EUROPEAN CHEMICALS AGENCY

Helsinki, 19 August 2016

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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For ethyl methacrylate, CAS No 97-63-2 (EC No 202-597-5)

Addressees: Registrant(s)[1] of ethyl methacrylate

This decision is addressed to the Registrant(s) of the above substance with active registrations pursuant to Article 6 of the REACH Regulation on the date on which the draft for the decision was first sent for comments. If Registrant(s) ceased manufacture upon receipt of the draft decision pursuant to Article 50(3) of the REACH Regulation, they did not become addressee(s) of the decision. A list of all the relevant registration numbers of the Registrant(s) that are addressees of the present decision is provided as an Annex to this decision.

Based on an evaluation by National Institute of Health on behalf of Ministry of health as the Competent Authority of Italy (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 20 March 2015, i.e. the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of Italy has initiated substance evaluation for ethyl methacrylate (EMA), CAS No 97-63-2 EC No 202-597-5 based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Human health/suspected CMR, sensitiser; Exposure/Wide dispersive use, consumer use, high (aggregated) tonnage ethyl methacrylate was included in the

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.

Community Rolling Action Plan (CoRAP) for substance evaluation to be evaluated in 2014. The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of Italy was appointed to carry out the evaluation.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns.

Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 26 March 2015

On 7 May 2015 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

Registrant(s) commenting phase

By 12 June 2015 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay.

The evaluating MSCA took into account the comments received from the Registrant(s) and where considered appropriate the draft decision has been amended accordingly.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH regulation, on 3 March 2016 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, some Competent Authorities of the Member States and ECHA submitted comments and proposals for amendment to the draft decision. The evaluating MSCA has reviewed the proposals for amendment received and where considered appropriate the draft decision has been amended accordingly.

On 8 April 2016 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

Referral to the Member State Committee

On 18 April 2016 ECHA referred the draft decision to the Member State Committee.

By 10 May 2016, the Registrant(s) provided comments on the proposals for amendment, in accordance to Article 51(5) and on the draft decision. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposal(s) for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposal(s) for amendment made and are therefore considered outside the scope of Article 51(5).

A unanimous agreement of the Member State Committee on the draft decision was reached on 23 May 2016 in a written procedure launched on 13 May 2016.

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

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test methods and instructions (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

1. *In vitro* gene mutation study in bacteria (test method: Bacterial reverse mutation test, OECD 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102, as specified in section III;
2. *in vitro* Mammalian Cell Micronucleus study (test method: OECD 487);
3. *in vitro* gene mutation study in mammalian cells (test method: OECD 476 or OECD 490), provided that both studies requested under 1. and 2. have negative results;
4. update of the registration dossier with relevant and available information on skin sensitization.

Deadline for submitting the required information

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **27 November 2017** an update of the registration(s) containing the information required by this decision[2], including robust study summaries and, where relevant, an update of the Chemical Safety Report.

The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

To clarify the suspected concerns for mutagenicity and carcinogenicity (and as a consequence the risk assessment to perform (DMEL or DNEL derivation for risk characterisation), ECHA adopted a tiered approach. The first step will be the evaluation of the *in vitro* genotoxicity potential of ethyl methacrylate (EMA).

The available information on mutagenicity is conflicting as explained further below. The information requested in this decision is necessary to elaborate reliable exposure scenario(s) in the registration dossier(s). Indeed, pending the results of the studies required below, the potential need of a DMEL (derived minimum effect level) derivation instead of a DNEL (derived no effect level) could significantly influence the elaboration of the exposure scenarios in the registration dossier(s). In case of positive results in the *in vitro* studies requested in this decision, there may be a need to follow up on these results with *in vivo* studies pursuant to Article 46(3) of the REACH Regulation possibly leading to a proposal for a harmonised classification for mutagenicity of the substance under Regulation (EC) No 1272/2008.

[2] The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).

Therefore ECHA judged that more information is required to clarify the identified concerns.

1. *In vitro* gene mutation study in bacteria (test method: Bacterial reverse mutation test, OECD 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102, as specified below

Two bacterial reverse mutation assays are available for EMA (Zeiger et al, 1987 and Waegemaekers et al, 1984). These two studies showed negative results but were performed before the publication of the current version of the OECD 471 guideline, therefore the strain set is incomplete according to the current guideline. The Registrant(s) are requested to perform the test on the missing strain of S. Thyphimurium TA102 or in E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101) as reported in the updated OECD 471 guideline.

In the comments to the draft decision, the Registrant(s) stated that retesting EMA for bacterial mutagenicity is unnecessary. In fact, the Registrant(s) deem that the read-across between EMA (claimed member of the C1 to C8 lower alkyl methacrylate, LAME category) and structurally related chemicals can be made to satisfy this endpoint thereby avoiding further testing.

ECHA considers that the arguments provided in the latest dossier update considered for the present evaluation are not sufficient to sustain a read-across approach for genotoxicity in vitro. The read-across justification presented is not in accordance with the requirements of Annex XI, 1.5 of REACH as it does not provide adequate basis for predicting properties of the registered substance from the data obtained with other substances. In particular, the current read-across adaptation is rejected because of (i) lack of analysis of structural differences and the impact of these differences for the category members and the possibility to predict their properties, (ii) lack of data on the corresponding alcohol metabolites and (iii) no endpoint specific justification for the proposed read-across. Moreover, in the comments to the draft decision, the Registrant(s) have "*proposed to update the EMA* [ethyl methacrylate] *dataset with the extended information from the revised category assessment*". However, this update was not made available in the registration dossier of EMA by the date until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are requested to perform an i*n vitro* gene mutation study in bacteria on the registered substance (test method: Bacterial reverse mutation test, OECD 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102, as specified above.

2. *in vitro* Mammalian Cell Micronucleus study (test method: OECD 487)

The available mammalian *in vitro* studies for EMA are the following:

- Mouse Lymphoma (gene mutation on L5178Y) (Moore et al, 1988 and Dearfield et al, 1989) positive but at concentration where the survival was less than 20%
- Chromosomal Abberation (CA) in CHO cells ([redacted]) negative
- CA in mouse lymphoma cells (Moore et al, 1988) weakly positive and non-linear response (cytotoxicity not reported)
- Sister Chromatid Exchange (SCE) in CHO cells, positive (1986, from OECD/SIDS)

While the bacterial studies were negative, mammalian *in vitro* studies, in particular addressing clastogenicity, gave positive results. However, it is not clear whether these positive outcome were a true indication of clastogenicity or were due at least in part to a

secondary effect of cytotoxicity. Therefore an *in vitro* micronucleus assay is requested in order to verify the genotoxic potential of the substance in mammalian cells.
In their comments to the draft decision the Registrant(s) considered methyl methacrylate (MMA) data as conclusive for assessing the in vivo genotoxicity of EMA. However, it is noted that the in vivo genotoxicity of MMA is still under evaluation.
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are requested to perform an *in vitro* micronucleus test, on the registered substance in accordance with the current 487 OECD guidelines.

3 *In vitro* gene mutation study in mammalian cells (test method: OECD 476 or OECD 490), provided that both studies requested under 1. and 2. have negative results.

In order to clarify the above mentioned concern, ECHA adopted a tiered approach and requires the Registrant(s) to perform two *in vitro* studies on EMA, performed in compliance with the current OECD guidelines: a bacterial reverse mutations assay on the missing strain (as reported in point 1 above) and an *in vitro* micronucleus test (as reported in point 2 above).

In case of negative results in both studies, a third *in vitro* gene mutation study is required before concluding on the genotoxic potential of the substance as studies currently available in the dossier are not sufficient.

ECHA notes that two *in vitro* gene mutation studies in mammalian cells are provided in the dossier for the registered substance. However, the first study (Dearfield et al, 1989, similar to OECD 476) was carried out on the registered substance but is deviating from the test guideline as it was performed only without metabolic activation and missing positive controls. Therefore, this study can not be considered adequate to cover the information requirement for this endpoint.

The second study ([redacted], a GLP study according to OECD 476) was performed on an analogue substance (2-ethylhexyl methacrylate) and it is considered invalid for EMA since the read-across justification presented is not in accordance with the requirements of Annex XI, 1.5 of REACH as it does not provide adequate basis for predicting properties of the registered substance from the data obtained with other substances. In particular, the current read-across adaptation is rejected because of (i) lack of analysis of structural differences and the impact of these differences for the category members and the possibility to predict their properties, (ii) lack of data on the corresponding alcohol metabolites and (iii) no endpoint specific justification for the proposed read-across. Moreover, in the comments to the draft decision, the Registrant(s) have "*proposed to update the EMA* [ethyl methacrylate] *dataset with the extended information from the revised category assessment*". However, this information was not made available in the registration dossier(s) of EMA considered for this decision.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are requested to perform an *in vitro* gene mutation study in mammalian cells on the registered substance (test method: OECD 476 or OECD 490), provided that both studies requested under 1. and 2. have negative results.

Note for consideration of the Registrant(s)

As reported above, this decision is based on the registration dossier(s) of 20 March 2015. While not related to any proposal for amendment submitted by a Member State competent authority or ECHA and thus outside the scope of the consultation pursuant to Article 51(5)

of the REACH Regulation, the following observations can be made towards the comments submitted in May 2016: The Registrant(s) suggest to take into account the recent modification and update of the read-across justification document. This updated justification for read-across will be taken into account in the course of the follow up of the substance evaluation process in accordance with Article 46(3) as the testing requested might be subject to adaptation provided that such adaptation has a scientific justification and an adequate and reliable documentation.

Moreover, in case of positive finding(s) *in vitro*, suitable *in vivo* study(ies) will be requested in order to verify if the genotoxic potential is expressed also *in vivo*. These results can trigger a classification for mutagenicity and possibly also the type of risk assessment to perform (DNEL or DMEL derivation for risk characterisation). For *in vivo* genotoxicity and for carcinogenicity studies the Registrant(s) proposed a category-based read-across approach. In particular, experimental data on substances within the OECD category of short-chain alkyl methacrylates are considered in order to address the concerns for EMA.

The available information for *in vivo* genotoxicity studies are the following:

- No data on EMA
- Most available studies on the reference substance methyl methacrylate (MMA) were performed before the publication of the current OECD guidelines and gave ambiguous results ([redacted] while the dominant lethal assay on MMA is negative ([redacted])
- the only recent MN study ([redacted]) has not been taken into account by ECHA because the read across with n-butyl methacrylate (n-BMA) is not considered acceptable. The main weaknesses of the read across approach were identified as (i) lack of analysis of structural differences and the impact of these differences for the category members and the possibility to predict their properties; (ii) lack of data on the corresponding alcohol metabolites; (iii) no endpoint specific justification for the proposed read-across (as reported above).

Further consideration on the need for the *in vivo* genotoxicity studies and on carcinogenicity will be made on the basis of the results on the *in vitro* genotoxicity studies requested with this decision. Negative results in the *in vitro* genotoxicity will overrule the initial concern for mutagenicity.

4. Update of the registration dossier with relevant and available information on skin sensitisation.

The available data for skin sensitisation in the registration dossier(s) are generally old and detailed information about the studies and results islacking.

A MSCA submitted a proposal for amendment suggesting that new, recently published and relevant data for skin sensitisation on EMA should be taken into consideration.

Therefore the Registrant(s) are required to update the registration dossier(s) with relevant and available information on skin sensitisation of EMA in humans. Based on these data the Registrant(s) may need to amend the chemical safety report in case the new data will influence the existing classification and whether a sub-categorisation for skin sensitisation in either category 1A or 1B is applicable.

In response to the proposal for amendment the Registrant(s) indicated their agreement to update the registration dossier for this end-point and at the same time to evaluate a possible sub-categorisation for skin sensitisation.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental studies, the sample of the substance to be used shall have a composition that is within the specifications of the substance compositions that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the tests subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the tests must be shared by the Registrant(s).

V. Avoidance of unnecessary testing by data- and cost-sharing

In relation to the experimental studies the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at: https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/datasharing_en.asp.

If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrants to perform the stud(y/ies) on behalf of all of them.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 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 the 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.

Authorised[3] by Leena Ylä-Mononen, Director of Evaluation

Annex: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

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

References

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K, Speck W, *Salmonella* Mutagenicity tests: III. Results from the testing of 255 chemicals, Environmental and Molecular Mutagenesis (1987), Volume 9, Issue Supplement S9, 62-109.

Waegemaekers THJM, Bensink MPM, Non-mutagenicity of 27 aliphatic acrylate esters in the Salmonella-microsome test, Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis (1984), 137(2-3):95-102.

Moore MM, Amtower A, Doerr CL, Brock KH, Dearfield KL, Genotoxicity of Acrylic Acid, Methyl Acrylate, Ethyl Acrylate, Methyl Methacrylate, and Ethyl Methacrylate in L51778Y Mouse Lymphoma Cells, Environ. Mol. Mutagen. (1988) 11: 49-63.

Dearfield KL, Millis CS, Harrington-Brock K, Doerr CL, Moore MM, Analysis of the genotoxicity of nine|acrylate/ methacrylate compounds in L5178Y mouse lymphoma cells, Mutagenesis (1989), 4(5): 381-393.