ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 16 December 2019

Substance name: 1,3-dioxolane
EC number: 211-463-5
CAS number: 646-06-0
Date of Latest submission(s) considered[1]: 03 October 2018
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressees: Registrant(s)[2] of 1,3-dioxolane

DECISION ON SUBSTANCE EVALUATION

1. Requested information

In accordance with Article 46(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), you must submit the following information on the registered substance:

1.1 In vitro study for skin irritation; test method: OECD TG 439 using the registered substance 1,3-dioxolane;

1.2 In vitro study for serious eye damage; test method: OECD TG 437 (BCOP test) and/or OECD TG 438 (ICE test) and/or OECD TG 460 (FL test) and/or OECD TG 491 (STE test) using the registered substance 1,3-dioxolane.

If the results from the first in vitro study for serious eye damage does not allow a conclusive decision whether classification for serious eye damage (Cat 1 of the CLP Regulation) is needed, you must perform (an)other in vitro study/ies.

You must 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 **16 March 2021**. 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.

[1] This decision is based on the registration dossier(s) on the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

[2] The terms Registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

2. Who performs the testing

In accordance with 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.

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[3] by Christel Schilliger-Musset, Director of Hazard Assessment

[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.

Appendix 1: Reasons

Based on the evaluation of all relevant information submitted for 1,3-dioxolane and other relevant available information, ECHA concludes that further information is required in order to enable the evaluating Member State Competent Authority to complete the evaluation of whether the substance constitutes a risk to human health.

The evaluating Member State Competent Authority will subsequently review the information submitted by you and evaluate if further information should be requested in order to clarify the concern for skin irritation and eye corrosivity.

The identification of a potential risk is based on a combination of exposure and hazard information.

According to information in the registration dossiers and the chemical safety reports the substance is used as a solvent in a wide range of solvent based (or solvent containing) products/formulations and applications/uses. 1,3-Dioxolane is used by professional workers e.g. in coatings, metal working fluids/rolling oils, cleaning agents, in de-icing and anti-icing applications, as lubricant, as binder as well as release agent. In addition the substance is used by consumers e.g. as coating and cleaning agent. Thus, significant exposure and therefore a potential risk of workers and consumers cannot be excluded.

1.1 Skin corrosion / skin irritation

The concern(s) identified

Based on the available in vivo data (as described in detail below) a concern for skin irritation was identified.

In the registration dossier(s), there is one in vivo acute dermal irritation/corrosion test in rabbits (1980) available for 1,3-dioxolane which was performed according to a standardised guideline (16CFR 1500.41). For two of the six treated rabbits erythema with mean scores (24 and 72 hours) of ≥ 2 have been observed which were not reversible within 72 h. As the test was already terminated after 72 h there is no information on reversibility of these observed skin lesions within the normal observation period of 14 days. Reversibility of skin lesions is important in evaluating irritant responses as a substance is considered to be an irritant if reactions (even those which do not directly lead to classification) in at least 2 animals persist to the end of the observation period (normally 14 days) (see CLP-Regulation, Section 3.2.2.8.2. and Guidance on IR & CSA, Chapter R7a section R.7.2.4). Thus, available data indicate a concern for skin irritation but do not allow a conclusive decision on classification.

Furthermore, in the Chemical Safety Reports you report the wide dispersive use of consumer and professional products containing 1,3-dioxolane for e.g. cleaning and coatings. Therefore, the skin contact is foreseeable.

As long as a substantiated assessment of the skin irritation potential of 1,3-dioxolane and adequate classification and labelling is not possible there is a potential risk for skin irritation of workers or consumers.

Thus, considering worker and consumer applications, there is necessity to clarify the concern for skin irritation.

Why new information is needed

In the in vivo study available in the dossier(s) (mentioned above), six rabbits were treated with 0.5 ml undiluted 1,3-dioxolane for 24 h with occlusive coverage. For 4 of 6 treated rabbits no irritating reactions (such as erythema or edema) were observed (mean scores of 24 h and 72 h = 0) treated on intact skin. The other two rabbits showed erythema with mean scores (24 h and 72 h) of 2 and 3.5, respectively treated on intact skin which were not reversible within 72 h. The study was terminated already 72 hours after the start of treatment. Thus, reversibility of the observed skin lesions in 2/6 rabbits (after 72 h) and subsequent irritation reactions could not be studied. Moreover, there are some methodological and documentation shortcomings of that study, such as missing data on substance purity, missing reading 48 h after begin of exposure and missing control data which reduce the overall reliability of the study.

From the available information a robust conclusion cannot be drawn as reversibility of observed skin lesions after treatment of rabbits has not been investigated in the normal observation period of 14 days.

A robust conclusion on the skin irritation potential and classification for 1,3-dioxolane, however, becomes possible by performing additional in vitro testing. New information on the skin irritation potential could lead to a realistic possibility for improved risk management measures, as it could lead to a new classification and labelling which could trigger such additional measures.

Currently, for human health hazard, there are no regulatory measures available (such as harmonised classification or restriction) which would be sufficient for the safe use. You have not classified 1,3-dioxolane as skin irritant.

Considerations on the test method and testing strategy

From the available skin irritation data it can be concluded that 1,3-dioxolane leads to slight irritation reactions which, based on scoring data, are not sufficient for classification. But as reversibility within 14 days of the observed reactions has not been investigated (72 h only) firm conclusions on skin irritation potential for the substance are not possible. Based on the existing data it is expected that the test substance is not corrosive. You have not classified 1,3-dioxolane for skin irritation but available data indicate a concern for skin irritation.

The selected test (OECD TG 439: In vitro skin irritation – reconstructed human epidermis test) should be used to generate the requested information as it is a validated in vitro method that may be used for hazard identification of skin irritants in accordance with the classification and labelling system laid down in the CLP Regulation. It is based on reconstructed human epidermis (RhE), which in its overall design closely mimics the biochemical and physiological properties of the upper parts of the human skin and it thus replaces an in vivo test using animals.

In case of positive results of the test (decrease of cell viability below defined threshold) the substance needs to be classified as skin irritant.

Alternative approaches and proportionality of the request

The information requested is necessary to clarify the identified concern of skin irritation and the obtained information will enable a robust conclusion on classification or non-classification for skin irritation. So far, you have not self-classified the substance as skin

irritant. However, if classification is justified based on the results of the new study requested this could lead to a realistic possibility for improved risk management measures. The requested study is an in vitro study and testing of vertebrate animals is not foreseen.

An in vitro test focussed on skin irritation (and not investigating skin corrosion) is considered to be the optimal solution to provide robust information for regulatory decision making. In case of positive results of the test the substance needs to be classified for skin irritation. In case of negative results the substance is considered not to be a skin irritant. Thus, the request is considered to be proportionate and suitable.

Another key option to provide the necessary information would be an OECD guideline-conforming in vivo skin irritation test. However, in vivo testing is more expensive than the proposed in vitro test and testing on vertebrate animals should only be undertaken as a last resort. Therefore, an in vivo study is considered to be disproportionate in the present case at the present state of knowledge.

As laid down in Annex VII, Section 8.1. of the REACH Regulation, skin irritation testing is a standard REACH information requirement for substances manufactured or imported in quantities of 1 tonne or more per annum. Currently, all addressees of the present decision have registered this substance at tonnages above this threshold. Consequently, this request is considered appropriate and proportionate.

Consideration of registrants' comments on the draft decision, the Proposals for amendment (PfAs) from Member States and the registrants' comments on the PfAs

You agree to conduct the requested study.

Conclusion

Therefore, ECHA concludes that you must carry out the following study using the registered substance 1,3-dioxolane subject to this decision: In vitro study for skin irritation; test method: OECD TG 439.

1.2 Serious eye damage/ eye irritation

The concern(s) identified

Based on the available in vivo data (as described in detail below) a concern for serious eye damage was identified.

There is one in vivo acute eye irritation/corrosion test in rabbits available in the registration dossier(s), which was performed according to the guideline 16 CFR 1500.42 (1980). 0.1 ml undiluted 1,3-dioxolane was introduced into the lower conjunctival sac on one eye of each of six animals. The contralateral eye served as control. The test was terminated after 72 h. Evaluation of eye irritation was done on 24, 48 and 72 h. The scoring system used was different compared to OECD TG 405. Positive scores (≥ 2) for conjunctival redness were exhibited by all six animals. This effect was not reversible in all animals within the test period of 72 h. 5/6 animals showed chemosis (up to mean score 1.3) and discharge (up to mean score 1.7) of conjunctivae which was not reversible in 72 h for 3/6 and 2/6 animals, respectively. 4/6 animals showed iridial irritation (up to mean score 1) which was not reversible for 2/6 animals within 72 h. In 4/6 animals corneal opacities were found with scores up to 1.3. These were not reversible in 4/6 animals. Moreover, in cornea area, stippling and ulceration (scores 0.6 to 4) were observed in 5/6 animals which were not reversible in all animals after 72 h. Thus, effects were observed to conjunctivae, iris and cornea which were not reversible in more than one animal within the 72 h observation

period. As the test was already terminated after 72 h a clear statement on reversibility of the observed effects within the foreseen period of 21 days (OECD TG 405) is not possible from the results of the test. According to criteria of the CLP-Regulation (Table 3.3.1) a substance is considered to produce serious eye damage (irreversible effects to the eye) if, when applied to the eye, at least in one animal effects on the cornea, iris or conjunctiva occur which are not expected to reverse or have fully reversed within an observation period of normally 21 d. A prompt classification of the substance as eye damaging based on the reported ulceration in the cornea is not considered to be justified as a different scoring system was used compared to OECD TG 405 and detailed information on this effect is missing in the study report.

Thus, available data indicate a concern for eye corrosion but do not allow a definitive conclusion on classification. You have self-classified 1,3-dioxolane as eye irritant.

Furthermore, in the Chemical Safety Reports you report the wide dispersive use of consumer and professional products containing 1,3-dioxolane for e.g. cleaning and coatings. Therefore, eye contact cannot be excluded.

As long as a substantiated assessment of the potential for serious eye damage of 1,3-dioxolane is not possible and classification and labelling has not adequately been performed there could be a potential risk for serious eye damage of workers or consumers.

Thus, considering worker and consumer applications, there is necessity to clarify the concern for eye corrosion.

Why new information is needed

The results of the in vivo study in the dossier(s) clearly indicate that the substance causes eye lesions. Effects were observed to conjunctivae, iris and cornea which were not reversible in more than one animal within the 72 h observation period. Thus, a clear statement on reversibility of these effects within the foreseen period of 21 d (OECD TG405) is not possible. Data indicate a concern for serious eye damaging of 1,3-dioxolane but are not sufficient for a prompt classification as corneal opacity was not ≥ 3 in 4/6 animals and iritis was not ≥ 1.5 in 4/6 animals. Serious effects observed such as corneal ulceration and opacity support the concern for corrosivity. The available information is considered to be not sufficient to draw a robust conclusion.

A robust conclusion on the serious eye damage potential and classification of 1,3-dioxolane, however, becomes possible by performing additional vitro testing. New information on the eye damaging potential could lead to a realistic possibility for improved risk management measures, as it could lead to a new classification and labelling. New classifications and labelling could trigger additional risk management measures.

Currently, there are no regulatory measures available (such as harmonised classification or restriction) which would be sufficient for the safe use.

Considerations on the test method and testing strategy

The selected in vitro methods (OECD TG 437, OECD TG 438, OECD TG 460 and OECD TG 491) are validated and regulatory accepted methods that can be used to clarify serious eye damage/eye irritation. According to the testing strategy as outlined in the Guidance on information requirements and chemical safety assessment (ECHA Guidance R.7a,

Chapter R.7.2.11: Testing and assessment strategy for serious eye damage/eye irritation)[4] and in the supplement to test method OECD TG 405, results of an in vitro test, if performed under valid conditions, in a weight of evidence with other available data, are considered to be sufficient to allow a robust conclusion on the eye damaging potential of the substance. Thus, the selected tests are considered to be most appropriate.

In vitro methods for serious eye damage/eye irritation are very substance specific. Thus, you can apply any of the four methods, if considered suitable for the substance.

If results of the first *in vitro* test allow a conclusive decision on the classification, further testing does not need to be conducted.

If the results from the first *in vitro* study do not allow a conclusive decision whether classification for serious eye damage (Cat 1 of the CLP Regulation) is needed, you must perform (an)other *in vitro* study/ies as specified by the request 1.2..

Alternative approaches and proportionality of the request

The information requested is necessary to be obtained to enable a robust conclusion on classification for eye corrosion. So far, you have not self-classified the substance for irreversible eye effects. Based on the available in vivo data there could be a concern for the potential of serious eye damaging of the substance 1,3-dioxolane. Thus, an in vitro eye irritation/corrosion test following the testing strategy as outlined in the Guidance on information requirements and chemical safety assessment (ECHA Guidance R.7a, Chapter R.7.2.11: Testing and assessment strategy for serious eye damage/eye irritation) and in the supplement to test method OECD TG 405 is considered to be the optimal solution to provide robust information for regulatory decision making.

In case of positive results from an in vitro test (e.g. OECD TG 437) the substance is considered to induce serious eye damage and in case of negative results the substance is, based on results of the available in vivo test, considered to cause eye irritation. If new information supports the concern for serious eye damaging potential and results in an altered classification there would be a realistic possibility for improved risk management measures. The requested study is an in vitro study and testing of vertebrate animals is not foreseen. Thus, the request is considered to be suitable and proportionate.

Another key option to provide the necessary information would be an in vivo eye irritation/corrosion test. However, in vivo testing is more expensive than the proposed in vitro test and testing on vertebrate animals should only be undertaken as a last resort. Therefore, an in vivo study is considered to be disproportionate in the present case.

As laid down in Annex VII, Section 8.2. of the REACH Regulation, eye irritation testing is a standard REACH information requirement for substances manufactured or imported in quantities of 1 tonne or more per annum. Currently, all addressees of the present decision have registered this substance at tonnages above this threshold. Consequently, this request is considered appropriate and proportionate.

[4] Guidance on information requirements and chemical safety assessment (ECHA Guidance R.7a), Chapter R.7.2.11: Testing and assessment strategy for serious eye damage/eye irritation: http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf

Consideration of registrants' comments on the draft decision, the PfAs of the Member States and the registrants' comments on the PfAs

In your initial comments to the draft decision you agreed to conduct the requested study.

A PfA proposed to include an additional available test method (OECD TG 491, STE test) in the request which is also suitable to conclude on serious eye damage based on the reasoning that *in vitro* methods for serious eye damage/eye irritation are very substance specific and you should be able to choose the most suitable of the available methods for your substance. ECHA agrees with the PfA and modified the decision accordingly.

In your comments to the submitted PfA you indicate that you disagree with the listing of specific TGs in the paragraph "Requested Information". You believe that the selection of the test method shall be at the registrant's discretion, as this would be in conformity with the REACH regulation stating that the standard information requirement (8.2.1. in Annex VII) does not specify any test method and Regulation (EC) 440/2008 lists in total five applicable TGs (OECD 437, 438, 491, 460 (added in 2017), and 492 (added in 2019)), which are considered suitable by you to generate the information of interest.

ECHA does not fully agree with your statement. In section "The concern(s) identified", it is clearly stated that based on the available in vivo data (as described in detail above) a concern for **serious eye damage** was identified, as no reversibility of effects was observed within 72 h after treatment. The three selected in vitro methods specified in section "Considerations on the test method and testing strategy" (OECD TG 437, OECD TG 438 and OECD TG 491) are validated and regulatory accepted methods that can be used to clarify serious eye damage/eye irritation (Category 1), as defined by Regulation (EU) 1272/2008 (CLP Regulation). The OECD TG 492 proposed by you, on the other hand, is only to be used to identify "chemicals (substances and mixtures) not requiring classification and labelling for eye irritation or serious eye damage in accordance with UN GHS". Hence, this test method is considered inappropriate to clarify the concern identified.

The OECD TG 460 proposed by you is used to identify "chemicals (substances and mixtures) as ocular corrosives and severe irritants" (Category 1), as defined by the CLP Regulation. Thus, this test method has been added to the selection of test methods that can be used for clarifying the identified concern. It is noted, however, that several of the in vitro test methods selected for the proposed testing strategy have a rather limited applicability domain (e.g. with regard to high volatility). Hence, ECHA emphasises that it is your obligation to ensure that the test substance falls within the applicability domain of the test method that you choose to perform.

Another PfA suggested to clarify that (an)other in vitro study/ies becomes necessary in case results from the first in vitro study do not allow a conclusive decision whether classification for serious eye damage is needed.

ECHA agrees with the PfA and modified the draft decision accordingly.

In your comments you disagree with the PfA based on the argumentation that in Annex VII, section 8.2.1, column 2 it is stated that a second study "shall be considered" if the results of the first study do not allow a conclusive decision on classification which has a slightly different meaning.

ECHA takes note of your reading of the wording in Annex VII. However, the present decision is neither a dossier evaluation decision under Article 41 of REACH nor does it involve an evaluation of the compliance of your dossier with the information requirement under Annex VII section 8.2.1, column 2. The present decision is rather a substance

evaluation decision under Article 46 of REACH. That provision allows ECHA to ask, if appropriate, for information not required in Annexes VII to X of REACH. The aim of the substance evaluation in the present case is the clarification of the concern related to serious eye damage as explained above. Therefore, ECHA considers that (a) further in vitro study/ies must be conducted if the results of the first study do not clarify the concern.

Conclusion

Therefore, ECHA concludes that you must carry out the following study using the registered substance 1,3-dioxolane subject to this decision: In vitro study for serious eye damage; test method: OECD TG 437 (BCOP test) and/or OECD TG 438 (ICE test) and/or OECD TG 460 (FL test) and/or OECD TG 491 (STE test) following the testing strategy as outlined in the supplement to test method OECD TG 405.

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 genotoxicity and reproduction toxicity, 1,3-dioxolane CAS No 646-06-0 (EC No 211-463-5) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2016. The updated CoRAP was published on the ECHA website on 22 March 2016. The Competent Authority of Germany (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 corrosivity and skin irritation.

The evaluating MSCA considered that further information was required to clarify the following concerns:

- Skin corrosion/skin irritation
- Serious eye damage/eye irritation.

Therefore, the evaluating MSCA 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 2017.

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

ECHA notified you of the draft decision and invited you and the other Registrant(s) to provide comments.

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took your comments, which were sent within the commenting period, into account and they are reflected in the reasons (Appendix 1). The request(s) and the deadline were not amended.

Proposals for amendment by other MSCAs and ECHA and referral to the 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 proposal(s) for amendment to the draft decision and modified the draft decision. They are reflected in the reasons (Appendix 1)

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

ECHA invited you to comment on the proposed amendment(s).

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-67 written procedure and ECHA took the decision according to Article 51(6) 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 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

   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.