EUROPEAN CHEMICALS AGENCY

Helsinki, 26 April 2017

Addressee: [redacted]

Decision number: CCH-D-2114359258-40-01/F
Substance name: ACETIC ACID' related multi constituent substance including 2-{(1S)-1-[(1R)-3,3-dimethylcyclohexyl]ethoxy}-2-oxoethyl propanoate
EC number: 607-255-2
CAS number: 236391-76-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 10.05.2013
Registered tonnage band: 100-1000T

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. **Name(s) in the IUPAC nomenclature or other international chemical name(s) (Annex VI, Section 2.1.1.) of the registered substance;**

2. **Composition (Annex VI, Section 2.3.) of the registered substance;**

3. **Description of the analytical methods (Annex VI, Section 2.3.7) of the registered substance;**

4. **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 modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy;**

5. **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 of the REACH Regulation. In order 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 an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **3 May 2019**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[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.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

IDENTIFICATION OF THE SUBSTANCE

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

1. Name or other identifier of the substance (Annex VI, Section 2.1.)

"Name or other identifier of the substance" is an information requirement as laid down in Annex VI, Section 2.1 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 you have identified the registered substance as multi-constituent with the chemical name "[redacted]" and the CAS number 236391-76-7 associated to the list number 607-255-2. Furthermore, in the description and synonyms fields another identifier referring to ELINCS number [redacted] and name "[redacted]" is mentioned to identify the substance.

ECHA points out that the identity of the substance is not clear as inconsistent information has been provided. The CAS name and number used for defining the registered substance refer to a substance containing all the possible isomers of "[redacted]". However, the submitted chemical name describes a substance containing 2 specific enantiomers of [redacted] and one main constituent containing "[redacted]" isomers.

Therefore, the CAS identifiers and the chemical name given to the registered substance are not consistent as they refer to different substances.

You are accordingly requested to provide appropriate identifiers corresponding to the specific multi-constituent substance covered in this registration. The chemical name shall follow the generic format "Reaction mass of [names of the main constituents]". All main constituents present in the registered substance shall be reflected in the name of the registered substance. All the constituents present at a concentration <10% (w/w) must be listed under impurities and not be part of the name. You shall also specify any available and appropriate CAS number and name reflecting the identity of the main constituents of the substance. You shall delete from the registration any information referring to different substances than the multi-constituent substance which is the subject of this registration.

You shall ensure that the identifiers are consistent with the composition required to be provided according to Annex VI, Section 2.3.

You shall note that in accordance with the criteria for substance sameness specified in the Guidance for identification and naming of substances under REACH and CLP (Version: 1.3, February 2014) - referred to as "the Guidance", multi-constituents substances with different main constituents shall be regarded as different substances under REACH.

You shall note that the registration is currently linked to chemical identifiers (including the list number 607-255-2) for the substance "[redacted]". In case the current identifiers are not appropriate to describe the registered substance, you should not remove or modify at this stage the chemical identifiers specified under the "EC inventory" section of your reference substance in IUCLID section 1.1 (including the List number 607-255-2) for technical reasons, the registration being linked to that List number in REACH-IT. To ensure unambiguous identification of the registered substance, you should however indicate, in the "Remarks" field of the reference substance in IUCLID section 1.1, the following: "The list number 607-255-2 currently assigned does not specifically correspond to the registered substance. This identifier cannot be modified or deleted at this stage in the present registration update for technical reasons". You should also specify, in the same "Remarks" field, any available and appropriate EC number for the substance. Any available CAS entry for the registered substance should be reported under the "CAS information" header of the reference substance in IUCLID section 1.1.

You should note that ECHA has established a process, subject to certain conditions, enabling you to adapt the EC identifier of your existing registration, while maintaining the regulatory rights already conferred to the substance concerned.

Pending the resolution of the non-compliances addressed in the present decision, any possible adaptation of the identifier can only become effective once ECHA is in a position to establish unambiguously the identity of the substance intended to be covered by you with this registration. Should the information submitted by you as a result of the present decision enable ECHA to identify the substance unambiguously and result in a need to modify the identifier of the substance, the process of adapting the identifier will be considered relevant. In that case, ECHA will inform you in due time as to when and how the identifier adaptation process shall be initiated.

In any case, you should note that the application of the process of adapting the identifier does not affect your obligation to fulfil the requirements specified in this decision.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you have indicated your intention to revise the chemical names and identifiers used in section 1.1 of your IUCLID dossier addressing the information requirement in an update of the registration dossier. ECHA will examine such information only after the deadline set in the adopted decision has passed and all the substance information requested in this decision has been submitted.

2. Composition of the substance (Annex VI, Section 2.3.)

The substance composition corresponds to the chemical representation of what the substance consists of and is therefore an essential part of substance identification and the cornerstone of all the REACH obligations.

Due to certain inconsistencies in the stereochemistry of the reported constituents, further compositional information of the registered substance is necessary, as required under Annex VI, Section 2.3 of the REACH Regulation.

ECHA observes that the identifiers and the stereochemistry of the second and third constituents are unclear as the submitted information is inconsistent. The provided substance identifiers refer to different isomers. More specifically, in IUCLID section 1.2,

- For the constituent 2
  - the IUPAC name refers to (1R,2'R) enantiomer;
  - the structural formula, SMILES notation and InChI code refer to the (1S,2'S) isomer;
  - reference substance name refers to the racemic mixture (1R*,2'R*).
- For the constituent 3
  - IUPAC name, refers to the (1R,1'R) isomer;
  - the structural formula, SMILES notation and InChI refers to the (1S,1'R) isomer.

As a result ECHA cannot confirm the identity of the registered substance and concludes that the compositional information has not been provided to the required level of detail.

You are accordingly requested to revise the consistency of all the identifiers of the constituents and to clarify the stereochemistry of the constituents reported in the composition of the registered substance, to have a complete chemical representation of what the substance consists of.

Regarding how to report the composition in IUCLID, the following applies: For each stereoisomer, at least one of the following identifiers shall be specified: chemical name, CAS number, EC number and/or molecular formula, as well as the minimum, maximum and typical concentration, in the appropriate fields in IUCLID section 1.2.

Further technical details on how to report the composition of multi-constituent substances in IUCLID are available in paragraphs 2.1 and 2.2.1.2 of the Data Submission Manual 18 on the ECHA website.

You shall ensure that the reported composition is verifiable and accompanied by a description of the analytical methods for the identification of the registered substance, as required under Annex VI, Section 2.3.7.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you have indicated your intention to revise the chemical names and identifiers used in section 1.2 of your IUCLID dossier addressing the information requirement in an update of the registration dossier. ECHA will examine such information only after the deadline set in the adopted decision has passed and all the substance information requested in this decision has been submitted.

3. Description of the analytical methods (Annex VI, Section 2.3.7.)

Annex VI, Section 2.3.7 of the REACH Regulation requires that each registration dossier contains a sufficiently detailed description of the analytical method used for establishing the composition of the registered substance and therefore its identity. This information shall be sufficient to allow the method to be reproduced.

ECHA notes that you have not provided sufficient information and appropriate description of the analytical methods used to determine the identity and composition of the registered substance. More specifically, you have provided a full set of analytical data (IR, UV, NMR and GC-MS).

However, the information provided in IUCLID section 1.4 is not sufficient for the identification and quantification of the stereochemistry of the constituents present in the composition of the substance and their respective concentration values.

You have provided a GC-MS in document "[redacted]" and a GC in the document "[redacted]" which contain each a chromatogram which show several major peaks. However, it is not clear how the assignment of the peaks refers to the stereoisomers present in the recorded composition of the substance.

Furthermore, the description of the methods with details of calibration and calculation used to identify the peaks and determine the concentration and the stereochemistry of the constituents were not included in the dossier. This information should allow the verification of the composition and its stereo-specific constituents listed in IUCLID section 1.2.

In addition, you have listed in the document "[redacted]" the constituents with a chemical name and a structural formula specific to an isomer and have provided the specific ^{1}H-NMR, ^{13}C-NMR spectra and MS signal assignments. However, with the absence of a detailed evaluation report ECHA could not conclude how the NMR and MS data support the specific isomer described by the chemical name and the structural formula. More specifically, the provided MS spectra show for each stereoisomer similar fragmentation pattern which does not allow the differentiation of the isomers of "[redacted]".

Consequently no sufficient description of the analytical methods required for the identification and quantification of the registered substance was included in the registration dossier.

In accordance with Annex VI, Section 2.3.7, you are therefore requested to provide a description of methods used for the identification and quantification of the registered substance including its constituents. This information shall be sufficient to enable the substance identity in IUCLID section 1.1 of the dossier and all constituents reported in IUCLID section 1.2 to be verified. The information is required to be sufficient for each method to be reproduced and shall include details of the experimental protocol followed, the calculations used and the results obtained.

As for the reporting of the above data in the registration dossier, the information should be attached in IUCLID section 1.4.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you have indicated your intention to consolidate the description of the analytical methods in your IUCLID dossier addressing the information requirement in an update of the registration dossier. ECHA will examine such information only after the deadline set in the adopted decision has passed and all the substance information requested in this decision has been submitted.

PROPERTIES OF THE SUBSTANCE

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

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

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 3.2 (a). You provided the following justification for the adaptation:

"Romandolide does not meet the classification criteria for any of the toxicological hazard classes. Moreover, no adverse effect was observed in studies conducted at the highest practicable & biologically-relevant concentration on toxicological endpoints:

- *In an acute oral toxicity study (LD50 > 2000 mg/kg bw),*
- *In a 28-day repeated-dose toxicity study by diet (NOAEL = 10910 ppm, i.e. 851 or 953 mg/kg bw/day for males or females, respectively),*
- *In a reproduction/developmental toxicity screening study toxicity (NOAEL = 11000 ppm, i.e 698 mg/kg bw/day for the males, 804-1467 mg/kg bw/day for the Main reprotoxicity phase females, 737 mg/kg bw/day for the Toxicity phase females). In this study, Romandolide was administered to rats for 7 weeks and investigations were extended with the inclusion of haematology, clinical biochemistry, organ weights (target organs, i.e. liver and kidneys), and histopathology (grossly abnormal tissues and target organs). After 7 weeks of administration, no additional adverse effects were observed compared to the 28-day study.*
  There were no increased incidence of findings and the NOAEL was similar. Although Romandolide and/or its metabolites may have an accumulative potential based on the log Kow value, prolonged exposure did not result in more potent adverse effects. Therefore, a sub-chronic toxicity study (90-day) is considered to be scientifically unjustified. Regarding the classification, no target organ toxicity was observed up to the highest and biologically-relevant dose, while damages to organs should have been observed in the 28-day and 7-weeks studies if Romandolide had been classified as STOT-RE. Therefore Romandolide is not classified as STOT-RE.
- *According to ECHA guidance part B (point B 8.4), this would normally indicate that no hazard has been identified and no DNEL can be derived and hence exposure assessment for that route of exposure, type of effect or protection target would not be needed. However, exposure scenarios were developed in order to justify exposure based adaptations to the tests to be performed for a substance in quantities of 100 to 1000 tpa. Indeed, according to REACH Annex XI Section 3, testing for sub-chronic study may be omitted based on the exposure scenario(s) developed in the Chemical Safety Report and the risk assessment performed in the dossier. For Romandolide:*
- *The results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified use*
- *DNELs derived from the results of available test data take into account the increased uncertainty resulting from the omission of the information requirement.*
- *The comparison of the derived DNEL with the results of the exposure assessment shows that exposures are always below the derived DNELs (i.e. for human health risk assessment: PEL/DNEL <1).*

Therefore, all criteria (according to REACH Annex XI section 3) being fulfilled to justify the waiving for the 90-day repeated dose toxicity study, no further testing was proposed. Adequate justification and documentation is provided in the respective sections of the CSR."

Pursuant to Annex XI, section 3, testing may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report. Pursuant to Annex XI section 3.2. an exposure based assessment must meet any one of the criteria set out in sub-sections (a) to (c). In all cases, an adequate justification and documentation shall be provided. In order to adapt in accordance with Annex XI, section 3.2 (a) three cumulative conditions need to be fulfilled.

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI, Section 3.2. (a), because you have not successfully demonstrated and documented that the three cumulative conditions set out in that section have been met:

First, contrary to what you have indicated, you have not shown that the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses.

There are a variety of industrial and professional worker as well as consumer uses described in the CSR. Such uses are in general considered as being accompanied by significant exposure to the substance used as conditions of use cannot be fully controlled. Whilst some of the industrial worker exposure scenarios describe closed systems, others do not. For example for exposure scenario 2, contributing scenario 3, mixing operations in batch process including filling equipment and sample collection, the inhalation and dermal long-term systemic exposure estimations from TRA Worker version 3, when compared with the respective DNEL yield RCRs of [redacted] and [redacted] respectively. A combined RCR of [redacted] certainly does not indicate the absence of exposure and support this exposure based adaptation. For consumer contributing scenario 2, furniture, floor & leather care: spray, when the inhalation, systemic, long-term exposure estimation from TRA Consumer version 3 is compared with the respective DNEL for the general population this yields an RCR of [redacted]. RCRs of [redacted] and [redacted] do not demonstrate absence of or no significant exposure. ECHA's *Guidance on information requirements and chemical safety assessment,* Chapter R.5: *Adaptation of information requirements* (version 2.1, December 2011), section R.5.1.5.4 states that to justify omission of testing in accordance with Annex XI Section 3.2(a) the risk characterisation ratio needs to be well below one.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you request information from ECHA on the exact level of an RCR that is considered by ECHA to be 'well below 1' and therefore acceptable in order to be in compliance in context of the Annex XI, Section 3.2 (a).

ECHA notes that, as explained above, the requirements of Annex XI, Section 3.2.(a) (ii) and (iii) cannot be met due to the absence of a suitable DNEL for comparison. According to ECHA's *Guidance on information requirements and chemical safety assessment,* Chapter R.5: *Adaptation of information requirements* (version 2.1, December 2011), section R.5.1.3.2. "*A quantitative risk characterisation establishes control of risk by demonstrating that the risk characterisation ratio is well below 1, taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes.*" Step 2 of figure R. 5-1 states "*Consider whether EBA can be justified based on no release, strictly controlled conditions, absence of exposure, or no significant exposure.*" Whilst ECHA has not stated an exact RCR that is well below 1, an acceptable value would be required to take into account the uncertainties of the non-standard study and the uncertainties in the exposure assessment. In your CSR you have used tier 1 exposure models to estimate exposure which delivers RCRs of [redacted] when compared with the respective DNEL.

ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.14: Occupational exposure assessment, section 14.4.2 provides further advice on relying on exposure assessment to support a case for substance-tailored exposure-driven adaptation:

"On occasions you may wish to rely on an exposure assessment to support a case for either a column 2 adaptation or for substance-tailored exposure-driven adaptation (Annex XI, Section 3). Generally the need is to demonstrate that there is sufficient evidence of absence of exposure, as defined through the application of strictly controlled conditions (Article 18(4)(a) to (f)).

Advice on how measurements may support an argument for strictly controlled conditions and absence of exposure is presented in Practical Guide 16: How to assess whether a substance is used as an intermediate under strictly controlled conditions and how to report the information for the intermediate registration in IUCLID. Various terms are used in the legal text as an indicator of the standard to be achieved, but in every case the evidence will need to be specific, adequate and suitable for that purpose. It is unlikely that exposure modelling alone will provide the level of proof required to demonstrate these highly controlled and rigorously contained conditions."

It should be noted that when a Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408), as requested in this decision is available, the exposure estimate when compared with the updated DNEL needs to result in RCRs below 1 to demonstrate safe use of the substance.

Finally, ECHA notes you have not provided an appropriate DNEL. The DNEL that you use to compare with the exposure estimates to calculate RCRs is based on results from a 28-day repeat dose toxicity study. REACH Annex XI section 3.2(a)(ii) contains a footnote which states "*... a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study.*" The lack of appropriate DNEL therefore means that you have not justified and documented how the second and third conditions in section 3.2 (a) have been fulfilled.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you note that "*the registered substance is not classified for any of the human health hazards and no adverse effects were observed up to the highest regulatory dose level in the sub-acute toxicity study (equivalent to 1000 mg/kg bw/day; in a dietary 28-day repeat dose toxicity study in rats). In this condition, risk assessment is not mandatory, according to the ECHA guidance document[2]*". Furthermore, you conclude that "*even if no 90-day study is available, the registrant performed a worst-case risk assessment based on a DNEL derived from effects which are not adverse at the highest recommended dose in the 28-day study and 7-weeks of exposure in a reproductive toxicity study. Those studies also indicate that there is no potential for cumulative toxicity with this substance that may be revealed in a 90-day study.*"

ECHA notes that the referenced ECHA guidance refers to risk assessment but does not allow for an adaptation of the standard information requirement of a sub-chronic toxicity study. Your adaptation of the sub-chronic toxicity study according to Annex XI, Section 3.2.(a) is not valid because the criteria are not met, as explained above (e.g. the dossier lacks an appropriate DNEL that can be used for an exposure-based adaptation accoding to REACH Annex XI, Section 3.2.(a)).

[2] Information Requirements and Chemical Safety Assessment. Part D: Framework for exposure assessment (version 2.0., August 2016)

Therefore, the standard information requirement remains to be fulfilled because the required exposure duration of 90 days is not met by the studies provided in the dossier (OECD 407 and 421).

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.

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 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure. Uses with spray application are reported in the chemical safety report. However, the reported concentrations are low (<[redacted]%). 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.

ECHA notes that in the sub-acute oral toxicity study and in the oral OECD TG 421 screening study present in your registration dossier, adverse effects due to the accumulation of urinary alpha 2 μ-globulin protein in the tubular epithelium were observed in the kidneys of male rats and not in female rats. The fact that these effects were only observed in male rats may indicate that the registered substance may induce alpha-2u-globulin-mediated nephropathy. ECHA accordingly considers that the kidney is a target organ of the registered substance. Since humans do not excrete alpha-2u-globulin and this mode of action is considered not relevant to humans the involvement of alpha-2u-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for risk assessment. For these reasons, ECHA considers that urinalysis is required to investigate kidney function (which is optional in paragraphs 3, 30 and 32 of OECD TG 408, and the relevant part of Section 1.5.2.2. of EU Method B.26.). Additionally, a full histopathological examination (paragraphs 3, 35 and 36 of OECD TG 408, Section 1.5.2.4. of EU Method B.26.), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you propose to conduct a repeated dose toxicity study using males only exposed sub-acutely (28 days), at the highest achievable and recommended dose level and concurrent vehicle only enabling determination of alpha-2u-globulin mediated pathology in a sighting study in order to avoid a 90-day toxicity study.

However, ECHA notes that the standard information requirement remains to be fulfilled, irrespectively from the additional kidney investigations as explained above.

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 modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

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

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 on the basis of Annex IX, Section 8.7.2, column 2 and Annex XI, Section 3.2.a. You provided the following justification for the adaptation

"Romandolide does not meet the criteria for any of the toxicological hazard classes. Indeed, the acute oral and the 28-day repeated dose oral toxicity studies identified no significant evidence of toxicity (LD50 > 2000 mg/kg bw and NOAEL = 881 mg/kg bw/day, respectively). Furthermore, no indication of reproductive and developmental toxicity in the screening study was observed leading to a NOAEL = 11000 ppm, i.e. 698 mg/kg bw/day for the males, 804-1467 mg/kg bw/day for the Main reprotoxicity phase females, 737 mg/kg bw/day for the Toxicity phase females). As a result, Romandolide is not classified as reproductive toxicant.

According to ECHA guidance part B (point B 8.4), this would normally indicate that no hazard has been identified and no DNEL can be derived and hence exposure assessment for that route of exposure, type of effect or protection target would not be needed. However, exposure scenarios were developed in order to justify exposure based adaptations to the tests to be performed for a substance of tonnage level 100-1000 tpa. Indeed, according to REACH Annex XI Section 3, testing for sub-chronic study may be omitted based on the exposure scenario(s) developed in the Chemical Safety Report and the risk assessment performed in the dossier. For Romandolide:

- *The results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified use*
- *DNELs derived from the results of available test data take into account the increased uncertainty resulting from the omission of the information requirement.*
- *The comparison of the derived DNEL with the results of the exposure assessment shows that exposures are always below the derived DNELs (i.e. for human health risk assessment: PEL/DNEL <1).*

In conclusion, even if absorption is expected, Romandolide is of low toxicological concern regarding the toxicity to reproduction and there is no or no significant human exposure. Thus, according to REACH Annex IX column 2 and REACH Annex XI Section 3, further studies to investigate reproductive and developmental toxicity are considered to be unjustified. Adequate justification and documentation is provided in the respective sections of the CSR."

Concerning your adaptation based on Annex IX, Section 8.7.2., column 2, ECHA notes that the third indent of that section provides that a pre-natal developmental toxicity study does not need to be conducted if the substance is of low toxicological activity, it can be proven from toxic-kinetic data that no systemic absorption occurs via relevant routes of exposure and there is no or no significant human exposure.

However, ECHA notes that your description of absorption in IUCLID section 7.1 shows that the registered substance is absorbed:

> *"The physical chemical characteristics described above suggest that Romandolide is of adequate molecular size to participate in endogenous absorption mechanisms within the mammalian gastrointestinal tract. Being lipophilic, Romandolide may be expected to cross gastrointestinal epithelial barriers even if the absorption may be limited by the inability of the substance to dissolve into gastro-intestinal fluids and hence make contact with the mucosal surface. Moreover, the absorption will be enhanced if Romandolide undergo micellular solubilisation by bile salts. Substances absorbed as micelles will enter the circulation via the lymphatic system, bypassing the liver."*

Therefore, the condition set out under the third indent of Annex IX, Section 8.7., column 2 that no systemic absorption occurs is not fulfilled. Accordingly, your adaptation does not meet the specific rules of adaptation set out in the third indent of Annex IX, Section 8.7., column 2.

With respect to your adaptation concerning Annex XI, Section 3.2(a), ECHA notes that pursuant to Annex XI, Section 3, testing may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report. Pursuant to Annex XI, Section 3.2. an exposure based assessment must meet any one of the criteria set out in sub-sections (a) to (c). In all cases, an adequate justification and documentation shall be provided.

In order to adapt in accordance with Annex XI, Section 3.2 (a) three cumulative conditions need to be fulfilled. However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI, Section 3.2. (a), because you have not successfully demonstrated and documented that the three cumulative conditions set out in that section have been met.

First, contrary to what you have indicated, you have not shown that the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses.

There are a variety of industrial and professional worker as well as consumer uses described in the CSR. Whilst some of the industrial worker exposure scenarios describe closed systems, others do not. For example for exposure scenario 2, contributing scenario 3, mixing operations in batch process including filling equipment and sample collection, the inhalation and dermal long-term systemic exposure estimations from TRA Worker version 3, when compared with the respective DNEL yield RCRs of [redacted] and [redacted] respectively. A combined RCR of [redacted] do not demonstrate absence of or no significant exposure.
For consumer contributing scenario 2, furniture, floor & leather care: spray, when the inhalation, systemic, long-term exposure estimation from TRA Consumer version 3 is compared with the respective DNEL for the general population this yields an RCR of [redacted]. RCRs of [redacted] and [redacted] do not demonstrate absence of or no significant exposure.

ECHA's *Guidance on information requirements and chemical safety assessment*, Chapter R.5: Adaptation of information requirements (version 2.1, December 2011), section R.5.1.5.4 states that to justify omission of testing in accordance with Annex XI, Section 3.2(a) the risk characterisation ratio needs to be well below one.

Second, ECHA notes you have not provided an appropriate DNEL. The DNEL that you use to compare with the exposure estimates to calculate RCRs is based on results from a combined 28-day repeated dose and reproductive/developmental toxicity screening study. REACH Annex XI, Section 3.2(a)(ii) contains a footnote which states "...a DNEL derived from a screening study for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study." The lack of an appropriate DNEL therefore means that you have not justified and documented how the second and third conditions in Section 3.2 (a) have been fulfilled.

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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid of very low vapour pressure, ECHA concludes that testing should be performed by the oral route.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you indicated your agreement to perform this study.

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 17 June 2016.

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

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

3. In carrying out the test(s) 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 test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.