EUROPEAN CHEMICALS AGENCY

Helsinki, 22 August 2018

Addressee: [redacted]

Decision number: CCH-D-2114440489-41-01/F
Substance name: Reaction mass of 2-methylbutyl acetate and pentyl acetate
EC number: 908-918-1
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26/04/2017
Registered tonnage band: [redacted]

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. **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**

   or

   Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance.

2. **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;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***31 August 2020***. You also have to 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 and 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, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation E1

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

Appendix 1: Reasons

1. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.) or long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)**

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] must contain, as a minimum, the information specified in Annexes VII to X to 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.
"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation.
Adequate information on these endpoints need to be present in the technical dossier for the registered substance to meet these information requirements.

In the technical dossier, you have provided a study record for a short-term toxicity study on *Pimephales promelas* ([redacted] 1974)[2]. This study reports a 96h-EC50 of 69 mg/L. The substance tested in that study was a mixture of primary amyl acetates similar to that of the registered substance but the proportion of the different isomers has not been specified. Therefore, it is not clear how similar the substance tested was to the registered substance.

ECHA notes that this study was conducted neither in accordance with a test method referred to in Article 13(3) of the REACH Regulation nor in accordance with GLP.

The general rules for adaptation presented in Annex XI, Section 1.1.2. of the REACH Regulation specify that studies not carried out according to GLP or to the test methods referred to in Article 13(3) of the REACH Regulation may still be considered if they meet some minimal quality criteria, e.g. if they are adequate for the purpose of classification and labelling and/or risk assessment, and if an adequate and reliable documentation of the study is provided.

However, ECHA notes that very few experimental details are reported for this study.

ECHA further notes that it was a static test with no analytical confirmation of the concentrations. The Henry's Law constant for the registered substance and its constituents is predicted to be 55.2 Pa m³/mol. Thus, losses of the test substance due to volatilisation may have occurred.

This is confirmed by the results of the analytical monitoring performed in the *Daphnia* study provided in your dossier ([redacted], 2003)[3]. The recovery rate reported for this study ranged from 30.8 to 43.2% of the nominal concentrations at the end of day 1. This *Daphnia* study was a semi-static test and the test medium was renewed after day 1. At the end of day 2, the new recovery rate was found to range between 23.8 and 47.4% of the nominal concentrations.

[2] [redacted]

One of the validity criteria for OECD test guideline 203 (Fish, Acute Toxicity Test), which is the recommended test guideline to cover the standard information requirement of Annex VIII, Section 9.1.3. of the REACH Regulation, requires that "*there must be evidence that the concentration of the substance being tested has been satisfactorily maintained, and preferably it should be at least 80 per cent of the nominal concentration throughout the test. If the deviation from the nominal concentration is greater than 20 per cent, results should be based on the measured concentration*". For the study provided in your dossier for short-term toxicity testing on fish, it is not clear what concentrations of the test substance the fish were actually exposed to since it was a static test with no analytical confirmation of the test concentrations. ECHA is of the opinion that this study is not valid and not adequate for classification and labelling or risk assessment.

Therefore, ECHA considers that the general rules for adaptation presented in Annex XI, Section 1.1.2. of the REACH Regulation are not met.

As explained above, the information provided on "Short-term toxicity testing on fish" does not meet the information requirement of Annex VIII, Section 9.1.3. of the REACH Regulation. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

Annex VIII, Section 9.1.3. of the REACH Regulation specifies that long-term toxicity testing on fish may be considered instead of short-term and that the short-term study does not need to be conducted if a long-term study on fish is available.

However, ECHA notes that you have sought to adapt the information requirement for long-term toxicity testing on fish (Annex IX, Section 9.1.6. of the REACH Regulation) by providing the following justification:

> "*No data on chronic toxicity to fish are available. However, in Annex IX of Regulation (EC) No 1907/2006, it is laid down that long-term toxicity to fish shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on fish. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of the mixture reveales* (sic) *neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, and for reasons of animal welfare, a long-term toxicity test in fish is not provided*".

As explained above, the available short-term study on fish is not adequate for the risk assessment and the classification and labelling of the registered substance because it is not clear what concentrations of the test substance the fish were exposed to. Assuming that the daily losses that occurred during the run of the short-term fish study were equivalent to those observed in the short-term *Daphnia* study, ECHA notes that the corrected 96h-EC50 for fish would be below the 48h-EC50 of 40.9 mg/L reported for the *Daphnia* study and that fish would then be identified as the most sensitive species. Consequently, the PNEC values would have to be recalculated. Would only short-term data be available, then the recalculated PNEC values would be lower and some risk characterisation ratios could exceed 1, indicating that risks are potentially not controlled.

Therefore, ECHA considers that the available information in your chemical safety assessment does not rule out the need to investigate further long-term effects on aquatic organisms.

In particular, you may need to perform long-term aquatic toxicity test(s) to refine the PNECs and the risk assessment. The magnitude of the assessment factors used for calculating the PNECs can indeed be reduced when information on long-term toxicity is available: this often leads to higher PNEC and to lower risk characterisation ratios.

If fish is less sensitive than *Daphnia*, then you will not need to modify the PNEC values and to refine the risk assessment. However if, based on short-term studies, fish is shown to be the most sensitive species, then the PNECs would have to be lowered and the risk assessment to be revised accordingly. ECHA notes that in this situation, some risk characterisation ratios could exceed 1. Because the data available for fish are not reliable, it is currently not possible to conclude definitively which species is the most sensitive, but as explained above, it cannot be excluded that fish is more sensitive than *Daphnia* (and algae). You may therefore choose to perform a long-term aquatic toxicity test instead of the requested short-term toxicity test on fish as the information currently available suggests that fish could be the most sensitive species and that risk characterisation ratios could exceed 1 if the PNECs are only based on short-term toxicity data.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4), a long-term test should be conducted on fish if there is indication that fish is substantially more sensitive than *Daphnia*. As explained above, the need to perform a long-term aquatic toxicity test will be triggered only if fish is substantially more sensitive than *Daphnia* so that the risk assessment needs to be refined. Therefore, if you choose to perform a long-term aquatic toxicity test, it should be conducted on fish.

With regard to the test methods to be used, ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) indicates that 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.

If you choose to perform a long-term test instead, then the fish early-life stage (FELS) toxicity test according to OECD test guideline 210 is to be preferred since it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Figure R.7.8-4).*

In your comments following the procedure set out in Article 50(1) of the REACH Regulation you acknowledged the deficiencies of the study provided in your dossier ([redacted] 1974) and indicated your agreement to conduct a new short-term toxicity test on fish (OECD TG 203) with the registered substance. You also indicated that you would not conduct a long-term toxicity study on fish before evidence arises that fish is the most sensitive aquatic species and that the substance is hazardous to the environment and therefore you regard the justification for the adaptation of the information requirement for long-term toxicity testing on fish as valid.

ECHA acknowledges your proposed approach but as indicated above, based on the available information, it is quite likely that fish will be the most sensitive species and that some RCRs could exceed 1. Hence, ECHA has maintained in the decision the option for you to perform long-term instead of short-term testing.

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) or Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Due to the high volatility of the registered 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 4.0, June 2017), 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).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] must contain, as a minimum, the information specified in Annexes VII to X to 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 the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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 provided

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

You have provided the following information in IUCLID section 8.7.1:

- End-point study record 1:- key study: screening for reproductive / developmental toxicity, rat, oral (OECD TG 422; GLP) with the analogue substance (3-methylbutan-1-ol, EC no: 204-633-5), [redacted], 2008 (study report), rel 1.

- End-point study record 2:-*"REACH allows the assessment of the reproductive toxicity of a given chemical with the help of findings from studies with repeated administration. This is in line with the idea that the information requirements under REACH are regarded as the evaluation of endpoints which does not necessarily require data from specific studies. The reaction mass of 2-methylbutyl acetate and pentyl acetate was tested in a 90 d repeated dose study ([redacted], 1985), in a 14 d repeated dose study ([redacted], 1984), in a prenatal OECD 414 study in rats ([redacted], 1994) and in rabbits ([redacted], 1994). None of these studies showed any concern regarding reproductive toxicity of the reaction mass of 2-methylbutyl acetate and pentyl acetate. Thus, a two-generation study is not necessary. This waiving argument is in line with the guidance document R7a and scientifically argumentation as below. Because of a high correlation, histopathology data and organ weights from repeated dose studies may be used to assess male fertility (Mangelsdorf, 2003). These parameters, taken from 90 day studies, were in fact shown to be more sensitive than fertility parameters that were measured during multi-generation studies. It could also be shown that exposure for 4 weeks suffices for an assessment of male fertility, although 90 day studies have been regarded as superior in the past because they cover a complete cycle of spermatogenesis (Mangelsdorf, 2003). If such a 28 day study shows neither relevantly elevated testis or ovary weights nor histopathological alterations in those organs, the weight of the evidence is that effects on reproduction are also not expected ([redacted] 2003). A comparison of more than one hundred 90 day studies with two-generation studies that used the same test substance additionally showed that the NOAELs differed by less than the variation limit of studies, i.e. a factor of two (Janer, 2007). Therefore, the information gained from a two-generation study can be regarded as minimal if a 90 day study has been performed. References -* [redacted] *- Janer G, Hakkert BC, Piersma, AH, Vermeire T, Slob W (2007). A retrospective analysis of the added value of the rat two-generation reproductive toxicity study versus the rat subchronic toxicity study. Reproductive Toxicol 24: 103-113 - Mangelsdorf I, Buschmann J, Orthen B (2003). Some aspects relating to the evaluation of the effects of chemicals on male fertility. Reg Toxicol Pharmacol 37: 356-369".*

- End point study record 3:- *"HYPOTHESIS FOR THE ANALOGUE APPROACH The reaction mass consists of three isomers of pentyl acetate, i.e., pentyl acetate itself, 2-methylbutyl acetate, and 3-methylbutylacetate. All components are rapidly,i.e., within minutes metabolized to their corresponding alcohols: pentanol, 2-methylbutanol, 3-methylbutanol, and acetic acid. Data are provided for one metabolite on the assumption, that all isomeric C5 metabolites as well as all corresponding acetates behave similarly- 2. SOURCE AND TARGET CHEMICAL(S) (INCLUDING INFORMATION ON PURITY AND IMPURITIES) Source: 3-methylbutanol, CAS: 123-51-3. Target: Reaction mass of 2-methylbutyl acetate and pentyl acetate (composition: app. 70% pentylacetate, 35% 2-methylbutylacetate, 5% 3-methylbutylacetate) no significant impurities in either source or target substance 3. ANALOGUE APPROACH JUSTIFICATION The available data for the alcohols (pentanol, 2-methylbutanol, 3-methylbutanol) indicate that they all behave similarly (see category approach for pentanols). All have low systemic toxicity and no indication of effects on reproduction. The same is expected for the acetates based on rapid metabolism and exposure mainly to the alcohols as metabolites.*
This statement is supported by the lack of any effects in a subchronic inhalation study up to the highest dose tested, as well as the lack of teratogenicity in the OECD

414 studies performed in two species. Consequently, the data from one metabolite, i.e., 3-methylbutanol, can be used to assess the reproductive toxicity of the registered substance. 4. DATA MATRIX Source Target LD50, oral >5000mg/kg >5000mg/kg LD50, dermal >2000mg/kg >2000mg/kg LC50, inhal sat. vapour >sat. vapour subchronic Tox. NOAEL (oral) NOAEC (inhal) =1250mg/kg = 500ppm (no effects) (no effects Fertility no effects no effects Teratogenicity, rat no effects noeffects Teratogenicity, rabbit no effects no effects."

While you have not explicitly claimed an adaptation, the provided information for the end-point study records could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.5 (read-across); and Annex XI, Section 1.2 (weight of evidence), respectively. ECHA has first evaluated the information you provided on read-across and then the information you provided on weight of evidence.

Read-across

ECHA has evaluated the information you provided on read-across according to the provision of REACH Annex XI, Section 1.5. ECHA has considered whether the information you have provided with the source substance 3-methylbutan-1-ol is sufficient to predict the properties of the registered substance with respect to reproductive toxicity.

Grouping of substances and read-across approach

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

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[4]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration.

Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation

[4] 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.

properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[5]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

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

Evaluation approach and conclusion on read-across

Based on the information provided, ECHA understands that the read-across hypothesis is based on:

1) Similar metabolism profile
2) Similar impurity profile
3) Similar toxicological profile for the metabolites

With regard to the metabolism profile, it is likely that both the source and registered substances are metabolised to the respective alcohols and the acid (acetic acid). ECHA notes that in your read-across justification you have stated that the metabolism will be rapid. However, you have not provided data to support your claim on the rate of metabolism for the source and registered substances.

With regard to the impurity profile, you have stated that the registered substance is "*Reaction mass of 2-methylbutyl acetate and pentyl acetate (composition: app. [redacted] pentylacetate, [redacted] 2-methylbutylacetate, [redacted] 3-methylbutylacetate) no significant impurities in either source or target substance*". However, ECHA notes that in IUCLID section 1.2., you have described the composition of the registered substance and indicated the source substance has an impurity with typical concentration of [redacted]. In addition, you have not provided the purity profile for the source substance. Therefore, ECHA cannot conclude on the impurity profile of the registered substance. In addition, ECHA considers that the source substance is not the main constituent of the registered substance.

With regard to the toxicological profile for the metabolites, you have stated that "*all have low systemic toxicity and no indication of effects on reproduction*". However, you have not provided data to support your claim that the alcohols do not have effect on toxicity to reproduction (fertility).

In your comments according to article 50(1) of the REACH Regulation, you provide improved explanations on the abovementioned aspects in the three preceding paragraphs and you outlined that you had provided data to support your claim on the rate of metabolism for the registered substance in the technical dossier assessed for this decision:

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

1) Metabolism of the two main constituents of the registered substance. The provided data supports that for the registered substance *"the time until virtual disappearance of the parent compound (conc. < 0.1nM)* [in the blood] *has been estimated to range between 14 and 70 seconds."*
2) Purity profiles of source and target substance. *"All substances in this group are of high purity. Impurities are also members of the category and only contained at low concentrations. None of the substances contains impurities that may have any toxicological or ecotoxicological impact."*
3) Toxicological profile of metabolites (source substances). The provided information relates to endpoints different from the request for toxicity to reproduction (fertility). More specifically, you explain that *"No study on fertility is available for the target substance"* and *"A screening study on the source substance 3-methylbutanol did not reveal a concern for toxicity to reproduction. An extended one-generation study has been scheduled for next year to further elaborate this endpoint. No other studies on fertility are available for the source substances, but two subchronic studies for pentan-1-ol and 3-methylbutan-1-ol in rats, as described above, did not reveal any changes in reproductive organs up to at least 1000mg/kg (Butterworth, et al., 1978; [redacted], 1990). The same is true for the subchronic study available for the target substance ([redacted], 1985). These studies thus support the conclusion that neither target nor source substances exert adverse effects on reproduction (fertility). Additional data on the source substances shall be used for the target substance once it becomes available."*

Furthermore, ECHA notes your intention to adapt this information requirement using results from an ongoing EOGRT study with the analogue source substance 3-methylbutan-1-ol.

ECHA observes that, (ad 1) the provided data supports the conclusion that the parent compound might be rapidly hydrolysed in different target tissues after it enters systemic circulation. However, some exposure to the parent compound during that time-frame is still possible, since the hydrolysis does not precede uptake into systemic circulation. The consequences have not been discussed so far. ECHA observes that, (ad 2) the information provided by you is broadly generalised and so far not supported by more detailed analytical data, nor eco-/toxicological data on the impurities.

Importantly, (ad 3) ECHA observes that you confirm an absence of studies investigating the effects on fertility by the target substance, and by the source substances pentan-1-ol and 2-methylbutan-1-ol. Instead, you refer to a category of pentanols, without providing robust study summaries of experimental studies conducted with category members, other than those already mentioned. ECHA reminds you that this category relates to metabolites and their analogues. As to how the prediction of properties of the registered substance is possible remains to be established for these analogue substances.

In the absence of sufficiently reliable data on the metabolites of the two main constituents (2-methylbutan-1-ol and pentan-1-ol), ECHA concludes that, with respect to fertility, it is not possible to predict hazardous properties of the registered substance with sufficient confidence based on the available information. Furthermore, you indicate that an EOGRT study is currently being performed with the analogous substance 3-methyl-butan-1-ol. This analogue substance would be the likely metabolite of a minor constituent of the registered substance ([redacted]). As explained above, an endpoint-specific comparison of toxicity profiles between this analogue and the other two main metabolites 2-methylbutan-1-ol and pentan-1-ol is lacking. Similarly, a comparison to the endpoint-specific toxicity profile to the registered substance is lacking.

Furthermore, ECHA observes in response to your comments on the draft decision that you confirm an absence of studies investigating the effects on fertility by the target substance. ECHA concludes that it is likely that the parent compound will be systemically available, albeit for possibly short time spans. The resulting uncertainty, together with those of the previous paragraph, could be reduced by comparing the toxicity profiles of analogous substances with those of the target substance, e.g. obtained through a bridging study (OECD TG 421/422) with the registered substance. Therefore, as indicated in the section on "Grouping of substances and read-across approach" above, a similar or regular pattern of toxicity, which is a core requirement of read-across adaptation, has not been demonstrated.

In addition, in your comments according to article 50(1) of the REACH Regulation, ECHA notes your indicated your intentions that "additional studies on the source substances will be added to the dossier with the next update (probably in QI 2018) to underline comparable systemic effects". You are reminded that this decision does not take into account any updates submitted after notification 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.

Hence, ECHA does not consider the read-across approach to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, your adaptation of the information requirement is rejected.

Based on your comments according to article 50(1) of the REACH Regulation, ECHA now considers the information from the OECD TG 422 study with source substance 3-methylbutan-1-ol ([redacted], 2008) in the weight of evidence approach. As a result, ECHA has modified the relevant sections in the evaluation of the weight-of-evidence approach, below (Sexual function and fertility and Effects on offspring).
However, ECHA still concludes that the read-across adaptation based on the source substance 3-methylbutan-1-ol is insufficient in its current form to predict the toxicity of the metabolites pentan-1-ol and 2-methylbutan-1-ol, as explained above (ad 3).

Weight of evidence (WoE)

Evaluation approach/criteria

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that this study provides, in addition to information to general toxicity, information in particular on two aspects, namely on sexual function and fertility in P0 and F1 generations (further referred to as 'sexual function and fertility') and on development and toxicity of the offspring from birth until adulthood due to pre- and postnatal and adult exposure in the F1 generation (further referred to as 'effects on offspring').

Relevant elements for 'sexual function and fertility' are in particular functional fertility (oestrous cycle, sperm parameters, mating behaviour, conception, pregnancy, parturition, and lactation) in the parental generation after sufficient pre-mating exposure duration and histopathological examinations of reproductive organs in both P and F1 generations. Relevant elements for 'effects on offspring' are in particular peri- and post-natal investigations of the F1 generation up to adulthood, including investigations to detect certain endocrine modes of action, and sexual development. Also the sensitivity and depth of investigations to detect effects on 'sexual function and fertility' and 'effects on offspring' need to be considered.

Furthermore, as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4., Section 4.4 (version 1.1, December 2011), ECHA has evaluated individually your provided sources of information with respect to relevance and reliability and has evaluated the overall provided information for consistency and coverage of the relevant elements as specified above.

Based on the criteria above, ECHA considers the following:

Sexual function and fertility

ECHA considers that the OECD TG 422 screening study with one of several possible source substances (3-methylbutanol) does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group.

These parameters are also not covered by the histopathological changes investigated in major reproductive organs in a 90-day study with the registered substance. Furthermore, this study does not provide information on functional fertility after 10 weeks exposure covering spermatogenesis and folliculogenesis, sexual maturation, sperm parameter analysis, oestrous cyclicity, and investigations related to hormonal modes of action. You claim that the available information from sub-chronic toxicity (90-days) study in the rat confirm that the reproductive organs are not affected after repeated exposure to the registered substance. However, ECHA notes that the histopathological methods for this study used fixation methods, 10 % formalin, are not recommended anymore and lack the sensitivity of the modern methods.
Furthermore, the literature references cited in your adaptation justification do not contain information on the registered substance nor do you explain why and how the information on various aspects of reproduction provided by an extended one-generation reproductive toxicity could be replaced or predicted for your substance by organ weights or histopathological examinations only.
Thus, the information you provided does not support your conclusion that the substance does not have a dangerous property with respect to sexual function and fertility.

Effects on offspring

ECHA notes that the provided studies according to OECD TG 414 in the rat and rabbit provide information only on effects observable pre-natally and not effects on offspring observable and/or due to postnatal exposure. However, the provided information does not

address key elements of offspring toxicity observable peri- and postnatally, such as survival, growth, certain endocrine modes of action and sexual development. ECHA considers that the OECD TG 422 screening study with one of several possible source substances (metabolites), 3-methylbutanol, does not provide the information required by Annex X, Section 8.7.3., because it does not cover key elements as stated above and an extensive postnatal evaluation of the F1 generation. Thus, the information you provided does not allow a conclusion on the hazardous property of the registered substance with respect to development and offspring toxicity observable peri- and post-natally. Thus, the information you provided does not adequately address all relevant elements with respect to effects on offspring.

Conclusion on weight of evidence

Hence, the information you provided to support your adaptation, considered individually or together, lacks information on critical elements of reproductive toxicity and does not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex X, Section 8.7.3.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2 of the REACH Regulation are not met and 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* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). 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.

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 24 July 2017.

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

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

ECHA took into account your comments and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

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

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.

4. If the required tests 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 on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show 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.