EUROPEAN CHEMICALS AGENCY

Helsinki, 10 December 2018

Addressee: [redacted]

Decision number: CCH-D-2114449851-43-01/F
Substance name: 1-(dimethylamino)propan-2-ol
EC number: 203-556-4
CAS number: 108-16-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 04/04/2017
Registered tonnage band: 10-100 (submission number [redacted] with latest tonnage band)

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. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, 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 ***17 December 2019***. 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

his 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 Claudio Carlon, Head of Unit, Evaluation E2

[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.

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Appendix 1: Reasons

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.
Your registration dossier contains adaptation arguments in the form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your grouping and read-across approach in general before the individual endpoint covered in this decision (section 1).

Grouping and read-across approach for toxicological information

You have sought to adapt the information requirements listed above by applying a read-across approach in accordance with Annex XI, Section 1.5., for the endpoint:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.).

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical and toxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance 1-(dimethylamino)propan-2-ol (EC No 203-556-4) using data of structurally similar substances 1,1'-iminodipropan-2-ol (EC No 203-820-9; hereafter cited as DIPA), 1-aminopropan-2-ol (EC No 201-162-7, hereafter cited as MIPA) and 1,1',1''-nitrilotripropan-2-ol (EC No 204-528-4; hereafter cited as TIPA) (hereafter the 'source substances').

You have provided a read-across documentation as a separate attachment in Section 13 of the IUCLID dossier.

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group:

- The target and source substances exhibit physico-chemical properties that are either very similar or that reflect incremental changes expected for an amino alcohol series,
- You consider that the physicochemical properties of the members of this group should lead to similar toxicokinetics and exposure patterns (all members of the group are expected to be readily absorbed through the gastrointestinal and respiratory tract epithelium by passive diffusion; you also state that the vapour pressure of the group members does not favour exposure to vapours),
- You specify that you used the OECD QSAR Toolbox v. 3.0 to identify structural alerts related to DNA/protein/oestrogen receptor binding, skin/eye irritation, or mutagenicity/carcinogenicity. You only report findings related to DNA binding and superfragments alerts. You found that the target substance and TIPA share the same DNA binding alert "aliphatic tertiary amine" and that superfragment alerts were found in the target substance and in DIPA and TIPA (but not 1-aminopropan-2-ol, EC number 201-162-7; cited as MIPA). You conclude that this observation supports the use of read-across for toxicological properties among the members of the group,
- Regarding experimental evidences on the toxicological properties of the target and source substances, you report that all substances are not genotoxic based on *in vitro* toxicity tests (you note that some tests may not have been conducted up to the highest attainable concentration). You also refer to the SIDS Initial assessment report for SIAM 29 and state that DIPA and TIPA are readily absorbed in rats and mostly excreted unchanged in the urine. You consider that available evidence show a decreasing trend in acute mammalian toxicity with increasing molecular weight among the members of the proposed category (you propose that the corrosive properties of the target substance and MIPA may be responsible for the greater acute toxicity). On the other hand you consider that, based on available data on repeated exposure to DIPA and TIPA, the members of the group target the kidney and that greater toxicity is to be expected with an increase in molecular weight. Finally, you consider that available data on MIPA, DIPA and TIPA support the fact

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

that none of the members of the group should be considered as leading to reproductive or developmental effects.

As an integral part of this prediction, you propose that the source and registered substances have similar properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical and toxicological properties between the source and registered substances is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical and toxicological properties does not necessarily lead to predictable or similar human health properties in other endpoints. Your justification based on structural similarity, similar physico-chemical and toxicological properties has not established why the prediction is reliable for the human health end-points for which the read across is claimed. More specifically, you have not addressed to what extent the differences in physico-chemical properties and in the chemical structure between the target and the source substances may impact the prediction of the toxicological properties of the target substance with regards to the selected endpoints.

You have also proposed that similar metabolism can lead to a basis for predicting the properties of the registered substance. One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination (ADME) of source and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target. However, ECHA notes that you did not provide any scientific evidence in section 7.1 of your technical dossier, in your read-across justification document or in your chemical safety report (CSR) on the toxicokinetic properties of the target and selected source substances to support that they share similar properties. You only refer in your read-across justification document to the SIDS Initial assessment report for SIAM 29 and you state that DIPA and TIPA are readily absorbed in rats and mostly excreted unchanged in the urine. ECHA considers that the information you provided does not allow an evaluation of whether your hypothesis is plausible or not. In the absence of adequate information, ECHA concludes that the hypothesis of similar metabolic pathways and of similar toxicodynamic properties cannot be considered as an adequate basis for predicting the toxicological properties of the registered substance from the data obtained with the source substances.
To support your hypothesis that the structural similarity of the target and source substances may lead to similar toxicological properties, you specify that you used the OECD QSAR Toolbox v. 3.0 to identify structural alerts related to DNA/protein/oestrogen receptor binding, skin/eye irritation, or mutagenicity/carcinogenicity. You state that the registered substance shares a similar DNA alert with TIPA and also superfragments with DIPA and TIPA (but not in MIPA). You consider that these results support the proposed read-across to predict toxicological properties among the members of the group. ECHA notes that you did not provide any justification on why these alerts may be relevant in the prediction of the toxicological properties for which a read-across is proposed. Accordingly, ECHA considers that this hypothesis is not a reliable basis for prediction of the toxicological properties of the registered substance from data with source substances.

Then, you argued that the members of the proposed category display a regular pattern in terms of toxicological properties. You state that available evidence support a "*trend of decreasing mammalian toxicity with increasing molecular weight*" among the members of the proposed category. ECHA notes that the data you provided in your technical dossier offer little support to this hypothesis. For instance:

- ECHA notes that the registered substance has a higher molecular weight than MIPA but the data you provided suggest that it exhibits greater acute oral and dermal toxicity.
- ECHA also notes that you provided an opposite hypothesis regarding repeated-dose toxicity as you state that "*the substances [...] target the kidney in repeated-dose studies (DIPA, TIPA, with the larger molecule showing greater toxicity)*". Based on this hypothesis, ECHA understands that you consider that DIPA and TIPA may represent worst-cases to evaluate the toxicological properties of the registered substance following repeated exposure. However, ECHA considers that the data included in your technical dossier are not sufficient to support this hypothesis. In your technical dossier you provided a robust study summary for a study conducted according to OECD TG 408 with DIPA and a study conducted according to OECD TG 422 with aminopropan-2-ol hydrochloride (EC No 231-948-5; i.e. the hydrocholoride salt of MIPA). ECHA notes that the exposure duration in these two studies are different and that the NOAEL cannot be directly compared. In addition, in your read-across justification document you report a NOAEL value of 272 mg/kg bw/day for TIPA obtained from a 102-104 days study in Beagles. However, ECHA notes that this study is not included in either the IUCLID dossier or the CSR and consequently the reliability of this information could not be evaluated. Accordingly, the information provided does not demonstrate that the members of the category having greater molecular weight show greater sub-chronic toxicity.

Based on the above, ECHA considers that the information you provided in your technical dossier does not support the aforementioned hypothesis of a regular pattern in mammalian toxicity among the category members.

Finally, you argued that none of the source substances (MIPA, DIPA and TIPA) showed any reproductive or developmental toxicity in the available studies ECHA understands that you consider that, based on available data on the members of the category, the registered substance is unlikely to show reproductive or developmental toxicity. ECHA notes that you did not provide any specific hypothesis to support why the prediction may be reliable. As already explained previously, ECHA considers that you did not adequately demonstrate that the target and sources substances share similar toxicological properties or that the properties of the substances included in the proposed category can be expected to show a regular pattern.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substances within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that there are specific considerations for the individual

endpoints which also result in a failure to meet the requirement of Annex XI, Section 1.5., and these are set out under the endpoint concerned.

As described above, further elements are needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

1. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

Instead, you have sought to adapt this information requirement according to Annex VIII, Section 8.7.1., column 2 of the REACH Regulation, by providing the following justifications for the adaptation:

- *'In accordance with column 2 of REACH Annex X, no two-generation reproduction toxicity study is needed since: 1) a reliable one-generation study in rats is available for TIPA; 2) no additional information is expected to be obtained from the second generation [Janer et al., Reprod. Toxicol. (2007), 24(1), 103-13]; 3) a reliable reproduction/developmental toxicity screening study (OECD 422) is available for (the hydrochloride salt of) MIPA; 4) repeated dose studies did not reveal any adverse effects on the gonads or other fertility effects.'*

Your adaptation argument refers to the following studies:

- *'Subchronic Oral Toxicity: 90-Day Study with TIPA In Utero Exposure and Feeding Study in Rats'*, methodology similar to a one-generation study, with 1,1',1''-nitrilotripropan-2-ol (EC number 204-528-4), GLP study, reliability score of 1, *DuPont, 1988*;
- *'Hydrochloride salt of isopropanolamine: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in Wistar rats'*, methodology according to OECD TG 422 (oral exposure by gavage), with 1-aminopropan-2-ol hydrochloride (EC number 231-948-5), GLP study, reliability score of 1; *BASF*, 2008.

ECHA understands from your argument that you aim at adapting the information requirement requirement according to Annex VIII, Section 8.7.1., column 2, by providing data on the members of the category, which must comply with Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that your adaptation cannot be accepted because, as explained above, ECHA has rejected your adaptation according to Annex XI, Section 1.5. (see section 'Toxicological information', sub-section 'Grouping of substances and read-across approach for toxicological information' above).

In addition to the insufficient justification on why the toxicological properties of the target substance may be predicted by the properties of the source substances, ECHA notes that there are significant deficiencies with the selected read-across studies.

ECHA notes that the first source study listed above, '*Subchronic Oral Toxicity: 90-Day Study with TIPA In Utero Exposure and Feeding Study in Rats'*, has been conducted with a methodology similar to a one-generation study. According to the provision of Annex VIII, Section 8.7.1, information on a screening study for reproductive/developmental toxicity study as specified in the OECD TG 421/422 shall be provided. ECHA points out that this study does not provide an adequate coverage of some key parameters expected to be investigated in a study performed according to the OECD TG 421/422 such as serum levels for thyroid hormones and gross pathology and histopathology of reproductive organs. Therefore, ECHA considers that this source study do not fulfil the requirements of Annex XI, Section 1.5. of the REACH Regulation for an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

Similarly, ECHA also notes that in the second study listed above, '*Hydrochloride salt of isopropanolamine: Combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in Wistar rats'*, the animals were sacrificed at 4 post-partum (as opposed to day 13 post-partum as specified in the OECD TG 421/422) and the overall exposure duration fo female was only 45 days. Therefore, ECHA considers that this source study does not fulfil the requirements of Annex XI, Section 1.5. of the REACH Regulation for an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3).

ECHA concludes that the source studies included in your technical dossier do not provide the information required by Annex VIII, Section 8.7.1., because it does not meet the requirements of Annex XI, Section 1.5.
Therefore, your adaptation of the information requirement is rejected.

In your comments on the draft decision, you acknowledged that you support the conclusion drawn by ECHA.

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 methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

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 6.0, July 2017) 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.

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: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

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. However, following your comments on the draft decision indicating a tonnage band downgrade, ECHA has taken into account the updated tonnage band (submission number [redacted] from 20 June 2018) only. No assessment of the updated registration has occurred. Based on the average production and/or import volumes for the three preceding calendar years, ECHA has changed the tonnage band as basis for the draft decision from 100-1000 tonnes per year (submission number: [redacted] from 04 April 2017) to 10-100 tonnes per year (submission number: [redacted]).

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

The compliance check was initiated on 13 September 2017.

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

ECHA took into account your comments and your information about tonnage band downgrade. This has resulted in the removal of the following decision requests: Sub-chronic toxicity study (90-day), oral route in rats (Annex IX, Section 8.6.2.) and Pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.). As a consequence the deadline for providing the information to meet the requests remaining in the draft decision has been set to 12 months.

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 relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally 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.