EUROPEAN CHEMICALS AGENCY

Helsinki, 7 March 2018

Addressee: [redacted]

Decision number: CCH-D-2114394624-40-01/F
Substance name: 3-methylpentane-1,5-diol
EC number: 224-709-1
CAS number: 4457-71-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11/04/2013
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Spectral data (Annex VI, Section 2.3.5.) of the registered substance;**
   - **Nuclear magnetic resonance or mass spectrum**
2. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**
3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **16 March 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to 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[1] by Kevin Pollard, Head of Unit, Evaluation E1

[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.

Appendix 1: Reasons

1. Spectral data (Annex VI, Section 2.3.5.)

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

"Spectral data" is an information requirement as laid down in Annex VI, Section 2.3.5. of the REACH Regulation. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA notes that the registration does not contain any nuclear magnetic resonance (NMR) spectrum or Mass spectrum (MS) which are required to support the identity of the registered substance.

ECHA regards this required information scientifically necessary for the identification of the registered substance. NMR spectroscopic analyses such as a ^{1}H-NMR or a ^{13}C-NMR are powerful tools for structure characterisation and elucidation due to characteristic chemical shifts and spin-spin coupling. Alternatively, a mass spectrum, is an appropriate analytical way to characterise the substance.

Accordingly, you are requested to provide a NMR spectrum, such as a ^{1}H-NMR or a ^{13}C-NMR or, alternatively, a mass spectrum.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you agreed to provide this information.

As for the reporting of the spectral data in the registration dossier, the information should be included in IUCLID section 1.4. You shall ensure that the description of the analytical methods used for the recording of the spectra is specified in the dossier, in line with the requirements under Annex VI section 2.3.7.

Further technical details on how to report the spectral data in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" (version: 4.0, May 2017) on the ECHA website.

2. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

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a) Information provided

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this provision.

You have provided the following justification for the weight of evidence: "*Annex XI to the REACH Regulation requires the waiving of additional animal testing in scenarios where adequate data exist, and further animal testing is not scientifically necessary to further substantiate the safety argument for the test substance. Given the following weight of evidence, as well as the availability of a OECD 422 subacute study of Klimisch 1 quality, we therefore conclude that it is scientifically unnecessary to generate additional mammalian data for MPD.*

- In an combined repeat dose and reproductive/developmental toxicity screening test [OECD TG 422], increased liver weight were observed in the females of the 1,000 mg/kg dose group only. No adverse effect in males and at lower doses were identified. The result fits well in studies available for structurally similar glycols and therefore does not justify a long term study of MPD. The following evidence can be cited:

> *a) the MPD isomer hexylene glycol (CAS 107-41-5, 2-Methyl-2,4-pentandiol), for which an OECD 408 subchronic study showed no systemic adverse effects. Other noted microscopic effects showed evidence of reversibility.*
>
> *b) for the MPD isomer 1,6-hexandiol (CAS 629-11-8) a large set of toxic data is available (see OECD SIDS Initial Assessment Report Hexamethylene glycol, June 2000). In valid OECD studies, tested up to the highest recommended dose of 1,000 mg/kg b.w. hexanediol revealed no effects of toxicological relevance besides a borderline effect on body weight.*

- the main metabolite of MPD has been identified as 3 -methyl glutaric acid (CAS 626 -51 -7), a well investigated human endogenic substance available in the blood stream at substantial concentrations. 3 -methyl glutaric acid is metabolitzed in humans to acetic acid CoA and acetylacetate by 3-methylglutaconyl coenzyme A hydratase (see Orly N. Elpeleg, Hanan Costeff, Adina Joseph, Yitzhak , Raphael Weitz, K. Michael Gibson, Developmental Medicine & Child Neurology Volume 36, Issue 2, pages 167–172, February 1994). Long term toxic effects due to accumulation in the body are not to be expected.

- MPD has been classified as hazardous (eye irritant) based on an single observation ([redacted] (1976)) which has not been confirmed by a later GLP study ([redacted] (1987)). The registrant has nevertheless adopted this worst case classification to create a further safety margin and provide risk management measures in the supply chain;

- a further quality assessment factor of 2 was included in the DNEL calculation to account for gaps in the repeat dose toxicity study set;

- Quantitative risk characterisation taking a worst-case approach (using the oral NOAEL = 300 mg/kg/day and worst case absorption rates of 100% for all routes) gave RCR values below 1 for all intended applications of the substance;

- Consumer exposure to MPD is limited to ink cartridges in ink jet printers, which are highly controlled and release the substance in controlled negligible amounts. Following the exposure assessment of MPD there is no reason for concern of toxic effects to the general public."

To support your weight of evidence adaptation you have solely provided the following source of information:

- Key study: combined repeated dose and reproduction/developmental toxicity screening test in rats via oral route (OECD TG 422) with the registered substance

b) ECHA's evaluation and conclusion of the information provided

Evaluation approach/criteria

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to a sub-chronic toxicity study (EU B.26/OECD TG 408). Relevant elements are in particular exposure route, duration and levels, two genders, sensitivity and depth of investigations to detect specific organ toxicity.

Furthermore, the relative values/weights of different pieces of the provided information needs to be assessed as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4., Section 4.4 (version 1.1, December 2011). In particular relevance, reliability and consistency of results/data and coverage (completeness) need to be considered.

Evaluation of the provided information

You have provided in the technical dossier a study record for a combined repeated dose and reproduction/developmental toxicity screening test in rats via oral route (OECD TG 422) with the registered substance. However, this study does not provide the information required by Annex IX, Section 8.6.2. because exposure duration is less than 90 days. Therefore, the data that you have provided under your weight of evidence adaptation is not considered complete, in regard of the specific information requirement.

ECHA also notes that the weight of evidence that you have developed is partly based on a read-across approach that includes information obtained from structurally similar substances (2-Methyl-2,4-pentandiol (CAS 107-41-5) and 1,6-hexandiol (CAS 629-11-8)) and the main metabolites of the registered substance that according to you are 3-methyl glutaric acid (CAS 626-51-7), acetic acid CoA and acetylacetate. Such sources of information are themselves adaptations, which are subject to specific conditions described in Annex XI, Section 1.5. including that adequate and reliable documentation of the applied method have to be provided.

However, there is no documentation for the read-across and therefore, your dossier is lacking a basis for predicting relevant human health properties of the registered substance from data for the source substances. In the absence of this information, ECHA cannot verify the adequacy of the read-across approach and that the properties of the registered substance can be predicted from the data on the source substance. Therefore, the read-across approach is rejected and, consequently, this information cannot be used as reliable source of information within a weight of evidence adaptation.

Furthermore, ECHA notes that while you refer to studies made with two read-across substances, notably with 2-Methyl-2,4-pentandiol (CAS 107-41-5,) and 1,6-hexandiol (CAS 629-11-8), you have not provided records of these studies in your dossier. Therefore, ECHA cannot assess the value that these studies may bring to the overall weight of evidence adaptation.

In your weight of evidence approach you have also indicated that you have self-classified the registered substance as Eye Irrit. 2 as a "worst case classification" to create a further safety margin and provide risk management measures in the supply chain. ECHA notes that this information seems to be not relevant for the weight of evidence approach as it does not address the specific dangerous (hazardous) properties of the registered substance with respect to a sub-chronic toxicity study (EU B.26/OECD TG 408). Nevertheless, ECHA would like to note that risk management measures put in place to control the eye irritant properties of the substance might not be adequate to control the risk derived from a hazard that could be identified in a sub-chronic toxicity study (90 day).

Finally, you have also indicated that in the DNEL derivation you have applied a further assessment factor of 2 to account for the "*gaps in the repeat dose toxicity study set*" and assumed a "*worst case absorption rates of 100% for all routes*" and in any case the RCR values are still below 1 "*for all intended applications of the substance*". In addition, you have also indicated that "*consumer exposure to MPD is limited to ink cartridges in ink jet printers, which are highly controlled and release the substance in controlled negligible amounts*".

ECHA notes that while you have not explicitly stated it, this information could be interpreted as an exposure-based adaptation according to Annex XI, Section 3.2.(a). However, ECHA notes that you have not demonstrated the absence of or no significant exposure in all scenarios. In addition, ECHA also notes that you have not demonstrated that the DNEL you have derived is relevant and appropriate and it takes full account of the uncertainty resulting from the omission of the sub-chronic toxicity study (EU B.26/OECD TG 408) also considering the footnote for Annex XI, Section 3.2.(a)(i). Therefore, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex XI, Section 3.2.(a).

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you agreed that the provided read-across approach was not adequate and stated your intention to provide a comprehensive read-across justification covering the criteria as laid out in the RAAF (March 2017). In this regard, ECHA also notes that you should consider that the different source substances differ in their similarities towards the target substance (distance between functional groups, branching, metabolism and toxicodynamics of primary vs. secondary vs. tertiary alcohols).

ECHA notes that the read-across justification and the data you are referring to is not available in the current submission of the registration dossier. As also mentioned in the Appendix 2 to this decision, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. Thus, an eventual update containing this information will only be examined after the deadline set in the adopted decision has passed.

ECHA also acknowledges that, in your comments, you stated that it is not your intention to apply for exposure based adaption and reduced testing requirements according to Annex XI Section 3.2.

Conclusion

The information you provided, together with your justification for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex IX, Section 8.6.2.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected. As explained above, the information provided 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.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, there is no concern for severe local effects following inhalation exposure and the available oral study indicates a concern for systemic toxicity that requires further information on repeated dose toxicity by the oral route. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

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3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422). However, this study does not provide the information required by Annex IX, Section 8.7.2. because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations. Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.
ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you indicated your intention to provide a read-across adaptation for this endpoint using data available from OECD TG 414 prenatal developmental studies for 1,6-hexanediol (CAS No. 629-11-8), 1,2-hexanediol (CAS No. 6920-22-5), 2-methylpentane-2,4-diol (CAS No. 107-41-5) and neopentylglycol (CAS No. 126-30-7).

In the context of explaining that you have an access to data for an OECD 414 study with 1,6-hexanediol, you also stated that the read-across justification will be an analogue read-across according to scenario 2 of RAAF (March 2017). ECHA notes further that apparently there is existing information from another source substance raising a higher concern (fetotoxicity NOAEL 300 mg/kg bw/d of 2-Methylpentane-2,4-diol; CAS 107-41-5), impacting on the prediction of hazardous properties for the target substance. ECHA concludes that you might therefore consider a category read-across adaptation since you referred to data from different source substances. In this regard, ECHA also notes that you should consider that the different source substances differ in their similarities towards the target substance (distance between functional groups, branching, metabolism and toxicodynamics of primary vs. secondary vs. tertiary alcohols).

ECHA notes further that the read-across justification and the data you are referring to is not available in the current submission of the registration dossier. As also mentioned in the Appendix 2 to this decision, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. Thus, an update containing this information ECHA will only examine after the deadline, set in the adopted decision, has passed.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 29 June 2017.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and did not amend the requests.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

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

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested 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 or imported. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

Furthermore, there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.