ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114312795-47-01/F Helsinki, 10 December 2015

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

For butyl methacrylate, CAS No 97-88-1 (EC No 202-615-1), 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 butyl methacrylate, CAS No 97-88-1 (EC No 202-615-1), 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 23 March 2015 the Registrant updated his registration with the submission number [redacted] concerning the information requirements of Annex VIII, 8.4.3., Annex IX, 9.1.6.1., Annex IX, Section 9.4.1., Annex IX, Section 9.4.2., Annex IX, Section 9.4.3. and Annex I, Section 3.3.

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.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) 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 VIII, IX, X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

***In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.; test method: EU B.17./OECD 476).**

B. 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 19 December 2016**. 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 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.

1. 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 [redacted] The Registrant states that the substances are typically of [redacted]% purity and the impurities consist of water and 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 endpoint: *In vitro* gene mutation study in mammalian cells.

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 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. In addition, an ECETOC Special report no. 14: n-Butyl Methacrylate, Isobutyl Methacrylate, OEL Criteria Document, and ECETOC report on Joint Assessment of Commodity Chemicals No. 36, n-Butyl Methacrylate, Isobutyl Methacrylate has been provided.

c. ECHA analysis of the grouping approach 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 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 as members of the category fall within the scope of this applicability domain presented 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 properties of the *in vitro* gene mutation in mammalian cells of the substance subject to this decision from data generated with other members of the category. Instead, ECHA considers that 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, adequate data has to be provided that allows 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 for human health endpoints

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.

For the *in vitro* gene mutation study in mammalian cells endpoint, the Registrant has provided a study record for a gene mutation study in mammalian cells conducted with a read-across substance 2-ethylhexyl methacrylate, 2-EHMA, and a justification based on the on the metabolism of lower methacrylate esters to methacrylic acid and the respective alcohol in several tissues, and states that "*In vitro gene mutation assays in mammalian cells, test method OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test), are available for category members: methyl methacrylate (CAS 80-62-6); ethyl methacrylate (CAS 97-63-2) and 2-ethyl-hexyl methacrylate (CAS 688-84-6)*" for which study records have been provided in the "Category CSR". In the Methacrylates Category Document he further refers to the EU Risk Assessments of MAA and MMA and the OECD SIAR and concludes that "*it can be concluded that all members of the category are not mutagenic or genotoxic and that there are no relevant data gaps*".

ECHA notes that since no data has been provided to explain the impact of the different structures of the category members and their alcohol metabolites on this endpoint, the read-across approach is not acceptable.

In the updated dossier, the Registrant provides further justification for the read-across approach regarding *in vitro* gene mutation in mammalian cells:

- testing is considered "*unnecessary due to the common and similar level of chemical reactivity of the lower alkyl methacrylates and the absence of any alerts whatsoever from the parent ester or both primary metabolites (see later discussion) to suggest that nBMA should be regarded any different than the other esters in the category*.
- n-BMA is not regarded as genotoxic since it does not induce chromosome aberrations *in vitro* and *in vivo*.
- the lower alkyl methacrylates have a common mode of chemical reactivity via the C=C double bond and Michael addition and as such this lends them the potential to be chemically reactive towards macromolecules such as protein and DNA though a mechanism of electrophilic attack. It has also been established that these esters are subject to hydrolysis by ubiquitous carboxylesterases. The resultant acid and alcohol metabolites are non genotoxic.
- read-across from negative results of MMA and 2-EHMA can be used to conclude that both n-BMA and i-BMA do not induce gene mutations.

ECHA notes that the Registrant states that testing n-BMA for gene mutation in mammalian cells is not necessary due to "*common and similar level of chemical reactivity*" of the category members and lack of any alerts from the parent ester or both primary metabolites.

ECHA notes that all category members do have the same double C=C bond and Michaels addition as explained by the Registrant. However, as also pointed out by the Registrant, the category members hydrolyse to methacrylic acid (MAA) and corresponding alcohols. The Registrant claims that there are no alerts for genotoxicity and that the metabolites are not genotoxic. However, ECHA notes that there is no data on *in vitro* gene mutation mammalian cells for MAA, i-BMA, i-butanol and n-butanol to support the Registrant's claim. ECHA further notes that results from the bacterial gene mutation and chromosome aberration

tests cannot be used to predict the mutagenicity of n-BMA in mammalian cells.

e. Conclusion on the grouping of substances and read-across approach

ECHA considers that the Registrant has not provided sufficient data to support the read-across approach regarding *in vitro* gene mutation in mammalian cells.

ECHA therefore concludes that the requirements of Annex XI, 1.5. are not met, and the read-across approach, as presented by the Registrant, is not acceptable.

2. Non-compliance with the endpoint 'In vitro gene mutation study in mammalian cells' (Annex VIII, 8.4.3.)

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained. ECHA notes that the registration dossier contains negative results for both of these information requirements. Therefore, 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 an *in vitro* gene mutation study in mammalian cells in the dossier that would meet the information requirement of Annex VIII, Section 8.4.3.

The Registrant has sought to adapt this information requirement and has provided a study record for a gene mutation study in mammalian cells conducted with a read-across substance 2-ethylhexyl methacrylate, 2-EHMA.

However, 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 section III.1.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.

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* mammalian cell gene mutation test (test method: EU B.17./OECD 476)

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.