L. The table of results indicate a statistical difference to control in concentration of 38.3 mg/L, thus the resulting NOEC is 11.3 mg/L (growth rate, measured). Geometric mean measured concentrations were 1.11, 3.64, 11.3, 38.3 and 111 mg/l. After 72-h the measured concentrations in the media were in the range of 29 to 33 % of the nominal values. The registrants report that the test outcomes can be considered as partial, because the measured concentrations were determined analysing only one of the two isomers present in the tested solutions. They do not report which isomer has been measured. ECHA considers this a sufficiently valid study.

*III.I.2.2 Experimental information considered as not adequate and/or not reliable by ECHA*

SC1

For 1-DSA#41098-56-0, the registrants provided a non-GLP limit test according to OECD TG 201 ("*Acute Toxicity of* [redacted] *trocken'to Green Algae (Growth Inhibition Tast [72 h] - OECD 201)*"). However, ECHA considers the study not reliable, mainly because no analytical monitoring has been performed. Further, the robust study summary lacks other information on the test, e.g. whether the study fulfils the validity criteria of the OECD TG 201. Cell density in replicate cultures over the time course of the test has not been reported and the information is needed to assess whether the test is valid. In addition, the pH shifted 2.5 log units (7.6-10.1) during the study, which is an order of magnitude more than recommended in paragraph 30 of OECD TG 201.

SC2

For 2-A#16090-02-1 the registrants have provided robust study summaries for three tests. The study "*Acute toxicity of* [redacted] *to Scenedesmus Subspicatus (OECD - algae growth inhibition test)*" is a GLP study indicating a 72-h EC50 value of 80.59 mg/L (nominal, cell number). In the robust study summaries they do not indicate if analytical monitoring has been performed. They further report that "*flocculation in the medium impaired the result and the reliability of the test*". Taken these together, ECHA considers that the test results may not be reliable.

The second study with 2-A#16090-02-1 ("*Untersuchungbericht nach OECD 201/EN ISO 8692/EU-Richtline C.3: toxiizität von* [redacted] *gegen Desmodesmus Subspicatus.sta*") is a static 72-h OECD TG 201 study (GLP not specified) indicating a 72-h EC50 of >100 mg/L (nominal, growth rate). In the robust study summary the registrants do not indicate if analytical monitoring has been performed. In addition, as they report "*Nevertheless the purity of the substance is unknown*", there is no information on the purity of the test material. Thus, ECHA cannot assess if the test material is representative of the main constituent of 2-A#16090-02-1. Further, the robust study summary lacks other information on the test, e.g. test conditions such as pH and whether the study fulfils the validity criteria of the OECD TG 201. ECHA considers that this test may not be reliable and/or adequate.

The third study with 2-A#16090-02-1 ("*Acute toxicity of* [redacted] *for Green Algae (72 hours screening test-OECD 201)*") the registrants consider to be reliability score 4 (not assignable) because "*Only a summary is available*". The study indicates a 72-h IC50 of 40 mg/L (nominal, growth rate). ECHA notes that many of the details in the robust study summary are missing, such as analytical monitoring, test type, test conditions, indication if the study has passed the validity criteria of OECD 201, and cell density over time course of the test. Therefore, with the current level of detail ECHA considers this study not reliable.

The study with 2-DSA#52301-70-9 ("*Acute toxicity of* [redacted] *300 % for Green Algae*") is a GLP compliant study indicating a 72-h EC90 of 1000 mg/L (cell number). ECHA considers the study not to be reliable and/or adequate due to following reasons. The registrants report that no analytical monitoring has been performed (even though the effect value is apparently based on measured concentrations) and the test type is not specified. Furthermore, there is no information on the purity of the test material. Thus, ECHA cannot assess if the test material is representative of the main constituent of 2-DSA#52301-70-9. Furthermore, the robust study summary lacks information on test conditions and cell density in replicate control cultures over the time course of the test which would allow ECHA to verify that indeed the study fulfils the validity criteria of the OECD TG 201, as is indicated by the registrants.

SC3a

The study with 3a-A(NaK)#70942-01-7 ("*Acute toxicity of* [redacted] *for Green Algae (72 hours screening test OECD 201)*") is a OECD TG 201 study (GLP not specified) indicating a 72-h EC50 of >100 mg/L (nominal, growth rate). ECHA considers the study not to be reliable and/or adequate due to following reasons. In the robust study summary the registrants do not indicate if analytical monitoring has been performed. In addition, test type is not specified, and the pH increase during the test was more than 1.5 log unit (7.8->10.4) which is against the recommendation of the paragraph 30 of OECD TG 201. They also indicate that validity criteria are fulfilled but there is no information on the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures to support the claim that validity criteria are met. Furthermore, there is no information on the purity of the test material. Thus, ECHA cannot assess if the test material is representative of the main constituent of 3a-A(NaK)#70942-01-7.

The study performed with 3a-A(Na)#4193-55-9 ("*Acute Toxicity of* "[redacted]" *to green algae (Growth inhibition test [72h] - OECD 201)*") is a limit test of non-GLP OECD TG 201 study indicating a 72-h EC50 of >100 mg/L (nominal, growth rate). In the robust study summary the registrants indicate that analytical monitoring has not been performed. Furthermore, ECHA has assessed the confidential information provided on the purity of the test material and considers that the test material is not representative for the registered substance 3a-A(Na)#4193-55-9, which consists of [redacted]% of the main constituent (i.e. CAS 4193-55-9). Therefore, ECHA considers that this study is not reliable and/or adequate for the substance 3a-A(Na)#4193-55-9.

The registrants provided two studies performed with 3a-MSA#16470-24-9: one GLP study ("*Acute Toxicity of* [redacted] *to Secenedesmus subspicatus (OECD - Algae growth inhibition test)*") and one which GLP status was not specified ("*Acute toxicity to* [redacted] *for Green Algae (72 hours screening test OECD 201)*"), both indicating a 72-h EC50 of >1000 mg/L (nominal, growth rate). ECHA considers both studies are not reliable for the following reasons. In the both robust study summaries the registrants do not indicate if analytical monitoring has been performed and the effect concentrations are based on nominal concentrations indicating that the exposure concentrations have not been measured. Furthermore, for the GLP study they do not indicate whether the validity criteria for this study are met but ECHA notes that, based on the reported cell numbers during the time course of the study, the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures may exceed 35%, which is against the recommendation of the paragraph 11 of OECD TG 201. For the non-GLP study, they indicate that validity criteria are fulfilled but there is no information on the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures to support the claim that validity criteria are met.

SC3b

The registrants provided results of a GLP study with 3b-A#13863-31-5 ("[redacted]*, Growth Inhibition Test with Pseudokirchneriella subcapitata, 72 hours*"), indicating a 72-h EC50 of 34.2 mg/L (measured, growth rate). However, they consider this study not reliable (reliability score 3). The registrants justify that "*Study conducted according to internationally accepted testing guidelines and performed according to the GLP. Nevertheless, in the main test the measured concentration of the test substance were very low and all test replicates foamed and showed a dose related opalescence*". They also claim that "*stilbene-type fluorescent whitening agents (FWAs) undergo photoisomerization and during the test it seems that only one of the two isomers present in the tested solutions was analyzed*". ECHA agrees that foaming of the test solution may influence the results and considers the disregarding of this study is justified.

SC3c
The registrants provided results from a static OECD TG 201 study for 3c-MSA#16324-27-9 (*"Acute Toxicity of [redacted] to Green Algae (Growth Inhibition Test [72 h] - OECD 201)"*) indicating a 72-h EC50 of >100 mg/L (nominal, growth rate). In the robust study summary the registrants do not indicate if analytical monitoring has been performed and the effect concentrations are based on nominal concentrations indicating that the exposure concentrations have not been measured. They also report that *"Study conducted according to internationally accepted testing guidelines. Low substance purity"*. They claim the test material details confidential. ECHA has assessed the information provided on the purity of the test material and considers that the test material indeed may not be representative for the registered substance 3c-MSA#16324-27-9, which mainly consists of the main constituent CAS 16324-27-9 ([redacted]%). The provided results from this limit test may not be adequate and/or adequate for the registered substance 3c-MSA#16324-27-9.

*III.I.2.3 Additional testing proposed by the registrants to consolidate the category approach*

In their testing strategy the registrants state that the results consistently show no concern for aquatic toxicity for all members of the category. However, they nevertheless agree that there is an issue with study reliability and agree to perform additional tests to better investigate the potential effects in the environment. On that basis, the registrants propose in their testing strategy to conduct algal toxicity studies with 1-MSA#42355-78-2, 2-A#16090-02-1, 3a-A(NaK)#70942-01-7 (or 3a-A(Na)#4193-55-9), 3a-DSA#68971-49-3, 3b-A#13863-31-5 and 3c-A#17958-73-5. [45]

***III.I.3. ECHA's Assessment***

Adequate and reliable information for growth inhibition of aquatic algae is available for 2-MSA#28950-61-0, 4-MSA#67786-25-8 and 5-A#27344-06-5. ECHA considers that these results do not cover the structural variations for R1 and R2 in the SFWA category. Furthermore, there is no evidence that within a subcategory the structural R1 variation would not influence the toxicity.

ECHA's general assessment of the registrants' adaptations based on grouping and read-across is provided in section II.C of this decision. ECHA does not accept the reasons with regard to their specific justification explained above. The registrants have provided no evidence to support their arguments that higher water solubility would indicate higher ecotoxicity. Furthermore, this argument contradicts with registrants' arguments in the category definition of the category justification document *"R1 variability would influence bioavailability and it is also known that an increase of sulphonated groups within an organic molecule will lower the general toxicity of a substance (Parkinson T.M., 1981)"* (see section II.B). In the absence of evidence to support any of these contradicting hypotheses related to the influence of sulphonation degree on ecotoxicity, the proposed adaptations within the subcategories are currently rejected. Furthermore, there is no evidence that would support their claim that the substance in SC3b has a similar reactivity compared to SC3a substances. Similarly, their arguments on the same metabolic and degradation pathways for substances in SC3b and SC3a are lacking evidence. The proposed adaptation from SC3a to SC3b substance is therefore also rejected.

With regards to *"ECOSAR predictions for algae"*, the registrants do not provide documentation of the applied ECOSAR method aiming at indicating the similarity of toxicity

[45] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

to algae. Therefore, ECHA cannot evaluate the reliability and adequacy of the provided results.

Regarding predictions for 3a-A(NaK)#70942-01-7, ECHA agrees to the registrants' argument that the presence of potassium ion has no relevant toxicological influence for the endpoint.

ECHA agrees to the registrants' proposed studies in their testing strategy to consolidate the category approach with additional experimental information. It is necessary to have sufficient information on all structural variations of the SFWA substances for this information requirement. This allows ECHA to decide then on the proposed adaptations for substances without experimental information on this information requirement and to determine whether more testing is needed, if the adaptations fail to meet the provisions in the REACH Regulation.

***III.I.4 ECHA requests to consolidate the registrants' category***

ECHA concludes that the information provided on this endpoint for the registered substances 1-MSA#42355-78-2, 1-DSA#41098-56-0, 2-A#16090-02-1, 2-DSA#52301-70-9, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-MSA#16470-24-9, 3a-DSA#68971-49-3, 3b-A#13863-31-5, 3c-A#17958-73-5 [46] and 3c-MSA#16324-27-9 does not meet the information requirement.

Therefore, the registrants of the above-mentioned substances are requested to provide the definitive studies, supporting studies and further justifications mentioned below (see also II.C.4). ECHA will reassess the eventual validity of the category approach after submission of this information.

*III.I.4.1 Experimental studies requested to fulfil the information requirement*

ECHA agrees that an OECD TG 201 study needs to be conducted with 1-MSA#42355-78-2, which has an amino diethyl function (R2) not otherwise present in constituents of the other subcategories.

ECHA agrees that an OECD TG 201 study needs to be conducted with 2-A#16090-02-1. This provides information for a morpholino function (R2) and amino aniline function (R1). While the morpholino function is addressed by an existing study on 2-MSA#28950-61-0, information on similarity in type and strength of effects across R1 function (amino aniline, amino monosulphonated aniline, and amino disulphonated aniline) on aquatic toxicity is currently not confirmed by data.

For the same reasons, and in addition to the tests proposed in the testing strategy, ECHA considers that also 2-DSA#52301-70-9, which has a morpholino function (R2) and amino disulphonated aniline function (R1), needs to be tested.

ECHA agrees that an OECD TG 201 study needs to be conducted with 3a-A(Na)#4193-55-9 and 3a-DSA#68971-49-3, which have bis(2-hydroxyethyl)amino function (R2). This functional group is not otherwise present in constituents of the other subcategories. Both 3a-A(Na)#4193-55-9 and 3a-DSA#68971-49-3 need to be tested as information on similarity in type and strength of effects across R1 function (amino aniline to amino disulphonated aniline) on aquatic toxicity is currently not confirmed by data.

[46] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

ECHA agrees that an OECD TG 201 study needs to be conducted with 3b-A#13863-31-5, which has a methyl (2-hydroxyethyl)amino function (R2) not otherwise present in constituents of the other subcategories.

ECHA agrees that an OECD TG 201 study needs to be conducted with 3c-A#17958-73-5, which has a 2-hydroxyethylamino function (R2) not otherwise present in constituents of the other subcategories. [47]

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrants of the substances indicated below are requested to submit the following information derived with their respective substance:

(request 44) 1-MSA#42355-78-2

(request 45) 2-A#16090-02-1

(request 46) 2-DSA#52301-70-9

(request 47) 3a-A(Na)#4193-55-9

(request 48) 3a-DSA#68971-49-3

(request 49) 3b-A#13863-31-5

(request 50) 3c-A#17958-73-5 [48]

Algae growth inhibition test, EU C.3./OECD TG 201).

*III.I.4.2 Updated justifications requested to adapt the information requirement*

The requested OECD TG 201 tests and the already existing OECD TG 201 studies will provide information on this information requirement to cover the structural variations of the substances in SFWA category. In particular, the impact of the R2 variations will be investigated at least for one substance in each SC by an OECD TG 201 study.

Furthermore, there will be information on the influence of R1 function (amino aniline, amino monosulphonated aniline, and amino disulphonated aniline) on the toxicity observed in OECD TG 201 studies.

For the other members of the SFWA category, for which the standard information of a growth inhibition toxicity study on algae applies but no experimental study exists, there will be information available from studies conducted according to OECD TG 201 with other SFWA substances. Results from these studies will allow the assessment of whether the toxicity profiles (= type and strength of effects) observed for substances in the category with definitive source studies (OECD TG 201) are indeed similar across the R1 function (e.g. SC2 and SC3a). In that respect, ECHA considers that the following criteria are decisive for the actual determination of similarity in toxicity:

- No adverse effects are observed up to the maximum concentration tested (e.g. maximum water solubility);
- Comparable effects (i.e. in terms of type and strength of effect) are observed at

[47] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

[48] *Idem*.

similar concentration level, or

- The strength of effects forms a trend across the category members.

Verifying that these criteria are met is an essential condition for the valid justification of the similarity of toxicity for the substances covered by the category and, hence, for meeting the provisions in Annex XI, Section 1.5 to adapt the information requirement.

In addition, ECHA points out there are explanations provided in the Read-Across Assessment[3] Framework on the elements assessed in justifications on grouping and read-across approaches.

Updated justifications need to be developed by the registrants to confirm that the existing and new studies to be generated on growth inhibition on aquatic algae can be used to predict the outcome of such studies for substances without experimental data.

Therefore, ECHA requests the registrants of the following substances to submit updated justifications explaining whether, why and how this information requirement can be adapted according to Annex XI, Section 1.5, taking into account the newly generated information obtained in the SFWA category, including the experimental studies requested above:

| | |
|---|---|
| (request 51) | 1-DSA#41098-56-0 |
| (request 52) | 3a-A(NaK)#70942-01-7 |
| (request 53) | 3a-MSA#16470-24-9 |
| (request 54) | 3c-MSA#16324-27-9 |

See table 4 in *Appendix 5* for an overview of ECHA's conclusions on ecotoxicity.

## III.J Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5)

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The SFWA substances 1-MSA#42355-78-2, 1-DSA#41098-56-0, 2-A#16090-02-1, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-MSA#16470-24-9, 3A-DSA#68971-49-3, 3c-A#17958-73-5 [49], 4-MSA#67786-25-8 and 5-A#27344-06-5 are registered at 100-1000 or above 1000 tonnes per year and information on Long-term toxicity testing on aquatic invertebrates is required.

### *III.J.1 The registrants' hypothesis to address this information requirement in the category*

The registrants have provided results obtained in experimental studies for some of the substances. Using the results obtained in these studies they have sought to adapt this information requirement for the substances without experimental data. The adaptation is based on Annex XI, Section 1.5. of the REACH Regulation in a category approach as explained under II.B.

[49] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

In addition to the general arguments explained in II.B the registrants have provided endpoint specific arguments to justify their category approach. There are currently data only for 3a-MSA#16470-24-9 in the SFWA category (e.g. Table 37 of the justification document). However, the registrants indicate that they plan to generate new data for 2-A#16090-02-1 which will be used as a source study for all the category members. The registrants state that this study will provide the worst case estimation of toxicity for the whole category and thus this study will provide representative results for the rest of the SFWA category members. They justified the approach by the following: "*Therefore it would be important to re-test CAS 16090-02-1 in a reproductive toxicity test on Daphnia Magna (OECD TG 211) with a suitable method, to properly assess the endpoint, in order to have a reliable test with representative results for the category. According to ECOSAR prevision the morpholino derivative (CAS 16090-02-1) is also the most representative conservative reference for the whole category, therefore a reliable result on this molecule will reasonably assess the whole category for the endpoint*". Based on this, ECHA understands that the registrants intend to perform a new study with 2-A#16090-02-1 and use the data to predict the properties of the all other SFWA category members.

In Table 38 of their justification document, the registrants have provided "*ECOSAR predictions for Daphnids chronic*" which lists toxicity values (*Daphnia* chronic value) for "*Triazines, Aromatic-acid*" and "*Melamines –acid*".

### *III.J.2 Available information to justify the category approach*

In table 37 of the justification document the registrants summarised the available information on the toxicity to aquatic invertebrates. Furthermore, the endpoint study summaries in the dossiers report the information provided in the justification document.

#### *III.J.2.1 Experimental information considered as adequate and reliable by ECHA*

The registrants have provided a 21-d toxicity GLP study on *Daphnia magna* according to OECD TG 211 for 3a-MSA#16470-24-9 ("*Chronische Daphnientoxizität von* [redacted]"), indicating a NOEC of 6.59 mg/L (measured, reproduction).

#### *III.J.2.2 Experimental information considered as not adequate and/or not reliable by ECHA*

The registrants have provided a 21-d toxicity study on *Daphnia magna* for 2-A#16090-02-1 ("*Chronische Daphnientoxizität von:* [redacted]"), indicating a NOEC of 1.0 mg/L and EC50 of 1.0-3.2 mg/L (nominal, reproduction).

ECHA notes that the registrants have disregarded the study with 2-A#16090-02-1, because of the issues with analytical measurements during the test, the possible formation of particles due to precipitation over time and possible (physical) effects of possible crystalline deposits on the antennae obstructing normal feeding and/or propulsion of the daphnids and/or respiration of the daphnids in the water column. The registrants further explain in their category justification document that the crystalline deposits have been interpreted as calcium complexes with the brightener. The substance forms strong ion-pairs with calcium ions in water and the octanol-water partition coefficients of the ion-pairs are two orders of magnitude higher than the partitioning coefficient of the substance.

ECHA acknowledges that if indeed the effects were caused only by physical interaction of the substance-$Ca^{2+}$ complex with the test organisms, the test results may not be reliable. Valid aquatic toxicity tests require the test substance to be dissolved in the water medium under the conditions recommended by the guideline, and the maintenance of a bioavailable exposure concentration for the duration of the test. ECHA, however, notes that the registrants have not provided evidence for occurrence of calcium complexes/precipitates and how they interacted with the test organisms. There is therefore no evidence that the

effects would not be caused by the substance or its degradation products. They indicate an intention to repeat the study and ECHA agrees to performing a new study with controlled conditions, including analytical measurements and detailed documentation of the precipitates attached to the daphnids (if precipitates are observed).

ECHA agrees that the study has shortcomings and uncertainties and is therefore not reliable.

*III.J.2.3 Additional testing proposed by the registrants to consolidate the category approach*

In their testing strategy the registrants state that the results consistently show no concern for aquatic toxicity for all members of the category. However, they nevertheless agree that there is an issue with study reliability and agree to perform additional tests to better investigate the potential effects in the environment. Contrary to their category justification document where the registrants propose to conduct only a new test with 2-A#16090-02-1, in their testing strategy they propose to test the following substances:

- 1-MSA#42355-78-2
- 2-A#16090-02-1
- 3a-A(NaK)#70942-01-7 (or 3a-A(Na)#4193-55-9)
- 3a-DSA#68971-49-3
- 3c-A#17958-73-5 [50]
- 4-MSA#67786-25-8
- 5-A#27344-06-5 (ECHA understands that there is a typing error in the registrants' document, identifying this substance as "CAS 23744-06-5" instead of CAS 27344-06-5)

ECHA understands that the registrants propose with this testing strategy to provide more information for some substances obtained in OECD TG 211 studies to cover more of the structural variations in the category with definitive data for this information requirement.

***III.J.3 ECHA's Assessment***

Except for 3a-MSA#16470-24-9, adequate and reliable information for toxicity aquatic invertebrates is not available for the SFWA substances. ECHA considers that this result alone does not cover the structural variations for R1 and R2 in the SFWA category.

In the table 38 of their justification document the registrants provide "*ECOSAR predictions for Daphnids chronic*" to support their prediction from 2-A#16090-02-1 to all the other SFWA category members, when the data for the substance 2-A#16090-02-1 becomes available. The values provided in the table 38 indeed indicates that 2-A#16090-02-1 may be the most toxic to the endpoints used for the ECOSAR prediction.

ECHA however notes several deficiencies in the registrants' justification. Firstly, ECHA notes that they have not provided any documentation that would allow evaluating the reliability of the ECOSAR predictions. ECHA further notes that it is doubtful that long-term toxicity to daphnids can be reliably predicted with ECOSAR for the category members. Although it is not clear what version of ECOSAR was used, ECHA assumes that the so-called ECOSAR QSAR equation for Triazines, Aromatic - DAPHNID ChV (Chronic Value) has been used and ECHA assumes that the values provided in the table 38 of the justification document are based on this equation. This equation has been build based on only three experimental data

[50] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

points and one cut-off value. Two of these three substances have the same calculated logKow, but the measured chronic values are two log units different. Generally for non-polar narcotic substances there is a relationship between increasing toxicity and increasing log Kow, which is not evident for the training set of the QSAR equation in ECOSAR in this case. Furthermore, the substances in the SFWA group have a higher molecular weight compared to the substances used to establish the ECOSAR DAPHNID ChV equation. In addition, many SFWA structural features are not addressed by the specific model on aromatic trazines, leading to high uncertainties in any prediction with the QSAR equation. In conclusion, the ECOSAR predictions provided in table 38 cannot reliably support the registrants' claim that the 2-A#16090-02-1 would be the most toxic to *Daphnia magna*.

Secondly, the registrants have not provided any other explanation or evidence how the structural variability in R1 and R2 functions may influence toxicity to aquatic invertebrates. ECHA therefore considers that their justification does not explain why the properties of all category members could be predicted from the test to be conducted with 2-A#16090-02-1. Their argument, stating that 2-A#16090-02-1 would be most toxic and thus provide a worst case estimation of toxicity for the rest of the category members, is not supported by reliable evidence. ECHA thus considers that this approach does not address the structural variations for R1 or R2 moieties for the property of long-term toxicity to aquatic invertebrates.

ECHA therefore rejects this adaptation based on the information currently available.

ECHA agrees to the studies proposed by the registrants in their testing strategy to consolidate the category approach with additional experimental information. It is necessary to have sufficient information on all structural variations of the SFWA substances for this information requirement. This allows ECHA to decide then on the proposed adaptations for substances without experimental information on this information requirement and to determine whether more testing is needed, if the adaptations fail to meet the provisions in the REACH Regulation.

***III.J.4. ECHA requests to consolidate the registrants' category***

ECHA concludes that the information provided on this endpoint for the registered substances 1-MSA#42355-78-2, 1-DSA#41098-56-0, 2-A#16090-02-1, 3a-A(NaK)#70942-01-7, 3a-A(Na)#4193-55-9, 3a-DSA#68971-49-3, 3c-A#17958-73-5 [51], 4-MSA#67786-25-8, 5-A#27344-06-5 does not meet the information requirement.

Therefore, the registrants of the above-mentioned substances are requested to provide the definitive studies, supporting studies and further justifications mentioned below (see also II.C.4). ECHA will reassess the eventual validity of the registrants' category approach after submission of this information.

*III.J.4.1 Experimental studies requested to fulfil the information requirement and to provide source studies for future adaptations*

ECHA agrees that an OECD TG 211 study needs to be conducted with 1-MSA#42355-78-2, which has an amino diethyl function (R2) not otherwise present in constituents of the other subcategories.

[51] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

ECHA agrees that an OECD TG 211 study needs to be conducted with 2-A#16090-02-1, which has a morpholino function (R2) not otherwise present in constituents of the other subcategories.

ECHA agrees that an OECD TG 211 study needs to be conducted with 3a-A(Na)#4193-55-9 and 3a-DSA#68971-49-3, which have bis(2-hydroxyethyl)amino function (R2). This functional group is not otherwise present in constituents of the other subcategories. Both, 3a-A(Na)#4193-55-9 and 3a-DSA#68971-49-3 need to be tested as information on similarity in type and strength of effects across R1 function (amino aniline to amino disulphonated aniline) on aquatic toxicity is currently not confirmed by data.

ECHA agrees that an OECD TG 211 study needs to be conducted with 3c-A#17958-73-5, which has a 2-hydroxyethylamino function (R2) not otherwise present in constituents of the other subcategories. [52]

ECHA agrees that an OECD TG 211 study needs to be conducted with 4-MSA#67786-25-8, which has bis(2-hydroxypropyl)amino function (R2) not otherwise present in constituents of the other subcategories.

ECHA agrees that an OECD TG 211 study needs to be conducted with 5-A#27344-06-5, which has (2-carbamoylethyl)(2-hydroxyethyl)amino function (R2) not otherwise present in constituents of the other subcategories.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrants of the substances indicated below are requested to submit the following information derived with their respective substance:

(request 55) 1-MSA#42355-78-2

(request 56) 2-A#16090-02-1

(request 57) 3a-A(Na)#4193-55-9

(request 58) 3a-DSA#68971-49-3

(request 59) 3c-A#17958-73-5 [53]

(request 60) 4-MSA#67786-25-8

(request 61) 5-A#27344-06-5:

*Daphnia magna* reproduction test (test method: EU C.20./OECD TG 211)

*III.J.4.2 Updated justifications requested to adapt the information requirement*

The requested OECD TG 211 studies and the already existing OECD TG 211 study will provide information on this information requirement to cover the R2 variations at least for one substance per SC. Furthermore, there will be information on the influence of R1 function (amino aniline, amino monosulphonated aniline, and amino disulphonated aniline) on ecotoxicity (III.I, III.J.).

Therefore, for the other substances of the SFWA category, for which the standard information of long-term toxicity to aquatic invertebrates applies but no experimental study

[52] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

[53] *Idem*.

exists, there will be information available from studies conducted according to OECD TG 211 and OECD TG 201. Results from these studies will allow the assessment of whether the toxicity profiles (= type and strength of effects) observed for substances in the category with definitive source studies (OECD TG 211) are indeed similar across the R1 function (e.g. SC2 and SC3a). In that respect, ECHA considers that the following criteria are decisive for the actual determination of similarity in toxicity:

- No adverse effects are observed up to the maximum concentration tested (e.g. maximum water solubility);
- Comparable effects (i.e. in terms of type and strength of effects) are observed at a similar concentration level; or
- The strength of effects forms a trend across the category members.

Verifying that these criteria are met is an essential condition for the valid justification of the similarity of toxicity for the substances covered by the category and, hence, for meeting the provisions in Annex XI, Section 1.5 to adapt the information requirement.

In addition, ECHA points out there are explanations provided in the Read-Across Assessment Framework[3] on the elements assessed in justifications on grouping and read-across approaches.

Updated justifications need to be developed by the registrants to confirm that the existing and new studies to be generated on toxicity on aquatic invertebrates can be used to predict the outcome of such studies for substances without experimental data.

Therefore, ECHA requests the registrants of the following substances to submit updated justifications explaining whether, why and how this information requirement can be adapted according to Annex XI, Section 1.5, taking into account the newly generated information obtained in the SFWA category, including the experimental studies requested above:

(request 62) 1-DSA#41098-56-0

(request 63) 3a-A(NaK)#70942-01-7

See table 4 in *Appendix 5* for an overview of ECHA's conclusions on ecotoxicity.

**III.K Long-term toxicity testing on fish (Annex IX, 9.1.6)**

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

The SFWA substances 1-MSA#42355-78-2, 1-DSA#41098-56-0, 2-A#16090-02-1, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-MSA#16470-24-9, 3A-DSA#68971-49-3, 3c-A#17958-73-5 [54], 4-MSA#67786-25-8 and 5-A#27344-06-5 are registered at 100-1000 or above 1000 tonnes per year. The information requirement applies for these substances.

[54] While the decision does not require the Registrant of substance 3c-A#17958-73-5 to perform any testing following the notification of his intention to cease manufacture, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category.

### *III.K.1 The registrants' hypothesis to address this information requirement in the category*

The registrants have sought to adapt this information requirement for all category members according to Annex IX, 9.1.6, column 2, by the following justifications:

- There is no risk to aquatic organisms:

  In the registration dossiers, adaptations of the registrants for this information requirement are based on unlikely direct and indirect exposure due to the risk management measures that will be applied at industrial level to avoid any release of the substances directly in the municipal waste water treatment. The registrants further state that the substances can be effectively removed from the waste waters, because of the affinity with the organic fraction. They refer to RCRs indicating no risk.

  The registrants further refer to further details in the justification document where they have calculated PECs, PNECs and RCRs for 3a-A(Na)#4193-55-9 and 3a-A#16470-24-9 and use these to be representative substances to claim no risk for category members. From the information in their justification document, ECHA understands the following are the arguments to adapt the information requirement on long-term toxicity to fish:

  **PEC** calculated for 3a-A#16470-24-9: the registrants state that these are overestimates for 2 reasons: 1) they state that "*it has to be considered that the water releases can be overestimated because the company declared a concentration under 0.01 %, which was the value used for the evaluation. Nevertheless, the effective discharges are expected to be lower (almost the half); also the STP is expected to be more effective than that estimated by the calculation tool*"; and 2) the tonnage for 3a-A#16470-24-9 is (much) higher than that of other category members so the PEC for this substance is an extreme worst-case for other category members.

  **Koc** used for PEC calculations: In their justification document the registrants describe that they have used the highest experimental Koc value to maximise the Predicted Environmental Concentrations in soil. To maximise the exposure of the water and sediment compartment they have used the lowest experimental Koc value for the risk assessment calculation. ECHA notes that the log Koc values they have used in the PEC calculations are 1.8 and 4.

  **PNEC**: for all the substances covered by the SFWA category the registrants derived a PNECaqua (freshwater) of 0.13 mg/L using an assessment factor of 50 to the lowest NOEC they consider reliable. The lowest NOEC they use is the 21 day NOECreproduction = 6.59 mg/L from the *Daphnia* study with 3a-MSA#16470-24-9 ("*Chronische Daphnientoxizität von* [redacted]"). The registrants justify that the AF of 50 is appropriate because the long-term toxicity results (i.e. algae and *Daphnia*) cover two trophic levels showing the lowest L(E)C50 in the short-term tests.

  **RCR**s: the registrants claim that "*Despite the water and sediment PECs resulted inevitably increased, the RCR resulted to be less than 1 in most cases, using the same Risk Management Measures*"

- The 14 day (prolonged acute) studies on fish for 2-A#16090-02-1 and 3a-A#16470-24-9 bring some supporting information on long-term toxicity to fish:

  The registrants provided two 14-day studies investigating mortality and behaviour with the following substances:

  - 2-A#16090-02-1 ("*Verlängerter Toxizitätstest beim Zebrabärbling; Prüfsubstanz:*

[redacted]"), indicating a 14-d NOEC of 61.8 mg/L (measured)
- 3a-A#16470-24-9 ("*Verlängerter Toxizitätstest beim Zebrabärbling; Prüfsubstanz:* [redacted]"), indicating a 14-d NOEC of >859 mg/L (measured)

In the justification document the registrants state that: "*Those two studies are not usually considered as chronic studies and they have been put into the acute toxicity section within the dossiers, but they are in any case performed on a repeated basis and they are useful to give an indication of the behaviour of the substances additional to other trophic levels like Daphnia.*"

- Fish is not considered the most sensitive species:

In the justification document the registrants argue that "*fish is not considered as the most sensitive species based on the results on both CAS 16090-02-1 and CAS 16470-24-9*". ECHA understands the registrants draw this conclusion based on the results of both 14 day fish studies and comparing these with the results from *Daphnia* and algae studies.

Based on these arguments in the justification document the registrants conclude that the exposure and risks for the environment resulted to be controlled for all compartments and for all the substances belonging to the category and that further testing on fish is not necessary. This implies that the registrants read-across the above presented arguments to all category members.

***III.K.2 Available information to justify the category approach***

In Table 37 of the justification document the registrants summarised the available information they consider relevant in relation to long-term toxicity. They indicate that no experimental data on long-term toxicity on fish performed according to (or similarly to) OECD TG 210 is available for SFWA category members.

*III.K.2.1 Other supporting information*

As explained above, the registrants have provided two 14-day fish studies which they use in their justification to show that fish are not more sensitive than *Daphnia* and algae:

- 2-A#16090-02-1 ("*Verlängerter Toxizitätstest beim Zebrabärbling; Prüfsubstanz:* [redacted]"), indicating a 14-d NOEC of 61.8 mg/L (measured)
- 3a-A#16470-24-9 ("*Verlängerter Toxizitätstest beim Zebrabärbling; Prüfsubstanz:* [redacted]"), indicating a 14-d NOEC of >859 mg/L (measured)

*III.K.2.2 Additional testing proposed by the registrants to consolidate the category approach*

Currently the registrants have not indicated further testing for this information requirement. They consider that "*It may be possible for the Registrant to first determine the exposure, PNEC and characterise the risk using the longterm invertebrate endpoint along with a larger assessment factor (e.g. AF of 50) before considering whether long-term testing of fish is necessary.*"

In case a risk is identified, the registrants propose that "*The decision to perform long term fish tests must be taken after having performed and assessed the daphnia studies, if the conditions for long term testing have been found, if some indications of more representative structures are available*".

***III.K.3 ECHA's Assessment***

In the absence of long-term toxicity data on fish the registrants have sought to adapt this information requirement for the category members as explained above under III.K.1. In the

next paragraphs describe ECHA's assessment of the reasoning and justification of the registrants for the adaptation.

- There is no risk to aquatic organisms:
  ECHA notes that based on the registrants' calculations with EUSES, exposure may still occur. They provided risk assessments for 2 representative substances in their justification document. ECHA has assessed their approach for PNEC, PEC and RCR calculations as follows:

  **PEC**: Firstly, ECHA notes that the registrants have not added information in the dossiers to justify why the value of 0.01% discharge is an overestimate, nor have they added any other values that would be more realistic than a 0.01% discharge. Similarly, the registrants have not explained and justified in the dossier how and why the STP efficiency would be higher than the values used for the PEC calculations, apart from the statement that the substances can be effectively removed from the waste waters, because of the affinity with the organic fraction.

  **Koc used for PEC calculations**: ECHA agrees that using the lowest experimental Koc value in PEC calculations would indeed maximise concentrations in water for both substances.

  **PNEC**: currently adaptation submitted by the registrants is based on a PNEC derived from an incomplete and largely unreliable data set as described below.

  As explained under section III.J, there is one reliable long-term toxicity study, on aquatic invertebrates for 3a-MSA#16470-24-9. This study indicates a NOEC of 6.59 mg/L (measured, reproduction) and is used for PNEC derivation for all the substances in the category. As described in Section III.J, this one study does not cover all the structural variations in R1 and R2 moieties in the SFWA category. Furthermore, as described below (see "Fish is not considered the most sensitive species") there are no reliable data to conclude that the existing long-term results on algae and daphnia cover the trophic levels showing the lowest L(E)C50 in the short-term tests as the applied assessment factor of 50 would require.

  **RCRs**: The registrants have indicated that they have used the actual conditions of use in their calculations. ECHA notes that, based on the provided tables in the justification document, for 3a-A#16470-24-9 which they identified as a representative substance, the RCRs for aquatic compartment exceed 1 for some exposure scenarios. Furthermore, the RCRs are based on PNEC derived with a single value from long-term toxicity study on *Daphnia* for substance with 3a-MSA#16470-24-9. As described in section III.J, the read-across approach cannot be currently accepted.

  ECHA thus considers that the argument of the registrants based on no risk seems to be incorrect. Furthermore, ECHA notes that their adaptation does not address the entire CSA according to Annex I, which is referred to in column 2 of Annex IX, section 9.1 . Annex I to the REACH Regulation Section 3 describes that Environmental hazard assessment of the CSA includes not only hazard assessment for PNEC derivation but also for classification and labelling. ECHA notes that some of the long-term toxicity tests provided for aquatic invertebrates are close to the threshold for classifying the substance for Category Chronic 3 (2-A#16090-02-1: a NOEC of 1.0 mg/L and EC50 of 1.0-3.2 mg/L (nominal, reproduction); 3a-MSA#16470-24-9: a NOEC of 6.59 mg/L (measured, reproduction)). As the read-across prediction from one substance to all SFWA category members is not accepted, it cannot be excluded that the substances with no experimental testing would produce toxicity below 1 mg/L and thus require

classification. Therefore, ECHA considers that the registrants' adaptation does not address the entire CSA as indicated in Annex IX, 9.1.6, column 2 and is thus insufficient.

- The 14 day (prolonged acute) studies on fish for 2-A#16090-02-1 and 3a-A#16470-24-9 bring some supporting information on long-term toxicity to fish:
There is no reliable information on long-term toxicity to fish. ECHA agrees to statement of the registrants that the provided studies cannot be considered as chronic studies under the REACH Regulation. ECHA notes that the exposure duration of the studies is 14 days. This study duration is shorter than the exposure period expected from a long-term toxicity study according to the OECD TG 210. Furthermore, the studies provide information only on survival and behaviour. A long-term toxicity study on fish performed according to the OECD TG 210 observations on hatching, survival, abnormal appearance, abnormal behaviour, weight and length should be reported. The submitted study fails to cover the key parameters of OECD TG 210. In conclusion, ECHA considers that the parameters addressed and the exposure duration of the test do not sufficiently follow the corresponding test method referred to in Article 13(3), and therefore the studies do not fulfil the requirement of Annex IX, Section 9.1.6 of the REACH Regulation. Based on the same reasons these studies also do not fulfil the requirement of Annex XI, Section 1.5. of the REACH Regulation and thus cannot be used as source studies within the category.

- Fish is not considered the most sensitive species:
ECHA understands that the registrants intend to use integrated testing strategy (ITS) outlined in ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4) by claiming that fish is not the most sensitive species. As explained above, the registrants come to this conclusion on the basis of, the available information on acute toxicity and the two 14-day studies on fish and then read-across this ITS-based waiving statement to the other SFWA members. The ITS in the above mentioned guidance document indicates that if based on (reliable) acute aquatic toxicity data fish or invertebrates are not shown to be substantially more sensitive than the other trophic levels, long-term studies may be required on both. In such a case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first and may allow adaptation of the fish testing. On the other hand, if fish or *Daphnia* are shown substantially more sensitive, only the more sensitive species needs to be tested.

  However, ECHA notes there are no reliable short-term data to support your argument that fish would not be the most sensitive species. As explained under section III.I (Growth inhibition to aquatic algae), ECHA notes that reliable short-term studies are available only for 2-MSA#28950-61-0 (a 72-h EC50 >100 mg/L, NOEC 22 mg/L, nominal, growth rate), 4-MSA#67786-25-8 (72-h EC50 >34.9 mg/L, NOEC 34.9 mg/L, growth rate, measured), and 5-A#27344-06-5 (72-h EC50 >111 mg/L, NOEC of 11.3 mg/L, growth rate, measured).

  For short-term toxicity to fish, although several studies have been submitted, ECHA notes that many of them were carried out without analytical monitoring or there was no information provided if the measurements of exposure concentrations were made. Out of 34 studies only six had analytical monitoring performed and reported in the robust study summaries. These six studies were performed with two substances: two studies with 3a-MSA#16470-24-9 and four with 2-A#16090-02-1.

  These six studies seem relatively reliable. Both of the two studies with 3a-MSA#16470-24-9 show effects in concentrations higher than 100mg/L (96-h LC50 and 14-d NOEC, mortality, measured). In a study with 2-A#16090-02-1 ("*Verlängerter Toxizitätstest*

*beim Zebrabärbling; Prüfsubstanz:* [redacted]") a 14-d NOEC of 61.8 mg/L (measured) was measured. In the robust study summary the registrants report that deaths occurred in the highest concentration i.e. 215 mg/L in 5 to 7 days of exposure, and no deaths occurred in lower concentrations i.e. in 100 mg/L in 4 days. Another study with 2-A#16090-02-1 ("*Report on the acute toxicity (96h) - OECD 203 - of* [redacted] *to Zebrafish*") reported a 96-h LC50 of 7.1 mg/L (measured). The registrants have disregarded this GLP study based on "*the measured concentration of the test substance were very low, indicating precipitation or other phenomena impairing the test*". ECHA notes that the test result is based on measured concentrations and thus the phenomena decreasing the test material concentration in the test has been considered in the test result. The registrants do not specify the phaenomena which would impair the test result. However, ECHA notes that there are several studies with the same substance 2-A#16090-02-1, including reliable GLP studies with analytical monitoring ("*Report on the acute toxicity (96h) - OECD 203 - of* [redacted] *to Zebrafish*", "*Report on the acute toxicity (96h) - OECD 203 - of* [redacted] *to Zebrafish*"), and they show an LC50 > 100 mg/L. Therefore, ECHA considers that the test result showing an LC50 of 7.1 mg/L may indeed be unreliable.

The rest of the studies either did not include analytical verification of test concentrations or it was not reported. Considering the adsorptive nature, isomerisation and photodegradation properties of these substances, the lack of critical analytical monitoring invalidates the studies. There were also other reliability issues in some of the studies, for example some studies do not cover an exposure duration comparable to the duration required in the OECD TG 203, i.e. 96-h. Many studies also were poorly reported and therefore their reliability could not be confirmed. Despite the issues with study reliability, the available experimental studies with SFWA member substances resulted mostly in LC50 values of > 100 mg/L.

There were two exceptions where an LC50 lower than 100mg/L in fish was reported: studies for 2-A#16090-02-1 (described above) and in two studies with 3b-A#13863-31-5 the LC50 concentrations were 86 mg/L (96-h, nominal)("*Acute toxicity of FA10, FA11, FA12 to rainbow trout (Salmo gairdneri) and channel catfish (Ictalurus punctatus)*") and 45 mg/L (48-h, nominal)("*Akute fischtoxizitaet*"). However, these studies were conducted without analytical monitoring and the registrants state in the robust study summaries that there is no evidence that the concentration of the substance being tested has been satisfactorily maintained throughout the test. While ECHA agrees that this invalidates the studies, it does not remove the concern that there would not be effects if the test would be reliably performed.

For short-term toxicity to aquatic invertebrates, the available experimental studies with SFWA member substances resulted in LC50 values of >100 mg/L. There are 6 GLP studies provided (two for 2-A#16090-02-1, one for 2-MSA#28950-61-0, one for 2-DSA#52301-70-9, two for 3a-MSA#16470-24-9). There were also 10 non-GLP studies or where GLP status was not specified (two for 1-DSA#41098-56-0, one for 2-A#16090-02-1, 3a-A(Na)#4193-55-9, 3a-A(NaK)#70942-01-7, 3a-MSA#16470-24-9, 3c-MSA#16324-27-9, two for 4-MSA#67786-25-8, and one for 5-A#27344-06-5). Out of all 16 studies, ECHA observes that only two had analytical monitoring performed (a study with 3a-MSA#16470-24-9 and one with 2-MSA#28950-61-0). These studies can be considered reliable. The rest 14 of the studies either did not include analytical verification of test concentrations or it was not reported. Considering the adsorptive nature, isomerisation and photodegradation properties of these substances, lack of analytical monitoring invalidates the studies. There were also other reliability issues in some of the studies. However, despite the reliability issues identified, the results consistently report LC50 values above 100 mg/L.

ECHA concludes that the short-term toxicity data provided for the SFWA members does not allow determining the relative species sensitivity due to data reliability issues described above. None of the substances have reliable short-term toxicity data for all trophic levels. This hampers the registrants' intention to determine relative species sensitivity based on information on short-term toxicity testing and therefore their justification "*Fish has not to be considered as the most sensitive species*" is not supported by reliable evidence. In fact, in short-term fish studies effects have been observed e.g. for 2-A#16090-02-1 and 3b-A#13863-31-5. Even though the registrants claimed these studies not reliable, ECHA considers that they may indicate concern for fish as no toxicity has been observed in (reliable or unreliable) short-term studies with aquatic invertebrates.

In their testing strategy the registrants propose to derive the PNEC with long-term toxicity data on invertebrates (and AF of 50) and risk characterisation and perform long-term fish testing if needed. ECHA considers that a PNEC cannot be derived based on the long-term *Daphnia* result with an assessment factor of 50. As explained in footnote c) of Table R.10-4 of Guidance document R.10: Characterisation of dose [concentration]-response for environment (May 2008), using such an assessment factor is allowed if "*An assessment factor of 50 applies to the lowest of two long term results (e.g. EC10 or NOECs) covering two trophic levels when such results have been generated covering that level showing the lowest L(E)C50 in the short-term tests.*"

As explained above, the short-term data provided for the SFWA category members are unreliable and no conclusions on the relative species sensitivity can be drawn from the data in the dossiers. Furthermore, short-term studies do not seem to be appropriate to conclude the entire CSA of the substances as the existing long-term studies seem to be close to a threshold of chronic toxicity classification. In this regard even a slight difference in species sensitivity or in toxicity of the SFWA category members may change the classification of the substance. Further, also existing human health studies indicate that category members exert toxicity.

In conclusion, there is no reliable information to conclude on potential need to classify the SFWA category members, nor to determine the relative species sensitivity for application of integrated testing strategy to conclude risk assessment. Furthermore, one reliable long-term toxicity study on *Daphnia magna,* which is used for PNEC derivation and risk assessment of all the category members, does not cover all the structural variations in R1 and R2 moieties in the SFWA category. The registrants claim that all the category members show no risk to aquatic organism is not justified. Therefore, the current approach to adapt fish testing is not accepted.

The registrants do not propose any testing for this information requirement in their testing strategy. ECHA considers that the category approach can be applied also to this information requirement and for that purpose experimental studies are needed. It is necessary to have sufficient information on all structural variations of the SFWA substances for this information requirement. This allows ECHA to decide the acceptability on the proposed adaptations for substances without experimental information on this information requirement and to determine whether more testing is needed, if the adaptations fail to meet the provisions in the REACH Regulation, Annex IX, 9.1.6 and Annex XI, 1.5.

Furthermore, despite the information gaps in short-term toxicity to fish and invertebrates ECHA considers that no further short-term toxicity studies on fish and *Daphnia* need to be performed in this case. Performing long-term testing on fish directly would minimise (vertebrate) testing as no further short-term testing would be needed to determine the relative species sensitivity first in order to potentially allow the registrants to adapt the

long-term testing in the future. ECHA considers that long-term aquatic testing for fish and invertebrates is of a greater value for the purpose of consolidating the category, considering the properties of the SFWA substances. Ultimately, when reliable long-term toxicity information will be available for the SFWA substances (either by experimental study or by updated adaptations), the information requirements for short-term toxicity endpoints can be considered fulfilled as per column 2 of sections 9.1.1 of Annex VII and 9.1.3 of Annex VIII.

***III.K.4 ECHA requests to consolidate the registrants' category***

ECHA concludes that the information provided on this endpoint for the registered substances 1-MSA#42355-78-2, 1-DSA#41098-56-0, 2-A#16090-02-1, 3a-A(NaK)#70942-01-7, 3a-A(Na)#4193-55-9, 3a-MSA#16470-24-9, 3a-DSA#68971-49-3, 3c-A#17958-73-5 [55], 4-MSA#67786-25-8, 5-A#27344-06-5 does not meet the information requirement.

Therefore, the registrants of the above-mentioned substances are requested to provide the definitive studies, supporting studies and further justifications mentioned below (see also II.C.4). ECHA will reassess the eventual validity of the category approach after submission of this information.

*III.K.4.1 Experimental studies requested to fulfil the information requirement and to provide source studies for future adaptations*

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, section 7.8.4.1.*

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

An OECD TG 210 study needs to be conducted with 1-MSA#42355-78-2, which has an amino diethyl function (R2) not otherwise present in constituents of the other subcategories.

An OECD TG 210 study needs to be conducted with 2-A#16090-02-1 which has a morpholino function (R2) not otherwise present in constituents of the other subcategories.

An OECD TG 210 study needs to be conducted with 3a-A(Na)#4193-55-9, which has a bis(2-hydroxyethyl)amino function (R2) not otherwise present in constituents of the other subcategories.

[55] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

An OECD TG 210 study needs to be conducted with 5-A#27344-06-5, which has a (2-carbamoylethyl)(2-hydroxyethyl)amino function (R2) not otherwise present in constituents of the other subcategories.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the registrants of the substances indicated below are requested to submit the following information derived with their respective substance:

(request 64) 1-MSA#42355-78-2

(request 65) 2-A#16090-02-1

(request 66) 3a-A(Na)#4193-55-9

(request 67) 5-A#27344-06-5

Fish early life stage (FELS) toxicity test (test method: OECD TG 210)

*III.K.4.2 Updated justifications requested to adapt the information requirement*

The requested OECD TG 210 tests will provide information on this information requirement to cover the structural variations of the substances in SFWA category. In particular, the impact of the R2 variations will be investigated for at least one substance in each SC by an OECD TG 210 study, except for SC4. Furthermore, there will be information on the influence of R1 function (amino aniline, amino monosulphonated aniline, and amino disulphonated aniline) on ecotoxicity (see III.I and III.J).

The supporting data obtained in OECD TG 211 studies are already requested under III.J. They will provide supporting information for the proposed adaptations for this information requirement (amongst others for SC4).

Therefore, for the other substances of the SFWA category, for which the standard information of long-term toxicity to fish applies but no experimental study exists, there will be information available from studies conducted according to OECD 211 across the category. Results from these studies will allow the assessment of whether the toxicity profiles (= type and strength of effects) observed for substances in the category with definitive source studies (OECD TG 210) are indeed similar to the target substances and if the structural variation in R1 moieties influence the prediction. In that respect, ECHA considers that the following criteria are decisive for the actual determination of similarity in long-term aquatic toxicity:

- No adverse effects are observed up to the maximum concentration tested (e.g. maximum water solubility); or
- Comparable effects (i.e. in terms of type and strength of effects) are observed at a similar concentration level; or
- The strength of effects forms a trend across the category members.

Verifying that these criteria are met is an essential condition for the valid justification of the similarity of toxicity for the substances covered by the category and, hence, for meeting the provisions in Annex XI, Section 1.5 to adapt the information requirement.

In addition, ECHA points out there are explanations provided in the Read-Across Assessment Framework[3] on the elements assessed in justifications on grouping and read-across approaches.

Updated justifications need to be developed by the registrants to confirm that the existing and new studies to be generated on toxicity to fish can be used to predict the outcome of such studies for substances without experimental data.

Therefore, ECHA requests the registrants of the following substances to submit updated justifications explaining whether, why and how this information requirement can be adapted according to Annex XI, Section 1.5, taking into account the newly generated information obtained in the SFWA category, including the experimental studies requested above:

(request 68) 1-DSA#41098-56-0

(request 69) 3a-A(NaK)#70942-01-7

(request 70) 3a-MSA#16470-24-9

(request 71) 3a-DSA#68971-49-3

(request 72) 3c-A#17958-73-5 [56]

(request 73) 4-MSA#67786-25-8

See table 4 in *Appendix 5* for an overview of ECHA's conclusions on ecotoxicity.

[56] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

**Appendix 2: Procedural history**

ECHA notes that the tonnage band for one member/several members are higher than the tonnage band for the lead registrant for some of joint submissions for the substances covered in the category.

For the purpose of the decision-making, this decision does not take into account any updates of the registrations after the date when the draft decision was notified to the registrants under Article 50(1) of the REACH Regulation.

**For substances 1-MSA#42355-78-2, 2-A#16090-02-1, 2-MSA#28950-61-0, 3a-A(NaK)#70942-01-7, 3a-A(Na)#4193-55-9, 3a-DSA#68971-49-3, 3b-A#13863-31-5, 3c-A#17958-73-5, 3c-MSA#16324-27-9, 5-A#27344-06-5**

The compliance checks were initiated in September 2013.

ECHA notified the registrants on 17 December 2013 of a first draft decision and invited them to submit comments within 30 days. They have provided comments to the draft decision during that period and have also updated the dossiers.

ECHA considered that the updated dossiers contained new scientific information that, for these specific cases, required ECHA to re-evaluate the provided information.

On 4 May 2015 ECHA informed the registrants on a temporary suspension of the further compliance check decision making process for the category members.

On 17 March 2017 ECHA has restarted the compliance check process in the context of a pilot project to encourage the use of category approaches.

In this context, ECHA has decided to provide the registrants with a new draft decision for their comments after the re-evaluation of the case in accordance with Article 50(1) of the REACH Regulation before referring the case to the Member State Competent Authorities.

On 06 November 2018, the Registrant of substance 3c-A#17958-73-5 indicated to ECHA that he has ceased the manufacture of it. In accordance with Article 50(3) of the REACH Regulation, he is not an addressee of this decision and he is not required to provide the information contained in the decision. However, the substance still falls within the scope of the category. This substance is therefore still covered by ECHA's assessment of the category. In addition the addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

**For substances 1-DSA#41098-56-0, 3a-MSA#16470-24-9, 4-MSA#67786-25-8**

There was a change of the Lead registrant after the initial draft decision had been sent on the 17 December 2013.

The compliance check on this new lead registration was initiated on 17 March 2017.

**For substance 2-DSA#52301-70-9**

This substance was registered on 19 April 2017. The compliance check was initiated on 22 September 2017.

**For substance 3a-A(NaK)#70942-01-7**

There was a change of the Lead Registrant from [redacted] to [redacted] on 28 March 2018 after the draft decision was notified to the Registrants. At the same time the tonnage band was upgraded from 100 to 1000 tonnes per year to 1000 tonnes or more per year. ECHA informed the Registrants that the compliance check procedure continued on the registration of the newly appointed Lead Registrant and that any further communication in relation to this compliance check will be addressed to him.

For the substances mentioned above, the registrants have also submitted via webform updated category justification and testing strategy documents on *10 August 2017* in response to a discussion between ECHA and the Registrants on the potential for improving the category justification. ECHA has taken those documents into consideration.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

All addressees of the decision submitted identical comments.

ECHA took into account your comments and did not amend the request(s).

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

ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-61 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

**Appendix 3: Further information, observations and technical guidance**

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

2. Failure to comply with the requests in this decision will result in a notification to the enforcement authorities of the Member States in which the registrants are established.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different compositions, the sample used for the new tests must be suitable to assess these compositions. Finally there must be adequate information on substance identity for the sample tested and the compositions registered to enable the relevance of the tests to be assessed.

4. As the required tests are to be used in the context of the read-across approach, the identity of the test material used to perform the test should be specified in line with ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the source substance(s) identified in the read-across approach and used to predict the properties of the target substance(s).

5. Specific precautions must be taken to ensure that the test material(s) used in the studies requested above is/are sufficiently characterised by analytical controls. The manufactured substances may photoconvert in solution from the trans-conformation to the cis-conformation, and photodegradation in aquatic solutions may follow the isomerisation of the substances. The analytical control of the dosing solutions therefore must be able to determine the test substance in cis- and trans-conformations. Furthermore, the test substances may associate to the test equipment and may also attach to constituents of the standard diet used in animal testing. The extent of such association for each test substance is currently unknown.

   It is therefore necessary to minimize the contact of the test material with diet constituents. In the future studies conducted by oral gavage as administration route, this must be achieved by removing the access to the diet 2 hours prior to the gavage administration for rats and 3 hours prior to the gavage administration for rabbits. Access to the diet must be given again earliest 2 hours after the gavage administration for rats and earliest 3 hours after the administration for rabbits. The determination of an appropriate fasting time before and after gavage administration takes into account the provisions of Directive 2010/63/EU. The time period for

fasting was determined based on the gastric emptying times of rats and rabbits. These are not fixed values but rather ranges varying depending on the diet, stress level, age and other factors. For rats, the passage of the majority of food through the stomach is estimated to be 2 hours[1]. For rabbits, the passage of food through the stomach is estimated to be 3 – 6 hours.[2]

Furthermore, in aquatic media containing Ca2+, the substances may form strong ion-pairs with calcium ions and crystalline deposits may be formed. The possible formation of such particles may decrease the substance concentrations in the test media and cause physical effects by accumulation to the gut or by attachment to the antennae of invertebrates obstructing normal feeding and respiration of the organisms in water. Therefore, when performing ecotoxicological studies, the test conditions should be well controlled to avoid issues with for instance precipitation or foaming, and/or potential formation of Ca-complexes. To ensure the reliability of the study results, analytical monitoring of the test media measuring the concentrations of the tested substance, its cis- and trans-isomers and their degradation products, is essential considering the adsorptive properties, potential precipitation, photoisomerisation and photodegradation for this group of substances. Furthermore, the formation of complexes with calcium need to be controlled to the extent possible and need to be well documented.

[1] R.A. Purdon and P. Bass (1973), Gastroenterology 64: 968-976
[2] R. R. Davies et al. (2003), Vet Clin Exot Anim 6: 139–153

**Appendix 4: Addressees of the decision and substances covered by the SFWA category**

| Addressees of the decision | Sub-category | Public Name | EC Number | CAS Number | Lead Reference number | Tonnage band (t/a) |
|---|---|---|---|---|---|---|
| [redacted] | 1 | tetrasodium 2,2'-ethene-1,2-diylbis[5-({4-[diethylamino]-6-[(4-sulfonatophenyl)amino]-1,3,5-triazin-2-yl}amino)benzenesulfonate] | 619-874-5 | 42355-78-2 | [redacted] | 100-1000 |
| [redacted] | 1 | hexasodium 2,2'-[vinylenebis[(3-sulphonato-4,1-phenylene)imino[6-(diethylamino)-1,3,5-triazine-4,2-diyl]imino]]bis(benzene-1,4-disulphonate) | 255-217-5 | 41098-56-0 | [redacted] | 100-1000 |
| [redacted] | 2 | disodium 4,4'-bis[(4-anilino-6-morpholino-1,3,5-triazin-2-yl)amino]stilbene-2,2'-disulphonate | 240-245-2 | 16090-02-1 | [redacted] | >1000 |
| [redacted] | 2 | tetrasodium 4,4'-bis[[4-morpholino-6-(p-sulphonatoanilino)-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate | 249-323-0 | 28950-61-0 | [redacted] | 1-10 |
| [redacted] | 2 | hexasodium 2,2'-[vinylenebis[(3-sulphonato-4,1-phenylene)imino[6-morpholino-1,3,5-triazine-4,2-diyl]imino]]bis(benzene-1,4-disulphonate) | 257-827-7 | 52301-70-9 | [redacted] | 10-100 |
| [redacted] | 3a | disodium 4,4'-bis[6-anilino-[4-[bis(2-hydroxyethyl)amino]-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate | 224-073-5 | 4193-55-9 | [redacted] | >1000 |
| [redacted] | 3a | potassium sodium 4,4'-bis[6-anilino-4-[bis(2-hydroxyethyl)amino]-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate | 275-031-8 | 70942-01-7 | [redacted] | >1000 |
| [redacted] | 3a | Tetrasodium 4,4'-bis[[4-[bis(2-hydroxyethyl)amino]-6-(4-sulphonatoanilino)-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate] | 240-521-2 | 16470-24-9 | [redacted] | >1000 |

| Addressees of the decision | Sub-category | Public Name | EC Number | CAS Number | Lead Reference number | Tonnage band (t/a) |
|---|---|---|---|---|---|---|
| [redacted] | 3a | hexasodium 2,2'-[vinylenebis[(3-sulphonato-4,1-phenylene)imino[6-[bis(2-hydroxyethyl)amino]-1,3,5-triazine-4,2-diyl]imino]]bis(benzene-1,4-disulphonate) | 273-468-9 | 68971-49-3 | [redacted] | >1000 |
| Not applicable | 3a | 4,4'-bis[4-[bis(2-hydroxyethyl)amino]-6-anilino-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonic acid | 224-548-7 | 4404-43-7 | [redacted] | intermediate |
| [redacted] | 3b | disodium 4,4'-bis[[6-anilino-4-[(2-hydroxyethyl)methylamino]-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate | 237-600-9 | 13863-31-5 | [redacted] | 10-100 |
| [redacted] | 3c | disodium 4,4'-bis[[4-anilino-6-[(2-hydroxyethyl)amino]-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate | 241-883-4 | 17958-73-5 | [redacted] | ~~100-1000~~ |
| [redacted] | 3c | tetrasodium 4,4'-bis[[4-[(2-hydroxyethyl)amino]-6-(m-sulphonatoanilino)-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate | 240-400-4 | 16324-27-9 | [redacted] | 10-100 |
| [redacted] | 4 | tetrasodium 4,4'-bis[[4-[bis(2-hydroxypropyl)amino]-6-[(4-sulphonatophenyl)amino]-1,3,5-triazin-2-yl]amino]-stilbene-2,2'-disulphonate | 267-097-1 | 67786-25-8 | [redacted] | >1000 |
| [redacted] | 5 | disodium 4,4'-bis[[4-anilino-6-[(2-carbamoylethyl)(2-hydroxyethyl)amino]-1,3,5,-triazin-2-yl]amino]stilbene-2,2'-disulphonate | 248-420-5 | 27344-06-5 | [redacted] | 100-1000 |

For substance with CAS number 4404-43-7, registered as on-site intermediate, the decision was not sent in accordance with Article 49 of the REACH Regulation.

The tonnage band in the last column is the highest tonnage band among active members of the joint submission for that substance.

[57] The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. However, the substance still falls within the scope of the SFWA category and is therefore still covered by ECHA's assessment of the category.

**Appendix 5: Figures and Tables**

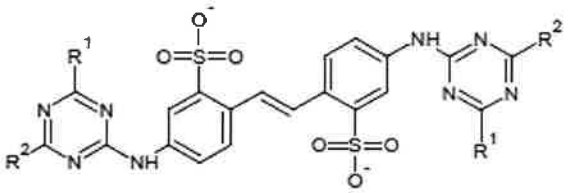


Figure 1 (page 6, justification document): Common core structure for the members of the SFWA category

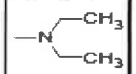
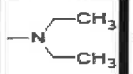
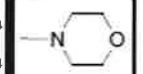
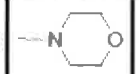
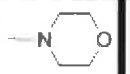
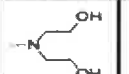
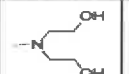
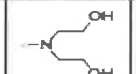
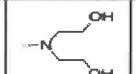
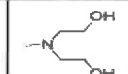
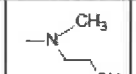
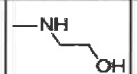
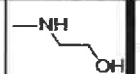
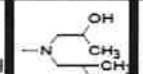
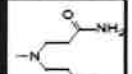
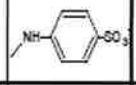
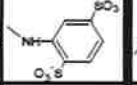
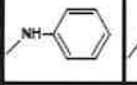
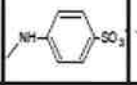
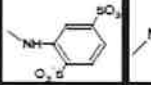
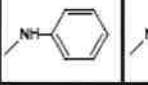
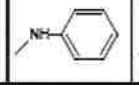
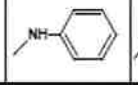
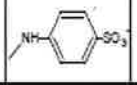
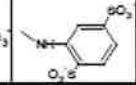
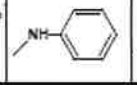
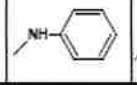
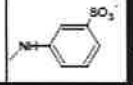
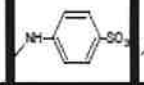
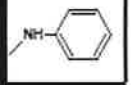
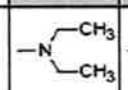
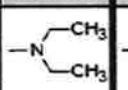
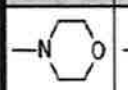
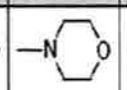
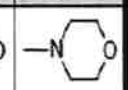
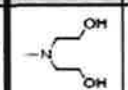
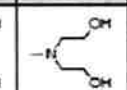
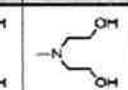
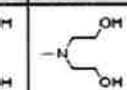
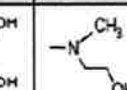
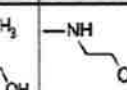
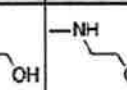
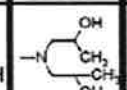
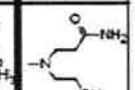
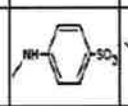
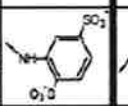
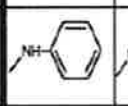
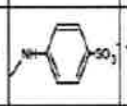
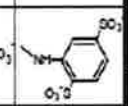
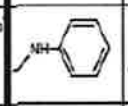
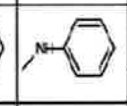
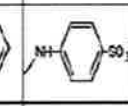
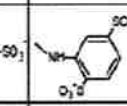
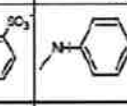
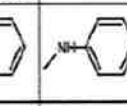
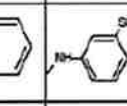
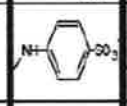
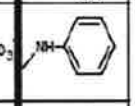
| | Group 1 | | Group 2 | | | Group 3 | | | | | | | | Group 4 | Group 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 3a | | | | | 3b | 3c | | | |
| EC | 619-874-5 | 255-217-5 | 240-245-2 | 249-323-0 | 257-827-7 | 224-548-7 | 224-073-5 | 275-031-8 | 240-521-2 | 273-468-9 | 237-600-9 | 241-883-4 | 240-400-4 | 267-097-1 | 248-420-5 |
| CAS | 42355-78-2 | 41098-56-0 | 16090-02-1 | 28950-61-0 | 52301-70-9 | 4404-43-7 | 4193-55-9 | 70942-01-7 | 16470-24-9 | 68971-49-3 | 13863-31-5 | 17958-73-5 | 16324-27-9 | 67786-25-8 | 27344-06-5 |
| R2 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| R1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cation | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | 4 $Na^+$ | 6 $Na^+$ | $H^+$ | 2 $Na^+$ | $Na^+/K^+$ | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | 2 $Na^+$ | 4 $Na^+$ | 4 $Na^+$ | 2 $Na^+$ |

Figure 2 (page 9, justification document): SFWA member substances with R1- and R2- substituents shown; subcategories formed according to R2 and ordered according to R1 (number of sulphonic acid moieties)

Substance with CAS number 4404-43-7 is registered as an on-site isolated intermediate and is considered in this decision as a potential source substance as data are available. However, as far as the present decision has not been addressed to its registrant in accordance with Article 49 of the REACH Regulation, this substance is not included in the tables developed by ECHA.

ECHA
EUROPEAN CHEMICALS AGENCY

Table 1: ECHA's data matrix on requirements on Annex VII 8.4.1, Annex VIII 8.4.2, 8.4.3 with study requests and future read-across

| | SC1 | | SC2 | | | SC3 | | | | | | | SC4 | SC5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 3a | | | | 3b | 3c | | | |
| Abbreviation | 1-MSA# | 1-DSA# | 2-A# | 2-MSA# | 2-DSA# | 3a-A(Na)# | 3a-A(NaK)# | 3a-MSA# | 3a-DSA# | 3b-A# | 3c-A# | 3c-MSA# | 4-MSA# | 5-A# |
| CAS | 42355-78-2 | 41098-56-0 | 16090-02-1 | 28950-61-0 | 52301-70-9 | 4193-55-9 | 70942-01-7 | 16470-24-9 | 68971-49-3 | 13863-31-5 | 17958-73-5 | 16324-27-9 | 67786-25-8 | 27344-06-5 |
| R2 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| R1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cation | 4 Na⁺ | 6 Na⁺ | 2 Na⁺ | 4 Na⁺ | 6 Na⁺ | 2 Na⁺ | Na⁺/K⁺ | 4 Na⁺ | 6 Na⁺ | 2 Na⁺ | 2 Na⁺ | 4 Na⁺ | 4 Na⁺ | 2 Na⁺ |
| Appl. Annex | IX | IX | X | VII | VIII | X | IX | X | X | VIII | IX | VIII | X | IX |
| OECD 471 | 471 GLP 2014<br>Neg | 471 -5th GLP 1989<br>Neg | 471 GLP 1991, 2015<br>Neg | 471 GLP 2008<br>Neg | RA from 16090-02-1 and 41098-56-0 | 471 GLP 1998<br>Neg | RA from 4193-550-9 | 471 1987, 1982<br>Neg | RA from 4193-550-9 | 471 GLP 5th only 2015 +WoE | 471 GLP 2014<br>Neg | RA from 17958-73-5 | Study request | 471 1980<br>Neg |
| OECD 473 or OECD 487 | 487 GLP 2014<br>Neg | RA from 42355-78-2 | 473 GLP 1991<br>Neg | n/a | RA from 16090-02-1 | RA from 16470-24-9 | RA from 16470-24-9 | 473 GLP 1991<br>Neg | Study request | RA from 42355-78-2, 16470-24-9 | Study request* | Future Adaptat. | Study request | Study request |
| OECD 476 or OECD 490 | 476 GLP 2015<br>Neg | RA from 42355-78-2 | 476 GLP 2014<br>Neg | n/a | RA from 16090-02-1 | RA from 68971-49-3 | RA from 68971-49-3 | RA from 68971-49-3 | 476 GLP 2014<br>Neg | RA from 42355-78-2, 68971-49-3 | Study request* | Future Adaptat. | 476 GLP 2014<br>Neg | 476 GLP 2015<br>Neg |

Adequate and reliable study
Accepted read-across or study with quality issues but used in WoE
Study request
Read-across from substance still to be tested
n/a = Information requirement not applicable

* The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

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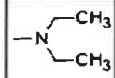
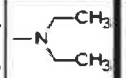
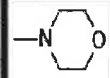
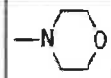
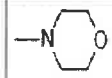
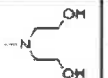
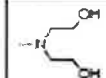
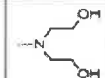
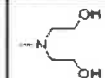
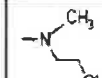
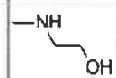
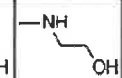
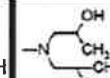
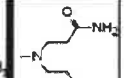
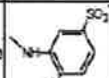
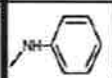
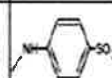
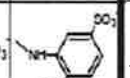
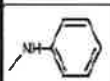
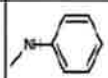
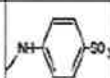
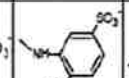
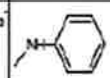
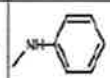
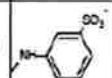
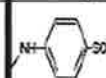
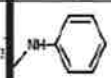
Table 2: Requirements on Annex VIII 8.6.1, 8.7.1, and Annex IX 8.6.2 with study requests and future read-across

| | SC1 | | SC2 | | | SC3 | | | | | | | SC4 | SC5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 3a | | | | 3b | 3c | | | |
| Abbreviation | 1-MSA# | 1-DSA# | 2-A# | 2-MSA# | 2-DSA# | 3a-A(Na)# | 3a-A(NaK)# | 3a-MSA# | 3a-DSA# | 3b-A# | 3c-A# | 3c-MSA# | 4-MSA# | 5-A# |
| CAS | 42355-78-2 | 41098-56-0 | 16090-02-1 | 28950-61-0 | 52301-70-9 | 4193-55-9 | 70942-01-7 | 16470-24-9 | 68971-49-3 | 13863-31-5 | 17958-73-5 | 16324-27-9 | 67786-25-8 | 27344-06-5 |
| R2 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| R1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cation | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | $Na^+/K^+$ | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | 2 $Na^+$ | 4 $Na^+$ | 4 $Na^+$ | 2 $Na^+$ |
| Appl. Annex | IX | IX | X | VII | VIII | X | IX | X | X | VIII | IX | VIII | X | IX |
| OECD 407 | not required | Not required | 407 OG, GLP 1991 NOAEL 825-HD No effects | n/a | Covered by OECD 422 | Not required | Not required | 407 OG, GLP 1987 NOAEL 200 or 50 Liv kid testes bl | Not required | Covered by OECD 422 | Not required | Future Adaptat. | Not required | Not required |
| OECD 408 | Study request | Similar to 408 feeding, 1969, liv kid testes bl | 2-y study feeding, 1978 | n/a | n/a | Fut.Adap. 2-y with 3a-A(free acid#4404-43-7 or RA | Fut.Adap. 2-y with 3a-A(free acid)#4404-43-7 or RA | Study request | Future Adaptat. | n/a | Future Adaptat.* | n/a | Similar to 408, OG, 1972, NOAEL 300-HD | Study request |
| OECD 422 | PNDT requested | EOGRTS requested | PNDT and EOGRTS requested | n/a | Study request | Study request | Future Adaptat. | PNDT and 2-gen available | Study request | Study request | Study request* | Future Adaptat. | Study request | PNDT requested |

■ Adequate and reliable study ☐ Study with quality issues ■ Study request ■ Potential adaptation based on future results ☐ n/a = Information requirement not applicable

* The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

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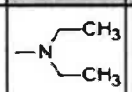
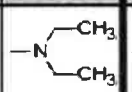
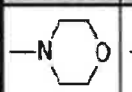
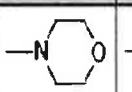
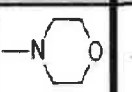
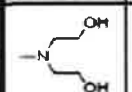
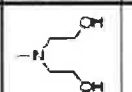
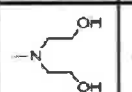
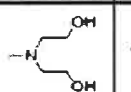
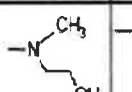
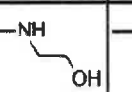
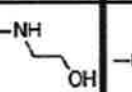
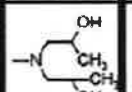
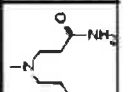
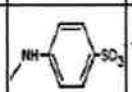
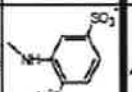
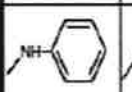
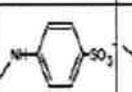
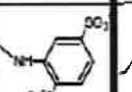
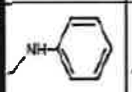
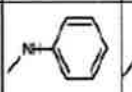
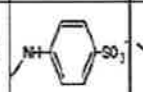
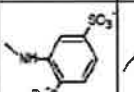
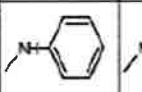
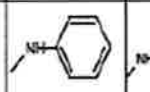
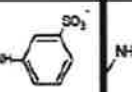
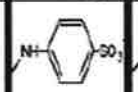
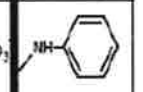
Table 3: Requirements of Annex VIII 8.7.1, Annex IX and X 8.7.2, and Annex X 8.7.3 with study requests and future read-across

| | SC1 | | SC2 | | | SC3 | | | | | | | SC4 | SC5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 3a | | | | 3b | 3c | | | |
| Abbreviation | 1-MSA# | 1-DSA# | 2-A# | 2-MSA# | 2-DSA# | 3a-A(Na)# | 3a-A(NaK)# | 3a-MSA# | 3a-DSA# | 3b-A# | 3c-A# | 3c-MSA# | 4-MSA# | 5-A# |
| CAS | 42355-78-2 | 41098-56-0 | 16090-02-1 | 28950-61-0 | 52301-70-9 | 4193-55-9 | 70942-01-7 | 16470-24-9 | 68971-49-3 | 13863-31-5 | 17958-73-5 | 16324-27-9 | 67786-25-8 | 27344-06-5 |
| R2 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| R1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cation | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | $Na^+/K^+$ | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | 2 $Na^+$ | 4 $Na^+$ | 4 $Na^+$ | 2 $Na^+$ |
| Appl. Annex | IX | IX | X | VII | VIII | X | IX | X | X | VIII | IX | VIII | X | IX |
| OECD 414 first species | Study request | Future Adaptat. | Study request | n/a | n/a | Future Adaptat. | Future Adaptat. | 414, GLP 1999, no effects | Future Adaptat. | n/a | Future Adaptat.* | n/a | Future Adaptat. | Study request |
| OECD 414 second species | n/a | n/a | Study request | n/a | n/a | Future Adaptat. | n/a | 414, GLP. 1999, mortality NOAELfoetus 400 | Future Adaptat. . | n/a | n/a | n/a | Study request | n/a |
| OECD 443 | RA to 41098-56-0 | Study request | Study request | n/a | n/a | Future Adaptat. | n/a | 416, GLP, Kidney, reproNOAEL 1000 | Future Adaptat. | n/a | n/a | n/a | Future Adaptat. | n/a |
| OECD 422 see table 3 | Not required | Not required | Not required | n/a | Study request | Study request | Future Adaptat. | Not required | Study request | Study request | Study request* | Future Adaptat. | Study request | Not required |

Adequate and reliable study | Study request | Potential adaptation based on future results | n/a = Information requirement not applicable

* The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.

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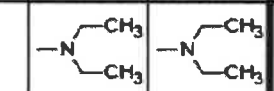
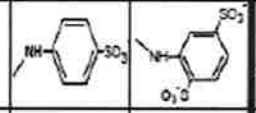
Table 4: ECHA's data matrix for requirements in Annex VII to X Section 9.1 with study requests and future read-across

| | SC1 | | SC2 | | | SC3 | | | | | | | SC4 | SC5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 3a | | | | 3b | 3c | | | |
| Abbreviation | 1-MSA# | 1-DSA# | 2-A# | 2-MSA# | 2-DSA# | 3a-A(Na)# | 3a-A(NaK)# | 3a-MSA# | 3a-DSA# | 3b-A# | 3c-A# | 3c-MSA# | 4-MSA# | 5-A# |
| CAS | 42355-78-2 | 41098-56-0 | 16090-02-1 | 28950-61-0 | 52301-70-8 | 4193-55-9 | 70942-01-7 | 16470-24-9 | 68971-49-3 | 13863-31-5 | 17958-73-5 | 16324-27-9 | 67786-25-8 | 27344-06-5 |
| R2 |  | | | | | | | | | | | | | |
| R1 |  | | | | | | | | | | | | | |
| Cation | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | $Na^+/K^+$ | 4 $Na^+$ | 6 $Na^+$ | 2 $Na^+$ | 2 $Na^+$ | 4 $Na^+$ | 4 $Na^+$ | 2 $Na^+$ |
| Appl. Annex | IX | IX | X | VII | VIII | X | IX | X | X | VIII | IX | VIII | X | IX |
| OECD 201 | Study request | Future Adaptat. | Study request | OECD 201, GLP (EC50 >100mg /L, NOEC 22 mg/L) | Study request | Study request | Future Adaptat. | Future Adaptat. | Study request | Study request | Study request* | Future Adaptat. | OECD 201, GLP (EC50 >34.9 mg/L, NOEC 34.9 mg/L) | OECD 201, GLP (EC50 >111 mg/L, NOEC 11.3 mg/L) |
| OECD 211 | Study request | Future Adaptat. | Study request | n/a | n/a | Study request | Future Adaptat. | OECD 211, GLP (NOEC of 6.59 mg/L, meas.) | Study request | n/a | Study request* | n/a | Study request | Study request |
| OECD 210 | Study request | Future Adaptat. | Study request | n/a | n/a | Study request | Future Adaptat. | Future Adaptat. | Future Adaptat. | n/a | Future Adaptat.* | n/a | Future Adaptat. | Study request |

Adequate and reliable study | Study request | Potential adaptation based on future results | n/a = Information requirement not applicable

* The Registrant of this substance has indicated to ECHA that he has ceased the manufacture of it. He is thus not an addressee of this decision and he is not required to provide the information contained in the decision. The addressees of the decision may nevertheless still consider the opportunity of performing the requested studies on this substance, if they consider it necessary to consolidate the justification of their category.