EUROPEAN CHEMICALS AGENCY

Helsinki, 15 December 2016

Addressee: [redacted]

Decision number: CCH-D-2114348081-58-01/F
Substance name: isopentyl acetate
EC number: 204-662-3
CAS number: 123-92-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 12.12.2014
Registered tonnage band: 1000+T

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. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten 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) without extension to mate the Cohort 1B animals to produce the F2 generation;**

2. **Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: Daphnia sp. Acute immobilisation test, EU C.2./OECD TG 202) with the registered substance;**

3. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203) 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 **23 December 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 Ofelia Bercaru, Head of Unit, Evaluation E3

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

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

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 X. If the conditions described in column 2 of Annex X 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

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement according to Annex XI, Section 1.2. in a weight of evidence approach. The evidence stems from read across according Annex XI Section 1.5 of the REACH Regulation. You provided study records for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) and a 90-day repeated dose toxicity study according to OECD TG 408 with a metabolite of the registered substance, 3-methylbutan-1-ol (EC no: 204-633-5). ECHA understands you assume that the registered substance had a complete hydrolysis within 2h to 3-methylbutan-1-ol and acetic acid, and hence that there was no (significant) systemic exposure to the parent compound. Hence the information from the hydrolysis products could be used to predict the systemic toxicology of the parent compound. ECHA understands that this hypothesis was the basis under which you predict the human health properties of the registered substance from the hydrolysis products.

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI, Sections 1.2 and 1.5, for the reasons discussed below.

ECHA notes that the provided studies, mentioned above, are not sufficient to meet the information requirements of Annex XI, Sections 1.2 and 1.5, for the following reasons:

- The screening study does not cover key parameters, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key parameters are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation.

- The 90-day repeated dose toxicity study does not cover key parameters, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key parameters are: 10 weeks pre-mating exposure duration, all the parameters for functional fertility, such as mating, pregnancy and littering, at least 20 pregnant females per group, and postnatal evaluation of a F1 generation. In the 90-day study only limited parameters regarding to reproductive toxicity have been investigated in males and non-pregnant females.

Hence, there is a failure to have adequate or reliable coverage of key parameters addressed in the corresponding test methods referred in Article 13(3) or cover an exposure duration comparable to or longer than the corresponding test method referred to Article 13(3) if exposure duration is a relevant parameter.

ECHA notes that the provided studies, mentioned above, are not sufficient to meet the information requirements of Annex XI, Section 1.5, for the following reason:

- You have not provided sufficient justification that the registered substance could be read-across to its metabolite, 3-methylbutan-1-ol (EC no: 204-633-5). The provided justification in particular did not sufficiently demonstrate the fast metabolism or hydrolysis of the parent compound (the substance subject to this decision) and therefore you have not demonstrated why systemic exposure to the parent compound can be ruled out.

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. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

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 ECHA Guidance, the starting point for deciding on the length of 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 because 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).

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 conducted 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.

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.

c) Outcome

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: 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:

- Ten 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) without extension to mate the Cohort 1B animals to produce the F2 generation.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion.

Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). You may also expand the 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 justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

ECHA notes that avoidance of unnecessary testing and duplication of information is a general aim of REACH as stated in Article 25. Also Article 13(1) of the REACH Regulation provides that "*Information on intrinsic properties of substances may be generated by other means of tests, provided that the provisions of Annex XI are met. In particular for human toxicity, information shall be generated whenever possible by means of alternative methods, for example ... from structurally related substances (grouping or read-across)*". ECHA notes that for the compliance check of 3-methylbutan-1-ol (EC no: 204-633-5) decision making is ongoing on the same endpoint. If you adequately address the deficiencies discussed above and a revised read-across justification meets the requirements of Annex XI, Section 1.5, you may want to approach the registrants of that substance in order to get access to said information.

In the comments to the draft decision, you asked ECHA to add details how to build a read-across adaptation. Please note that ECHA is not in a position to provide case-specific advice. On the contrary, it is your responsibility to appropriately justify an adaptation according to REACH Annex XI, Section 1.5., read-across.

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

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

"Short-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex VII, Section 9.1.1. 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.

According to the Table R.7.8—2 in ECHA's Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7b (Version 3.0 February 2016) degradation and volatility are a critical parameters for aquatic toxicity testing. It is noted in this Guidance that "*one of the key issues for difficult substances is the ability to quantify actual exposure of the test organisms to the test substance*" and that for substances which are likely to be lost from the water column "*in the absence of analytically measured concentrations at least at the start and end of the test, no valid interpretation can be made and the test should be considered as invalid*".

According to OECD Guidance Document Number 23 on aquatic toxicity testing of difficult substances and mixtures (OECD, 2000) if Henry's law constant " *is greater than 100 Pa*m^3/mol, more than 50% of the substance could be lost from the water phase in 3-4 hours (Mackay, 1992). However, other factors in the test system may affect the rate of loss, principally test vessel size and shape, depth and temperature of the medium and rate of aeration. The losses due to volatilisation may become significant for substances with Henry's law constants of 1-10 Pa*m^3/mol under vigorous mixing conditions where the opportunity for water/air exchange is high*". Furthermore, it is noted that "*If the substance is likely to be unstable, a decision to test the parent substance and/or its degradation products, if identified, should be based on a consideration of its half-life under test and real-world conditions [...]*

The testing of degradation products imposes a requirement for an analytical method to determine their concentration. This will be additional to the method required to determine the parent substance."

The Henry's law constant reported in the registration dossier is approximately 59.5 Pa*(m^3/mol). Furthermore, ECHA observes that in the toxicity study with Algae analytical verification of the test concentrations showed the decrease of concentrations of the registered substance in the testing system due to the degradation, but also possibly due to volatilization of the substance. Thus, ECHA considers that the substance has potential for volatilisation as well as for degradation and can be lost from the test system during aquatic toxicity testing. Therefore, in order to gather adequate results for the purpose of classification/labelling and risk assessment, analytical verification of exposure concentrations of the substance (and its degradation products, if necessary) is necessary for the aquatic toxicity testing, especially for the static test design.

In the registration dossier you have reported results of two short-term toxicity studies with aquatic invertebrates. One of the reported studies has been performed according to the Test Guideline "DIN 38412, Teil 11" with a read-across substance (named by you as amylacetat). You claimed this study as disregarded. ECHA agrees with your conclusion to disregard this study. ECHA observes that exposure concentrations were not analytically verified during the test, the test duration was 24 hours and ECHA considers that the results of this study reported in the registration dossier are not adequate for the purpose of classification/labelling and risk assessment. Furthermore, ECHA notes that there is no documentation with justification of read-across hypothesis applied submitted in the registration dossier.

Thus, ECHA considers that the proposed read-across approach does not satisfy requirements of Annex XI, section 1.5., which requires adequate and reliable documentation, and consequently does not allow predicting the (eco)-toxicological properties of the registered substance from the data available for the analogue substance. Therefore the information on the analogue substance is not appropriate to fulfil the information requirement of the substance subject to the present decision for short-term toxicity testing with aquatic invertebrates.

Furthermore, ECHA observes that for the second reported study (performed according to the Test Guideline "DIN 38412, Teil 11" with the registered substance) you noted that there is no information available on the analytical verification of exposure concentrations during the test. Therefore, ECHA considers that the results of this study are not adequate for the purpose of classification/labelling and risk assessment.

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 ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 3.0, February 2016) Daphnia sp. acute immobilisation test (test method EU C.2. / OECD TG 202) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.1.

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: *Daphnia* sp. acute immobilisation test, EU C.2./OECD TG 202).

Notes for your consideration

Due to the high volatility and potential for degradation of the substance you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, February 2016), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

3. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

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

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. 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.

According to the Table R.7.8—2 in ECHA's Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7b (Version 3.0 February 2016) degradation and volatility are a critical parameters for aquatic toxicity testing. It is noted in this Guidance that "*one of the key issues for difficult substances is the ability to quantify actual exposure of the test organisms to the test substance*" and that for substances which are likely to be lost from the water column "in the absence of analytically measured concentrations at least at the start and end of the test, no valid interpretation can be made and the test should be considered as invalid.

According to OECD Guidance Document Number 23 on aquatic toxicity testing of difficult substances and mixtures (OECD, 2000) if Henry's law constant " *is greater than 100 Pa*m3/mol, more than 50% of the substance could be lost from the water phase in 3-4 hours (Mackay, 1992). However, other factors in the test system may affect the rate of loss, principally test vessel size and shape, depth and temperature of the medium and rate of aeration. The losses due to volatilisation may become significant for substances with Henry's law constants of 1-10 Pa*m3/mol under vigorous mixing conditions where the opportunity for water/air exchange is high*". Furthermore, it is noted that "*If the substance is likely to be unstable, a decision to test the parent substance and/or its degradation products, if identified, should be based on a consideration of its half-life under test and real-world conditions [...] The testing of degradation products imposes a requirement for an analytical method to determine their concentration. This will be additional to the method required to determine the parent substance.*"

The Henry's law constant reported in the registration dossier is app. 59.5 Pa*(m3/mol). Furthermore, ECHA observes that in the toxicity study with Algae analytical verification of the test concentrations showed the decrease of concentrations of the registered substance in the testing system due to the degradation, but also possibly due to volatilization of the substance.

Thus, ECHA considers that the substance has potential for volatilisation as well as for degradation and can be lost from the test system during aquatic toxicity testing. Therefore, in order to gather adequate results for the purpose of classification/labelling and risk assessment, analytical verification of exposure concentrations of the substance (and its degradation products, if necessary) is necessary for the aquatic toxicity testing, especially for the static test design.

ECHA observes that to cover this information requirement you have reported the key study performed according to the OECD TG 203 with the registered substance. In the registration dossier you noted that the test type was static and that exposure concentrations were not verified during the test. Therefore, ECHA considers that the results of this study are not adequate for the purpose of classification/labelling and risk assessment.

Furthermore, ECHA observes that in the dossier in addition to the key study you have reported results of the supporting study, which has been performed according to the methodology based on the static fish test with the Goldorfe with a read-across substance (named by you as amylacetat). ECHA considers that you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing this non-GLP study conducted with the analogue substance.

First, under Annex XI, Section 1.5, results should have adequate and reliable coverage of the key parameters addressing in the corresponding test method referred to in Article 13(3). For this study two concentrations of the substance which kills 50 percent of fish (LC50s) after 48 hours of exposure are reported. ECHA notes, however, that the standard result of Fish, acute toxicity test (EU C.1. and OECD 203), which is used for the purpose of classification and labelling and/or risk assessment, is 96 hours LC50.

Second, exposure concentrations were not analytically verified during the test, which - as explained above - is required for volatile and chemically unstable substances. As consequence, ECHA considers that the results of this study reported in the registration dossier are not adequate for the purpose of classification/labelling and risk assessment, as required under Annex XI, Section 1.5.

Third, in accordance with Section 1.1.2. of Annex XI of the REACH Regulation, data from experiments not carried out according to the test methods referred to in Article 13(3) shall only be considered equivalent to data generated from the standard test method if they fulfil the cumulative conditions outlined in that provision. At least the first and the third (exposure duration is a relevant parameter of the short-term fish toxicity study) of the listed conditions are not fulfilled by the submitted short-term study.

Fourth, ECHA notes that Section 1.5. of Annex XI of the REACH Regulation sets out the conditions to be met when the read-across approach is used to cover standard information requirements listed in Annexes VII-X of REACH Regulation. It is a requirement of Annex XI, Section 1.5., that "adequate *and reliable documentation of the applied method shall be provided*". In the present case, ECHA notes that there is no documentation with justification of read-across hypothesis applied submitted in the registration dossier. The table in section R.6.2.6.1 "Reporting Format for the analogue approach" of ECHA's Guidance on information requirements and chemical safety assessment, R.6 (May 2008), sets out aspects which must be addressed to justify a read-across hypothesis.

Thus, ECHA considers that the proposed read-across approach does not satisfy requirements of Annex XI, section 1.5., and consequently does not allow predicting the (eco-)toxicological properties of the registered substance from the data available for the analogue substance. Therefore the information on the analogue substance is not appropriate to fulfil the information requirement of the substance subject to the present decision for short-term toxicity testing with fish and your adaptation of the information cannot be accepted.

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 ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 3.0, February 2016) fish acute toxicity test (test method EU C.1. / OECD TG 203) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.1.3.

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: Fish, acute toxicity test (test method: EU C.1./OECD TG 203).

Notes for your consideration

Due to the high volatility and potential for degradation of the substance you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, February 2016), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision requested an Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) in rats, oral route with the registered substance. However, a decision making of 3-methylbutan-1-ol (EC no: 204-633-5) is ongoing on the same endpoint and there the deadline for providing the requested information is 36 months. For the data sharing reasoning, also your deadline for providing requested information in the form of an updated registration is extended to 36 months from the date of the adoption of the decision.
The decision was modified accordingly.

Appendix 2: Procedural history

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

The compliance check was initiated on 29 March 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 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 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.

4. In case the required test(s) is/are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with ECHA's Practical Guide 6 "How to report on read-across". This is required to demonstrate that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.