Helsinki, 19 December 2018

Substance name: Methyl salicylate
EC number: 204-317-7
CAS number: 119-36-8
Date of Latest submission(s) considered[1]: 14 March 2016
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
The present decision is addressed to all registrants of the substance

DECISION ON SUBSTANCE EVALUATION

1. Requested information

Based on Article 46(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), you are requested to submit the following information on the registered substance:

1.1 **Eye irritation and human health risk assessment:**

1.1.1 Short time exposure (STE) *in vitro* test method for identifying i) chemicals inducing serious eye damage and ii) chemicals not requiring classification for eye irritation or serious eye damage (test method: OECD 491).

1.1.2 Update of the DNELs and the risk characterisation for human health, as specified in Appendix 1.

You shall provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the Chemical Safety Report by **26 June 2019**. The deadline takes into account the time that you, the Registrant(s), may need to agree on who is to perform any required tests.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision.

2. Who performs the testing

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all Registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

[1] This decision is based on the registration dossier(s) at the end of the 12 month evaluation period

3. Appeal

You can appeal this decision to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals

Authorised[2] by Leena Ylä-Mononen, Director of Evaluation

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

Appendix 1: Reasons

Based on the evaluation of all relevant information available for methyl salicylate and other relevant available information, ECHA concludes that further information is needed in order to enable the evaluating Member State Competent Authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to human health and the environment.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in order to clarify the concern for eye irritation.

As explained in the initial draft decision the evaluating MSCA also has a concern for endocrine disruption. Therefore, in the initial draft decision the evaluating MSCA requested for a larval amphibian growth and development assay (test method OECD 241) as well as a Fish sexual development test (test method OECD 234).

In your comments to the draft decision you indicated among others that any endocrine disrupter testing based on concerns for salicylic acid (SA) as premature and are of the opinion that the conclusion on the ED assessment of SA performed in the scope of the Biocidal Products Regulation (BPR), according to the new scientific criteria, should be awaited.

The evaluating MSCA is aware that the possible endocrine disrupting properties of salicylic acid are currently being assessed within the scope of the BPR. On this basis the evaluating MSCA agrees to wait for the outcome of the ED assessment for SA before including requests for the possible ED concern for methyl salicylate. On this basis, the requests to investigate the ED concern for methyl salicylate have been removed. ECHA however informs the registrant that, based for example on the outcome of the ED assessment for SA under the BPR, it may issue a new substance evaluation decision requesting further information to clarify the ED concern for methyl salicylate.

1.1. Eye irritation and human health risk assessment

ENDPOINT 1.1.1: EYE IRRITATION

<u>The Concern Identified</u>
Contradictory eye irritation results were found with methyl salicylate but none of the available study is considered as fully acceptable. In one eye irritation study (Longobardi, 2001) submitted by the Registrant as a key study, chemosis, discharge and redness of the conjunctiva (score of 1) were only observed at 1 hour, but not thereafter. Since this result was not confirmed in 2 additional animals as recommended in the OECD TG 405, no final conclusion can be made from this study. In contrast, additional data report ocular irritation but were assigned with a reliability of 3 or 4 due to very low level of details and/or major deficiencies in the experimental design. Contradictory results were also reported for methyl salicylate in the Cosmetic Ingredient Review (Cir, 2003).

Hazards could be predicted from salicylic acid, which is the main hydrolysis product of methyl salicylate. In June 2015, a classification as Eye Damage 1 was agreed by the

Committee for Risk Assessment (RAC) for this substance. Even if it cannot be totally assumed that methyl salicylate needs to be classified in the same way that salicylic acid, this raises a concern that methyl salicylate could also be an eye irritant.

At this time, no harmonized classification is available for methyl salicylate and no consensus has been reached among the notified classifications for eye irritation. Considering the wide dispersive uses of methyl salicylate, in particular consumer uses, a potential risk of eye splashes cannot be excluded and adequate harmonized classification and labelling are needed to ensure a safe use.

Why new information is needed

Considering the available information described above, no final conclusion can be made on eye irritation properties of methyl salicylate. This is reflected by the different self-classifications notified in the Classification and Labelling Inventory for methyl salicylate showing that the notifiers were unable to come to an agreement. Read-across to salicylic acid raises the concern that methyl salicylate can also induce eye damage. This effect might be due to methyl salicylate itself or be secondary to hydrolysis, if enough salicylic acid is produced when methyl salicylate enters in contact with the eye. However, it is not clear if the classification as Eye Dam. 1 of salicylic acid can directly be extrapolated to methyl salicylate or if methyl salicylate requires a lower/no classification.

In conclusion, a concern for eye damage/irritation is identified for methyl salicylate and a new eye irritation study is required. This study will allow to conclude on the need of a harmonized classification in the absence of consensus in the current self-classifications. Therefore, this request can result in implementation of new risk management measures (i.a. labelling, personal protective equipment) to ensure a safe use of methyl salicylate and control the potential risk.

Considerations on the test method and testing strategy

The Registrant(s) are required to perform a Short time exposure (STE) *in vitro* test method OECD 491. The aim of this study is to identify substances inducing serious eye damage (CLP classification category 1) as well as those that do not require classification for either serious eye damage or eye irritation. In case of equivocal results in this OECD 491 study, the evaluating MSCA will potentially propose suitable assay(s) in a succeeding decision to establish a definitive classification.

Alternative approaches and Proportionality of the request

Since the purpose of the Short time exposure (STE) *in vitro* test is to identify the need of a classification, this study adequately responds to the concern identified for methyl salicylate. Other *in vitro* tests for ocular irritation also exist, such as reconstructed human cornea-like epithelium (RhCE) test method (OECD TG 492), isolated chicken eye test method (OECD TG 438) and bovine corneal opacity and permeability test method (OECD TG 437). These studies can be proposed by the registrant as an alternative of the required STE test but should be scientifically justified in the light of the limitations described in the corresponding test guidelines. Finally, the request is judged proportionate since no testing on animals will be involved and considering the wide dispersive uses of the methyl salicylate leading to a potential eye exposure.

Consideration of Registrants' comments
In your comments you recognize that the data may lead to different conclusions regarding the classification and that none are fully acceptable. Thus, you agree to conduct the required test.

Conclusion
Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the registered substance subject to this decision: Short time exposure (STE) *in vitro* test method for identifying i) chemicals inducing serious eye damage and ii) chemicals not requiring classification for eye irritation or serious eye damage (test method: OECD 491).

ENDPOINT 1.1.2: UPDATE OF THE DNELS AND THE RISK CHARACTERISATION FOR HUMAN HEALTH

The Concern Identified
New data related to reproductive and developmental toxicity (available in FDA review (2006)) have been made available by the Registrant(s) during the commenting period on the first draft decision. However the Chemical Safety Assessment (CSA) has not been updated yet in order to include these new data and assess their potential impact on risk assessment. Indeed, a higher risk for workers and consumers can be anticipated if these new data lead to a reduction of the DNELs.

Why new information is needed
You are requested to consider the new data to recalculate the DNELs if appropriate, and to re-iterate the risk characterisation for worker and consumers. The information currently available in the registration dossier is not sufficient to enable the evaluating MSCA to perform such an assessment, because there are several flaws in the current exposure assessment and risk characterisation (refer to separate decisions on exposure-related requests) and because the evaluating MSCA does not have a sufficient knowledge of the real use conditions to be able to iterate the risk characterisation.

What is the possible regulatory outcome

Update of the CSA and Chemical Safety Report (CSR) is necessary to communicate appropriate conditions of safe use of substances along the supply chain.

Consideration of Registrants' comments
In your comments, you agree to make every effort to gain access to the requested data, and to update the dossier based to the data legally available to you.

Conclusion
You are requested to consider the new data to recalculate the DNELs if appropriate, and to re-iterate the risk characterisation for worker and consumers so as to demonstrate safe use, also taking into account requests 1 of the separate decisions on exposure-related requests as appropriate.

Deadline to submit the requested Information

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a larval amphibian growth and development assay (test method OECD 241) and a Fish sexual development test (test method OECD 234). As these studies are not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration is 6 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

References

Cosmetic Ingredients Review (CIR) Expert Panel. 2003. Safety Assessment of Salicylic Acid, Butyloctyl-, Calcium-, C12-15 Alkyl Salicylate, Capryloyl Salicylic Acid, Hexyldodecyl-, Isocetyl-, Isodecyl-, Magnesium-, MEA-, Ethylhexyl-, Potassium-, Methyl, Myristyl-, Sodium-, TEA-, and Tridecyl Salicylate. Int J Toxico.; 22(S3):1-108.

Food and Drug Administration (FDA). Center for Drug Evaluation and Research. 2006. Pharmacology / Toxicology review and evaluation. FS-67 Patch (10% Methyl salicylate & 3% l-menthol Topical patch). NDA number 22-029.

Other references listed in this draft decision are provided in the registration dossier.

Appendix 2: Procedural history

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, exposure/consumer use and aggregated tonnage, methyl salicylate CAS No 119-36-8 (EC No 204-317-7) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2015. The updated CoRAP was published on the ECHA website on 17 March 2015. The Competent Authority of France (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

Pursuant to Article 45(4) of the REACH Regulation the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding eye irritation, endocrine disrupting properties adsorption/desorption screening and exposure to worker/general population/environment.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns: eye irritation, endocrine disruption properties and toxicity to reproduction, adsorption/desorption screening and exposure to worker/general population/environment. 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 17 March 2016.

Registrant(s)' commenting phase (I)

On 26 April 2016 the initial draft decision was sent to you for comments.

ECHA received your comments on 1 June 2016 and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took into account your comments, which were sent within the commenting period. In addition, you provided additional references, including a pharmacology review and evaluation of a medical patch containing methyl salicylate (the Food and Drug Administration, FDA, 2006). This new data provides adequate information to allow removal of the initial requests related to genotoxicity (i.e. an *in vitro mammalian cell micronucleus test (test method OECD 487*) and reproductive toxicity (i.e. an *Extended one-generation reproductive toxicity study (test method: OECD 443))*.

However new concerns emerged based on the provided information: potential endocrine disruption for environmental organisms.

You also provided additional information which demonstrates that methyl salicylate is not expected to present any surface active properties. Indeed, you explained that based on its chemical structure methyl salicylate does not allow forming emulsions and/or microemulsions and/or micelles. Furthermore, you agreed to provide additional justification to demonstrate that the Kow QSAR approach is appropriate and if necessary an adsorption/desorption test according to the OECD TG 121 method. Consequently, the

initial request on the Kow QSAR approach for the Koc estimation of methyl salicylate has been withdrawn.

Consequently the evaluating Member State considered necessary to revise the requests to be made and it submitted to ECHA a revised draft decision.

ECHA notified you of the revised draft decision and invited you to provide comments again.

Registrant(s)' commenting phase (II)

On 25 April 2018 the revised draft decision was sent to you for comments.

ECHA received your comments on 31 May 2018 and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took into account your comments, which were sent within the commenting period. Therefore the requests were amended and as explained in Appendix 1 the requests related to the endocrine disruption were removed.

Proposals for amendment by other MSCAs and ECHA and referral to Member State Committee

The evaluating MSCA notified the draft decision to the Competent Authorities of the other Member States and ECHA for proposal(s) for amendment.

Subsequently, the evaluating MSCA received one proposal for amendment to the draft decision according to which the decision was amended.

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendment. Any comments on the proposal for amendment were taken into account by the Member State Committee and are reflected in the Reasons (Appendix 1).

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-62 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(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.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the required experimental study/ies, the sample of the substance to be used shall have a composition that is within the specifications of the substance composition 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 test(s) 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.

4. In relation to the required update of the registration dossier on exposure assessment, it is reminded to the Registrant(s) that new OECD Harmonised Templates (available in IUCLID6) shall be used for reporting exposure endpoints.

5. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). You 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?CaseNumber=SEV-204-317-7-1

   Further advice can be found at
http://echa.europa.eu/regulations/reach/registration/data-sharing. 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.