EUROPEAN CHEMICALS AGENCY

Helsinki 31 May 2017

Addressee: [redacted]

Decision number: CCH-D-2114361700-57-01/F
Substance name: 3-p-cumenyl-2-methylpropionaldehyde
EC number: 203-161-7
CAS number: 103-95-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08.06.2015
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. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance provided that the study requested under 1. has negative results;**

3. **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;**

4. **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;**

5. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **At least two weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;**

6. **Classification and labelling (Annex VI, Section 4.): Apply classification and labelling on the registered substance for reproductive toxicity *or* provide a justification for not classifying.**

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 **7 December 2020** except for the information requested under point [3] for a sub-chronic toxicity study (90-day) and under point [6] for classification and labelling, which shall be submitted in an updated registration dossier by **7 June 2018**. You may only commence the extended one-generation reproductive toxicity study as requested under point [5]) after **7 September 2018**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also 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. 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 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.

Appendix 1: Reasons

For the endpoints In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.), and Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.), your registration dossier contains adaptation arguments in form of a grouping and read-across approach under Annex XI, 1.5 of the REACH Regulation using data of a structurally similar substance, Florhydral (EC No 412-050-4) (hereafter the 'source substance'). ECHA has considered first the scientific and regulatory validity of your read-across approach in general in Section 0 before assessing the individual endpoints (sections 1 and 3).

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".
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 property-specific context.

0.1 Description of the grouping and read-across approach proposed by the Registrant

In the technical dossier you have provided a justification document for read-across, under IUCLID Section 13. You claim that "the output from the OECD [Q]SAR toolbox shows that the profiles of the target substance and the source substance are sufficiently similar such that available toxicological data from the source substance" Florhydral (EC No 412-050-4) can be used to read-across to the registered substance. This toolbox output addresses structural, physico-chemical, toxicological and 'mechanistic action' similarities, and ECHA accordingly understands that your read-across justification is based on these similarities. You have proposed that the source and registered substances have comparable properties for the above-mentioned information requirements.

ECHA considers that this information is your read-across hypothesis, which provides the basis whereby you predict the properties of the registered substance from the source substance.

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

You have proposed that structural, physicochemical and toxicological similarity are the basis for predicting the properties of the registered substance. However, any structural similarity and similarity in physicochemical or toxicological properties are only useful, if they are supplemented by a justification of why they would allow a prediction of similar properties for human health.
Structural similarity is a prerequisite for applying the grouping and read-across approach but ECHA does not accept in general or this specific case that structural similarity per se is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties.

Specifically, ECHA notes that there is not a well-founded hypothesis of (bio)transformation to a common compound(s), or that different compounds have the same type of effect(s), to allow a prediction of human health properties that does not underestimate risks.

Similarly, physicochemical/toxicological similarity per se cannot be considered as sufficient to enable the prediction of human health properties of a substance, since physicochemical and toxicological similarity or regular properties in one toxicological endpoint does not always lead to predictable or similar human health properties in other toxicological endpoints.

As described above, to justify the predictability of the human health and environmental properties, you have proposed that there are 'mechanistic action' similarities, and that this is a basis for predicting the properties of the registered substance. The 'mechanistic action' similarities in Table 1 are listed under the heading "human hazard assessment information". There are a list of issues (e.g. "DNA binding ability (OECD)"), together with an assessment for these issues. There is no explanation of what these issues are and no explanation of the methodology for performing the assessment. ECHA is unable to assess this information. Consequently, ECHA considers that this material provides no support for your claim that physicochemical and toxicological similarities enable the prediction of relevant human health properties. ECHA considers that there is a failure of adequate and reliable documentation.

ECHA considers that this grouping and read-across approach does not provide a robust basis whereby the human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach), and hence does not comply with the general rules of adaptation as set out in Annex XI, 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, 1.5, and these are set out under the endpoint concerned further below.

0.3 Conclusion on the read-across approach

The adaptation of the standard information requirements for the endpoint *in vitro* cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.) and the Sub-chronic toxicity study (90-day) (using a short-term repeated dose toxicity study (28 day) (Annex VIII, Section 8.6.1.)) in the technical dossier is based on the proposed read-across approach examined above. ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation in the endpoints mentioned above does not comply with the general rules of adaptation as set out in Annex XI, 1.5.

1. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 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.

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. 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 not provided any study record of an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the dossier that would meet the information requirement of Annex VIII, Section 8.4.2.

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 an *in vitro* chromosome aberration study according to OECD TG 473 (RCC, 2005) on the analogue substance Florhydral (EC no 412-050-4). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Additionally, in the technical dossier there is an *in vivo* study used to assess chromosome aberration (Micronucleus Assay) (<[redacted], 1991), with the same analogue substance (Florhydral). However, as already mentioned above, the read-across approach fails to meet the requirements of Annex XI, Section 1.5. Hence, the adaptation for Annex VIII, Section 8.4.2., column 2, cannot be used since there is no "*adequate data from an in vivo cytogenicity test*" available.

In the comments to the draft decision you disagreed with the information requirement in the draft decision. You outlined how you could address the information requirement by using "*read across to an in vitro cytogenicity study in mammalian cells performed on Lilial (CAS 80-54-6) that has a Klimisch score of 2. Read across justification is contained in Annex I of this document.*" Annex I contains a 'Read-across Assessment Framework' for the cytogenicity and gene mutation endpoints. The read-across hypothesis whereby "*Lilial is considered to be acceptable as the read-across substance of choice*" in Annex I is based on: (a) section 1.1 is titled "*Read-across hypothesis based on (bio) transformation to common compounds*", and you describe the metabolism of the registered substance and Lilial (the source substance) (b) in view of the high purity of the registered substance and the source substance, it is not necessary to make specific provisions in the read-across justification for the toxicity of any impurities (c) the similarity in structure, physico-chemical and toxicological properties, and (d) the predictions from a computer programme.

In respect of the read-across argumentation, ECHA has addressed the arguments set out above:

a) The proposed adaptation argument is that the "similar" metabolites are formed by both the target and source substances when metabolized in rat hepatocytes, and this is under the heading "Read-across hypothesis based on (bio) transformation to common compounds". ECHA considers that no case has been made that there is production of common compounds, nor that toxicity is mediated by these common compounds. ECHA considers that the description of metabolism to "similar", non-common compounds does not, by itself, form a basis for explaining why the properties of one substance can be used to predict the properties of a different substance.
b) ECHA agrees that it is not necessary to make specific provision for the impurities when making the read-across justification in the circumstances of this case.
c) Your proposed adaptation argument is that the similarity in structure/ physico-chemical/ toxicological properties between the source and target substance is a sufficient basis for predicting the properties of the substance. This argument is limited and is in principle not capable of being sufficient. You have not provided any other basis for predicting the properties of the registered substance (except (d), see below).

Similarity in structure/ physico-chemical/ toxicological properties is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that similarity in structure/ physico-chemical/toxicological properties per se is sufficient to enable the prediction of human health properties of a substance. This is because similarity in structure/ physico-chemical/ toxicological properties does not always lead to predictable or similar human health properties. Further elements are needed[2], such as a well-founded hypothesis of (bio)transformation to a common compound(s), or that different compounds have the same type of effect(s), to allow a prediction of human health properties that does not underestimate risks.

d) You have provided predictions of the properties of the registered substance and source substance in "Table 5. Read-Across Profile Using the OECD [Q]SAR Toolbox" and in "Table 5. The OECD [Q]SAR Toolbox Prediction for DNA Binding/Interaction". ECHA considers that there is not an adequate and reliable description of the methodology used to predict these properties, nor of precisely what properties are being predicted. Consequently, ECHA cannot independently evaluate this information and cannot take these predictions into account.

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, ECHA considers that the arguments when taken all together do not provide a basis for predicting the properties of the registered substance. ECHA considers that this grouping and read-across approach does not provide a robust basis whereby the human health effects may be predicted from data for reference substance(s) within the group, and hence does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

Finally, you did not provide the *in vitro* chromosome aberration assay. Hence, ECHA is not in a position to assess the study record referred to in your comments.

In view of the above, ECHA considers that this grouping and read-across approach does not provide a robust basis whereby the human health effects concerned may be predicted from data for reference substance within the group, and hence does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

Furthermore, ECHA notes that this decision does not take into account any updates submitted after the submission of the draft decision. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after the deadline for complying with the final decision has expired).

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 considers that the *in vitro* mammalian chromosome aberration test (OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

[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 and 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).

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: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

2. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 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.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

You have not provided any study record of an *in vitro* gene mutation study in mammalian cells in the dossier that would meet the information requirement of Annex VIII, Section 8.4.3.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex VIII, Section 8.4.3. or with the general rules of Annex XI for this standard information requirement.

In your comments to the draft decision you disagreed with the information requirement and outlined how "*The registrant will read across to an in vitro gene mutation study in mammalian cells performed on Lilial (CAS 80-54-6) that has a Klimisch score of 2. Read across justification is contained in Annex I of this document.*" The read-across adaptation is rejected for the same reasons as set out for the *in vitro* cytogenicity endpoint (under request 1), with the exception that you failed to provide an *in vitro* gene mutation study in mammalian cells and hence ECHA is not in a position to assess the study record referred to in your comments.

In view of the above, ECHA considers that this grouping and read-across approach does not provide a robust basis whereby the human health effects may be predicted from data for reference substance within the group, and hence does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

Furthermore, ECHA notes that this decision does not take into account any updates submitted after the submission of the draft decision. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after the deadline for complying with the final decision has expired).

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 considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

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: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the study requested under section 1. has negative results.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 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.

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 not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

In the technical dossier you have provided two study records for this endpoint:
1. Key study: 14-day repeated dose toxicity study, in rabbits, via the oral route, with the registered substance (Charles River Labs, 2011); and
2. Supporting study: 28-day repeated dose toxicity study, in rats, via the oral route, with the analogue substance, Florhydral (ß-methyl-3-(1-methylethyl)benzenepropanal EC no 412-050-4) ([redacted], 1991).

However, these studies do not provide the information required by Annex IX, Section 8.6.2., because of the following reasons:
- In both studies exposure duration is less than 90 days and ECHA considers that there is not exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3), and that exposure duration is a relevant parameter.
- The number of animals tested per dose group is significantly lower than required by the test guideline. In the 14-day and the 28-day studies, only five males and 12 animals (6 males and 6 females) were used, respectively. According to OECD TG 408, the 90-day study requires "*at least 20 animals (ten female and ten male)...at each dose level*". Therefore, the sensitivity of a 14-day and a 28-day study is much lower than that of a 90-day study. In the 14-day study conducted on rabbits, no data was provided for the following parameters: ophthalmological, haematology and urinalysis; these parameters need to be examined under the 90-day as per OECD TG 408. ECHA accordingly considers that there is not adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3).
- Finally, the 28-day study report is not reliable information for this endpoint since, not only it has been assigned a reliability score of 4, but the study has been performed with the analogue substance Florhydral. As explained in Appendix 1, section 0 of this decision, the read-across adaptation to Florhydral (EC no 412-050-4) cannot be accepted.

Therefore, your adaptation of the information requirement is rejected.

Upon receipt of the draft decision you submitted comments explaining that "*the oral (gavage) one-generation reproduction study...in rats provides information which clearly fulfils this endpoint request.*" You also claim that "*in a weight of evidence approach, the registrant will also read across a sub-chronic toxicity study (90-day), oral route (OECD TG 408) in rats performed on Lilial (CAS 80-54-6).*"

However, ECHA notes that the one-generation reproductive toxicity study according to OECD 415 ([redacted], 2009), provided in the technical dossier, does not fulfil the standard information requirement of Annex IX, Section 8.6.2. This study does not provide equivalent information to that expected from a 90-day repeated dose toxicity study, required to comply with this standard information requirement. According to Annex XI, Section 1.1.2., data from experiments not carried out according to the test methods referred to in Article 13(3) cannot be considered equivalent to the data generated by the corresponding test methods, if no "*adequate and reliable documentation of the study*" is provided. More specifically, the one-generation reproductive toxicity study does not provide information on haematology, and as regards the organ weights, there is no data on kidneys, thymus, spleen and heart.

Moreover, it is not clear whether the histopathology examinations were only limited to reproductive organs, liver, adrenal glands, brain and pituitary. As indicated in OECD TG 408, there is a list of organs/tissues that should be examined; however, in the study by [redacted] (2009), no data is found on a number of organs/tissues, including: spinal cord, thyroid, parathyroid, thymus, oesophagus, salivary glands, stomach, small and large intestines, pancreas, kidneys, spleen, heart, lymph nodes, urinary bladder, peripheral nerve and bone marrow. Moreover, the female rats in this one-generation reproductive toxicity study ([redacted] 2009) were only exposed to the registered substance for 77 days (< 90days), hence the data provided in this study cannot be considered to be equivalent to the data generated by the corresponding test method since the exposure duration for females is less than the corresponding test method. Hence the "use of existing data" adaptation as set out in conditions (3) and (4) of Annex XI, Section 1.1.2. is not met.

As regards the sub-chronic toxicity study (90-day), oral route (OECD TG 408) in rats performed on the read-across substance Lilial (CAS 80-54-6), ECHA notes that you provided a summary of this study, and you refer to Annex I for the justification for read-across. However, ECHA notes that there is not a robust study summary of this study present in the dossier, and ECHA has insufficient information to be able to evaluate this study, irrespective of whether the newly provided information may be sufficient to meet the information requirement for the registered substance. In respect of the read-across justification in Annex I, ECHA's comments for the *in vitro* cytogenicity endpoint (under request 1.) also apply for this endpoint, with the exception of the comment on the availability of the *in vitro* cytogenicity study.

Furthermore, ECHA notes that this decision does not take into account any updates submitted after the submission of the draft decision. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after the deadline for complying with the final decision has expired).

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. The registered substance has a very low vapour pressure (0.3 Pa at 20°C) and a very high boiling point (234°C). The substance has a significant exposure to both professionals and consumers (PROCS 4/8/10/11/13) and it may be found in sprays and aerosols. 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 occupational inhalation exposure (8 hour TWA, mg/m^3) are low (maximum [redacted] mg/m^3). Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

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

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

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 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.

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 not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 8.7., column 2, 3rd sub-paragraph. You provided the following justification for the adaptation: "*In a Reproduction and Developmental Toxicity Screening Test (OECD Guideline 415, Klimisch 1) the test substance Cyclamen Aldehyde Extra was administered to rats via the oral route at 25, 75 and 150 mg/kg/day. This evidence from this study suggests that this substance had no adverse effects on the reproductive cycle at a dose level of 25 mg/kg/day. However a further study into the metabolism of Cyclamen Aldehyde Extra in hepatocytes, comparing rat metabolism to human, rabbit and mouse, showed clear differences in metabolism between the rat and other species. It was proposed that the adverse effects observed in rat studies were misleading due to the observed differences in metabolism of the test substance.*

This hypothesis was supported by a long term study performed in the Rabbit which showed no effects at the highest concentration of 300 mg/kg bw/day, the metabolism study highlights the similarity between human and rabbit metabolisms of cyclamen aldehyde as opposed to that of human to rat, and thus the test substance should not be classified. In addition, acute oral toxicity testing (LD50 >2000 mg/kg/day), acute dermal toxicity testing (LD50 >5000 mg/kg/day) and sub chronic toxicity (NOAEL 300 mg/kg/day) confirms that Cyclamen Aldehyde Extra is of very low toxicity. The expected route of exposure to this substance is considered to be dermal rather than oral or inhalation which suggests that systemic exposure via the dermal route would be low. As the test substance has been shown to be of low concern regarding any adverse toxicity in reproductive screening or sub chronic study, up to and including the accepted high dose levels, further reproductive toxicity testing is not deemed appropriate. The evidence does not support the necessity to perform additional animal studies."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.7., column 2, third sub-paragraph, because the cumulative conditions of the adaptation requirement, whereby the study does not need to be conducted if *"(i) the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), (ii) it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure, and (iii) there is no or no significant human exposure*", are not met.

ECHA makes the following observations:

(i) In your justification you state that the acute oral and dermal toxicity and sub-chronic toxicity studies confirm the "*very low toxicity*" of the registered substance. However, the available studies presented in the dossier show evidence of toxicity, which is contrary to your claim. Hence, condition (i) of Annex IX, Section 8.7.2., column 2, third sub-paragraph is not met, since the substance should have "*no evidence of toxicity seen in any of the tests available*".

a. In the technical dossier, there are no 28-day or 90-day repeated dose toxicity studies with the registered substance, however, there is clear evidence of adverse effects in the one-generation study in rats [redacted], 2009) and the 14-day repeated dose toxicity in rabbits (Charles River Laboratories, 2011).

i. The one-generation study ([redacted], 2009) shows "*adverse effects on sperm analyses and histopathological changes to the epididymides*" of the parental animals, "*observed at 150mg/kg bw/day dose level.*" "*In treated female rats, reduced gestational body weight...Reduced pup body weights...reduced number of implantation sites and a reduced fertility index were observed at the 150mg/kg bw/day dose level.*" A NOAEL was also established for the parental and F1 generation: 75 and 25 mg/kg bw/day for males and females, respectively.

ii. In the 14-day study (Charles River Laboratories, 2011) "*a slight trend in the mean number of motile sperm...and total sperm count...from ejaculated samples in the cyclamen aldehyde-treated groups was observed",* though this was not considered as an adverse finding.

b. Apart from the above-mentioned adverse effects related to reproductive toxicity, you self-classified the registered substance as a skin irritant category 2 and a skin sensitiser category 1B due to the adverse effects observed in two skin irritant studies in rabbits ([redacted], 1984; 1986) and a Local lymph node assay in mice [redacted] 2001).

(ii) There is no proof that no systemic absorption occurs via relevant routes of exposure:

a. According to the toxicokinetics endpoint, under IUCLID section 7.1, though no further studies have been carried out, it has been reported that the registered substance is "*likely to be absorbed via dermal, inhalation and gastric routes following exposure.*" The acute and sub-chronic toxicity data indicate that the test substance is "*is absorbed following administration by gavage and metabolised by the liver.*"
The values used for the chemical safety assessment include: 50% absorption rate for oral and dermal and 100% for inhalation. In the CSR, in all routes of exposure it has been reported that there may be a "*low potential for significant rate of absorption*", however it has not been proved that "*no systemic absorption occurs via relevant routes of exposure*". Hence, condition (ii) of Annex IX, Section 8.7.2., column 2, third sub-paragraph is not met.

(iii) The registered substance has a significant exposure to both professionals (PROCS 4/8/10/11/13) and consumers (PC 3/8/28/31/35/39) and it may be found in sprays and aerosols. Hence condition (iii) of Annex IX, Section 8.7., column 2, third sub-paragraph is not met.

You have cited uses involving likely human exposure, specifically PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises; PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities; PROC 10: Roller application or brushing; PROC 13: Treatment of articles by dipping and pouring; and PROC 11: Non industrial spraying. Also PC 3: Air care products; PC 8: Biocidal products (e.g. disinfectants, pest control); PC 28: Perfumes, fragrances; PC 31: Polishes and wax blends; PC 35: Washing and cleaning products (including solvent based products); PC 39: Cosmetics, personal care products.

In view of the above observations, none of three cumulative conditions is met. 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, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you agree to conduct the pre-natal developmental toxicity study in rabbits via the dermal route. As regards the choice of the dermal route over the oral route, ECHA notes that according to the test methods for reproductive toxicity, which focus on the detection of reproductive hazards, the oral route (gavage, in diet, or in drinking water) is the "default" route, except for gases.

According to the ECHA Guidance document[3], "*testing via dermal route might be necessary…for substances with high dermal penetration and indications for a specific toxicity following dermal absorption*.
" In the technical dossier there are no specific studies on the absorption, distribution, metabolism and elimination (ADME) of the registered substance. In the chemical safety report, you claim that the acute and sub-chronic toxicity data indicate that the registered substance "*is absorbed following administration by gavage and metabolised in the liver.*" Furthermore, you state, that "*the physicochemical and toxicological properties suggest low potential for significant rate of absorption through the skin.*" Additionally, the results of the *in vivo* animal studies in the technical dossier show low acute dermal toxicity. Hence, the information provided in the dossier does not indicate that the registered substance has either a "*high dermal penetration*" or a "*specific toxicity following dermal absorption*". There is also no data on toxicokinetics indicating that the use of oral administration of the substance would not be relevant for assessing human health hazards via the oral route.

ECHA also notes that this substance has been classified as a skin irritant (Skin Irrit. 2) and a skin sensitiser (Skin Sens. 1B). According to the guidance document, irritating substances should be tested, preferentially, via the oral route.

Finally, as regards "*the significant absorption of Lilial across the skin*", and the hypothesis that absorption of the registered substance is "*expected to be very similar*", ECHA considers the following: In respect of the read-across justification in Annex I, ECHA's comments for the *in vitro* cytogenicity endpoint (under request 1.) also apply for this endpoint, with the exception of the comment on the availability of the *in vitro* cytogenicity study. The read-across approach proposed by the Registrant does not provide a robust basis whereby the human health effects concerned may be predicted from data for reference substance within the group, and hence does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

In summary, the proposed reasons for adopting the dermal route are not sufficient, and there are no reasons provided which suggest that the oral route is less appropriate. ECHA concludes that the oral route is most appropriate.

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.

5. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 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.

[3] Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance Version 4.1 (October 2015), R.7.6.2.3.2 Procedure for adaptations and testing approaches, Stage 4: (iv) Route of administration for reproductive toxicity studies (page 368)

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

ECHA considers that adverse effects on reproductive organs or tissues and other concerns in relation with reproductive toxicity are observed. More specifically, the one-generation reproductive toxicity study ([redacted] 2009; according to OECD TG 415) provided in the dossier shows changes in reproductive organ weights (increased absolute and relative weights of epididymides in males; decreased absolute and relative weights of the non-gravid uterus (with the cervix) as well as left and right ovary in females; 150 mg/kg/day), histopathological changes in the epididymides (presence of masses on the cauda epididymis and moderate to marked sperm granulomas; 150 mg/kg/day), reduced sperm count and density from the cauda epididymis (75 mg/kg/day), and reduced sperm motility reflecting the presence of drifting debris and headless sperm (75 and 150 mg/kg/day) which correlates with the infertility of male rats at 150 mg/kg/day. Furthermore, in females treated with 150 mg/kg/day, there was a reduction in the average number of implantation sites, a significant reduction in the average number of pups delivered per litter and the average number of live born pups per litter, and a significant increase in pup mortality on days 1 to 5 postpartum with a corresponding significant reduction in the viability index.

In addition, you have provided a repeated dose toxicity study ("*A 14-Day Study of cyclamen Aldehyde by Oral (Stomach Tube) Administration in Male New Zealand White Rabbits* ", Charles River Laboratories, 2011; "*in accordance with OECD guidelines*"). Even though you state that "*individual values were highly variable*", the study showed a "slight trend" (decrease) in the mean number of motile sperm and total sperm count, which is considered as a concern in relation with reproductive toxicity.

Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for registrations of the registered substance. In the technical dossier you have provided a study record for a "one-generation reproduction toxicity study" ([redacted] 2009; test method: OECD TG 415). However, this study does not provide the information required by Annex IX, Section 8.7.3., because it does not cover key parameters, exposure duration, and life stages of an extended one-generation reproductive toxicity study. The main missing key aspects/element is an extensive postnatal evaluation of the F1 generation. In addition, the criteria for extension of the Cohort 1B are met for the registered substance.

Thus, the provided one-generation study does not cover the key parameters of an extended one-generation reproductive toxicity study (see Annex XI, 1.1.2 of REACH) and does therefore not fulfil the information requirement.

Additionally, in the registration dossier you have provided an adaptation statement that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 8.7., column 2, third indent of first paragraph ("*the substance is of low toxicological activity..., that no systemic absorption occurs... and there is no or no significant human exposure.*"). You provided the following justification: "*One Generation Reproduction Study: In a Reproduction and Developmental Toxicity Screening Test (OECD Guideline 415, Klimisch 1) the test substance Cyclamen Aldehyde Extra was administered to rats via the oral route at 25, 75 and 150 mg/kg/day. This evidence from this study suggests that this substance had no adverse effects on the reproductive cycle at a dose level of 25 mg/kg/day.*
However a further study into the metabolism of Cyclamen Aldehyde Extra in hepatocytes, comparing rat metabolism to human, rabbit and mouse, showed clear differences in metabolism between the rat and other species. it was proposed that the adverse effects observed in rat studies were misleading due to the observed differences in metabolism of the test substance. This hypothesis was supported by a long term study performed in the Rabbit which showed no effects at the highest concentration of 300 mg/kg bw/day, the metabolism study highlights the similarity between human and rabbit metabolisms of cyclamen aldehyde as opposed to that of human to rat, and thus the test substance should not be classified.
In addition, acute oral toxicity testing (LD50 >2000 mg/kg/day), acute dermal toxicity testing (LD50 >5000 mg/kg/day) and sub chronic toxicity (NOAEL 300 mg/kg/day) confirms that Cyclamen Aldehyde Extra is of very low toxicity. The expected route of exposure to this substance is considered to be dermal rather than oral or inhalation which suggests that systemic exposure via the dermal route would be low. As the test substance has been shown to be of low concern regarding any adverse toxicity in reproductive screening or sub chronic study, up to and including the accepted high dose levels, further reproductive toxicity testing is not deemed appropriate. The evidence does not support the necessity to perform additional animal studies."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.7., column 2, third indent of first paragraph as outlined above (see request 4). Therefore, your adaptation of the information requirement is rejected.

ECHA also notes that you have provided a weight of evidence adaptation according to Annex XI, Section 1.2. Hence, ECHA has evaluated your adaptation and has assessed whether you have provided "*sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the substance has or has not a particular dangerous property*" with respect to the information requirement of Annex IX, Section 8.7.3., columns 1 and 2 for an extended one-generation reproductive toxicity study.

Your weight of evidence is based on the following sources of individual information:

- A reference to "*section 7.5.1 repeated dose toxicity: oral – Weight of Evidence/Repeated dose toxicity: oral/20010310 of this dossier*"
    - The content of this section is a GLP-compliant key study for "*A 14-Day Study of cyclamen Aldehyde by Oral (Stomach Tube) Administration in Male New Zealand White Rabbits*", with the registered substance, Charles River Laboratories 2011 (study report), reliability score 2.
- A non-guideline, GLP-compliant study "*to compare the in vitro metabolism by hepatocytes of Cyclamen aldehyde between 4 species (mouse, rat, rabbit and human)*". [redacted] 2011 (study report), reliability score 2.

- A summary of examinations conducted:
  - *"In vitro metabolism study comparing rat to human, rabbit and mouse*
  - *Confirmation of the putative toxic metabolite in rats*
  - *Confirmation of lack of reproductive toxicity in a more relevant species"*

You have provided the following conclusion for the weight of evidence adaptation:
"*Conclusions on toxicity and classification*
Overall the data can be summarised as follows:
• *The toxic metabolite of Cyclamen aldehyde (4-isopropyl benzoic acid) has been confirmed.*
• *This metabolite is found in rats in vitro and in vivo but is not found in rabbits, mice and humans in a metabolism study.*
• *Cyclamen aldehyde does not cause reproductive organ effects in a more relevant species (rabbit).*
• *Therefore, the effects seen in rats are unlikely to be relevant to the human route and levels of exposure.*
• *The hazardous property will not be expressed in humans and classification is not warranted."*

ECHA concludes that none of the individual studies meets the information requirement of Annex IX, Section 8.7.3.:

- The 14-day repeated dose toxicity study in male rabbits does not provide the information required by Annex IX, Section 8.7.3., because it does not cover key parameters, exposure duration, and life stages of an extended one-generation reproductive toxicity study. The main missing key aspects/element are: Mating of the P0 generation to generate the F1 generation and therefore no investigations on male and female reproductive performance (such as gonadal function, mating behaviour, conception, development of the conceptus and parturition), and extensive postnatal evaluation of the F1 generation (peri- and post-natal investigations of the F1 generation up to 14 weeks of age (such as growth, survival/mortality, certain external malformations, investigations related to hormonal modes of action like anogenital distance, nipple retention, thyroid hormone measurements, and sexual maturation), investigations in a second offspring generation. As the study was only performed with male rabbits, also oestrus cyclicity was not investigated.
- Also the *in vitro* metabolism study does not meet the requirements of an extended one-generation reproductive toxicity study for obvious reasons (e.g. study is performed *in vitro* and does not use living animals; study does not address the key parameters).

ECHA has the following observations on your weight of evidence justification:

- The provided *in vitro* study using rat, rabbit, mouse and human hepatocytes is not sufficient to prove that a certain metabolite is not produced in certain species as the liver is not solely responsible for metabolism. You have not shown that other tissues/organs are unable to metabolise the registered substance.
- Furthermore, you have not shown that only the metabolite 4-isopropyl benzoic acid is responsible for the toxicological effects observed. Testing of one metabolite does not exclude the possibility that other metabolites or, in this case, even the parent substance could cause toxicity.

- In this respect, ECHA observes that the 14-day repeated dose toxicity study in male rabbits actually shows reproductive effects (a "slight trend"(decrease) in the mean number of motile sperm and total sperm count although you indicate that these effects are not noteworthy). Because the exposure duration in this study is significantly shorter compared to that of male rats in the one-generation reproductive toxicity study (OECD TG 415), the non-observance of other effects on reproductive tissues and organs may be linked to this shorter exposure duration.
- ECHA concludes that the provided data does not support that (a) 4-isopropyl benzoic acid is only produced in rats; (b) 4-isopropyl benzoic acid is solely responsible for the observed toxicity; (c) toxicity is limited to rats; (d) toxicity does not occur in rabbits.
- Based on these conclusions, your assumption that "*the hazardous property will not be expressed in humans*" is also not supported.

ECHA also notes that the provided studies together (i.e. the 14-day repeated dose study in male rabbits, the *in vitro* metabolism study in hepatocytes and the one-generation reproductive toxicity study) do not meet the information requirement of Annex IX, Section 8.7.3. because even together they do not address key parameters of the extended one-generation reproductive toxicity study (see Annex XI, Section 1.1.2.) such as evaluation of the F1 and F2 generations.

Hence, ECHA considers that the individual sources of information you provided, taken together with your justification for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous property with respect to the information requirement for Annex IX, Section 8.7.3. Therefore, your weight of evidence 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. Thus, an extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the required study

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, along with other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015), the starting point for deciding on the length of the premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter premating exposure duration for parental (P) animals may be considered. However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex IX are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

The use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals because the registered substance is used by professionals (PROCs 2, 4, 8a, 10, 11, 13) and consumers in air care products, biocidal products, perfumes and fragrances, polishes and wax blends, washing and cleaning products as well as cosmetics and personal care products.

In addition, there are indications for endocrine-disrupting modes of action because the one-generation reproductive toxicity study ([redacted] 2009; according to OECD TG 415) provided in the dossier shows changes in reproductive organ weights (increased weights of epididymides; decreased weights of the non-gravid uterus (with the cervix) and ovaries), histopathological changes in the epididymides (presence of masses on the cauda epididymis and sperm granulomas), reduced sperm count and density from the cauda epididymis, and reduced sperm motility. Furthermore, the 14-day repeated dose toxicity study (Charles River Laboratories, 2011; "*in accordance with OECD guidelines*") conducted with the registered substance on male rabbits showed a "slight trend" (decrease) in the mean number of motile sperm and total sperm count.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance are leading to significant exposure of professionals and consumers and the available one-generation reproductive toxicity study and repeated dose study indicate endocrine-disruption modes of action for the registered substance.

Species and route selection

According to the test method EU B.56/ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in 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 4.1, October 2015) R.7a, chapter 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 perform the extended one-generation reproductive study with the registered substance. However, you propose to conduct the study in rabbits via the dermal route.
You consider that "*the rabbit, not the rat, is the most appropriate animal model for human health risk assessment of the registered substance*". Your justification is based on (1) clear species differences in the metabolism of the substance in rats (which produce 4-isopropyl benzoic acid (4-IPBA), the putative toxic metabolite) vs. mice, rabbits and humans (which do not); (2) that 4-IPBA is a highly potent reproductive toxin; (3) that all the adverse effects of the registered substance in rat are caused by the species-specific metabolism to 4-IPBA. You propose (4) that there is no toxicity of reproductive organs in an appropriate species, the rabbit.

In respect of species-specific metabolism, ECHA notes that the species differences in the metabolism of the registered substance, and consequently the formation of the putative toxic metabolite 4-IPBA exclusively in rats, is only examined in an *in vitro* study using hepatocytes. You have not taken into account any extrahepatic metabolism, and the alleged species-specific metabolism has not been confirmed in an *in vivo* study. ECHA considers that you have not established that there is species-specific metabolism in the intact animal to produce 4-IPBA.

ECHA agrees that, on the basis of the very limited information provided, 4-IPBA appears to be a potent reproductive toxin.

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You propose that all the adverse effects of the registered substance in rats are caused by the species-specific production of 4-IPBA. In the one-generation study (OECD TG 415) provided in the dossier, the registered substance caused specific adverse effects in female (decreased absolute and relative weights of the non-gravid uterus (with the cervix) as well as left and right ovary, and a reduction in the average number of implantation sites) and in male (increased absolute and relative weights of epididymides, histopathological changes in the epididymides (presence of masses on the cauda epididymis and moderate to marked sperm granulomas, reduced sperm count and density from the cauda epididymis, and reduced sperm motility reflecting the presence of drifting debris and headless sperm).

In your comments, you refer to a 5-day male rat study conducted with 4-IPBA, and a 5-day male rat study conducted with the registered substance. Firstly, ECHA notes that these are not present in the dossier, and there is not sufficient information to evaluate these studies. ECHA cannot reliably conclude based on these studies. Secondly, on the basis of the information provided, ECHA notes that in these 5-day male rat studies, the registered substance had no adverse effects, whereas 4-IPBA causes effects in testes and epididymides. ECHA concludes that 4-IPBA and the registered substance cause different effects in the 5-day study, and that under any circumstances, the effects reported from 4-IPBA in the 5-day study are different from those reported in the one-generation study on the registered substance. It has not been shown that the 4-IPBA causes the effects seen in females in the one-generation study (OECD TG 415) provided in the dossier. Consequently, you have not demonstrated that 4-IPBA is causing all the adverse effects seen in the rat one-generation study.

Regarding the claimed no toxicity in the rabbit, you have provided a 14-day male rabbit study conducted with the registered substance and consider that there is no toxicity to reproductive organs, which you hold to be a consequence of the putative species-difference in metabolism. ECHA notes that you recorded a "slight trend" for a decrease in mean sperm count and number of motile sperm in the rabbit study. ECHA considers that the exposure duration is a key parameter, as witnessed by comparison of the effects of the registered substance in a one-generation study, and the absence of effects in a 5-day study. Accordingly, ECHA considers it is not possible to draw conclusions on the toxicity of the substance to the rabbit, based solely on the results of a 14-day study.

Based on the data you have provided, it cannot be concluded that 1) there is species-specific metabolism, with the putative toxic metabolite 4-IPBA only formed in rats; 3) that 4-IPBA alone is causing all the adverse effects in males and females; 4) rabbit shows no toxicity when exposed to the registered substance. You have established that 4-IPBA is toxic to the parts of the male reproductive tract.

As regards the choice of the dermal route over the oral route, ECHA notes that you have not provided evidence on the dermal absorption of the registered substance, nor any indication for a specific toxicity following dermal absorption. Consequently, ECHA considers that it is not certain that dermal exposure would lead to systemic exposure to the registered substance, and a robust evaluation of the hazardous properties of the registered substance. Furthermore, the substance has been classified as skin irritant (Skin Irrit. 2) and skin sensitiser (Skin Sens. 1B). These properties would tend to reduce the amount of substance to which an animal could be exposed, before there would be unacceptable damage to the skin. In consequence, this would reduce the amount of possible systemic exposure, and hence the ability to evaluate the hazardous properties of the substance. In view of these limitations of the dermal route of exposure, ECHA considers that the oral route of exposure is the most appropriate route of exposure.

c) Outcome

Based on the available information, 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: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least two weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;

Currently, the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request *3*) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by **7 June 2018**.

If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by **7 September 2018** (i.e. within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by **7 September 2018**, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision **7 December 2020**.

Notes for your consideration

When submitting the study results of the sub-chronic toxicitystudy (90-day) you are invited to also include in the registration update your considerations whether changes in the EOGRTS study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 5.0, December 2016*).

Furthermore, after having commenced the EOGRTS study in accordance with the ECHA decision, you may also expand the EOGRTS study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Pending your conclusion on request 6 for classification and labelling, you should consider adaptation possibilities, in particular Column 2 of Section 8.7. of Annex IX; i.e. "*If the substance is known to have an adverse effect on fertility, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage fertility (H360F), and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for developmental toxicity must be considered*".

An extended one-generation reproductive toxicity study provides information on fertility but also on development and toxicity to offspring up to the adulthood which cannot be obtained from prenatal developmental toxicity studies. Thus, it must be considered if information from peri-and postnatally observable effects on development and offspring toxicity is relevant information for risk management and/or risk assessment even though the substance were (self-)classified to Repr 1B for fertility.

6. Classification and labelling (Annex VI, Section 4.): Apply classification and labelling on the registered substance for reproductive toxicity *or* provide a justification for not classifying

Pursuant to Article 10(a)(iv) of the REACH Regulation your technical dossier shall contain information on classification and labelling of the substance as specified in Annex VI, Section 4 of the REACH Regulation in conjunction with Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation).

Annex VI, section 4.1. clarifies that the hazard classification of the substance shall result from the application of Title I and II of the CLP Regulation. In addition, for each entry, the scientifically justified reasons why no classification is given for a hazard class or differentiation of a hazard class should be provided. According to Article 5(1) of Title I of the CLP Regulation, a substance shall be classified on the basis of available information.

Furthermore, the technical dossier must include the resulting hazard label for the substance in line with Title III of the CLP Regulation (Annex VI, section 4.2 of the REACH Regulation).

For reproductive toxicity, you have provided a one-generation study (OECD 415) in rats, showing several adverse effects in reproductive parameters in the mid-dose (75 mg/kg bw/day) and high-dose groups (150 mg/kg bw/day). These include e.g. changes in the epididymis (increased weight, sperm granulomas), decreased weights of uterus and ovaries, changes in sperm motility, and male infertility. There is also a 14-day repeated dose study in male rabbits showing a "slight trend" (decrease) on sperm count and number of motile sperm.

According to Annex I, Section 3.7. of the CLP Regulation, classification of the substance as reproductive toxicant, Category 1B is indicated when there is clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate. The above effects demonstrate adverse effects on sexual function and fertility. You have not self-classified the substance for reproductive toxicity despite the several adverse effects observed in the one-generation study and in the 14-day repeated dose study. Furthermore, ECHA observes that the dossier does not contain any justification for non-classification, but only the statement: *"The hazardous property will not be expressed in humans and classification is not warranted."* In particular, it is unclear why the hazardous property should not be relevant for humans.In your comments to the draft decision, you have provided a justification for not applying classification and labelling on the registered substance for reproductive toxicity.

You consider that "*the hazardous property will not be expressed in humans and classification as substance to be suspected of damaging fertility is not warranted*". Your justification is based on (1) the registered substance-induced reproductive toxicity is species-specific and only limited to rat with no relevance for humans, (2) CLP Regulation Section 3.7.2.3.2 indicating that a substance should not be classified if the mechanism or mode of action has no relevance for humans, and (3) consumer and occupational exposure is almost exclusively via the dermal route with low exposure.

With regards to species-specific effects on reproductive toxicity and their relevance to humans, ECHA notes that based on the data you have provided, it is not possible to conclude on the species-specific metabolism of the registered substance, or on the formation of the putative toxic metabolite 4-IPBA and consequently the adverse effects on reproductive organs to be specific to rats, as outlined above (see request 5).

In your comments, you have provided information for the "*relevance of route of administration to humans*", including an estimation of exposure based on the "*assumed worst-case scenario as for Lilial*" (a proposed structural analogue). ECHA notes that this information is irrelevant for the purposes of providing a justification for not classifying the registered substance, as classification should be based on hazard identification and not exposure estimation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to classify and label the registered substance taking into account the information above. In the alternative, you are requested to provide the scientifically justified reasons why no such classification is given. You are also reminded that for a differentiation of a hazard class, scientifically justified reasons need to be provided.

Deadline

A Proposal for Amendment was received, asking that the timeline for the submission of information on "Classification and labelling (Annex VI, Section 4.): Apply classification and labelling on the registered substance for reproductive toxicity or provide a justification for not classifying" be reduced to 12 months. ECHA considers that this information would be pertinent for ECHA's assessment of all relevant information on the information requirement of the EOGRTS study, including the design and conduct of the study, when you submit the information on the 90-day study. ECHA has accordingly amended the decision so that this information should be submitted 12 months from the date of the decision.

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 August 2016.

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

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

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

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

ECHA received proposal(s) for amendment and modified the draft decision.

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

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendments were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-53 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

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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 relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally 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.