EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114319706-47-01/F Helsinki, 07 June 2016

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For 2-ethylhexyl methacrylate, CAS No 688-84-6 (EC No 211-708-6), registration number: [redacted]

Addressee: [redacted]

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

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for 2-ethylhexyl methacrylate, CAS No 688-84-6 (EC No 211-708-6), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates submitted after 3 September 2015, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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

The compliance check was initiated on 13 November 2013.

On 13 November 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 11 December 2014 ECHA received comments from the Registrant on the draft decision agreeing to ECHA's draft decision.

On 20 March 2015 the Registrant updated his registration with the submission number [redacted] concerning the information requirements of Annex IX, Section 9.4.1., Annex IX, Section 9.4.2., Annex IX, Section 9.4.3. and Annex I, Section 3.3, and agreeing to ECHA's draft decision concerning the information requirements of Annex VIII, 8.1.1 and Annex IX, 8.7.2.

The ECHA Secretariat considered the Registrant's update. On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 3 September 2015, ECHA notified the competent authorities of the Member States of its draft decision and invited them to propose amendments to the draft decision under Article 51 of the REACH Regulation.

Subsequently, proposals for amendment to the draft decision were proposed.

On 9 October 2015 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendments received and amended the draft decision.

On 19 October 2015 ECHA referred the draft decision to the Member State Committee.

By 9 November 2015 the Registrant did not provide any comments on the proposals for amendment.

After discussion in the Member State Committee meeting on 7–11 December 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 9 December 2015.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(e), 13 and Annexes VII, IX, and X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance 2-ethylhexyl methacrylate:

1. Skin irritation (Annex VII, Section 8.1*): in vitro* study for skin irritation (test method: OECD TG 439;

2. Pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route.

B. Information related to chemical safety assessment and chemical safety report

Pursuant to Articles 41(1), 41(3), 10(b), 14 and Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report:

1. Identification of DNEL (Annex I, Section 1.4.): derive long-term DNEL(s) for workers, inhalation route, using the assessment factors according to ECHA Guidance R.8 for DNEL derivation.

2. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for human health: generate a quantitative exposure assessment considering inhalation route for all 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 of the REACH Regulation. In order 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 an adequate and reliable documentation.

C. Deadline for submitting the required information

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **14 June 2017**. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 10(a)(vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

With respect to the information in the technical dossier derived from the sequential application of the Annexes VII to XI, the Registrant has used a read-across and grouping approach based on Annex XI, 1.5. of the REACH Regulation. ECHA has considered the documentation and the scientific validity of the proposed read-across and grouping approach, before assessing whether the information provided for information requirements is compliant with the REACH Regulation.

0. Grouping of substances 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*".

Annex XI, 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. The following analysis presents the Registrant's justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context.

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant

According to the Registrant, the substance subject to this decision can be grouped with other substances for the purpose of read-across in a category that is named Basic Short Chain (Lower) Alkyl Methacrylates. Category members include methacrylic acid (MAA, CAS No 79-41-4, EC No 201-204-4), methyl methacrylate (MMA, CAS No 80-62-6, EC No 201-297-1), ethyl methacrylate (EMA, CAS No 97-63-2, EC No 202-597-5) n-butyl methacrylate (n-BMA, CAS no 97-88-1, EC No 202-615-1), iso-butyl methacrylate (i-BMA, CAS No 97-86-9, EC No 202-613-0) and 2-ethylhexyl methacrylate (2-EHMA, CAS No 688-84-6, EC No 211-708-6), the registered substance. The Registrant states that the substances are typically of [redacted]% purity and the impurities consist of water and of the corresponding alcohol. The Registrant further supports the grouping approach by referring to a common metabolism pathway of the category members leading to a common metabolite, methacrylic acid, and the corresponding alcohols. The Registrant also identified trends and structure activity relationships with environmental toxicity, distribution and fate, and mammalian toxicity. The Registrant further states that methyl methacrylate "*provides a robust reference chemical for this category*".

According to the Registrant, the category hypothesis is based on the following: "*The esters are rapidly metabolized to methacrylic acid (CAS: 79-41-4) and the structurally corresponding alcohol by non-specific carboxylesterases in several tissues. Methyl methacrylate (MMA) (CAS: 80-62-6), the C1 ester, is the largest volume methacrylate ester that has been studied extensively and reviewed in the OECD HPV Chemical Program. As such MMA provides a robust reference chemical for this category*". The Registrant qualifies the category applicability domain by referring to a "*set of inclusion and/or exclusion rules*", and provides the following category justification: "*Due to trends observed in environmental toxicity, distribution and fate, mammalian ADME (adsorption, distribution, metabolism and excretion), and toxicology between basic short chain (C2-C8) unsaturated linear and branched alkyl methacrylates, a category approach was used for these compounds. The category is defined as methacrylate esters of straight and branched C2 to C8 alcohols. The basic short chain (C2-C8) unsaturated linear and branched alkyl methacrylates included in this category show structure activity relationship with respect to environmental toxicity, distribution and fate, and mammalian toxicity*".

The Registrant further states that "*There are extensive data available for the methyl ester (MMA) and this has been reviewed in the EU Risk Assessment (2002). Sufficient data is available to confirm applicability of this data across all members of the category and this has been reviewed in the OECD SIAR (2009). Data on MAA, the common metabolite, has been reviewed in the EU Risk Assessment (2002)*".

The Registrant has used the grouping and read-across approach to predict the properties of the substance subject to this decision for the following endpoints: pre-natal developmental toxicity and as part of the adaptation justification for the skin irritation.

b. Information submitted by the Registrant to support the grouping approach and read-across hypothesis

Concerning the grouping approach and read-across hypothesis, the Registrant has provided a category definition, applicability domain and justification, and a category data matrix. For the category members, the Registrant has provided experimental data conducted with the respective registered substance and source substances (robust study summaries), which he has further summarised and provided in the Methacrylates Category Document.

c. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

Based on the information provided, ECHA understands that the category hypothesis is based on i) the structural similarity ("*methacrylate esters of straight and branched C2 to C8 alcohols*"), ii) the metabolism of the parent substances to methacrylic acid and structurally corresponding alcohols, and iii) trends and structure activity relationship with environmental fate and distribution, as well as mammalian toxicity.

ECHA notes that

(i) In the Methacrylates Category Document the following definition for the applicability domain has been provided: "*methacrylate esters with side chain groups larger than 2-EHMA are excluded from the category due to low water solubility and vapour pressure*". ECHA concludes that based on the information provided by the Registrant on the category members as outlined above and the exclusion criteria the applicability domain of the category has been adequately described. Also, that all substances presented by the Registrant as members of the category fall within the scope of this applicability domain as defined by the Registrant.

Whereas the Registrant has provided a general structural formula for the category members he has not addressed the structural differences, such as branching and different chain length of the parent compounds, and the impact of these differences on the toxicokinetic and (eco)toxicological properties of the category members as explained further below.

(ii) ECHA notes that based on the data provided, a common metabolite (methacrylic acid) and non-common metabolites (corresponding alcohols) are formed from category members. However, due to linear and branched carbon chains with different lengths (C2-C8) of the parent substances, the alcohols formed are structurally different. For the environmental endpoints, the Registrant has not properly justified why MAA and MMA are part of the category. Based on the information submitted, ECHA concludes that MAA and MMA do not fit within the category definition presented by the Registrant because MAA is a free acid and MMA is an ester with a C1 alcohol while the category definition refers to C2-C8 alcohols. The Registrant has not addressed the structural differences and their impact on the half-life, further metabolism, elimination and toxicity of the respective alcohols formed.

In view of the structural differences of the parent compounds and of the corresponding alcohols and in the absence of additional supporting information on the toxicity of the alcohol metabolites, ECHA concludes that the predictions of hazard properties might lead to an underestimation of hazard of the non-tested category members.

(iii) The Registrant indicated that "*structure activity relationship with respect to environmental toxicity, distribution and fate, and mammalian toxicity*" has been observed. However, he has not provided a detailed demonstration of this structure-activity relationship and did not explain how the structural differences observed between the category members relate to their toxicological properties.

ECHA understands that the Registrant has identified a trend for the ADME properties of the category members based on the increasing molecular weight of the substances which results in decreased absorption rate and increased half-life, but he has not elaborated on this argument to demonstrate how this trend can be used to predict the toxicological properties of category members from data generated from other category members. Moreover, the Registrant has not considered the influence of all the metabolism products, in particular the alcohols, of the category members in the establishment of this trend. Due to lack of data on the alcohol metabolites, ECHA considers that the trend for toxicokinetic properties of the category members has not been fully established and therefore, ECHA does not consider that this trend constitutes a solid basis for predicting properties among category members.

(iv) The Registrant states that MMA provides a robust reference substance for this category. ECHA notes that other category members (e.g. n-BMA) have been also used as reference substances. The Registrant did not justify the selection of MMA as reference substance for the category and of n-BMA as source substance in the read-across approach. The Registrant also failed to demonstrate that predictions based on data obtained from these reference substances do not lead to an underestimation of the properties of the other category members.

ECHA concludes that the Registrant has not provided any endpoint-specific justification supporting the prediction of the in vitro/in vivo skin irritation and developmental toxicity properties of the substance subject to this decision from data generated with other members of the category. Instead, the Registrant has only used general statements as an attempt to justify why human health and environmental data from other category members can be used to predict properties for other category members and fill in respective data gaps for these members.

ECHA notes that the provision of the underlying data, documentation of the read-across approach and a robust justification is always necessary even if the category or read-across approach has already been used in another regulatory or international context (see Annex XI, 1.5. last subsection and the introduction to Annex X, second paragraph of the REACH Regulation). Within the REACH context a registration dossier shall be compliant for each substance and each endpoint. Where registrants seek to adapt the standard information requirements, data need to be provided that will allow ECHA to conclude that the endpoint requirement is met.

For example, simply stating that a substance is a member of an OECD category is not by itself a sufficient justification for read-across because it does not allow a conclusion on endpoint-compliance and neglects that grouping by OECD has a different objective than under the REACH Regulation.

d. ECHA analysis of the endpoint-specific read-across approach

According to Annex XI, 1.5. (2), the similarities of a group may be based on: the common precursors and/the likelihood of common breakdown products via physical and biological processes, which results in structurally similar chemicals. The Registrant claims that due to rapid hydrolysis, toxicity is due to the methacrylic acid, which is a common breakdown product for all category members. However, the Registrant has not provided any data to explain why *"MMA provides a robust reference chemical for this category"* other than it *"is the largest volume methacrylate ester that has been studied extensively"*. In addition, as stated in section III.0.c. above, the analysis of the structural differences of parent compounds and the corresponding alcohol metabolites and their impact on the properties and (eco)toxicity profile of the category members is missing.

Skin irritation

The Registrant has provided two *in vivo* skin irritation studies conducted with the registered substance, 2-EHMA, and concludes that *"Although the observation period of the two available studies was too short to establish reversibility, by analogy to the other esters of the category, for which reversibility has been established, it is assumed that the skin irritation caused by 2 -EHMA will be reversible"*.

ECHA notes that the Registrant has not specified which substance(s) he is using as a source substance(s) but only refers to *"the other esters"*, and has not provided any substance-specific reasoning for the assumption that the effects of 2-EHMA will be reversible. In addition, as the other category members are classified as either as Skin Corr. 1A (MAA) or Skin Irrit. 2 (MMA, EMA, n-BMA and i-BMA), the claim about reversibility *"by analogy to the other esters"* does not support a non-irritating property of 2-EHMA. Annex XI, 1.5. foresees that classification and labelling on basis of an applied group concept. In the case at hand neither properties can be predicted from the presented data nor is there a coherent approach concerning classification and labelling. Therefore, ECHA concludes that due to lack of supporting data for non-irritating property of 2-EHMA and classification of the other category members either as skin irritant or corrosive, the read-across for this endpoint is not considered acceptable.

Pre-natal developmental toxicity

With regard to the prediction of properties between category members, the Registrant has provided the following justification: *"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"*. ECHA notes that based on the results in the data set provided by the Registrant, it is evident that the category members do have different effects on mammalian toxicity as explained in detail below.

In the technical dossier, the Registrant has provided a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) conducted with the registered substance (2-EHMA) and a pre-natal developmental toxicity studies (oral and inhalation) conducted with the category member n-BMA. In the CSR he concludes that 2-EHMA "*is not expected to be a developmental toxicant*". In the Methacrylates Category Document the Registrant further concludes that for 2-EHMA "*the developmental toxicity has been derived by read-across logic using a weight-of-evidence approach relying on the data available for all members of the category*".

ECHA notes that the results of the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) conducted with 2-EHMA and n-BMA (study submitted in n-BMA registration dossier) indicate that 2-EHMA causes more severe effects on fertility since it caused a lower number of oestrus cycles, prolonged gestation and decreased parturition index compared to control group, which were not observed after n-BMA exposure.

In an oral pre-natal developmental toxicity study in rabbits, n-BMA caused abortions, decreased foetal body weight and bone alterations in the foetuses at the dose level that caused maternal toxicity (1000 mg/kg bw/day) whereas MMA administration did not cause any adverse effects on foetuses. However, the highest dose of MMA tested was 450 mg/kg bw/day and therefore, the potential developmental effects of higher doses of MMA on rabbits remains unclear. Similarly, in an inhalation pre-natal developmental toxicity study in rats, n-BMA exposure showed decreased foetal body weight and skeletal variations at 600 ppm and higher concentrations whereas MMA had no effects on foetuses at 2038 ppm.

The results show that both 2-EHMA and n-BMA have adverse effects on the development and/or fertility. In addition, combined repeated dose toxicity studies with the reproduction/developmental toxicity screening test (OECD 422) suggests that 2-EHMA has more severe effects on fertility than n-BMA. ECHA concludes that based on the studies submitted, it is likely that 2-EHMA has more severe effects on the reproductive toxicity than the source substances MMA and n-BMA.

Hence, the Registrant proposes read-across from a less toxic substance, which would, in case read-across approach was accepted, most likely lead to an underestimation of the hazard of the registered substance and thereby not allow to be adequate for the purpose of classification and labelling and risk assessment as foreseen by Annex XI, 1.5 of the REACH Regulation.

e. Conclusion on the grouping of substances and read-across approach for human health endpoints

ECHA concludes that the grouping and read-across approach for the Basic Short Chain (Lower) Alkyl Methacrylates is not adequately and reliably documented as the analysis of the structural differences of parent compounds and the corresponding alcohol metabolites and their impact on the properties and (eco)toxicity profile of the category members is missing.

Consequently, ECHA considers that the category "Basic Short Chain (Lower) Alkyl Methacrylates" does not fulfil the requirement defined in Annex XI, 1.5. of following a regular pattern as a result of structural similarity and does not allow the Registrant to meet the objective pursued by the REACH Regulation.

ECHA concludes that the Registrant has not demonstrated that the properties/adverse effects of the registered substance can be predicted from the source substance(s) within the group irrespective of the status of these substances under other legal/assessment systems. ECHA notes that the Registrant has provided a generic read-across justification without a clear distinction to the specific endpoints. ECHA stresses that, in so far as the prediction possibility may vary from one endpoint to another, read-across justification shall be endpoint-specific.

According to Annex XI, 1.5., there is a prerequisite that the results of a grouping of substances and read-across approach should in all cases be adequate for the purpose of classification and labelling and/or risk assessment. As explained above this cannot be concluded for the case at hand.

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements in the technical dossier, based on the read-across and grouping of substances, does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5. Consequently, where an adaptation according to Annex XI, 1.5. has been presented by the Registrant, the information in the technical dossier is not sufficient to comply with the standard information requirements.

Irrespective of the unsuitability of the grouping approach, ECHA has considered the read-across approach separately for each endpoint in which this approach has been applied.

Non-compliance of individual endpoints listed in Annexes VII to X.

1. ***Skin irritation (Annex VII, Section 8.1): in vitro study for skin irritation (test method: OECD TG 439***

"Skin irritation or corrosion" is a standard information requirement as laid down in Annex VII, Section 8.1. of the REACH Regulation: "The assessment of this endpoint shall comprise the following consecutive steps: (1) an assessment of the available human and animal alternative data, (2) an assessment of the acid or alkaline reserve, (3) *in vitro* study for skin corrosion, (4) *in vitro* study for skin irritation". Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. "*In vivo* skin irritation" is a standard information requirement as laid down in Annex VIII, Section 8.1.1. of the REACH Regulation, but it may be adapted based on the information obtained as specified in section 8.1 of Annex VII. 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 the Registrant has provided two study records conducted with the registered substance subject to the present decision for skin irritation conducted according to 1) and 2). However, these studies do not provide the information required by Annex VIII, Section 8.1.1., due to reasons explained below.

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.

While the Registrant has not explicitly claimed an adaptation pursuant to Annex XI, 1.1.2., he has provided information that could be interpreted as an attempt to do so. However, ECHA notes that this adaptation does not meet the general rules for adaptation of Annex XI, 1.1.2.(1)(2) and (3) because as the Registrant himself indicates (*"Although the observation period of the two available studies was too short to establish reversibility..."*), the observation period being too short to adequately and reliably assess the reversibility of the effects. Therefore the results are not adequate for classification and labelling and/or risk assessment (see below).

Furthermore, ECHA notes that the argument provided by the Registrant tries to combine the studies (found to be insufficient by themselves) with a read-across argument, thus claiming weight of evidence (Annex XI, Section 1.2.). An adaptation based on weight of evidence would require that there are several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property while the information from a single source alone is regarded insufficient to support this notion.

According to the first study, the registered substance is not irritating but it is slightly irritating according to the second study result as erythema and edema were not fully reversible within 72 hours. The Registrant concludes the following: *"Although the observation period of the two available studies was too short to establish reversibility, by analogy to the other esters of the category, for which reversibility has been established, it is assumed that the skin irritation caused by 2 -EHMA will be reversible".*

The studies conducted according to [redacted] (second study) may be used for classification purposes although the study protocol deviates from the OECD 404 guideline. However, according to the Guidance on the Application of the CLP Criteria (EC) No 1272/2008, Version 4.0, 2013, "*in case of pronounced responses at the 72 hours time point an expert judgement is needed as to whether the data is appropriate for classification*".

ECHA notes that the proposed read-across approach is not sufficiently justified by the Registrant as explained in section III.0.d above. Moreover, the Registrant's approach to use the read-across substances to support the reversibility and non-irritating property of the registered substance is illogical as the other category members are classified either as skin irritant or corrosive.

Therefore, as the studies submitted are not adequate and reliable and the read-across approach is not acceptable, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

As explained above, the information available 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.

In his comments the Registrant agreed to conduct the originally requested study for *in vivo* skin irritation according to test method EU B.4/OECD TG 404.

A proposal for an amendment was submitted by a Member State Competent Authority to remove the request for an *in vivo* skin irritation test and to replace the request with an *in vitro* skin irritation test (OECD TG 439). ECHA agrees on the proposal for amendment to change the request from an *in vivo* skin irritation study to an *in vitro* skin irritation study, for the reasons given below:
Firstly, for the present registration in the tonnage band above 1000 tonnes, the information generation should start with the Annex VII information requirement. Only in case it is not possible to conclude on the skin corrosion/irritation endpoint based on the information specified in Annex VII, section 8.1., information would need to be generated according to Annex VIII, section 8.1. This means that the Annexes shall thus be considered as a whole, and in conjunction with the overall requirements of registration, evaluation and the duty of care (ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.2.2.2 (October 2015)). In particular the guidance states as follows:

"*Before new tests are carried out to determine the properties listed in Annex VIII, all available in vitro data, in vivo data, historical human data, data from valid (Q)SARs and data from structurally related substances (read-across approach) must be assessed first. Due to the sequential nature of the REACH standard information requirements, the reader is reminded that at quantities of ≥10 tpa, the information requirements of Annex VII to the REACH Regulation also apply. This means that before a new in vivo test is performed, the appropriate in vitro testing must be undertaken according to the rules set out in section 8.1 of Annex VII and must be documented in the technical dossier (IUCLID). Finally, the information generated at Annex VII level must be taken into account in determining whether an in vivo test at Annex VIII level is really needed*".

Secondly, the choice of the *in vitro* test to be performed is justified based on the *in vivo* studies provided in the dossier, as it does not provide indications that the substance could be corrosive to the skin. Therefore, information obtained from *in vitro* skin irritation test alone is sufficient to conclude on the skin corrosion/irritation endpoint, and there is no need to generate separately the information on *in vitro* skin corrosion (Annex VII, 8.1, column 1, step 3).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision:

in vitro study for skin irritation (test method: OECD TG 439).

2. Pre-natal developmental toxicity study (Annex IX, 8.7.2.)

A pre-natal developmental toxicity study 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.

The Registrant has not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

In the technical dossier the Registrant has provided a study record for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) conducted with the registered substance. 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.

Furthermore, the Registrant has sought to adapt this information requirement and has provided study records for pre-natal developmental toxicity studies conducted with the proposed read-across substance butyl methacrylate (n-BMA) via oral (rabbit) and inhalation (rat) routes. Due to more toxic effects caused by 2-EHMA compared to n-BMA the read-across approach for pre-natal developmental toxicity endpoint is not acceptable and thus the justification of the adaptation given by the Registrant does not meet the general rules for adaptation of Annex XI, 1.5. as explained in detail in section III.0.d. above.

Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

As explained above, the information available 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 the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

In his comments the Registrant agreed to conduct the requested study.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 414) in rats or rabbits by the oral route.

Notes for consideration by the Registrant:

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if weight of evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that no study on a second species is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2.

B. Information related to the chemical safety assessment and chemical safety report

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

1. Identification of DNEL (Annex I, Section 1.4.)

Article 14(3)(a) and Annex I, Section 1.4.1. of the REACH Regulation require the Registrant to establish DNEL(s) "*reflecting the likely route(s), duration and frequency of exposure*". It is also required that "*taking into account the available information and the exposure scenario(s) in Section 9 of the Chemical Safety Report it may be necessary to identify different DNELs for each relevant human population (e.g. workers, consumers and humans liable to exposure indirectly via the environment) and possibly for certain vulnerable sub-populations (e.g. children, pregnant women) and for different routes of exposure.*"

Further, Annex I, Section 1.4.1 of the REACH Regulation requires that the following factors shall, among others, be taken into account when deriving DNELs:

a) the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
b) the nature and severity of the effect;
c) the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
d) and that the DNELs reflect the likely route(s), duration and frequency of exposure.

The ECHA Guidance on information requirements and chemical safety assessment Chapter R.8 (version 2.1, November 2012) provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information to fulfil the REACH obligations.

ECHA notes that the Registrant has disregarded the DNEL derivation for the inhalation route since he concluded that "*based on phys-chem properties and toxicokinetic information, the inhalation pathway is not considered a relevant route of exposure*". However, ECHA notes that his conclusion is not supported by the data provided by the Registrant:

- the vapour pressure provided for the registered substance is not very low (6.5 Pa at 20 C);
- the Registrant himself has stated that the registered substance is of "*high volatility*" considering the results obtained for the Henry's law constant (07 Pa m^3/mol);
- process categories in the exposure scenarios indicate exposure via inhalation route during activities like roller and brushing application, loading, transfer or dumping (e.g. PROCs 5, 8a, 8b, 9, 10) and the consequent risk for workers cannot be excluded.

Thus, ECHA notes that the inhalation route is a relevant route of exposure and a risk assessment of the substance including the inhalation route needs to be performed to demonstrate that the registered substance is used safely and consequently, the Registrant needs to derive DNEL(s) for the exposure via the inhalation route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to derive long-term DNEL(s) for workers, inhalation route, using the default assessment factors and other recommendations of ECHA Guidance R.8 for DNEL derivation and revise the risk characterisation accordingly.

Notes for consideration by the Registrant

The results of the studies requested with this decision shall be taken into account when deriving the DNELs.

2. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.)

According to Article 14(4), the CSR must include an exposure assessment and risk characterisation, if the substance is assessed to be a PBT or vPvB or fulfils the criteria for any of the hazard classes or categories set out in Annex I to Regulation (EC) No 1271/2008.

Annex I section 5 of the REACH Regulation requires the Registrant to generate exposure scenarios and exposure estimations for the registered substance. Each relevant route of human exposure (inhalation, oral, dermal and combined through all relevant routes and sources of exposure) shall be addressed.

Annex I section 6 of the REACH Regulation requires the Registrant to characterise the risk for each exposure scenario and shall 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 reasonably foreseeable, under the assumption that the risk management measures described under exposure scenario in the Section 5 have been implemented. The risk characterisation includes the comparison of the exposure of each human population known to be or likely to be exposed with the appropriate DNEL.

The Registrant classified the substance as Skin Irrit. 2, Eye Irrit. 2, Skin Sens. 1, STOT Single Exp. 3 (inhalation, respiratory tract) and Aquatic Chronic 3 and therefore needs to include an exposure assessment and a risk characterisation in the CSR.

ECHA notes that the Registrant did not generate an exposure assessment and risk characterisation for the exposure via the inhalation route since he concluded that "*based on phys-chem properties and toxicokinetic information, the inhalation pathway is not considered a relevant route of exposure*". However, as explained above in section B.1. of the present decision, this is not supported by the data provided by the Registrant. Thus, a risk for workers by exposure via the inhalation route cannot be excluded and an exposure assessment and risk characterisation of the substance including the inhalation route needs to be performed to demonstrate that the registered substance is used safely.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation of the REACH Regulation, the Registrant is requested to generate an exposure assessment and risk characterisation for human health including the exposure via the inhalation route. The chemical safety report shall be amended accordingly.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all 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 substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

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

Authorised1 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.