EUROPEAN CHEMICALS AGENCY

Helsinki, 12 December 2017

Addressee: [redacted]

Decision number: CCH-D-2114381426-45-01/F
Substance name: 2-butylaminoethanol
EC number: 203-904-5
CAS number: 111-75-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28/04/2017
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. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD [421/422]) in rats, oral route with the registered substance;**

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 **19 June 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.

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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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

In the registration, you have adapted the standard information requirements for

- Screening for reproductive/developmental toxicity (Annex VIII, 8.7.1)
- Sub-chronic (90-day) toxicity (Annex IX, 8.6.2.)
- Pre-natal developmental toxicity (Annex IX, 8.7.2.)

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context.

0.1. Information provided on the grouping and read-across approach

You have provided read-across justification document "[redacted]" as an attachment within Section 13 of the technical dossier. In this document you provide data matrices of physico-chemical and toxicological properties of the registered (target) and source substances, an assessment of toxicokinetics, and an evaluation of similarity between the target and source substances based on profiling and metabolism simulation results generated by the OECD QSAR Toolbox. In addition, toxicological data on other structurally related ethanolamines (supporting substances) has been provided.

You propose to use grouping and read-across approach to adapt the standard information requirements listed above for the registered substance butylaminoethanol (BEA, CAS no 111-75-1, EC no 203-904-5, the target substance) by using the source substance dibutylethanolamine (DBEA, CAS no 102-81-8, EC no 203-057-1,). The supporting substances are: DEA (Diethanolamine, CAS 111-42-2), Methyldiethanolamine (MDEA, CAS 105-59-9), a methylation product of DEA, DEEA (Diethylethanolamine, CAS 100-37-8), Monomethylethanolamine (MMEA, CAS 109-83-1), Dimethylethanolamine (DMAE, CAS 108-01-0), Triethanolamine (TEA, CAS 102-71-6), and Monoethanolamine (MEA, CAS 141-43-5).

You have provided the following hypothesis in the read-across justification document:

"The target substance Butylethanolamine (BEA) is both primary aliphatic alcohol and secondary amine that can be described by the structure H-N(R)-R', with R representing alkyl chain (in this case butyl) and R' an aliphatic alcohol group (ethanol). The source chemical 2-dibutylaminoethanol (DBEA) is a tertiary amine with two butyl tail chains and an ethanol group. Hence, the common structure of DBEA is R-N(R')-R" with R" representing additional alkane chain. Both substances belong to the class of alkanolamines (N-alkylated aminoalcohols) that possess both amine and alcohol functional groups. The nitrogen atom of both substances has an unshared electron pair that can accept a proton forming a substituted ammonium ion. Generally, tertiary amines possess a more basic character than the secondary amines. The tendency to share these electron pair underlies the entire chemical behaviour of amines as a group and this was considered as main / basic parameter, which is suitable for read across within an analogue approach. Further common features which were considered for regrouping the amines within the analogue group were the following:

- *A structure that contains alkane and alcohol substituents*
- *Elemental compositions of carbon, hydrogen, nitrogen and oxygen in both structures*
- *Same aliphatic chains (butyl) and ethanol tail are constituents in both compounds, however, DBEA possesses the aliphatic chain twice*
- *Molecular weights of < 200 g/mol, classifying both amines as low molecular weight aliphatic amines*
- *The substances share the same ethanolamine moiety, which is known to be linked to their mode-of-action i.e. effects on choline homeostasis and therefore have the same target organs (liver and kidney). The substances could also be considered as derivatives of mono-ethanolamine (CAS 141-43-5). Ethanolamines have structural similarity with choline, an ubiquitous physiological molecule (e.g. involved in phospholipid synthesis like phosphatidylcholine and acetylcholine). In this regard, since the data set for BEA is not completed, toxicological data on other structurally related ethanolamines (here named supporting substances) have been taken into account to strengthen the read-across approach. In this regard, the data on other derivatives of ethanolamine i.e. DEA (Diethanolamine, CAS 111-42-2), Methyldiethanolamine (MDEA, CAS 105-59-9), a methylation product of DEA, DEEA (Diethylethanolamine, CAS 100-37-8), Monomethylethanolamine (MMEA, CAS 109-83-1), Dimethylethanolamine (DMAE, CAS 108-01-0), Triethanolamine (TEA, CAS 102-71-6), and Monoethanolamine (MEA, CAS 141-43-5) will be compared with the data of butyl derivatives to conclude whether the same mode of action can also extended for the whole group of short-alkyl-chain (i.e methyl-butyl) ethanolamines.*

According to the information of the RAAF (2015), the read-across hypothesis for BEA from DBEA is based on the structural similarity of the substances which produce the same type of effects via common underlying mechanisms (choline impairment) (Scenario 2 of RAAF, 2015 is proposed).".

0.2. ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

ECHA understands that your read-across hypothesis is based on structural similarity of the substances, similar physico-chemical properties and toxicokinetics and similar or regular pattern as a result of structural similarity (including common mode of action involving the potential of impairment of choline homeostasis). ECHA considers these elements interlinked and analysed them in the following section:

Structural similarity

In order to meet the provisions in Annex XI 1.5 to predict physicochemical and toxicological properties from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

You state that the target and source substances are alkanolamines (N-alkylated aminoalcohols) that possess both amine and alcohol functional groups, the target substance (BEA) is both primary aliphatic alcohol and secondary amine and the source substance (DBEA) is a tertiary amine with two butyl tail chains and an ethanol group. You further state that "*the nitrogen atom of both substances has an unshared electron pair that can accept a proton forming a substituted ammonium ion. Generally, tertiary amines possess a more basic character than the secondary amines. The tendency to share these electron pair underlies the entire chemical behaviour of amines as a group and this was considered as main / basic parameter, which is suitable for read across within an analogue approach*". Further common structures are (i) alkane and alcohol substituents, (ii) "*elemental compositions of carbon, hydrogen, nitrogen and oxygen*" and (iii) one (butyl) aliphatic chain and ethanol in the target substance and two butyl chains and ethanol in the source substance.

ECHA observes that although both the target and source substances share a similar core structure, i.e. nitrogen atom, butyl chain and ethanol, the target substance is a secondary amine, whereas the source substance is a tertiary amine with two butyl chains. ECHA notes that you have not provided adequate information to support how the structural difference, i.e. secondary vs tertiary amine structure, may impact the predicted human health hazard properties.

Regarding the different lengths of the alkyl groups between the target and source supporting substances, ECHA notes that you consider that the different alkyl lengths do not impact the toxicity of the target, source and supporting substances. In particular, under "Conclusion for repeated dose toxicity" of the read-across justification document you conclude that "*Therefore, it seems that the structural difference: presence of alkyl groups of different lengths (methyl, ethyl or butyl) does not strongly influence the observed toxicity*", and "

Since capability of ethanolamine moiety to impair choline homeostasis (depletion of cellular choline, affection of metabolism pathway and synthesis of aberrant phospholipids) is the underlying mode of action of ethanolamines, structural differences do not influence the read-across validity because the functional amino alcohol group with its assumed effect on choline homeostasis is thought to be of greater importance in this case than the structural differences due to alkyl tail".

ECHA notes that based on the results presented in the read-across justification document, the conclusions made are not based on experimental evidence with the target substance, and that other mode(s) of action cannot be excluded that would be due to the presence of the additional butyl- alkyl chain in the target substance.

Furthermore, you have provided information on predicted metabolites of the target and source substance (generated by the OECD QSAR Toolbox metabolism simulation data). The prediction provided indicates a number of different metabolites that are likely to be formed between the target and source substances. ECHA notes that you have not explained how the different predicted metabolites will impact the toxicity of the substances as explained in section "Toxicokinetics" below.

Consequently, there is not a robust basis for predicting the properties of the target substance from the data of the source substance and the supporting substances.

Physico-chemical properties and Toxicokinetics

Annex XI 1.5 provides that "Substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances." One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the comparison of absorption, distribution, metabolism and elimination of source and target substances to allow assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.

You have provided data on physico-chemical properties and an assessment of the toxicokinetic (absorption, distribution, accumulation and excretion) properties of the target and source substances. ECHA considers that the physico-chemical properties are in the same/similar range and the toxicokinetic properties regarding absorption, distribution, accumulation and excretion can be considered similar for the target and source substance.

However, regarding metabolism, you explain that both the target and source substances have a common metabolic pathway and can undergo Phase I reactions (hydroxylation, oxidation, oxidative deamination and further possible reactions). In addition, you have provided information generated by the OECD QSAR Toolbox metabolism simulation ("Rat liver metabolism simulator"). Based on this, you conclude that the predicted metabolites are "*very similar*" for the target and source substances, the source substance can be metabolised to the target substance, which "*strongly supports the read-across approach*", and four identical metabolites are predicted to be formed from the target and source substances.

ECHA observes that although four identical metabolites are predicted and that the source substance can be metabolised to the target substance, there are non-common metabolites

predicted to be formed from the target and the source substances. In addition, ECHA notes that the prediction does not provide information on the target and source substances regarding:

1. the rate and quantity of metabolism of the source substance to the target substance,
2. the rate of metabolism,
3. the (relative) quantity of each metabolite that may be formed from the target and source substance,
4. the completeness (i.e. complete/limited metabolism of the parent substances) of the metabolism, and consequently the impact of the parent substances on toxicity,
5. how the non-common metabolites may impact the toxicity of the target and source substances (four and seven non-common metabolites are predicted to be formed from the target and source substance, respectively), and
6. other metabolism pathways (e.g. glucuronidation or sulfonisation).

ECHA concludes that based on the above there is not sufficient evidence to conclude on the similarity of the metabolism of the target and source substances. The explanation provided is not considered adequate to establish the link between the structural similarity and the prediction. For this reason, too, ECHA considers that there is no adequate basis for predicting the properties of the target substance from the source substance.

Support of a similar or regular pattern as a result of structural similarity

Annex XI, 1.5 provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties or follow a regular pattern. One important aspect in this regard is the data matrix comparing properties of source and target substances.

You have provided a data matrix on human health endpoints in your read-across justification document. Based on this data, you conclude that the substances have "*quite similar profiles especially regarding acute systemic toxicity, genetic toxicity and irritation/corrosion potential*". You have provided a combined repeated dose and reproduction/developmental toxicity screening test (OECD 422) conducted with the source substance. ECHA observes that acute toxicity, irritation/corrosivity, sensitisation and genotoxicity profiles of the target and source substance are similar. ECHA notes that acute/irritation/corrosivity/genotoxicity data alone is not sufficient to establish the toxicological profile of a substance with regard to repeated dose/reproduction/pre-natal developmental toxicity and that no higher tier studies (systemic toxicity) are available for the target substance. Thus, comparison of toxicological profiles of the target and source substances is not possible.

You have also provided OECD QSAR Toolbox profiling results to substantiate the similarity between the target and the source substance in a Weight of Evidence approach. Regarding human health endpoints you state that there are no alerts for DNA binding, for genotoxicity or non-genotoxic carcinogenicity, or protein and estrogen receptor binding and the target and source substances are not expected to cause sensitization. ECHA notes that OECD QSAR Toolbox profiling results and the absence of specific alerts on the basis of structural components of the target and source substance cannot cover the parameters required for the hazard assessment regarding repeated dose, reproductive and pre-natal developmental toxicity. Therefore, they are not considered sufficient information that can be used for the endpoints of repeated dose, reproductive and pre-natal developmental toxicity.

You have further provided an analysis for similar or regular pattern of toxicological properties for the endpoint Repeated Dose toxicity that includes the following information within the read-across justification document:

1. A summary of findings with the source and supporting substances
2. Analysis of liver and kidney as primary target organs in studies with ethanolimines
3. Mode of action considerations involving perturbation of choline homeostasis ("Ethanolomines perturb choline homeostasis in vitro studies" and "Ethanolamines perturb choline homeostasis (in vivo studies)"
4. Carcinogenicity effects as consequence of choline deficiency induced by ethanolamines
5. Local effects are primary effects of ethanolamines as a group.

You have concluded that "*Since capability of ethanolamine moiety to impair choline homeostasis is the underlying mode of action of ethanolamines, structural differences do not influence the read-across validity because the functional amino alcohol group with its assumed effect on choline homeostasis is thought to be of greater importance in this case than the structural difference due to alkyl tail. Morever, similarity in irritation effect of respiratory tract and their strength identified in the inhalation studies with the source substance DBEA, target substance BEA and other ethanolamines supports the hypothesis for the read-across*"

ECHA agrees that the target, source and supporting substances might have similar effects after repeated exposure on the basis of the common functional group (ethanolamine). However, ECHA observes that the most severe liver and kidney effects were observed with the secondary amine DEA and MMEA whereas the tertiary amines caused less severe effects.

You claim that the read-across is based on the mode of action mediated via the ethanolamine group and that the differences in the alkyl tail have less impact on read-across approach.

ECHA notes that in order to substantiate claims of established common mode of action, description of consistency and specificity of the effects observed needs to be presented for both the target and source and supporting substances. In addition, the exclusion of other mode(s) of action regarding target organ toxicity needs to be presented on the basis of the structural differences and the predicted different metabolites between the target and source and the supporting substances.

ECHA notes that there are no systemic toxicity studies available with the target substance to allow concluding on presence or absence of similar effects compared to the source and supporting substances.

ECHA notes that the studies with the target substance regarding cholinesterase inhibition have been performed in vitro and in vivo via the intraperitoneal route. Although the findings from these studies are useful for the specific mode of action arguments and the potency for choline perturbation, they are not sufficient to address the toxicological profile of the target substance for repeated exposure administration because they do not address the presence or absence of other toxicological effects via relevant routes of exposure.

Therefore, ECHA concludes that the information available does not allow to conclude on the presence or absence of target organ toxicity after repeated exposure and the impact on hazard assessment for the purpose of classification and labelling and/or risk assessment.

You have further provided an analysis for similar or regular pattern of toxicological properties for the endpoint Reproductive / Developmental toxicity that includes the following information within the read-across justification document:

1. A summary of findings with the source and supporting substances
2. An analysis of interrelationship of perturbation of choline homeostasis and reproductive/developmental toxicity effects observed with ethanolamines

You have concluded that: *"the link between the Ethanolamine mediated perturbation of choline homeostasis and the resulting systemic toxicity thereof with the reproductive findings induced by ethanolamines (i.e. affected male reproductive system (DEA, DEEA, MMEA and only a slight tendency for DBEA, implantation loss (MEA, DEA, TEA, MDEA), no lifeborn pups (MMEA), postpartum deaths of pups (MMEA, DMAE) as a secondary consequence of choline-homeostasis perturbation appear plausible". "Ethanolamines administration during pregnancy can perturb choline homeostasis affecting a lot of maturation systems of embryos i.e. cellular uptake of choline, its metabolism pathway, synthesis of aberrant phospholipids".*

ECHA has assessed the information provided within the read-across justification document. ECHA agrees with the fact that the source substance and the supporting substances had different impact on some reproductive/developmental toxicity related parameters. ECHA agrees that ethanolamines can affect maturation systems of embryos on the basis of the information provided. Based on the information provided the target, source and supporting substances seem to impact choline homeostasis.

ECHA notes that in order to substantiate claims for established common mode of action for the target and the source and the supporting substances, elaboration of consistency and specificity of the effects observed needs to be presented. In addition, the exclusion of other mode(s) of action regarding target organ toxicity needs to be presented on the basis of the structural differences and the predicted different metabolites between the target and source and the supporting substances.

ECHA notes that the studies with the target substance regarding cholinesterase inhibition have been performed in vitro and in vivo via the intraperitoneal route. Although the findings from these studies are useful for the specific mode of action arguments, they are not sufficient to address the toxicological profile of the registered substance for the evaluation of reproductive and developmental toxicity because they do not address the presence or absence of other toxicological effects.

ECHA notes that there are no reproductive and developmental toxicity studies available with the registered substance to allow concluding on presence or absence of similar effects compared to the source and supporting substances.

Therefore, ECHA concludes that the information available does not allow to conclude on the presence or absence of reproductive and developmental toxicity and the impact on hazard assessment for the purpose of classification and labelling and/or risk assessment.

Based on the above, ECHA notes that in the absence of adequate experimental evidence with the registered substance to allow comparison for presence of common effects and absence of different effects the argument of one potential common mode of action cannot be accepted to support the read-across plausibility for the endpoints under consideration within this draft decision.

In your comments to the draft decision you have expressed your intention to further justify the read-across approach by providing the studies conducted with the registered substance (OECD 422 and OECD 414 first species) and the source substance (Dibutylethanolamine, OECD 413 and OECD 414).

You are further proposing sequential testing, i.e. the need to test the sub-chronic (90-day) study with the registered substance will be decided once the results of the OECD 442 and OECD 414 with the registered substance are available.

In addition, you intend to perform metabolome analysis and include choline measurements in the OECD 422 study to be conducted with the registered substance.

ECHA understands that you intend to include data also from a supporting substance, butyldiethanolamine, (CAS 102-79-4, EC 203-055-0), in support of the read-across approach.

ECHA acknowledges your intention to reconsider the read-across approach depending on the outcome of the studies by providing new data as explained above. However, based on the information currently available, ECHA cannot conclude whether the potential updated read-across approach would comply with the requirements of Annex XI, section 1.5. of the REACH Regulation.

ECHA notes that the information presented in the comments to the draft decision need to be included in an updated technical dossier. While for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage.
ECHA concludes that for the reasons explained above the available data provided in the technical dossier and read-across justification document does not provide sufficient

information to conclude on a similar or regular pattern of toxicity regarding the endpoints in consideration. Therefore, ECHA considers that there is no adequate basis for predicting properties of the registered substance from the source substance and the supporting substances.

0.3. Conclusion of the read-across approach

ECHA considers that the read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. of the REACH Regulation, because the information provided is not considered adequate to demonstrate structural similarity, toxicokinetic similarity or similar toxicological profiles between the target and source substance and the supporting substances. Therefore, this adaptation is not acceptable and there is a data gap for the endpoints covered by this read-across approach.

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

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.

"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 adequate information is presented in the technical 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 sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Screening study for reproductive/developmental toxicity (OECD 422) via inhalation with the analogue substance dibutylethanolamine (DBEA, CAS no 102-81-8, EC no 203-057-1). However, as explained above in Appendix 1, section 0 of the present decision, your adaptation of the information requirement is rejected.

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.

In your comments to the draft decision you agree to fulfil this request.

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).

The registrant should also carefully consider the order of testing especially the requested screening (OECD TG 421/211) and the developmental toxicity studies (OECD TG 414) to ensure unnecessary animal testing is avoided, paying particular attention to the end point specific guidance, ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a (version 6.0, July 2017)..

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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) via inhalation with an analogue substance dibutylethanolamine (DBEA, CAS no 102-81-8, EC no 203-057-1).

In addition, you have provided the following justification:

"The sub-chronic toxicity study (90 days) does not need to be conducted since reliable Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test in Rats (Crl: WI(Han) (OECD 422; Inhalation exposure: OECD413; [redacted], 2013; Project No.: [redacted]) is available for the nearest structural analogue dibutylethanolamine, for which the observed NOAEL, with an application of an appropriate assessment factor, allow the extrapolation towards the NOAEL-90 days for the same route of exposure. Systemic effects observed were only transiently reduced food consumption, body weight and body weight gain. Histopathological findings of nasal cavities display local effects which prevail over systemic effects (local NOAEC (20.6 mg/m³) < systemic NOAEC (236.3 mg/m³). An additional repeated dose toxicity study will not deliver new results".
However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected. Further, the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals examined per dose group for histopathology and clinical chemistry is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408).

Therefore, your adaptation of the information requirement is rejected.

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. ECHA notes that you have also provided the following justification within the endpoint study record for the "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test":
"According to Annex IX, testing of the subchronic toxicity (90 days) is only relevant for the most likely exposure route. Due to the vapour pressure of the substance (13.94 Pa at 20°C), the substance is volatile and can easily evaporate into the air. In conclusion, testing via oral route is not necessary. For the hazard assessment purpose (DNEL derivation), a NOAEL from the combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test in rats (OECD 422; Inhalation exposure: OECD413; [redacted], 2013; Project No.: [redacted]), with application of an appropriate assessment factor, allows extrapolation towards repeated oral route administration", and

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 default 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, the exposure concentrations reported in the chemical safety report for the inhalation route are low (maximum [redacted] mg/m³) compared to the toxicity profile of the substance.

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.

In your comments to the draft decision you propose sequential testing, i.e. the need to test the sub-chronic (90-day) study with the registered substance will be decided once the results of the OECD 442 and OECD 414 with the registered substance are available. ECHA acknowledges your comment on considerations of sequential testing strategy for the request of the sub-chronic toxicity study. ECHA has already indicated in the statement of reasons of the decision (Section 0.2) the elements that need to be considered to substantiate a robust read-across approach when additional experimental evidence becomes available.

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.

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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) via inhalation with an analogue substance dibutylethanolamine (DBEA, CAS no 102-81-8, EC no 203-057-1).

In addition, you have provided the following justification:

"The Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test according to OECD TG 422 ([redacted], 2013) with 2-dibutylaminoethanol covers reproductive performance, developmental toxicity and offspring observations until day 4. No effects on reproduction and development were observed at any dose-level. The NOAEC for reproduction / developmental toxicity was considered to be 236.3 mg/m³/day (highest dose tested). It was therefore concluded that an additional Developmental

Toxicity / Teratogenicity study is not necessary as no adverse effects were detected in the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test."

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected. Further, 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.

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 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.

In your comments to the draft decision you agree to fulfil this request.

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 23 March 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 request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) 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.