EUROPEAN CHEMICALS AGENCY

Helsinki, 23 November 2017

Addressee
[redacted]

Decision number: CCH-D-2114378296-37-01/F
Substance name: Tetramethylene dimethacrylate
EC number: 218-218-1
CAS number: 2082-81-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 24.04.2014
Registered tonnage band: 100-1000T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **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) with the registered substance using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102;**

2. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

4. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some 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;**

5. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203) with the registered substance;**

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

7. **Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment: generate an exposure assessment for all relevant exposure scenarios and revise the risk characterisation accordingly.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **31 May 2021** except for the information requested under point 2 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **30 November 2018**. You may only commence the extended one-generation reproductive toxicity study as requested under point 4 after **4 March 2019**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

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[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

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

Appendix 1: Reasons

You have applied a grouping and read-across approach according to Annex XI, Section 1.5. of the REACH Regulation for certain toxicological and ecotoxicological standard information requirements which are addressed in the current decision. ECHA has assessed first the scientific and regulatory validity of your grouping and read-across approach in general (Section 0 below) before the corresponding individual endpoints (sections 1-5).

0. Grouping and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

0.1. Information provided by the Registrant on the proposed grouping and read-across approach

In your registration dossier, you have reported a grouping and read-across approach as supporting evidence for the standard information requirement for sub-chronic (90-day) toxicity and *in vitro* gene mutation study in bacteria, and have adapted the standard information requirements for

- Pre-natal developmental toxicity (Annex IX, Section 8.7.2), and
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3)

Your dossier contains a category information section and you have provided a category justification document ("[redacted]").

According to the information reported in the category information section of your technical dossier, the substance subject to this decision is a member of the "*the category of* [redacted] *which provide a consistent set of structure-property- and structure-activity relationship throughout all endpoints. Furthermore, they share common metabolic pathways. Where data gaps exist for one category member, they can be satisfied by read-across to data from other members of the category.*" You have identified the members of the category (8) and substances identified as supporting chemicals (3) – see table 1 below- in the Category justification document. You have grouped the members of the category in two subfamilies, the oxyethylene subfamily and the alkyldiol/triol subfamily and you have outlined two distinct trends between these two subfamilies, associating the variations of the partition coefficient to the molecular weight and volume of the members of the each subfamily. You concluded on this basis that "*This is a category with clear trends in the physicochemical properties of its members, related to molecular weight, molecular size and hydrophilicity*". You have also listed the category members in the category information section, listing only four (1,4-BDDMA, EGDMA, 1,3-BDDMA and TREGDMA) substances.

Table 1- Category membership

Name	EC No	CAS No	Role
Triethylenegycol dimethacrylate (TREGDMA)	203-652-6	109-16-0	Category member - oxyethylene subfamily
Ethylene glycol dimethacrylate (EGDMA)	202-617-2	97-90-5	Category member - oxyethylene subfamily
Diethyleneglycol dimethacrylate (DEGDMA)	219-099-9	2358-84-1	Category member - oxyethylene subfamily
1,4-Butanediol dimethacrylate (1,4-BDDMA	218-218-1	2082-81-7	Category member – alkyldiol/triol subfamily
1,3-Butanediol dimethacrylate (1,3-BDDMA)	214-711-0	1189-08-8	Category member – alkyldiol/triol subfamily
Glycerol 1,3-dimethacrylate (GDMA)	217-388-4	1830-78-0	Category member – alkyldiol/triol subfamily
1,6-Hexanediol dimethacrylate (1,6 HDDMA)	229-551-7	6606-59-3	Category member – alkyldiol/triol subfamily
Trimethylpropane trimethacrylate (TMPTMA)	221-950-4	3290-92-4	Category member – alkyldiol/triol subfamily
Methacrylic acid (MAA)	201-204-4	79-41-4	Supporting substance
Methyl methacrylate (MMA)	201-297-1	80-62-6	Supporting substance
Hydroxyethyl methacrylate (HEMA)	212-782-2	868-77-9	Supporting substance

You have provided a category justification document ([redacted]) which contains a basis for read-across. You have also presented results of physico-chemical, environmental fate, human health and environmental studies conducted with some of these substances to support this basis.

In the category justification document, you use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: on the basis of structural similarity/ similarity in physico-chemical/ ecotoxicological/ toxicological properties, and that they share common metabolic pathways, it is possible to predict the human health/ ecotoxicological properties of the registered substance. You propose that the source and registered substances have similar properties for the above-mentioned information requirements.

ECHA considers that this information is your read-across hypothesis.

0.2. ECHA's analysis of the grouping approach

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation.

According to provisions of Annex XI, section 1.5., application of the group concept requires that physico-chemical properties, environmental fate and (eco)toxicologal properties may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group(read-across approach). Based on the information provided in the category justification section included in your dossier, ECHA understands that your read-across hypothesis is based on structural similarities among the members of the category, the identification of common metabolic pathways for these substances and the observation of two distinct trends between the physicochemical properties of the members of the two subfamilies and their molecular weight or size.

ECHA has assessed your grouping approach against the requirements of Annex XI, section 1.5. and observes the following deficiencies.

ECHA notes that the grouping of substances does not define unambiguously the applicability domain of this category. You have provided one listing of category members (consisting of four substances) in the category information section, another listing of category members of eight substances in the justification document, and you have also indicated that there are two sub-families within the category (oxyethylene and alkyldiol/triol), without indicating the relevance for the category applicability domain. Information on applicability domain is necessary to outline possible differences among the category members and constitutes a set of inclusion and exclusion rules establishing the molecular structure(s) that a substance must have to be part of the category and describing the accepted structural differences within the category. You have not defined these inclusion and exclusion criteria, such as branching, whether mono and diesters can be part of the category and what is the minimum/maximum number of ethylene glycol moieties allowed in the alcohol carbon chain in the oxyethylene subfamily or the accepted range of alkyl chain length in the alkyldiol/triol subfamily. According to ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6, such criteria should be described in order to identify the range of values within which reliable estimations can be made for the members of the category and to define the borders of the category. ECHA considers that the general statement included in the category information section of your technical dossier does not characterise boundaries of the category in general and of the two subfamilies that you identified within the category.

Given that the category definition is not clear, ECHA is unable to verify that the substances in the category can be used so that human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

Nevertheless, the determination that the grouping is insufficiently defined, and thereby fails to provide a basis for prediction in accordance with Annex XI, 1.5. does not affect the possibility for you to invoke a read-across approach in order to predict human health or environmental effects of these substances individually on the basis of a one-to-one analogue approach.

0.3. ECHA's analysis of the read-across approach for human health endpoints

ECHA has summarised your read-across hypothesis from the category justification document in section 0.1. The individual arguments supporting this read-across hypothesis are analysed below.

Consistent structure-property and -activity relationships throughout all endpoints

Your proposed adaptation argument is that the similarity in structures, similarity/trends in physico-chemical properties and toxicological properties between the source and target substance is a sufficient basis for predicting the properties of the substance. This argument is limited and is in principle not capable of being sufficient. Similarity in structures, similarity/trends in physico-chemical properties and toxicological properties is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that similarity in structures, similarity/trends in physico-chemical and toxicological properties per se is sufficient to enable the prediction of human health properties of a substance. This is because similarity in structures, similarity/trends in physico-chemical and toxicological properties does not always lead to predictable or similar human health properties, and consequently cannot on its own constitute sufficient evidence of predictable or similar human health properties. Further elements are needed[2], as pointed out below, such as a well-founded hypothesis of (bio)transformation to a common compound(s), or that different compounds have the same type of effect(s), to allow a prediction of human health properties that does not underestimate risks.

The description of the members of the category included in the category justification document suggests elements of structural similarity among these substances. However, in Category information section (0.2 Related information) you have not provided a detailed demonstration of this structure-property and structure-activity relationship regarding human health and environmental properties of the substances. In the read-across justification document attached you have provided a structure-property explanation regarding physico-chemical properties of the category members.

ECHA understands that you have identified subfamilies in the category based on different physico-chemical properties/trends in the category:

- oxyethylene subfamily (EGDMA, DEGDMA, TREGDMA and GDMA) with similar logP values and a trend to increasing water solubility with increasing length of the oxyethylene chain length, and

- alkyldiol/triol subfamily (1,3-BDDMA, 1,4-BDDMA, HDDMA and TMPTMA) with increasing logP values and decreasing water solubility with increasing molecular weight/volume.

ECHA acknowledges that you have linked structural differences with water solubility and log Kow. However, you have not explained how the structural differences and trends in physicochemical properties are linked with the predicted environmental and human health hazard properties, neither within a subfamily nor between the subfamilies which are currently part of the same claimed category.

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals and ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

More specifically, you have not explained how the structural differences such as different chain lengths of the parent compounds between the category members (within and between the subfamilies) relate to their toxicokinetic, especially metabolism, and toxicological properties. Furthermore, the subfamily of alkyldiol/triol includes also other structural differences than alkyl chain length, e.g. branching, and it has not been explained how such differences may influence the predicted properties. Consequently, there is not a robust basis for predicting the properties of the registered substance.

Shared common metabolic pathways
ECHA understands that regarding human health your read-across hypothesis is based also on the identification of common metabolic pathways for these substances. You have provided evidence in your category justification document demonstrating a rapid hydrolysis of the esters. ECHA considers that this is adequate to establish that the systemic exposure to the category members in their native form, i.e. as diesters, and the impact of such exposure on the properties of the substances may be low. However ECHA stresses that similarities in metabolic pathways may constitute a reason for grouping of substances together but this does not constitute a sufficient basis for predicting that the properties of these substances will be similar or follow a regular pattern. Additional information characterising the metabolic reactions involved and addressing the toxicodynamic properties of the different metabolites are required to establish a basis for making such predictions. Further, ECHA notes that no further information on the toxicological properties of the ultimate common metabolite of the category members, i.e. methacrylic acid, and on the properties of the non-common alcohols formed has been provided in the dossier. ECHA considers that in the absence of supporting information on the toxicity of the alcohol metabolites, it is not possible to predict the properties of the target substance from the data obtained with the source substance(s).

Evidence contradicting your hypothesis of similar properties
In a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD 422) conducted with the source TREGDMA no adverse repeated dose or reproductive toxicity effects were observed up to the highest dose (1000 mg/kg bw/day). In a OECD 422 study conducted with HEMA, the first metabolite of source EGDMA (ECHA considers that information about HEMA is informative about the properties of EGDMA), slight effects in kidney and no adverse reproductive effects were observed up to the highest dose (1000 mg/kg bw/day). However, in the OECD 422 study with the registered (target) substance effects on e.g. kidney (increased weight), thymus (decreased weight), stomach (mild diffused hyperplasia) and liver (minimal degree of multifocal perilobular hepatocytic vacuolation) were observed. In addition, fertility index was markedly reduced and litter and mean pup weights were reduced in the high dose group (1000 mg/kg bw/day). ECHA considers that the source substance TREGDMA, and the first metabolite of EGDMA, HEMA, have different systemic and reproductive toxicity profiles from the registered (target) substance.

This information contradicts your hypothesis of consistent structure-activity relationships, and is therefore an additional reason why your read-across hypothesis is not an adequate basis for predicting the properties of the registered substance.

ECHA observes that in your dossier you have used studies generated with the source substance TREGDMA (CAS no 109-16-0, EC no 203-652-6) as supporting studies to fulfil the information requirements for the *in vitro* gene mutation in bacteria and for the sub-chronic (90-day) toxicity and a study generated with the source substance EGDMA (CAS no 97-90-5, EC no 202-617-2) to fulfil the information requirement for the pre-natal developmental toxicity. ECHA notes that both source substances belong to the oxyethylene subfamily whereas the registered (target) substance belongs to the alkydiol/triol subfamily. These subfamilies are characterised by differences in the structures of their members, as presented in your category justification document. ECHA highlights that you have not explained how the structural differences between the members of these subfamilies, in their native form or via their non-common metabolites, may impact the toxicity of the substances and thus affect the possibility to predict properties of the target substance from the data obtained with the source substances. This is particularly important since the information from the repeated dose/screening studies conducted with these substances reveal that their toxicological properties differ, as explained above.

In your comments to the draft decision you acknowledge that "the current category document submitted in 2014 does not fully meet" the current expectations regarding adaptations based on grouping of substances and read-across. You reported that based on the available information on the hydrolysis of the methacrylate esters and taking into account the information available on the metabolites formed, you have a high confidence in this read-across approach. You noted though that the reporting of the data on the metabolites currently included in the dossier is insufficient. You expressed your intentions to revise the overall category approach and the endpoint specific sections in compliance with the RAAF. Specifically, information on the hydrolysis of the parent ester 1,4-BDDMA, on the further metabolism of 1,4-butane diol would be provided and the use of information on analogous substances on the alcohol metabolite further discussed in this revision.
You also pointed out in your comments to the draft decision, that "if the situation arises that new studies are required for both BDDMA isomers, we suggest to test only 1,4-BDDMA (Tetramethylene dimethacrylate), due to higher production amounts and thus potentially higher exposure of the population, and to use read-across for 1,3-BDDMA".

ECHA acknowledges your intentions to revise their adaptation in accordance with ECHA's RAAF by providing further information characterising the hydrolysis of 1,4-BDDMA, clarifying the further metabolism of the metabolite 1,4-butanediol and by elaborating on the possibility to use information on analogue substances to 1,4-butanediol in order to predict the properties of the registered substance.

As a general rule, ECHA stresses that for a read-across approach based on metabolism (RAAF Scenario 1), reliable data establishing rapid and complete hydrolysis of the parent substance is essential to support the read-across hypothesis. Furthermore, adequate and reliable information on the toxicological properties of the metabolites needs to be provided.

ECHA further stresses that reliability and adequacy of the source and supporting studies, and particularly in case of old non-guideline studies, need to be accounted for, e.g. duration of the studies and the parameters examined in the studies need to be compared to current OECD/EU guidelines. The impact of possible deficiencies is to be addressed and the relevance and reliability of the studies evaluated accordingly.

In summary, ECHA stresses that the selection of the source substance needs to be scientifically justified and in particular the read-across should not lead to an underestimation of the effect(s) as per RAAF Scenario 1.

Endpoint-specific comments to the draft decision by you:

In vitro gene mutation study in bacteria:

You referred in your comments on the draft decision to a mode of action-based approach whereby "the potential MoA is the electrophilic reaction of the methacrylate double bond with DNA, another aspect is potential mutagenicity of the alcohol". In order to support this approach, you expressed your intention to refer to existing information from an Ames test conducted with 1,4 butane diol. You also mentioned the existence of "at least two methacrylates with the complete set of strains in the category – both negative" and a "fundamental summary of Ames tests with methacrylates (~ 45 esters all with the same reactive group) - all tests are negative and approx. 50% are with the full complement of five strains including either TA102 or E.coli WP2 uvrA" in their comments. On that basis you conclude on a high level of confidence in this read-across approach.

ECHA understands that you intend to refer to supporting information in the form of an Ames test conducted with 1,4-butane diol to establish that the alcohol is not mutagenic. Since no further information on this study is provided, ECHA cannot assess the reliability and adequacy of this information in the context of this read-across approach.

In your "MoA: Level 1" argument, you refer to complete sets of strains available on at least two methacrylates. No information on the identity of these two other methacrylates is provided, and no details on the studies included in these data sets are reported.

In your "MoA: Level 2" argument, you refer to an analysis of results from Ames tests conducted with multiple methacylates with "~ 45 esters all with the same reactive group" specifying that "50% are with the full complement of five strains including either TA102 or E.coli WP2 uvrA " and that "all tests are negative". No further information on the underlying data set considered in this analysis is provided. The limited information provided in the comments on the draft decision by you prevents ECHA from assessing the reliability and adequacy of these scientific arguments in the context of this read-across approach.

Sub-chronic (90-day) toxicity:

ECHA understands that you intend to strengthen your current read-across approach (available screening for reproductive/developmental toxicity study (OECD 422) with the registered substance) according to which "1,4 BDDMA is metabolized rapidly to 1,4-butanediol and methacrylic acid" using additional existing information on the metabolites 1,4-butane diol and methacrylic acid. You also indicate your intention to use information on γ-butyrolactone to inform on the properties of 1,4-butane diol and of methyl methacrylate as a precursor of methacrylic acid. On that basis you conclude on a high level of confidence in this revised read-across approach.

Pre-natal developmental toxicity:

ECHA understands that you intend to strengthen your current read-across approach (available screening for reproductive/developmental toxicity study (OECD 422) with the registered substance) using additional existing information on the developmental toxicity of the metabolites 1,4-butane diol and methacrylic acid. You also indicate your intention to use information on γ-butyrolactone to inform on the properties of 1,4-butane diol and of methyl methacrylate as a precursor of methacrylic acid. You also state that there are no developmental toxicity studies in rabbits but point out that no developmental toxicity was observed in studies conducted with e.g. ethylene glycol and propylene glycol.

You conclude that "As the second species is not fully covered for all metabolites, a developmental toxicity study in rabbits could be considered if the level of confidence is considered to be insufficient".

On that basis you conclude on a high level of confidence in this revised read-across approach for rats and a moderate confidence for rabbits.

Extended-one generation reproductive toxicity:

ECHA understands that you intend to strengthen your current read-across approach (available screening for reproductive/developmental toxicity study (OECD 422) with the registered substance) using additional existing information on reproductive toxicity of methyl methacrylate, 1,3-butane diol, small molecular weight diols like ethylene glycol and propylene glycol, and of 1,4-butanediol.

On that basis you conclude on a high level of confidence in this revised read-across approach.

ECHA outlines that reliable information characterising the claimed "short half-life and rapid ultimate metabolism to CO2 and water" is required to support the claim of limited potential of 1,4-butane diol to cause direct reproductive toxicity.

ECHA acknowledges your intention to revise and strengthen your read-across adaptation. However, ECHA notes, very limited information introducing the data set on which this revision of the read-across approach is intended to be based on has been provided in your comments to the draft decision.

ECHA stresses that should information from other source substances such as 1,3-butane diol, γ-butyrolactone, other small MW diols like ethylene and propylene glycol, and methyl methacrylate be used as source or supporting information, adequate and reliable documentation establishing the relevance of this information needs to be provided in an updated dossier. In case multiple source substances are used to predict the properties of the target substance, details on the use and integration of the multiple source data needs to be unambiguously and transparently reported, in an updated dossier.

Based on your comments to the draft decision ECHA considers that all the intentions, do not address the deficiencies indicated above regarding read-across approach provided for toxicological endpoints. For the reasons presented above, ECHA is not in a position to conclude on whether the revised read-across approach will comply with the requirements of Annex XI, section 1.5 of the REACH Regulation.

ECHA emphasizes that this decision does not take into account the dossier update you submitted on 30 June 2017 (submission number [redacted]), i.e. after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. ECHA will further assess the information provided in an updated dossier in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in the decision.

Summary for toxicological endpoints

In the light of the deficiencies as described above, both for the general read-across hypothesis, ECHA considers that this grouping and read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. of the REACH Regulation. Therefore, this adaptation cannot be accepted and there is a data gap for the endpoints covered by this read-across approach.

0.4. ECHA's analysis of the read-across approach for environmental endpoint

ECHA has summarised your read-across hypothesis from the category justification document in section 0.1. The individual arguments supporting this read-across hypothesis for environmental endpoint (Short-term toxicity to fish) is analysed below.

For the short-term toxicity to fish you have provided a 48-h toxicity study on the structural analogue 1,3-BDDMA (CAS No 1189-08-8, EC No 214-711-0).

ECHA understands from the information provided in the technical dossier and Category justification document that you intend to predict Short-term toxicity to fish based on the following hypothesis: "*For acute fish toxicity there is a trend of increasing toxicity (96 h LC50) with increasing logP, while the glycol dimethacrylate subfamily with similar logP also shows similar ecotoxicity*".

Lack of evidence supporting your hypothesis of similar properties

ECHA notes that both the source substance and the registered substance belong to the alkydiol/triol subfamily. The description of the members of the category included in the category justification document suggests elements of structural similarity between these substances. However, ECHA notes some deficiencies in your read-across justification.

In your read-across justification document you provide data matrices listing toxicity values in several environmental hazard endpoints (Short-term toxicity to fish, Long-term toxicity to fish, Short-term toxicity to aquatic invertebrates, Long-term toxicity to aquatic invertebrates, Effects on algae and aquatic plants) for the eight category members. However, ECHA notes that you do not provide toxicity data for both the registered substance 1,4-BDDMA and the source substance 1,3-BDDMA in any of the endpoints which would allow anchoring the toxicity levels.

Therefore, ECHA concludes that based on the presented information it is not possible to confirm that the source and target substances would have similar properties regarding toxicity to fish. In the absence of such information there is not an adequate basis for predicting the properties of the target substance from the data obtained with the source substance.

Reliability of the submitted study

Furthermore, ECHA notes that the study performed with the source substance was performed in a static freshwater system, exposing *Idus melanotus* for 48 hrs to the source substance. However, in accordance with Annex XI, Section 1.5., in all cases results 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.

ECHA notes that the exposure duration was set at 48 hours. A standard test duration for a short-term toxicity test on fish according to OECD TG 203 (1992), Fish, acute toxicity test is 96 hours. Therefore, the exposure duration of the test provided is not comparable to or longer than the corresponding test methods referred to in Article 13(3). Furthermore, ECHA observes that there is no information provided in the technical dossier on the experimental conditions, such as the dissolved oxygen concentration of the test solutions.

ECHA concludes that the toxicity study on fish provided in the registration dossier does not fulfil the conditions of Annex XI, 1.5. for being recognised as equivalent to data from the test method referred to in Article 13(3).

Considerations of impurities

In addition, ECHA emphasises that the substance characterisation of the source substance(s) need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA practical guide 6 "How to report on Read-Across" it is recommended to follow the ECHA Guidance for identification and naming of substances under REACH and CLP (version 2.1, May 2017) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

ECHA acknowledges that in the technical dossier of the registered substance you have provided the following information on the tested material and its degree of purity:EC name 1-methyltrimethylene dimethacrylate; EC number 214-711-0; CAS number 1189-08-8; *Analytical purity: not given in the study; according to supplier's information: reactive ester content ca. 98 %, purity ca. 90%.*

ECHA observes that the reported purity of the tested material is only ca. 90% and the impurity profile of the tested substance is not provided (*"Impurities (identity and concentrations): no data"*). ECHA considers that currently the composition and the impurity profile of the source and target substances cannot be adequately compared using the information provided in the registration dossier. Therefore, ECHA cannot analyse the impact of the possible differences in the composition and impurity profiles that the source and target substances may have on the proposed prediction. Hence ECHA cannot reach a conclusion that the source substance can be used to predict and does not underestimate properties of the registered substance.

In the absence of unambiguous information on the composition and impurity profile of the test sample used to generate the source data, ECHA cannot verify the adequacy of this information for the purpose of classification and/or risk assessment of the registered substance, as required by the provisions of Annex XI, Section 1.5 of the REACH Regulation.

Consistent structure-property and -activity relationships throughout all endpoints

Your proposed adaptation argument is also that the similarity in structures, similarity/trends in physico-chemical properties and ecotoxicological properties between the source and target substance is a sufficient basis for predicting the properties of the substance. This argument is limited and is in principle not capable of being sufficient. Similarity in structures, similarity/trends in physico-chemical properties and ecotoxicological properties properties is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that similarity in structures, similarity/trends in physico-chemical properties and ecotoxicological properties per se is sufficient to enable the prediction of environmental properties of a substance. This is because similarity in structures and similarity/trends in physico-chemical properties does not always lead to predictable or similar environmental properties, and consequently cannot on its own constitute sufficient evidence of predictable or similar environmental properties. Further elements are needed[3], as pointed out above, such as supporting evidence to show similarity in ecotoxicological effects, or that the impurities would not contribute to the prediction, to allow a prediction of environmental properties that does not underestimate risks.

The description of the members of the category included in the category justification document suggests elements of structural similarity among these substances. However, in Category information section (0.2 Related information) you have not provided a detailed demonstration of this structure-property and structure-activity relationship regarding human health and environmental properties of the substances.

In the read-across justification document attached you have provided a structure-property explanation regarding physico-chemical properties of the category members.

ECHA understands that you have identified subfamilies in the category based on different physico-chemical properties/trends in the category:

- oxyethylene subfamily (EGDMA, DEGDMA, TREGDMA and GDMA) with similar logP values and a trend to increasing water solubility with increasing length of the oxyethylene chain length, and

- alkyldiol/triol subfamily (1,3-BDDMA, 1,4-BDDMA, HDDMA and TMPTMA) with increasing logP values and decreasing water solubility with increasing molecular weight/volume.

ECHA acknowledges that you have linked structural differences with water solubility and log Kow. However, you have not explained how the structural differences and trends in physicochemical properties are linked with the predicted environmental and human health hazard properties, neither within a subfamily nor between the subfamilies which are currently part of the same claimed category.

[3] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals and ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

More specifically, you have not explained how the structural differences such as different chain lengths of the parent compounds between the category members (within and between the subfamilies) relate to their ecotoxicological properties. Furthermore, the subfamily of alkyldiol/triol includes also other structural differences than alkyl chain length, e.g. branching, and it has not been explained how such differences may influence the predicted properties. Consequently, there is not a robust basis for predicting the properties of the registered substance.

Summary for Short-term toxicity to fish
In the light of the deficiencies as described above, both for the general read-across hypothesis and the endpoint-specific justifications, ECHA considers that this grouping and read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. of the REACH Regulation. Therefore, this adaptation cannot be accepted and there is a data gap for the endpoints covered by this read-across approach.

In your comments to the draft decision, you explained your intention to update the read-across/category justification document. You indicated an intention to provide data on metabolic pathways and toxicological data for the metabolites to improve the read-across adaptation. ECHA considers that these intentions do not address the deficiencies indicated above regarding read-across approach provided for ecotoxicological endpoints i.e. Lack of evidence supporting your hypothesis of similar properties; consistent structure-property and -activity relationships throughout all endpoints; and considerations of impurities. Therefore, it is ECHA's understanding of your comments on the draft decision, that you intend to improve read-across and grouping only to predict Human Health properties.

ECHA emphasizes that this decision does not take into account the dossier update you submitted on 30 June 2017 (submission number [redacted]), i.e. after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. ECHA will further assess the information provided in an updated dossier in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in the decision.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

In accordance with Articles 10(a) and 12(1) of 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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.
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 the registered substance to meet this information requirement.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four S. typhimurium strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or S. typhimurium TA102 which have an AT base pair at the primary reversion site.

You have provided two *in vitro* gene mutation in bacteria tests with the registered substance:

1) from the year 1995 according to OECD TG 471 and GLP with an assigned reliability score of 1. The test used five different strains of S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and TA 1538.
2) from the year 1984 equivalent or similar to OECD 471, publication, non-GLP, with an assigned reliability score of 2. The test used five different strains of S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and TA 1538.

The tests did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).

However, since the tests were conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided studies do not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.
ECHA concludes that a test using E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 has not been submitted and that the test using one of these is required to conclude on in vitro gene mutation in bacteria.

In addition, in the CSR you have provided the following statement: "*In both Ames tests S. typhimurium TA 102 or E. coli WP2 are missing. However, data sets including S. typhimurium TA 102 are available for other methacrylates from the category*".

ECHA notes that based on the information you provided in the category justification document (but not in the dossier), *S. typhimurium TA 102* has been examined with one category member, TREGDMA (CAS no 109-16-0, EC no 203-652-6).

In your comments to this draft decision you explained your intention to update the read-across/category justification document and provide further information to improve the read across approach. Your comments to the draft decision are addressed in section 0 "Grouping and read-across approach". As explained above in section 0. "Grouping and read-across approach" of this decision, your category and read-across approach is not considered acceptable.

In addition, *S.typhimurium TA 102* has been examined only with one claimed category (TREGDMA) member and therefore, it cannot be concluded if the other claimed category members would have similar mutagenicity profile. Further this study is not provided in the IUCLID dossier and so cannot be considered for the information requirement.

ECHA emphasizes that this decision does not take into account the dossier update you submitted on 30 June 2017 (submission number [redacted]), i.e. after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. ECHA will further assess the information provided in an updated dossier in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in the decision.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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, you are requested to complete following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

In accordance with Articles 10(a) and 12(1) of 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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

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.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) with the registered substance. However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days.

In addition, you have provided a study record for a 78-wk dermal study in mice (US EPA guideline) with the analogue substance TREGDMA (CAS no 109-16-0, EC no 203-652-6) as a supporting study.

In your comments to this draft decision you explained your intention to update the read-across/category justification document and provide further information to improve the read across approach. Your comments to the draft decision are addressed in section 0 "Grouping and read-across approach". However, as explained above in section 0. "Grouping and read-across approach" of this decision, your category and read-across approach is not considered acceptable. ECHA further notes that the study is not considered adequate as sufficient dermal absorption of the test substance has not been demonstrated.

ECHA emphasizes that this decision does not take into account the dossier update you submitted on 30 June 2017 (submission number [redacted]), i.e. after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. ECHA will further assess the information provided in an updated dossier in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in the decision.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 6.0 July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and no human exposure via inhalation is reported. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

In accordance with Articles 10(a) and 12(1) of 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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./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 substance to meet this information requirement.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422). However, this study does not provide the information required by Annex IX, Section 8.7.2. because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations. Therefore, your adaptation of the information requirement is rejected.

You have provided the following justification:

"According to REACH regulation, Annex XI, 1, a prenatal developmental toxicity study is scientifically not necessary. The available data for the members of the multifunctional methacrylates category are sufficient for classification, labelling and risk assessment. Thus, no further testing is proposed.
A prenatal developmental toxicity study (similar to OECD guideline 414) is available for EGDMA. No developmental toxicity was observed in this study up to the highest tested dose of 500 mg/kg bw/d.
For the members of the category of lower alkyl methacrylates, based on studies in experimental animals, there is no evidence of selective toxicity to the reproductive system. This is corroborated by the fact that the esters are rapidly metabolised in vivo and the primary metabolites, methacrylic acid, as well as the corresponding alcohol (1,4-butanediol), demonstrates an absence of concern for specific reproductive toxicity".

ECHA understands that you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by referring to a pre-natal developmental toxicity study conducted with EGDMA.

In your comments to this draft decision you explained your intention to update the read-across/category justification document and provide further information to improve the read across approach. Your comments to the draft decision are addressed in section 0 "Grouping and read-across approach". However, as explained above in section 0. "Grouping and read-across approach" of this decision, your category and read-across approach is not considered acceptable. ECHA further notes that you have not provided this study in your registration dossier.

ECHA emphasizes that this decision does not take into account the dossier update you submitted on 30 June 2017 (submission number [redacted]), i.e. after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. ECHA will further assess the information provided in an updated dossier in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in the decision.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

4. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

In accordance with Articles 10(a) and 12(1) of 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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./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 IX of the REACH Regulation, 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 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 in ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 6.0, July 2017).

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

a) The information requirement

ECHA considers that adverse effects on reproduction are observed. More specifically, in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) provided in the dossier, the high dose group (1000 mg/kg/day) shows a markedly reduced fertility index (40% compared to 90% of the control group), reduced litter and mean pup weights compared to controls, and an increased percentage of cumulative pup loss on Day 4 post-partum. Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for registrations of the registered substance.

You did not consider the information requirement for reproductive toxicity in Annex IX, Section 8.7.3., column 1, because no adverse effects on reproductive endpoints have been observed in the available repeated dose toxicity studies. You have provided the following justification: *"According to column 1 of Annex IX, section 8.7.3 of REACH regulation a decision on the need to perform a two generation study at this tonnage level should be based on the outcome of all other relevant available data. In the available screening study no substance-related adverse effects on reproductive endpoints were found.*

The effects seen at the highest dose level (reduced number of pregnant females, reduced litter and mean pup weights) were nonspecific effects and only observed in the presence of general toxicity. This is consistent with findings with other methacrylates in the category of multifunctional methacrylates as well as with monofunctional methacrylates. Thus, the conduct of a two generation study is scientifically not justified".

However, ECHA points out that the information requirement according to Annex IX, Section 8.7.3. has been changed by Commission Regulation (EU) 2015/282, and that the new information requirement, i.e. the extended one-generation reproductive toxicity study, is an information requirement if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD 421 or 422 screening studies) or if these studies reveal other concerns in relation with reproductive toxicity. ECHA considers that such concerns in relation with reproductive toxicity are observed: the OECD TG 422 screening study shows effects such as reduced fertility index, reduced litter and pup weights, and increased pup loss which are considered as a concern in relation with reproductive toxicity.
These severe findings are not considered by ECHA as secondary to described slight maternal toxicity: "*Slight toxic effects were seen in parental animals as indicated by the reduced body weight, body weight gain and food consumption in the animals receiving 1000 mg/kg bw/d.*" and "*no clinical signs of toxicological significance were reported*"

You also state that the observed reproductive toxicity, considered as non-specific effects by you, are consistent with "*findings with other methacrylates in the category of multifunctional methacrylates as well as with monofunctional methacrylates".* However, you have not provided scientific justifications explaining why and how the observed slight general toxicity would produce such severe effects in reproduction with this category of methacrylates.

In your comments to this draft decision you explained your intention to update the read-across/category justification document and provide further information to improve the read across approach. Your comments to the draft decision are addressed in section 0 "Grouping and read-across approach". As explained above in section 0. "Grouping and read-across approach" of this decision, your adaptation of the information requirement is rejected.

Hence, an extended one-generation reproductive toxicity study is an information requirement.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422). However, this study does not provide the information required by Annex IX, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3. is required. The following refers to the specifications of this required study.

ECHA emphasizes that this decision does not take into account the dossier update you submitted on 30 June 2017 (submission number [redacted]), i.e. after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. ECHA will further assess the information provided in an updated dossier in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in the decision.

b) The specifications for the required study

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

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that 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* R.7a, chapter R.7.6 (version 4.1, October 2015). The sub-chronic toxicity study 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 the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015), the starting point for deciding on the length of the 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* R.7a, chapter R.7.6 (version 4.1, October 2015).

The highest dose level shall aim to induce some toxicity 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 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.

Species and route selection

According to the test method EU B.56/ 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

Based on the available information, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral 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 some 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;

Currently, the extension of Cohort 1B and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request 2) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by **30 November 2018**. 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 you by **4 March 2019** (i.e. within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to 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 you do not receive a communication from ECHA by **4 March 2019**, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision **31 May 2021**.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter 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, you 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.

5. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

In accordance with Articles 10(a) and 12(1) of 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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. You provided a study record for a Fish, acute toxicity test (guideline DIN 38 412 part 15, key study, reliability 2, [redacted] 1987) with the analogue substance 1,3-BDDMA (CAS no 1189-08-8, EC no 214-711-0). However, as explained above in section 0. "Grouping and read-across approach" of this decision of this decision, your adaptation of the information requirement cannot be accepted.

In particular, ECHA notes that this study was performed in a static freshwater system, exposing *Idus melanotus* for 48 hrs to the analogue substance. However, this study does not provide the information required by Annex VIII, Section 9.1.3., because you did not provide data generated by the corresponding test method referred to in Article 13(3) of the REACH Regulation, i.e. Fish, acute toxicity test (test method EU C.1./OECD TG 203), as explained in section 0.4. above.

In your comments to this draft decision you explained your intention to update the read-across/category justification document. However, as described above in section 0 "Grouping and read-across approach", it is ECHA's understanding that you intend to improve read-across and grouping only to predict Human Health properties.

In your comments to this draft decision you also stated the following regarding the requests 5-7: "*Illustrate current knowledge of near-baseline toxicity as relevant MoA for methacrylates, including 1,4-BDDMA, based on QSAR*". Based on this statement, ECHA understands that you may refer to adapting the information requirement by (Q)SAR models. ECHA acknowledges that (Q)SAR models may be used instead of testing if conditions set out in Section 1.3 of Annex XI to the REACH Regulation are met. The use of QSARs to adapt information requirements is further specified in the ECHA Guidance on information requirements and chemical safety assessment (May 2008), Chapter R.6.

ECHA emphasizes that this decision does not take into account the dossier update you submitted on 30 June 2017 (submission number [redacted]), i.e. after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. New information/approach provided in an updated dossier will be evaluated in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in the decision.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 3.0, February 2016) fish acute toxicity test (test method EU C.1. / OECD TG 203) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.1.3.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: fish acute toxicity test (test method EU C.1. / OECD TG 203).

6. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

In accordance with Articles 10(a) and 12(1) of 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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"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.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: `*Long-term testing in fish is waived for 1,4-BDDMA since the substance is readily biodegradable. The risk characterization shows that the PEC/PNECaqua ratio for the aquatic environment is <1, indicating no need for further information or testing. According to REACH regulation Annex IX, 9.1. column 2, long-term testing shall only be considered when the chemical safety assessment indicates the need for further investigations.*

Because there is no indication of major differences in sensitivity between trophic levels and in the absence of any significant long-term bioaccumulation potential it is not necessary to perform further chronic fish test with the substance. The environmental risk assessment can be performed with sufficient reliability with the available long-term ecotoxicity data. Thus, no long-term toxicity testing is required for 1,4-BDDMA.`

ECHA notes that contrary to your claim, information present in your dossier indicates the need to investigate further the effects on aquatic organisms, as explained below.

Firstly, although your statement pointing out that "*the substance is readily biodegradable*" may allow conclusion of PBT properties of the substance, it, however, does not allow to conclude risk assessment and thus the entire CSA. Ready biodegradability does not exclude the potential of toxic effects, neither exclude completely exposure of the aquatic environment.

Secondly, you have argued that "*Because there is no indication of major differences in sensitivity between trophic levels and in the absence of any significant long-term bioaccumulation potential it is not necessary to perform further chronic fish tests with the substance*". ECHA understands that you refer to integrated testing strategy (ITS) described 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). ECHA notes that according to this ECHA Guidance, if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially less sensitive than other trophic levels (i.e., fish, invertebrates, algae), long-term studies may be required on both fish and invertebrates. In such case, according to the integrated testing strategy, the Daphnia study is to be conducted first. If based on the results of the long-term Daphnia study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, ECHA notes that this ITS approach cannot be applied in this case because there is no reliable information provided in the technical dossier on short-term toxicity to fish or daphnia that would allow determination of relative species sensitivity. Therefore the standard information requirement of long-term toxicity to fish cannot be adapted based on ITS for aquatic pelagic toxicity.

Thirdly, you have not provided evidence to justify your claim that "*risk characterization shows that the PEC/PNECaqua ratio for the aquatic environment is <1*". ECHA notes that the registration dossier does not include a qualitative risk characterisation (RCR, PEC/PNECaqua ratio) that would allow you to adapt this information requirement. In the CSR you provided, the exposure assessment for the environment is missing (section 7 to this decision). Furthermore, in the absence of reliable short-term hazard data on fish (request 5 in this decision), it is not possible to perform a reliable risk characterisation. In the absence of quantitative risk characterisation your justification for adapting long-term toxicity to fish based on the assumed PEC/PNECaqua ratio for the aquatic environment of <1, is not substantiated.

Therefore, your adaptation of the information requirement cannot be accepted.

In addition to your comments to this draft decision which you provided and ECHA addressed in request 7 above, Short-term toxicity testing on aquatic invertebrates, you also indicated that you intend to "*modify the respective PNEC assessment factors*" and "*update also the respective exposure assessment and risk assessment*". As you also state that "*Initial PEC/PNEC calculations provide confidence that we can address your concerns without further testing of vertebrates animals*", ECHA understands that you intend to adapt the information requirement for long-term toxicity to fish by provisions set out in column 2 of section 9.1 of Annex IX. As described above, the column 2 adaptation currently provided in the technical dossier is rejected. Therefore you should consider all the issues described above when updating this adaptation. ECHA acknowledges that you have indicated in the comments to the draft decision to update the exposure assessment and risk characterisation but also to "*Discuss different sensitivies of the trophic levels*". ECHA points out that such comparison on sensitivity should be based on reliable short-term toxicity data on daphnia and fish which are currently not present in the technical dossier.

ECHA emphasizes that this decision does not take into account the dossier update you submitted on 30 June 2017 (submission number [redacted]), i.e. after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. The new information/approach provided in an updated dossier will be evaluated in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in the decision.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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, Figure R.7.8-4).

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).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Before conducting the requested test you shall consult the ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b, Section R.7.8.5 to determine the necessity to conduct long-term toxicity testing on fish.

Currently the long-term toxicity testing is needed in the absence of reliable short-term toxicity data on fish (Request 5 in this decision) and exposure assessment and risk characterisation (Request 7 in this decision). However, you may consider adapting long-term toxicity testing when reliable data on short-term toxicity to fish become available, you perform the exposure assessment and update the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

If you come to the conclusion, following the ECHA Guidance as mentioned above, that no further investigation of effects on aquatic organisms is required, you shall update your technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.6. taking into account the new data generated by the short-term toxicity study and exposure assessment and risk characterisation requested by the present decision.

7. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report (CSR) which shall document the chemical safety assessment (CSA) conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

Pursuant to Article 14(4), if the substance fulfils the criteria for any of the hazard classes listed in that provision or is assessed to be a PBT or vPvB, the CSA shall include exposure assessment and risk characterisation.

Annex I, Section 5 of the REACH Regulation requires the Registrant to generate exposure scenarios and exposure estimations for the registered substance. The exposure assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the identified hazards.

Annex I, Section 6 of the REACH Regulation requires the Registrant to characterise the risk for each exposure scenario and to consider the human population (exposed as workers, consumer or indirectly via the environment and if relevant a combination thereof) and the environmental spheres for which exposure to the substance is known or reasonable foreseeable, under the assumption that the risk management measures described under exposure scenario in Section 5 of the same Annex have been implemented. In addition, the overall environmental risk caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments.

In the CSR you provided, the exposure assessment for the environment is missing. You claimed that no exposure assessment is necessary for the environment by stating for each exposure scenario that *"As no environmental hazard was identified no environmental-related exposure assessment and risk characterization was performed".*

ECHA notes that you have classified the substance as Skin Sens. 1B (H317) and thus, fulfilling the criteria set out in Article 14(4) of the REACH Regulation to require an exposure assessment and a risk characterisation in the chemical safety assessment.

With regard to the scope of the required exposure assessment, as stated above and in accordance with Annex I, section 5.0., it has to cover all hazards that have been identified according to sections 1 to 4 of Annex I of REACH Regulation.

It is clear from your dossier that effects were observed in some environmental toxicity studies. For example, in the long-term aquatic invertebrate (*Daphnia*) study, a 21-d NOEC value of 5.09 mg/L and EC10 value of 7.51 mg/L were reported for the registered substance, and in the algae toxicity study the reported NOEC and EC10 values based on growth rate were 2.11 mg/L and 4.35 mg/L. The EC10 of 4.35 mg/L determined in an algal toxicity study was considered for the calculation of the PNECfreshwater. Therefore, exposure assessment and risk characterisation for environment are needed to address the hazards identified for the environment.

As further outlined in Guidance *on information requirements and chemical safety assessment*, Part B: Hazard Assessment, Section B.8.1. (version 2.1, December 2011), such identified hazards (among others) necessitating exposure assessment are the *"hazards for which there are classification criteria and there is information on these properties of the substance showing that it does have these properties, but the severity of the effects is lower than the criteria for classification and so the substance is not classified"*. Moreover, the above mentioned guidance specifies further (in Section 8.4.2.2.) that *"If there are ecotoxicity data showing effects in aquatic organisms, but the substance is not classified as dangerous for the aquatic environment, an aquatic PNEC can nevertheless be derived thus indicating a hazard to the aquatic environment.(...) Hence, quantitative exposure assessment, i.e. derivation of PECs, is mandatory for the water, sediment and soil environmental compartments."*

Based on your comments to this draft decision, ECHA understands that you intend to perform the exposure assessment and risk characterisation as requested. ECHA emphasizes that this decision does not take into account the dossier update you submitted on 30 June 2017 (submission number [redacted]), i.e. after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. The new information provided in an updated dossier will be evaluated in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in the decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to generate an environmental exposure assessment for all relevant exposure scenarios and subsequently perform the risk characterisation for each exposure scenario to demonstrate the safe use of the substance, and update the dossier accordingly.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 23 November 2016.

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.

ECHA took into account your comments and did not amend the request(s).

Note in request 1, 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) with the registered substance, for clarity, the strains mentioned in Appendix 1 of the draft decision were included as follows:"using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102".

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposal(s) for amendment and modified 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.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-56 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, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

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.

4. 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.

5. If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.