EUROPEAN CHEMICALS AGENCY

Helsinki, 19 September 2017

Addressee: [redacted]

Decision number: CCH-D-2114371485-43-01/F
Substance name: REACTION MASS OF 2-METHYLBUTYL SALICYLATE AND PENTYL SALICYLATE
EC number: 911-280-7
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 09.03.2016
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. **Skin sensitisation (Annex VII, Section 8.3) with the registered substance:**
   i) ***in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins, inflammatory response in keratinocytes and activation of dendritic cells (Annex VII, Section 8.3.1); *and***
   ii) ***in vivo* skin sensitisation information (Annex VII, Section 8.3.2; test method: EU B.42./OECD 429) with the registered substance in case the Registrant can justify that the *in vitro/in chemico* test methods specified under point i) are not applicable for the substance or that the results obtained are not adequate for classification and risk assessment;**

2. ***In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

3. ***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;**

4. ***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 studies requested under 2 and 3 have negative result;**

5. **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;**

6. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421 or 422) in rats, oral route with the registered substance;**

7. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

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

You have to submit the requested information in an updated registration dossier by **26 March 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

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

0. Grouping of substances and read-across approach

You have sought to adapt the information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation.

The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis for the endpoints sub-chronic toxicity (Annex IX, Section 8.6.2.), screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) and pre-natal developmental toxicity (Annex IX, Section 8.7.2.). Your read-across and category approaches for the endpoints *in vitro* bacterial mutagenicity and, *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.) are addressed under the respective section.

Description of your grouping and read-across approach

You propose read-across from the substance cyclohexyl salicylate (EC No. 400-410-3) (hereafter the 'source substance') for each of the above-mentioned information requirements. You conclude that information relating to this source substance can be used to close data-gaps in the health hazard assessment of the registered substance reaction mass of 2-methylbutyl salicylate and pentyl salicylate (EC No. 911-280-7) (hereafter the 'target substance') as you consider the read-across approach is scientifically acceptable with high confidence based on your examination of the adequacy and scientific robustness of the provided read-across justifications and corresponding information using assessment elements (AE) of the ECHA Read-across assessment framework (RAAF).

Your read-across hypothesis and justification is the following "*This read-across is based on the hypothesis that the target substance and source substance have the same expected mode of action and similar physicochemical properties relevant for the read-across endpoints. The experimental data presented in the paper by Belsito et al, shows that all salicylates undergo hydrolysis which yields salicylic acid and the alcohol of the corresponding alkyl, alkenyl, benzyl, phenyl, phenethyl side chain. This is consistent with information on other alkyl- and alkoxy- benzyl derivatives whereby aromatic esters are hydrolyzed in vivo by carboxylesterases, or esterases, especially the A-esterases.*"

Information provided for the read-across approach

With respect to repeated dose toxicity you have provided a sub-chronic toxicity study (90 days) in rats by the oral route (OECD TG 408; [redacted] 1995, Rel. 2,) performed with the source substance cyclohexyl salicylate (EC No. 400-410-3).

With respect to reproductive toxicity, you have provided a one-generation reproductive toxicity study (OECD TG 415; [redacted], 1995, Rel. 2,) and a pre-natal developmental toxicity study (OECD TG 414; [redacted] 1996, Rel. 2) both performed with the source substance cyclohexyl salicylate (EC No. 400-410-3).

You have also provided attached to the IUCLID section 13

- read-across (category) justification document "[redacted]" [1]
- justification for read-across to support the REACH registration of Amyl Salicylate (CAS 2050-08-0; EC 218-080-2) for mammalian toxicity endpoints (acute toxicity, sub-acute toxicity, sub-chronic toxicity, screening for reproduction/developmental toxicity, developmental toxicity and one generation reproduction toxicity) with empirical and mechanistic chemical profile of amyl salicylate and cyclohexyl salicylate [2]

ECHA analysis of the grouping and read-across approach

With regard to the proposed read-across adaptations for repeated dose toxicity and reproductive toxicity, ECHA has the following observations:

Read-across hypothesis

ECHA understands that your read-across hypothesis is supported by information from the source substance. ECHA further understands that you assume that the source substance and the target substance are metabolised to a common metabolite (salicylic acid) and to the alcohol of the corresponding side chain. You did not specify which alcohols are to be expected for the source and the target substances. However, based on Table 2 of your justification document and the structure of the substances, ECHA understands that it would be pentyl alcohol and 2-methylbutanol for the target substance and cyclohexanol for the source substance.

Structural similarity

You indicate that the target substance is a reaction mass of 2-methylbutyl salicylate and pentyl salicylate (EC No. 911-280-7) with typical concentrations of [redacted]% and [redacted]%, respectively.

In your read-across justification document [1] you state that "*The source substance has a >60% structural similarity with Amyl salicylate*". Furthermore, you indicate that "*Both substances are salicylic acid esters and the structural differences are not expected to influence the in vivo interaction of either the target or source substances.*"

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you state that the 60% structural similarity of the target and source substance would justify read-across.

ECHA acknowledges the similarity between the target and source substances with respect to the salicylic acid group, but notes that structural similarity alone cannot justify the use of the source substance for read-across purposes because the predictive property of the source substance for the target substance properties are still to be demonstrated. ECHA also notes the significant differences of the target and source substances. More specifically, the two constituents of the target substance have different (linear and branched) side chains whereas the source substance has a cyclic side chain. Such structural difference might result in differences in toxicity of the parent compounds, differences in enzymatic hydrolysis of the parent compounds and also in differences in the toxicity of metabolites (e.g. as indicated in Table 2 of read-across justification document for mutagenicity). However, you did not provide sufficient information to support your claim the structural differences are not expected to influence the *in vivo* interaction of either the target or source substances (see below).

Predicted Metabolites

ECHA acknowledges the similarity of the target and source substances with respect to the salicylic acid group and its predicted metabolite salicylic acid.

In your read-across justification document [1] for "repeated dose toxicity and reproductive toxicity", Table 1, you present the structure of an analogue substance benzyl salicylate instead of the structure of the target substance indicated by the identifiers. Furthermore, in Table 2 you present predicted metabolites for "amyl salicylate" including benzoic acid, amyl alcohol and benzaldehyde. Such metabolites are not reported in your justification document [4] for "Mutagenicity" for "amyl alcohol". Furthermore, predicted metabolites for 2-methylbutyl salicylate are not presented.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you state that "*data are available on the 2 primary metabolites (cyclohexanol and salicylic acid) which support the lack of concern and allow to fulfil the endpoints for genotoxicty, repeat dose and developmental and reproductive toxicity. The data on cyclohexyl salicylate provide additional supporting evidence in the RAAF document. This data is available on the ECHA dissemination web site.*"

ECHA acknowledges the assumed main metabolites of the source substance (cyclohexanol and salicylic acid). However, in absence of further supporting information of the target substance constituents, parent structure toxic properties and metabolic behavior, ECHA considers that you have not sufficiently explained or demonstrated why the differences in the target and source substance metabolic pattern would not influence or lead to underestimating the toxicological properties of the target substance.

Hence, the currently provided information on predicted metabolites seems to be partially inconsistent and as important information on metabolites from 2-methylbutyl salicylate is missing, it is not possible to conclude that "*The available data for the metabolites indicates no safety concerns for salicylates.*"

Metabolism rate

You explain that "*salicylates undergo hydrolysis which predominantly yields the major metabolite salicylic acid. This is consistent across all the salicylates and therefore the relevant experimental data for salicylic acid is also presented in Table 5 for both the acute oral LD50 and one-generation reproductive toxicity tests.*"

ECHA understands that your read-across hypothesis is supported by metabolism (enzymatic hydrolysis) of the target and the source substance to one common metabolite, salicylic acid and respective alcohols. However, you did not provide information on the metabolic rate to support your assumption.

Hence your claim that "*both parent substances will have the same impact with regard to metabolite production*" is not sufficiently supported and it is not possible to conclude on the "*impact*" of the parent substances or the toxicity of the metabolites.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you state that *"the metabolic rate is not considered to be a critical factor in comparing the toxicity of the target and source substances"* and that *"both target and source substances will be metabolised rapidly in the liver to the corresponding alcohols and salicylic acid."* However, ECHA considers the metabolic rate can have impact on the bioavailability of the parent compounds and thereby affect the toxic potential of the target and source substances which are structurally different.

Toxicological effects

You have provided information on a sub-chronic toxicity study (OECD TG 408), a pre-natal developmental toxicity study (OECD TG 414), and a one-generation study (OECD TG 415) with the source substance cyclohexyl salicylate to fulfil the standard information requirement for the target substance. However, you did not provide any information on repeated dose toxicity and reproductive toxicity with the target substance to demonstrate toxicological similarity between source and target for the endpoint in question.

Furthermore, your hypothesis is arguably supported by formation of the common metabolite salicylic acid and the corresponding alcohols and further metabolites.

ECHA, however, points out that Table 2 comprising a list of predicted metabolites shows that all the metabolites of the source substance and the target substance, with the exception of the metabolite salicylic acid, are different. For example, potential metabolites of the target substance are pentanol, pentanal and pentanoic acid, whereas potential metabolites of the source substance are cyclohexanol, cyclohexanone, and cyclohexane diols. ECHA notes that you referred to some existing information on repeated dose toxicity of salicylic acid, pentanol, and pentanal, but respective study summaries were not provided in the dossier.

Furthermore, you did not provide comparable information on the repeated dose toxicity and reproductive toxicity of the other main constituent of the target substance (2-methylbutyl salicylate) and its further metabolites.

ECHA would expect you to provide a robust study summary in IUCLID for information that is most relevant to support the read-across approach. For information supporting the read-across, either detailed information on the results should be provided in the read-across justification document or a study summary with appropriate reference to publicly available information. ECHA also notes that your reference to an evaluation of primary alcohols by JECFA (2001) does not include a specific link, but only a generic reference to "International Joint FAO/WHO Expert Committee on Food Additives". Hence, ECHA cannot consider this as supporting information. In the absence of such information, the similarities and/or differences in toxicity of the resulting alcohols it cannot be taken into consideration.

Furthermore, according to the information provided in Table 5 of your read-across justification document [1], the source substance cyclohexyl salicylate does not seem to be an appropriate source substance. More specifically, in Table 5 of you document, you mentioned a NOAEL of 47 mg/kg bw/d for "isoamyl salicylate" (EC No. 201-730-4), which is an isopentyl salicylate. Since the registered substance is a reaction mass of pentyl salicylate and isopentyl salicylate, read-across from an isopentyl salicylate might be more obvious than from cyclohexyl salicylate. Furthermore, for cyclohexyl salicylate a NOAEL of 360 mg/kg bw/d was provided, which is clearly higher than the NOAEL you provided for "isoamyl salicylate". Hence, ECHA considers that the selected source substance seems to underestimate the hazard and is thus not a suitable source to predict human health effects for the target substance reliably.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you state the following

- *"the read-across hypothesis is supported by profiling information on the target and source substance as per the OECD [Q]SAR Toolbox. Additionally, information on the metabolites of the target and source substances strengthens the lack of toxicological classification for genotoxicity and reproductive/developmental toxicity."*
- *"We have already provided substantial information in the RAAF documents which leads to conclude to a low concern for repeat-dose toxicity with benzyl salicylate. In addition, the available experimental data within the REACH dossiers on the metabolites of Amyl salicylate, salicylic acid (4-Week, NOEL 237 mg/kw bw/day) indicates low toxicity via the oral route. Neither substance is classified for repeat dose toxicity."*
- *"study data on isoamyl salicylate was referenced in the OECD [Q]SAR Toolbox and should have been listed as LOEL and not NOAEL. However, this 1975 study was deemed to be a Klimisch 3 study as no actual data could be found."*
- *"In the OECD 414 tests on cyclohexyl salicylate and salicylic acid, the NOAEL for were 360 and 150 mg/kg bw/day respectively. This indicates that salicylates have the magnitude of toxicity in a Pre-natal developmental toxicity study test and no effects on either parent or offspring at >150 mg/kg bw/day."*
- *"In the OECD 415 tests on cyclohexyl salicylate and salicylic acid, the NOAEL for were 180 and 100 mg/kg bw/day respectively. This indicates that salicylates as a group have the same magnitude of toxicity in a reproductive test with no effects on either parent or offspring at >100 mg/kg bw/day. This is also in confirmed by the NOAEL on methyl salicylate in the OECD 415 at 150 mg/k bw/day."*

Furthermore, you propose to update the dossier with supporting robust study summaries as additional argument and in order to fulfil the sub-chronic toxicity information requirement alongside with the updated read-across justification document if ECHA accepts the Registrant's comments to the draft decision.

ECHA notes that the toxicological comparison of the salicylates made by you omits toxicological data with the target substance as you disregard the isoamyl salicylate study reference (Table 5) and thereby also its LOEL of 47 mg/kg bw/day. In addition, low toxicological concern, equal level of toxicity or lack of toxicological classification among given analogue substances does not support the read-across hypothesis by which you intend to predict the toxic properties of the target substance because a comparison of target and source substance toxic properties is not possible under endpoint specific read-across adaptations.

Therefore, based on the structural differences of the target (pentanol- and 2-methylbutyl-side chain) and the source substances (cyclohexyl-side chain), ECHA considers that read-across adaptations for sub-chronic toxicity and reproductive toxicity would require further supporting information (*e.g.*, a combined repeated dose toxicity study with the reproductive/developmental toxicity screening test on the target substance). ECHA notes that, for read-across adaptations, it is critical to demonstrate that the structural differences of the target and source substance will not have an impact on the toxicity and that the human health effects can indeed be predicted from the data for the source substance.

Read-across assessment framework (RAAF)

You conclude that information from the source substance can be used to close data-gaps in the health hazard assessment of the registered substance as you consider the read-across approach is scientifically acceptable with high confidence based on your examination of the adequacy and scientific robustness of the provided read-across justifications and corresponding information using assessment elements (AE) of the ECHA Read-across assessment framework (RAAF).

ECHA notes that the used RAAF applicability domain did not allow it to be used for assessing multi-constituent read-across adaptations and that further extension to RAAF addressing specifically multiconstituent substances and UVCBs was published in March 2017[2].

Conclusion

ECHA concludes that your comments on the draft decision do not provide new information that can be used as a basis to demonstrate that the target substance's toxicological properties can be predicted from data on the source substance. Furthermore, you have not sufficiently explained or demonstrated why the differences in the target and source substances' chemical structures would not influence the prediction of the toxicological properties of the target substance.

ECHA considers that, in the absence of further supporting information, relevant differences in the toxicological properties of target and source substance and/or their metabolites cannot be ruled out. Furthermore, ECHA disagrees with your RAAF assessment element scoring supporting the acceptance of the read-across with high confidence. Therefore, it is currently not possible to assume/conclude if human health effect of the target substance with respect to sub-chronic toxicity, screening for reproduction/developmental toxicity and pre-natal developmental toxicity can be predicted from the information provided on the source substance. Hence, your read-across adaptation does not comply with the general rules of Annex XI, Section 1.5. of the REACH Regulation.

1. Skin sensitisation (Annex VII, Section 8.3.)

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

"Skin sensitisation" is a standard information requirement as laid down in Annex VII, Section 8.3. of the REACH Regulation (as amended by Commission Regulation (EU) 2016/1688 of 20 September 2016): "*Information allowing: - a conclusion whether the substance is a skin sensitiser and whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A) and -risk assessment, where required*". According to subsection 8.3.1 this includes information from *in vitro/in chemico* test addressing each of the following key events of skin sensitisation: (a) molecular interactions with skin proteins, (b) inflammatory response in keratinocytes, and (c) activation of dendritic cells. Provided that the *in vitro/in chemico* test methods are not applicable, or the results obtained from those studies are not adequate for classification and risk assessment according to point 8.3, also information from an *in vivo* study is required according to subsection 8.3.2.

[2] Read-across assessment framework (RAAF) - considerations on multiconstituent substances and UVCBs: https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316 n

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

In the technical you have provided a study record for a Guinea pig sensitisation test ([redacted] 1981). However, this study does not provide the information required by Annex VII, Section 8.3., because i) ECHA considers the concentrations used in the test not appropriate and ii) the study has been conducted with insufficient number of animals. More specifically, the selected doses in the provided study for induction and challenge applications were 40% and 10%, respectively. ECHA notes that, according to OECD TG 406 (Skin sensitisation), a substance used for each induction exposure should be well-tolerated systemically, the highest dose should cause mild-to-moderate skin irritation and that the concentration used for the challenge exposure should be the highest non-irritant dose. However, according to the preliminary (patch) irritation test results reported in the dossier concentrations of [redacted]% and [redacted]% did not lead to reaction apart from one animal in the [redacted]% group which caused barely perceptible erythema (4 animals per dose group).

In addition, a minimum of 20 animals in the treatment group and 10 in the control group is required according to OECD TG 406, when it is not possible to conclude that the test substance is a sensitiser, while only 10 animals in the treatment group and 4 in the control group were used in the provided study. In addition, no information concerning positive control group was provided to demonstrate the sensitivity and reliability of the experimental technique. ECHA therefore considers that the provided preliminary irritation test indicates that higher concentrations should have been used in conduct of the study. Based on all of the above, the provided study cannot be regarded as valid information on skin sensitisation.

Furthermore, there is a concern that the registered substance might lead to skin sensitisation. More specifically, in a publication (Belsito et al. 2007, Food Chem Toxicol 45: S318 - S361) it is mentioned that "*With regard to the alkyl-side chain salicylates, sensitization reactions were observed with methyl salicylate and pentyl salicylate at concentrations higher or equal to 30%.*" ECHA notes that pentyl salicylate is a constituent of the registered substance.

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.

To address the skin sensitisation endpoint *in vitro/in chemico* methods have been developed. The ECHA Guidance on information requirements and chemical safety assessment (version 5.0, December 2016), Chapter R.7.3 describes the applicability and the limitations of the currently adopted test methods. ECHA Guidance also lists the *in vitro/in chemico* methods that have either already been validated or are under validation assessment at the time of the publication. It is your responsibility to select the test methods which are most appropriate for the registered substance.

Provided that an *in vivo* study is required, the murine local lymph node assay (LLNA; EU B.42./OECD TG 429) is the first-choice method for *in vivo* testing.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you agree to perform *in vitro* KeratinoSens (OECD TG 442E) and *in chemico* DPRA (OECD TG 442C) test methods to fulfil the information requirement and support it with an appropriate Weight of Evidence if required. ECHA acknowledges the described approach but notes that further key event(s) (e.g. activation of dendritic cells) might need to be investigated if classification and risk assessment is not possible based on the results of those two tests.

Furthermore, ECHA notes that it is in the discretion of the Registrant to consider adaptation possibilities according to Annex XI, section 1.2. Weight of Evidence with other additional information.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information on skin sensitisation derived with the registered substance subject to the present decision:

i. *in vitro/in chemico* information on molecular interactions with skin proteins, inflammatory response in keratinocytes and activation of dendritic cells (Annex VII, Section 8.3.1.) and
ii. in case the *in vitro/in chemico* test methods specified under point i) are not applicable for the substance or the results obtained are not adequate for classification and risk assessment:
local lymph node assay (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429) with the registered substance.

2. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)

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

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation.

Information provided for the read-across approach

For the endpoint *in vitro* gene mutation in bacteria you have provided an *in vitro* Salmonella mutagenicity test (Haworth et al., 1983) performed with the source substance benzyl salicylate (CAS 118-58-1; EC 204-262-9).

You have also provided attached to the IUCLID section 13

- read-across (category) justification document "[redacted]" [3]
- justification for read-across to support the REACH registration of Amyl Salicylate (CAS 2050-08-0; EC 218-080-2) for *in vitro* gene mutation study in bacteria with empirical and mechanistic chemical profile of amyl salicylate and benzyl salicylate [4]

Furthermore, ECHA notes that in Table 5 of the justification document [3] you refer to an *in vitro* bacterial reverse mutation assay performed with "amyl salicylate". However, such test was not provided in the dossier. Furthermore, from Table 5 it is not obvious whether this test was performed with the registered substance (EC 911-280-7) or with pentyl salicylate, one of the two main constituents of the registered substance.

Description of your grouping and read-across approach

You indicate that "*This is a category approach for which the read-across hypothesis is based on different compounds which have the same type of effect(s). […] The category is based on 11 salicylic substances […]. All 11 category members have similar profiling alerts for mutagenicity […] and the structural differences are not expected to influence the degree of DNA interaction and therefore the mutagenicity of either the target or source substances.*"

You provided the following read-across hypothesis and justification: "*This read-across is based on the hypothesis that the target substance and source substances have similar mutagenicity properties as a result of structural similarity, the same expected mode of action and similar physicochemical properties relevant for the read-across mutagenicity endpoints.*" You conclude that "*the salicylates as a group are concluded to be without mutagenic/genotoxic potential.*"

In the justification documents [3] and [4] you identified three main source substances, benzyl salicylate (EC No. 204-262-9), cyclohexyl salicylate (EC No. 400-410-3) and ethyl hexyl salicylate (EC No. 204-263-4) (hereafter the 'source substances). In the justification document [3] you state that cyclohexyl salicylate and ethyl hexyl salicylate "*share structural similarities and also mechanistic action similarities which are both general and endpoint specific.*" In the justification document [4] you state that target substance and benzyl salicylate "*are sufficiently similar such that available toxicological data from the Source Substance can be used to address the following endpoints in the REACH registration dossier for the Target Substance. In vitro gene mutation study in bacteria - Ames test.*"

ECHA analysis of the grouping and read-across approach

ECHA observes that especially for "Mutagenicity" you are supporting your read-across approach with information from a category. However, you did not define the applicability domain of your category and you did not describe inclusion and exclusion criteria. ECHA notes that the listed 10 potential source salicylic acid compounds contain a range of saturated, unsaturated, branched and unbranched side chains. Furthermore, ECHA notes that benzyl salicylate is the only salicylic acid category member among the analogue substances having an aromatic side chain. Hence, such substances might be considered as "outliers" of the category. Therefore, in the absence of a category definition with appropriate inclusion and exclusion criteria the source substance cannot be considered as appropriate member of your category.

Furthermore, as mentioned above, a study performed with "amyl salicylate" seems to be existing which would be the most relevant study either to address the standard information requirement for this endpoint (in case the study was performed with the target substance itself) or as most relevant information within your read-across and category approach (in case the study was performed with one constituent of the target substance). In addition, you list a study with "isoamyl salicylate" (EC 201-730-4), but a robust study summary of the study is not available. If valid, such a study performed with an isopentyl salicylate would also be a key element in a read-across approach.

ECHA also notes that, in Table 5 of your read-across justification document [3], you are referring to information from BlueScreen tests as supporting information to your read-across adaptations but you did not provide a study summary of these tests in IUCLID. You state that BlueScreen test "specificity" is currently 96% and "sensitivity" 87% and that "*available fragrance industry data comparing BlueScreen data to the available experimental data for genetox testing indicates that the "specificity" is 90%.*" Furthermore, since this is not a test method approved by OECD, it would be necessary to provide more detailed information on this test. For example, clarification on the study principle and more detail on its ability to detect gene mutations and/or cytogenicity is required. Please note that ECHA expects you to provide robust study summary/summaries in IUCLID for information that is addressing either a standard information requirement and/or that is most relevant to support your read-across approach.

You conclude that information from the main source substances mentioned above can be used to close data-gaps in the health hazard assessment of the registered substance as you consider the read-across approach is scientifically acceptable with high confidence based on your examination of the adequacy and scientific robustness of the provided read-across justifications and corresponding information using assessment elements (AE) of the ECHA Read-across assessment framework (RAAF). ECHA notes that the current RAAF applicability domain does not allow it to be used for assessing multi-constituent read-across adaptations and that further extension to RAAF addressing specifically multiconstituent substances and UVCBs was published in March 2017[3].

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you state that "*there are 5 other non-aromatic side chain substances which have Ames negative data in the absence and presence of S9-mix. Therefore, the exclusion of Benzyl Salicylate (6th category member) does not reduce the power of the category and the argument that data on salicylates (complete category) are negative in the in vitro bacterial reverse mutation assay.*" In addition, you clarify that "*in vitro bacterial reverse mutation assay performed with amyl salicylate result was taken from literature reference. However, this result could not be confirmed and was included as additional weight of evidence.*"

You also included in your comments two OECD QSAR toolbox reports "Prediction of Gene mutation for benzoic acid, 2-hydroxy-, pentyl ester" which you state, "*confirm that as a group, the target substance is not mutagenic".* However, the data matrix has not been provided and no further references or study reports are made available. In addition, the read-across substances included in the report are mostly different from the substances listed in read-across justification document [3].

You conclude that "*[Q]SARs in the absence and presence of S9-mix have been conducted and confirm that as a group, the target substance is not mutagenic.*" You also note that "*from the category it can clearly be seen that these structural differences including the aromatic side on benzyl salicylate, do not result in differences to the following:*

- *Toxicity of the parent compounds.*
- *Differences in enzymatic hydrolysis of the parent compounds.*
- *Potential toxicity due to metabolite formation.*
- *Overall mutagenicity/genotoxicity*"

[3] Read-across assessment framework (RAAF) - considerations on multiconstituent substances and UVCBs: https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

ECHA acknowledges the supporting documentation provided in the comments but notes that robust study summary/summaries for information that is addressing either a standard information requirement and/or that is most relevant to support your read-across approach have not been provided and therefore an independent evaluation of the read-across supporting documentation is not possible.

As explained above, ECHA considers that, in the absence of further supporting information, differences in target and source substance toxicological properties cannot be ruled out and therefore disagrees with your RAAF AE scoring supporting the acceptance of the read-across with high confidence. ECHA considers that it is not possible to assume/conclude if human health effect of the target substance with respect to mutagenicity can be predicted from the information provided on the source substance.

Conclusion on your read-across approach

For the reasons as set out above, ECHA considers that this grouping and read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. Therefore, this adaptation cannot be accepted and there is a data gap for the endpoints covered by this read-across approach.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

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

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

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 sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation.

Information provided for the read-across approach

You have provided the following information:

- *in vitro* mammalian chromosome aberration test (OECD test method not indicated) with the source substance methyl salicylate (CAS No. 119-36-8; EC No. 204-317-7)

- *in vivo* mammalian erythrocyte micronucleus test (equivalent or similar to OECD TG 474) with the source substance ethyl hexyl salicylate (CAS No. 118-60-5; EC No. 204-263-4)
- *in vivo* mammalian erythrocyte micronucleus test (according to OECD TG 474) with the source substance cyclohexyl salicylate (CAS No. 25485-88-5; EC No. 607-733-0[4])

You have also provided attached to the IUCLID section 13

- read-across (category) justification document [redacted] [3]
- justification for read-across to support the REACH registration of Amyl Salicylate (CAS No. 2050-08-0; EC No. 218-080-2) for *in vitro* cytogenicity study in mammalian cells (chromosome aberration) with empirical and mechanistic chemical profile of amyl salicylate and methyl salicylate [5]
- justification for read-across to support the REACH registration of Amyl Salicylate (CAS No. 2050-08-0; EC No. 218-080-2) for *in vivo* mutagenicity test (micronucleus test or UDS assay) with empirical and mechanistic chemical profile of amyl salicylate and ethyl hexyl salicylate [6]

Description of your grouping and read-across approach

You indicate that "*This is a category approach for which the read-across hypothesis is based on different compounds which have the same type of effect(s). […] The category is based on 11 salicylic substances […]. All 11 category members have similar profiling alerts for mutagenicity […] and the structural differences are not expected to influence the degree of DNA interaction and therefore the mutagenicity of either the target or source substances.*"

You provided the following read-across hypothesis and justification: "*This read-across is based on the hypothesis that the target substance and source substances have similar mutagenicity properties as a result of structural similarity, the same expected mode of action and similar physicochemical properties relevant for the read-across mutagenicity endpoints.*" You conclude that "*the salicylates as a group are concluded to be without mutagenic/genotoxic potential.*"

In the justification documents [3], [5] and [6] you identified three main source substances, methyl salicylate (EC No. 119-36-8), cyclohexyl salicylate (EC No. 400-410-3) and ethyl hexyl salicylate (EC 204-263-4) (hereafter the 'source substances'). In the justification document [3] you state that cyclohexyl salicylate and ethyl hexyl salicylate "*share structural similarities and also mechanistic action similarities which are both general and endpoint specific.*"

You state that "*the source and target substance have similar human health properties as a result of structural similarity, the same expected mode of action for mutagenicity and similar physicochemical properties.*" In the justification document [5] you state that target substance and methyl salicylate "*are sufficiently similar such that available toxicological data from the Source Substance can be used to address the following endpoints in the REACH registration dossier for the Target Substance. In vitro cytogenicity study in mammalian cells (chromosome aberration).*"

[4] The Registrant uses two different EC identifiers for cyclohexyl salicylate in IUCLID (EC No. 607-733-0 and 400-410-3)

In the justification document [6] you state that target substance and ethyl hexyl salicylate "*are sufficiently similar such that available toxicological data from the Source Substance can be used to address the following endpoints in the REACH registration dossier for the Target Substance. Other in vivo mutagenicity test: micronucleus test (OECD 474) or UDS assay (OECD 486).*"

ECHA analysis of the grouping and read-across approach

Category definition

ECHA observes that especially for "Mutagenicity" you are supporting your read-across approach with information from a category. However, you did not define the applicability domain of your category and you did not describe inclusion and exclusion criteria. ECHA notes that the listed 10 potential source salicylic acid compounds contain a range of saturated, unsaturated, branched and unbranched side chains. Hence, in the absence of a category definition with appropriate inclusion and exclusion criteria and demonstrating that the respective groups not common to all the category members do not affect the anticipated toxicity, the target and source substance cannot be considered as appropriate members of your category.

Read-across/category hypothesis

With respect to structural similarities and structural differences you mention that "*The 10 source category members have > 60% structural similarities with the target amyl salicylate. This high degree of structural similarity increases the confidence along with the profiling as discussed, that this category will react in a similar manner in both an in vitro and in vivo test system.*" However, ECHA notes that a quantified structural similarity by itself is not sufficient basis for read-across adaptation and that the remaining structural dissimilarities between the main source and target substances clearly suggest different properties with regard to mutagenicity, as explained below in context with predicted metabolites. Therefore, ECHA considers that the structural similarities described as > 60% do not add confidence in your read-across adaptations of mutagenicity endpoints between target substance and the 10 category members.

ECHA observes that in Table 5 you cited negative results on *in vitro* and/or *in vivo* tests on cytogenicity (chromosomal aberration or micronucleus) from four category members. However, salicylate with a pentanol and/or isopentanol side chain are not included.

In your read-across justification document [1] for repeated dose toxicity and reproductive toxicity you refer to your hypothesis that the parent compounds are metabolised to salicylic acid and alcohols. In your read-across justification document [3] for mutagenicity, you listed results of *in vitro* and *in vivo* genotoxicity tests performed with predicted metabolites of "amyl salicylate", cyclohexyl salicylate and ethyl hexyl salicylate.

It is to be noted that positive results were mentioned for metabolites of "amyl salicylate". More specifically, pentanal (valeraldehyde) was positive e.g., in an *in vitro* mouse lymphoma test with S9 and pentanoic acid in an *in vitro* "mammalian germ cell cytogenicity" test. However, for the predicted metabolites of the source substances cyclohexyl salicylate and ethyl hexyl salicylate, the reported results for mammalian tests were either negative or no information is available. Those results indicate a genotoxic potential of the target substance in mammalian system but not for the source substances of the category.

Hence, your current approach underestimates the hazard. ECHA concludes therefore that human health effect of the target substance with respect to *in vitro* cytogenicity in mammalian cells cannot be predicted from the information provided on the source substance(s).

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you state that "*the REACH dossiers on the metabolites of the target and source substances (salicylic acid and cyclohexanol) are available for consultation on the ECHA website following registration*" and that "*there is no indication of an increase in the in vitro chromosome aberration for either substance in the absence and presence of S9-mix.*" In addition,

You also included in your comments a QSAR toolbox report "Prediction of chromosome aberration for benzoic acid, 2-hydroxy-, pentyl ester" which, you state, "*confirms that the target substance does not cause chromosome aberrations in mammalian cells*". However, the data matrix has not been provided and no further references or study reports are made available. In addition, the read-across substances included in the report are mostly different from the substances listed in read-across justification document [3].

You note that "*from the category it can clearly be seen that these structural differences including the aromatic side on benzyl salicylate, do not result in differences to the following:*

- *Toxicity of the parent compounds.*
- *Differences in enzymatic hydrolysis of the parent compounds.*
- *Potential toxicity due to metabolite formation.*
- *Overall mutagenicity/genotoxicity*"

ECHA acknowledges the supporting documentation provided in the comments but notes that robust study summary/summaries for information that is addressing either a standard information requirement and/or that is most relevant to support your read-across approach have not been provided and therefore an independent evaluation of the read-across supporting documentation is not possible.

ECHA considers that to clarify the concern for potential genotoxicity of the registered substance, is necessary to provide information on *in vitro* cytogenicity in mammalian cells with the registered substance.

Conclusion on your read-across approach

For the reasons as set out above, and taking into account all of your arguments, ECHA considers that this grouping and read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. Therefore, this adaptation cannot be accepted and there is a data gap for the endpoints covered by this read-across approach.

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 (test method 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.

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).

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

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

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.

ECHA notes that information requirements of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. have been adapted using invalid read-across adaptation (see below) and the registration dossier does not contain a valid study record for this information requirement. Therefore, adequate information *on in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement provided that the study requested under 2 and 3 have negative results.

You have sought to adapt this information requirement according to Annex VIII, Section 8.4.3. You provided the following justification for the adaptation:

"According to Regulation (EC) No. 1907/2006, Annex VIII, section 8.4.3, an in vitro gene mutation study in mammalian cells is not required if negative results are obtained in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. Since adequate data from reliable in vivo mammalian gene mutation tests are available, testing for this endpoint is not required."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex VIII, Section 8.4.3., because an *in vitro* gene mutation study in mammalian cells is required if *negative* results are obtained in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. Furthermore, as explained above, your read-across adaptations for *in vitro* gene mutation in bacteria (Annex VII, Section 8.4.1.) and for *in vitro* cytogenicity in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.) based on *in vitro* and *in vivo* information from source substances is rejected.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you state that "*the REACH dossiers on the metabolites of the target and source substances (salicylic acid and cyclohexanol) are available for consultation on the ECHA website following registration*" and that "*there is no indication of an increase in the in vitro mammalian gene mutation for these substances in the absence and presence of S9-mix.*"

You also included in your comments a QSAR toolbox report "*Prediction of gene mutation for benzoic acid, 2-hydroxy-, pentyl ester*" which, you state, "*confirms that the target substance does not cause gene mutations in mammalian cells*". However, the data matrix has not been provided and no further references or study reports are made available. In addition, the read-across substances included in the report are mostly different from the substances listed in read-across justification document [3].

ECHA acknowledges the supporting documentation provided in the comments but notes that robust study summary/summaries for information that is addressing either a standard information requirement and/or that is most relevant to support your read-across approach have not been provided and therefore an independent evaluation of the read-across supporting documentation is not possible. In addition, as explained above in Appendix 1, sections 2 and 3 of this decision, your read-across adaptations of the mutagenicity information requirements is rejected.

Therefore, your adaptation of the information requirement for *in vitro* mammalian gene mutation test is also rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA 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 studies requested under 2 and 3 has negative result.

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

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

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Repeated Dose 90-Day Oral Toxicity in Rodents (OECD TG 408) with the source substance cyclohexyl salicylate (EC No. 400-410-3).

You provided comment(s) on the draft decision according to Article 50(1) of the REACH Regulation which have been acknowledged and discussed above in Appendix 1, section 0 of this decision.

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

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and the reported concentrations applied in uses with industrial / professional spray applications are low (<1%). 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.

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

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

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a one-generation reproduction toxicity study (OECD TG 415) with the source substance cyclohexyl salicylate (EC No. 400-410-3).

You provided comment(s) on the draft decision according to Article 50(1) of the REACH Regulation which have been acknowledged and discussed above in Appendix 1, section 0 of this decision.

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

Hence, 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 methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, section R.7.5 and 7.6 (version 4.1, October 2015). You should also carefully consider the order of testing especially the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure unnecessary animal testing is avoided, paying particular attention to ECHA's end point specific guidance document[5].

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

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a prenatal developmental toxicity study (OECD TG 414) with the source substance cyclohexyl salicylate (EC No. 400-410-3).

You provided comment(s) on the draft decision according to Article 50(1) of the REACH Regulation which have been acknowledged and discussed above in Appendix 1, section 0 of this decision.

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

[5] ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance Version 5.0, December 2016, p 461-2 (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf).

Hence, 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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Appendix 2: Procedural history

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

The compliance check was initiated on 1 March 2017.

Concerning your comment on the initiation date for the compliance check, ECHA notes that the compliance check initiation date in the decision is not correctly reflecting the initiation of evaluation work of your dossier. This inconsistency is due to an IT-system update during the evaluation and root cause technical by nature. Therefore, the assessment of the dossier and the attached read-across justifications started in practise earlier on 30 November 2016. ECHA considers that full and comprehensive assessment has not been compromised.

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.