EUROPEAN CHEMICALS AGENCY

Helsinki, 13 March 2018

Addressee: [redacted]

Decision number: CCH-D-2114386909-26-01/F
Substance name: HOMOSALATE
EC number: 204-260-8
CAS number: 118-56-9
Registration number: [redacted]
Submission number: [redacted]
Submission date: 10.05.2013
Registered tonnage band: 100-1000T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **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;**

2. **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;**

3. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **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;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity); and**
   - **Cohort 3 (Developmental immunotoxicity).**

4. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method 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 are required to submit the requested information in an updated registration dossier by **20 September 2021**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing. The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 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

TOXICOLOGICAL INFORMATION

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.

Your registration dossier contains for several endpoints adaptation arguments in form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints.

Grouping of substances and read-across approach

You have sought to adapt the information requirements for the following endpoints by – *inter alia* - applying a read-across approach in accordance with Annex XI, Section 1.5.:

- Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Extended One-Generation Reproductive Toxicity Study (Annex IX, Section 8.7.3.)

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.

Description of your grouping and read-across approach

You propose read-across from the structurally similar substance methyl salicylate (EC 204-317-7, CAS 119-36-8) (hereafter the 'source substance') for each of the above-mentioned information requirements. You conclude that this analogue substance can be used to close data-gaps in the health hazard assessment of the target substance as the target and source substances share the following properties:

(i) Impurities are comparable or not present;
(ii) Similar metabolic pathways;
(iii) Comparable modes of action with regard to systemic toxicity.

You state that *"Methyl Salicylate was registered in 2010 and has a similar metabolic profile to homosalate in that it is rapidly metabolised to salicylic acid which is the driver for the toxicity of the substance. The additional metabolite from homosalate, trimethylcyclohexanol is not considered to present a significant hazard. The SCCP (now SCCS) opinion on homosalate also makes reference to the metabolism of homosalate and the comprehensive database of the metabolites (SCCP 2007).*
This primary piece of information makes a read across from Methyl salicylate to homosalate applicable and appropriate. [...]

Given the above data and taking a conservative approach in the read across by utilising the NOAEL of 50 mg/kg bw/ day identified in the 2 year repeated dose study with Methyl salicylate and correcting for the difference in molecular weights the NOAEL used for derivation of the oral and dermal DNELs for homosalate is 86 mg/kg bw/day.

Similarly, the inhalation DNELs makes use of the data from the subacute inhalation study for methyl salicylate and correcting for the difference in molecular weights the NOAEL used for derivation of the inhalation DNELs for homosalate is 1207 mg/m3."

Furthermore, you state that "*given both homosalate and methyl salicylate can be considered to have similar pathways for biotransformation and consequently comparable modes of action with regard to systemic toxicity (supported by justification in the disseminated dossier for methyl salicylate), read-across from data available for methyl salicylate for the following endpoints is considered appropriate for evaluating the safety of homosalate: Reproductive toxicity, Developmental toxicity, Long term repeat dose Toxicity*"

Information provided for the read-across approach

For the endpoints mentioned above, you have provided an OECD TG 422 screening study performed with the registered (target) substance 3,3,5-trimethylcyclohexyl salicylate and sub-acute, sub-chronic and chronic toxicity studies as well as a two-generation reproductive toxicity study performed with the alleged analogue substance methyl salicylate (EC 204-317-7, CAS 119-36-8).

You have also provided a read-across justification document attached to the IUCLID dossier.

ECHA analysis of the grouping and read-across approach

ECHA notes that the OECD TG 422 screening study performed with the registered substance has relevant shortcomings. More specifically, you describe that a technical error (constant lightening) occurred which you consider as the principal reason for the increased infertility observed in all groups: "*This effect was distributed in a dose level independent manner: number of pregnancies in the groups 2, 3 and 5 were very low whereas the number in the control group and group 4 was similar to the normal background values (8 and 7, respectively). The low number of pregnancies per group might have had an impact on evaluation of data on breeding and reproduction at the dose levels of 60, 120 and 750 mg /kg bw/day. Eight pregnancies in the control group and seven pregnancies at the dose level of 300 mg/kg bw/day enabled reliable evaluation of the data."* ECHA observes that you assigned reliability 2 (reliable with restrictions) to this study.

ECHA further notes the shortcomings you indicated for the studies performed with the source substance. More specifically, you mentioned that in the repeated dose toxicity studies "*limited histopathological examinations of key organs and tissues*" were performed and in the three-generation reproductive toxicity study "*several currently recommended observations and parameters determinations were not performed.*"

With regard to the proposed prediction for human health endpoints ECHA has the following observations:

Firstly, you consider that *"salicylic acid [...] is the driver for the toxicity of the substance. The additional metabolite from homosalate, trimethylcyclohexanol is not considered to present a significant hazard."* However, ECHA notes that provided information on the target and source substance demonstrate different systemic toxicity. More specifically, the organs affected in the OECD 422 screening study with the target substance were e.g., liver, kidneys, thyroid glands, thymus, and epididymides. However, in the sub-chronic toxicity study with the claimed analogue substance methyl salicylate no histopathological effects were reported, whereas in the chronic toxicity study pituitary gland lesions occurred. Furthermore, you conclude that substance-related adverse effects on reproduction and development were observed in the OECD TG 422 screening study with the target substance, whereas no effects on reproduction were reported in the three-generation reproductive study with the source substance. Consequently, your assumption that *"salicylic acid is the driver for the toxicity of the substance"* is not supported by that provided information. Hence, read-across adaptation fails because the properties of the target and source substances have not been demonstrated to be similar.

Secondly, with respect to your conservative approach for DNEL derivation, ECHA acknowledges that the NOAEL derived in the chronic study with the source substance (e.g., 50 mg/kg bw/d) is lower than the NOAEL derived in the OECD 422 screening study performed with the target (registered) substance (300 mg/kg bw/d). However, since the properties of the target and source substances have not been demonstrated to be similar, a "conservative approach" on its own is not sufficient to justify a read-across approach.

Thirdly, you state that *"given both homosalate and methyl salicylate can be considered to have similar pathways for biotransformation and consequently comparable modes of action with regard to systemic toxicity."* You further state that *"Homosalate or 3,3,5-trimethyl cyclohexyl salicylate is rapidly transformed into salicylic acid and trimethyl cyclohexanol [...] Similarly, the source substance methyl salicylate is rapidly hydrolysed to salicylic acid and methanol."* ECHA understands that your read-across hypothesis is based on the formation of the common metabolite salicylic acid. You argue that *"trimethylcyclohexanol is not considered to present a significant hazard"*. However, you did not provide supporting information to demonstrate said rapid hydrolysis and that the presumed metabolite 3,3,5-trimethyl cyclohexanol would indeed not present a significant hazard. In the light of the observed differences in toxicity and affected target organs of the target and source substances, as explained above, it must be suspected that the target substance either does not hydrolyse as assumed or its presumed metabolite 3,3,5-trimethyl cyclohexanol contributes to the hazard of the target substance subject to this decision. Hence, your read-across approach fails because it is not possible to predict the toxicity of the target substance from the source substance.

In your comments, following the procedure set out in Article 50(1) of the REACH Regulation, you acknowledge that the approach *"contains some weaknesses and that methyl salicylate may not be the best suitable source substance",* and you refer to many existing registration dossiers on salicylates stating that *"a number of these salicylates bear greater chemical and toxicological similarities with homosalate than does methyl salicylate. As such, the registrant believe that other read-across strategies still need to be investigated in order to avoid additional vertebrate animal testing."*

ECHA acknowledges your comments and your intention to investigate whether the read-across approach and justification can be strengthened, using other source substances. Furthermore ECHA notes that it is not sufficient merely to establish a similar toxicological profile; rather it is necessary to establish a basis for predicting the properties of the registered substance, according to Annex XI, 1.5.[2]

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.

Consideration on uses of the substance

In your comments to the proposal for amendment for an extended one-generation reproductive toxicity study and as you further clarified at the member state committee you explained for the first time that the substance is used exclusively in cosmetic products but there is formulation taking place in the EU. The registration dossier indeed indicates formulation, and thus worker exposure, with no indication of strictly controlled conditions. ECHA's factsheet on the interface between REACH and Cosmetics Regulations, which was developed jointly with the European Commission[3], provides that registrants of substances that are exclusively used in cosmetics may not perform animal testing to meet the information requirements of the REACH human health endpoints. The exception is any testing required to assess the risks from exposure to workers in the absence of strictly controlled conditions.

The requested human health tests are therefore justified for the purposes of assessing hazards for workers. Such testing would not trigger the testing and marketing bans under the Cosmetics Regulation as the testing is to be performed for the purposes of meeting the requirements of the REACH Regulation; see Commission Communication of 11 March 2013 on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics (COM(2013)135)).

1. Sub-chronic toxicity study (90-day), (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.

[2] You can find more information at https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
3 Please see https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf

In the technical dossier you have provided an OECD TG 422 screening study performed with the registered substance. In addition, you have sought to adapt this information requirement according to Annex XI, Section 1.5. (read-across) by providing study records for chronic and subacute oral toxicity studies in dogs, rats, and rabbits (Webb 1963), a subacute inhalation toxicity of 109 industrial chemicals (Gage 1970) and a sub-chronic dermal toxicity study in rabbits (Webb 1963) all performed with the analogue substance methyl salicylate (CAS No 119-36-8). However, as explained above (see paragraph "Grouping and read-across approach"), your adaptation of the information requirement according to Annex XI, Section 1.5., read-across, is rejected.

Furthermore, you indicated that the OECD TG 422 screening study with the registered substance and the oral chronic toxicity study with the claimed analogue substance were used in a 'weight of evidence' approach.

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. Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance at equivalent level as investigated in a sub-chronic toxicity study (EU B.26/OECD TG 408). Relevant elements are in particular exposure route, duration and levels, two genders, sensitivity and depth of investigation to detect specific organ toxicity.

However, the provided sources of information do not sufficiently address the properties of the registered substance with respect to sub-chronic toxicity. More specifically, the information you provided on the registered substance (OECD TG 422 screening study) does not cover to a sufficient extend exposure duration of a sub-chronic toxicity study (47 days instead of 90 days) and it does not have the sensitivity to detect specific target organ toxicity due to a lower number of animals per dose group (less than 10 compared to 20 animals per dose group). Furthermore, the provided sources of information on sub-chronic and chronic toxicity with the analogue substance methyl salicylate cannot be considered as relevant because the toxicological properties of the target and source substances seem to be different and hence, as explained above, your read-across approach is rejected.

Hence, the information you provided to support you weight of evidence adaptation does not allow to conclude on the dangerous (hazardous) properties of the registered substance with respect to the information requirement for Annex X, Section 8.6.2. 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.

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 6.0, July 2017) 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 no uses with spray application are reported that could potentially lead to aerosols of inhalable size. 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.

In your comments, following the procedure set out in Article 50(1) of the REACH Regulation, you claim that *"the requested sub-chronic toxicity study (90-d), oral route, in rat would only be required in case an amendment of the read-across strategy would not be justifiable."* And that *"if based on the amended read-across strategy, homosalate requires further testing , oral dosing is most appropriate and the rat species is preferred".*

ECHA has already included above detailed scientific considerations on why the weight-of evidence (and read-across) cannot be accepted. ECHA considers these considerations are still valid.

ECHA notes that you agree regarding the route of administration and animal species.

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 toxicity study (test method: EU B.26./OECD TG 408) oral in rats.

2. 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.

In the technical dossier you have provided an OECD TG 422 screening study performed with the registered substance. In addition, you have sought to adapt this information requirement according to Annex XI, Section 1.2. of the REACH Regulation by providing the following justification: *"According to regulation (EC) 1907/2006 Annex XI (weight of evidence), testing for developmental toxicity is not considered to be required based on WoE considerations taking into account results from the OECD 422 screening study with homosalate, results from the 3-generation reproduction toxicity study with the read-across substance methyl salicylate and additional data on developmental toxicity available for acetylsalicylic acid, salicylic acid and other salicylates in several animals species and in humans (see read-across justification document in IUCLID section 13 resp. in the appendix to the CSR) that has concluded that salicylic acid and its esters should not be considered a developmental toxicants in humans."*

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. Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance at equivalent level as investigated in a pre-natal developmental toxicity study (EU B.31/OECD TG 414).

Relevant elements are in particular exposure route, duration and levels, sensitivity and depth of investigation to detect pre-natal developmental toxicity (including growth, survival, external, skeletal and visceral malformations) as well as maternal toxicity.

However, the provided sources of information do not address the same properties of the registered substance as a pre-natal developmental toxicity study. More specifically, neither the OECD TG 422 screening study performed with the registered substance nor the three-generation reproduction toxicity study performed with the source substance provide information e.g., on examinations of foetuses for skeletal and visceral alterations. In addition, as explained above in section 'Grouping of substances and read-across approach', your read-across adaptation according to REACH Annex XI, Section 1.5. is rejected, and thus the three-generation reproduction toxicity study cannot be considered within the weight of evidence approach. For other source substances of the group of salicylates you have not provided any read-across justification.

Hence, the information you provided to support the weight of evidence adaptation, does not allow to conclude on the dangerous (hazardous) properties of the registered substance with respect to the information requirement for Annex X, Section 8.7.2. "Prenatal developmental toxicity". 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.

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

In your comments, following the procedure set out in Article 50(1) of the REACH Regulation, you claim that *"the prenatal developmental toxicity study would only be required in case an amendments of the read-across strategy would not be justifiable."* And that *"if based on the amended read-across strategy, homosalate requires further testing, appropriate species and route of administration will be based on the available information".* Furthermore you refer to a paper from Schardein *et al.* (1985) to argue that there is *"information available in the species sensitivity towards salicylates".*

ECHA has already included above detailed scientific considerations on why the weight-of evidence (and read-across) cannot be accepted. ECHA considers these considerations are still valid. Regarding the selection of animal species, it is your responsibility to justify your choice based on available information and this will be reviewed when the study is submitted.

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.

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

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.

a) The information requirement

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

ECHA considers that adverse effects on reproductive organs and tissues in line with Annex IX, Section 8.7.3 of the REACH Regulation are observed in the provided OECD TG 422 study. ECHA notes that probably due to a technical error, fertility was reduced (see paragraph "Grouping and read-across approach"). Nevertheless, you indicate that "*test item-related effect on fertility and gestation at the high-dose level should be considered*". More specifically, increase in post-implantation loss occurred at mid dose level (300 mg/kg bw/day). At the high dose (750 mg/kg bw/day) changes in sperm morphology and sperm motility correlating with reduced weights of prostate and seminal vesicles were observed. Furthermore, increased incidence and/or severity of diffuse hypertrophy of the follicular epithelium was reported in thyroid glands in females at the dose level of 300 mg/kg bw/day and in both sexes at the dose level of 750 mg/kg bw/day. In addition, an *in vitro* androgen receptor binging assay showed that the registered substance inhibited (32 to 41 % at 100 mM) the binding of the test ligand methyltrienolone to the androgen receptor investigated.

Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for the registered substance.

In your comments, following the procedure set out in Article 50(1) of the REACH Regulation, you claim that the request is not triggered at this tonnage band because there is not "*sufficient evidence for triggering the basic EOGRTS with extension of the F2 generation and Cohorts 2 & 3*" and that "*additional available data on the potential read-across source substances have to be taken into account*". You also consider that "*the* [OECD TG 422] *study was biased by the continuous lighting schedule and the relevance of the effects is questionable*" and speculate that the concerns in relation with reproductive toxicity at the highest dose "*might be secondary findings in rats, not directly relevant to humans*" due to a "*known rat-specific mechanism of thyroid hypertrophy*".

ECHA notes that you have not disregarded the OECD TG 422 screening study ([redacted] 2013) due to the problems with light/dark cycle, although with limitation and consequently conducted a new study. Instead, you state that the problem light system has reduced the reliability of the study and therefore assigned Klimisch score 2 (i.e., reliable with restriction) for the study. More specifically, you state that such technical problem results increased infertility in all groups except that the number in the control and treated group 4 (300 mg/kg bw/day) was similar to the normal background value. As a result, you have used the findings from the control and the group treated at 300 mg/kg bw/day for the reliable evaluation of data on breeding and reproduction.

Hence, ECHA understands that the result of this study provides relevant information on the effect of the registered substance with regard to reproductive health. More specifically, ECHA notes the following in the robust study summary of OECD TG 422 screening study ([redacted] 2013):

- No adverse effect in the control animals were reported despite that both the treated and control animals are subjected to the same cage environment (including exposure to continuous light),
- You have concluded that some of the results reported for the study are test substance related effects. More specifically, you state that *"test item-related effect on fertility and gestation at the high-dose level should be considered".* The effects on post implantation loss at 300 mg/kg bw/day (note: the data at 750 mg/kg bw/day is considered as not conclusive since only one female was evaluated), sperm morphology and sperm motility at 750 mg/kg bw/day, and reduction in weights of prostate and seminal vesicles at 750 mg/kg bw/day were considered by you as test material related adverse effect,
- You consider the effects observed in the thyroid (increased incidence and/or severity of diffuse hypertrophy of the follicular epithelium in thyroid glands in females at 300 mg/kg bw/day and in both sexes at 750 mg/kg bw/day) as secondary to the liver enzyme induction. However, you have failed to justify that the observed changes in thyroid are mediated by thyroid hormone metabolism, or that the specific mechanism involved would be irrelevant for human, thus ECHA considers the effects relevant for triggering, and
- The effects in eosinophils, globulin, and thymus at 300 and/or 750 mg/kg bw/day are reported by you as test item related.

Hence, for the reason mentioned above, there is no supportive evidence to justify that the findings in the OECD 422 screening study ([redacted] 2013) used for triggering are secondary to continuous light. Thus, ECHA concludes that the results of the OECD TG 422 screening study are relevant and sufficient to be used as triggers for the extended one-generation reproductive toxicity study and to expand the study design.

Furthermore, ECHA notes that in addition to the effects seen at the highest doses in both males and females, effects remained observed at the mid-doses and cannot be dismissed. They raise concerns, which need to be clarified. Further, you have not demonstrated that the changes in thyroid are mediated by effects on thyroid hormone metabolism, or that the specific mechanism involved would be irrelevant for human. Consequently, the results may be relevant for humans.

Therefore, ECHA considers the extended one-generation reproductive toxicity study is triggered for the reasons explained above, as the triggers are there to clarify "*concerns in relation with reproductive toxicity*", and the 'secondary' nature of these effects seem to be speculation.

b) Information provided

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. You have provided the following justification for the adaptation: "*WoE was done based on the an oral OECD 422 reproduction toxicity screening study with homosalate and a 3-generation oral reproduction toxicity study with the read-across substance methyl salicylate. The two studies gave consistent results with a NOAELs of 430 mg/kg bw/day in the 3-generation study and no evidence of reproductive effects at 120 mg/kg bw/day in the OECD 422 study. A read-across justification is provided as attachment to IUCLID section 13 respectively as appendix to the CSR.*"

In the technical dossier you have provided an OECD TG 422 screening study performed with the registered substance. In addition, you have provided a study record for a three generation reproductive toxicity study (Collins et al. 1971) performed with the proposed analogue substance methyl salicylate (CAS no 119-36-8). You have further provided two supporting studies (Androgen receptor binding assay, and estrogen receptor binding assay).

ECHA's evaluation and conclusion of the provided information

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.

Therefore, your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance at equivalent level as the required study. An extended one-generation reproductive toxicity study provides relevant information on two aspects, namely on a) sexual function and fertility in P1 and F1 generations (further referred to as 'sexual function and fertility') and b) on developmental toxicity observable peri- and postnatally in the F1 generation (further referred to as 'post-natal developmental toxicity'). Relevant elements for 'sexual function and fertility' are in particular functional fertility (mating behaviour, conception, pregnancy, parturition, and lactation) in the parental generation after sufficient pre-mating exposure and histopathological examinations of reproductive organs in both P and F1 generations. Relevant elements for 'post-natal developmental toxicity' are in particular peri- and post-natal investigations of the F1 generation up to adulthood, investigations on developmental neurotoxicity, and investigations on developmental immunotoxicity. Furthermore, the relative values/weights of different pieces of the provided information needs to be assessed as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4.4. In particular relevance, reliability and adequacy for the purpose as well as consistency of results/data need to be considered.

With respect to the aspect of 'sexual function and fertility' of P and F1 generation, you have provided an OECD 422 screening study that provides information on histopathological changes in major reproductive organs and on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition.

Due to a technical error, fertility was decreased (see above paragraph "Grouping of substances and read-across"). However, based on the findings, you indicate and ECHA agrees that this study demonstrates adverse effects on reproduction and development. ECHA further notes that the statistical power of this study is lower than that of the extended one-generation reproductive toxicity study, and certain investigations are not included, such as histopathology of the reproductive organs in F1 animals in adulthood. Therefore, this source of information provides only limited information on 'sexual function and fertility'.

In addition, you have provided a three-generation reproductive toxicity study performed with the analogue substance methyl salicylate (EC no 204-36-8). However, as explained above in section 'Grouping of substances and read-across approach', your read-across adaptation according to REACH Annex XI, Section 1.5. is rejected. Furthermore, as you reported, this study contains *"several deficiencies in relation to OECD Guideline 416 in terms of parameters studied."* ECHA considers that based on the combined shortcomings of read-across supporting information and the evident shortcomings of the source study itself lead, the information cannot be considered as adequate to conclude on the toxicological properties of the substance subject to this decision concerning sexual function and fertility as investigated by an extended one-generation reproductive toxicity.

With respect to the aspect of 'post-natal developmental toxicity', you have provided only limited information. More specifically, the OECD TG 422 screening study investigates developmental toxicity only until postnatal day 4. However, peri- and post-natal investigations of the F1 generation up to adulthood, investigations on developmental neurotoxicity and investigations on developmental immunotoxicity are not addressed at all. In addition, you have provided a three-generation reproductive toxicity study performed with the proposed analogue substance methyl salicylate. (EC no 204-36-8). However, as explained above in section 'Grouping of substances and read-across approach', your read-across adaptation according to REACH Annex XI, Section 1.5. is rejected. Furthermore, as you reported, this study contains *"several deficiencies in relation to OECD Guideline 416 in terms of parameters studied."* Hence, you did not provide enough reliable information to support your assumption/conclusion that the substance does not have a dangerous property with respect to post-natal developmental toxicity.

The information from the provided *in vitro* estrogen and androgen receptor binding assays, which are screening tests to detect the ability of the substance to interact with estrogenic or androgenic receptors, respectively, do not directly provide information on "sexual function and fertility" and/or "developmental toxicity".

Hence, the sources of information you provided, do not allow to conclude on the presence or absence of the dangerous property of the registered substance 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 to Annex IX, Section 8.7.3. is required. The following refers to the specifications of this required study.

c) *The specifications for the required study*

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017), the starting point for deciding on the length of the premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017). In this specific case ten weeks exposure duration is supported by the lipophilicity of the substance (log Kow > 6) to ensure that the steady state in parental animals has been reached before mating.

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

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

In your comments to the proposal for amendment, you stated that the substance is used in cosmetic products but potential consumer exposure is out of the scope of REACH and therefore cannot justify the trigger for the extension of Cohort 1B under REACH, which was initially proposed in the draft decision.

ECHA considers your comment and agrees that the registered substance is used exclusively in cosmetics and the foreseen exposure is limited to workers in industrial setting. Hence, the extension of Cohort 1B is not met because the criteria set out in column 2, first paragraph, lit. (a) of section 8.7.3., Annex IX is not fulfilled. Consequently, ECHA has removed the extension of Cohort 1B request from the decision.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex IX. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA notes that existing information on the registered substance derived from the available combined repeated dose toxicity study with the reproduction / developmental toxicity screening test ([redacted] 2013) show evidence of neurotoxicity.

More specifically, a greater incidence and severity of diffuse hypertrophy of the follicular epithelium in thyroid glands in females at the mid dose level (300 mg/kg bw/day) and in both sexes at the high dose level (750 mg/kg bw/day) was reported. This effect in the thyroid gland could be an indication to specific mechanisms/modes of action of the substance with an association to (developmental) neurotoxicity.

ECHA concludes that the developmental neurotoxicity cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified study with the registered substance.

In your comments, following the procedure set out in Article 50(1) of the REACH Regulation, you claim that the neurotoxicity is not triggered because there are species differences between rat and human in thyroid hormone metabolism and so you cannot extrapolate between rat and human for rat thyroid changes, and you conclude that the results are not relevant for humans.

ECHA considers that you have not demonstrated that the changes in thyroid are mediated by effects on thyroid hormone metabolism, or that the specific mechanism involved would be irrelevant for human. Consequently the results may be of relevance for humans.

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

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex IX.

ECHA notes that existing information on the registered substance derived from available combined repeated dose toxicity study with the reproduction / developmental toxicity screening test show evidence of immunotoxicity. More specifically, lower number of eosinophils in males at all dose levels (60, 300 and 750 mg/kg bw/day), lower globulin level in males at the high dose level ((750 mg/kg bw/day), and reduction in thymus weight (absolute, relative to body the brain and/or body weight) in both sexes at the highest dose level. In addition, histopathological examination showed a greater incidence and/or severity of decreased cortical lymphocytes of thymus in males at the mid and high dose levels and in females at the high dose level.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* study with the registered substance itself.

In your comments, following the procedure set out in Article 50(1) of the REACH Regulation, you argue that the immunotoxicity cohort is not triggered because "*the high dose group for homosalate was excessively toxic and should be disregarded. The remaining findings are isolated (eosinophils and lymphocytes) and are not sufficient to trigger the study.*" However ECHA considers that the totality of the evidence in the dose-response curve is sufficient to establish consistency, and that the top-dose level should be taken into account. The overall picture establishes a concern for (developmental) immunotoxicity.

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

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

In your comments, following the procedure set out in Article 50(1) of the REACH Regulation, you argue that there are difficulties (thyroid stimulation and prostaglandin synthesis inhibition) which "*render the EOGRTS test technically impossible*".

ECHA does not consider this to be a valid reasoning as to why the test is technically impossible, as foreseen in Annex XI, Section 2 of the REACH Regulation.

Furthermore, the data the statement relies on is not provided (in the dossier) and therefore ECHA cannot assess it.

a) Outcome

Based on the available information, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- 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;
- Cohorts 2A and 2B (Developmental neurotoxicity); and
- Cohort 3 (Developmental immunotoxicity).

ECOTOXICOLOGICAL INFORMATION

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.

4. Identification of degradation products (Annex IX, 9.2.3.)

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX 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.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 9.2.3., column 2 and Annex XI, Section 1.2. : *"From structural information on the test item provided by the sponsor, the test item contains an ester group which is expected to hydrolyse to the associated acid and alcohol.*

In this case this would be salicylic acid (2-hydroxylbenzoic acid) and 3,3,5-trimethylcyclohexanol. As the hydrolysis of esters is a common reaction it was not considered necessary to identify the hydrolysis products".

You also claim that: *"With a half-life time of < 16 days (9 days for pH 7) the criteria for rapid degradation according to the CLP/GHS criteria are fulfilled as the degradation products salicylic acid (2-hydroxylbenzoic acid) and 3,3,5-trimethylcyclohexanol are not classified as hazardous to the aquatic environment."* And: *"Even though the substance is not considered as dangerous, an exposure assessment for the environment (surface water, sediment, soil) was carried out on the basis of the inherent biodegradability and hydrolysis of the test substance. As the environmental risk assessment leads to the conclusion "no risk" (RCR <1) for surface water, sediment and soil, there is no need for further testing of the biodegradability (see R7b, R.7.9.6.2)".*

According to Annex IX, Section 9.2.3., column 2 of the REACH Regulation, identification of degradation products is not needed if the substance is readily biodegradable. ECHA notes that based on the OECD TG 301F test available in the dossier, the registered substance is not readily biodegradable in (degradation 21% in 28 days).

Furthermore, ECHA notes that you have not provided sufficient justification in your chemical safety assessment (CSA) or in the technical dossier for why there is no need to provide information on the degradation products.
Pursuant to Annex XIII of the REACH Regulation "*the identification* [of PBT and vPvB substances] *shall also take account of the PBT/vPvB-properties of relevant constituents of a substance and relevant transformation and/or degradation products*". ECHA Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), Chapter R.11.4.1. further specifies that "*constituents, impurities and additives are relevant for the PBT/vPvB assessment when they are present in concentration of ≥ 0.1% (w/w). This limit of 0.1% (w/w) is set based on a well-established practice rooted in a principle recognised in European Union legislation*. [...] *Similar arguments apply to relevant transformation/degradation products. The PBT/vPvB assessment should normally be carried out for each relevant transformation or degradation product*". ECHA guidance Chapter R.11.4.1.1. also explains that "*concern for P/vP screening cannot be removed by significant and substantial loss of parent substance by hydrolysis alone*" and that "*as abiotic degradation is primary degradation, careful consideration will need to be given to the formation of stable degradation products with PBT/vPvB properties. Hydrolysis products should be identified in accordance with the recommendations contained in the test guidelines (e.g. OECD TG 111).*" ECHA notes that your CSA does not contain any information on whether the degradation products could be PBT/vPvB or not.

Information on degradation products shall also be taken into account for the exposure assessment (Annex I, Section 5.2.4. of the REACH Regulation) and for the hazard assessment (e.g. column 2 of Annex X, Section 9.4 and Annex X, Section 9.5.1 of the REACH Regulation). Finally, information on degradation products is required for the preparation of Section 12 of the safety datasheet (Annex II of the REACH Regulation).

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

ECHA would like to clarify that following the above provisions you must identify transformation products generated not only from potential hydrolysis but also from biodegradation. Aerobic mineralisation in surface water – simulation biodegradation (test method EU C.25. / OECD TG 309) is an appropriate test to obtain information on the primary degradation (both biotic and abiotic) and the formation of major transformation products for substances that are not highly insoluble in water. Based on the information provided in your registration dossier, ECHA notes that the water solubility of the substance is 0.4 mg/L, therefore the registered substance cannot be regarded as highly insoluble in water. The analytical methods to be applied will have to be substance-specific in order to identify the transformation products. When analytically possible, the identification, stability, behaviour and molar quantity of those transformation products relative to the parent compound should be evaluated. In addition, degradation half-life, log Kow and potential toxicity of the transformation products may be investigated. As specified in the OECD 309 test guideline, higher concentrations of the test substance (e.g., >100 µg/L) could be used for the identification and quantification of major transformation products to overcome potential analytical limitations.

In your comments, following the procedure set out in Article 50(1) of the REACH Regulation, you agree to perform the test but you indicate your wish to perform a QSAR before testing to assess which degradation pathways may be more relevant for the registered substance.

ECHA would also like to further clarify that the main purpose of this request is to identify such stable degradation products that fulfil the P criterion.

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:

Identification of the degradation products (Annex IX, Section 9.2.3.) by using an appropriate and suitable test method, as explained above in this section.

Deadline to submit the requested information

In the draft decision communicated to you the time indicated to provide the requested information was 42 months from the date of adoption of the decision. In your comments on the draft decision, you requested an additional 12 months to develop a step-wise approach to improve your read-across strategy. However, such suspension of the compliance check is not foreseen in the REACH Regulation and registrants should submit compliant information already when they register.

In your comments to the Member States' proposals for amendment (PfAs) you requested an extension of the deadline from 42 months to 54 months to require more time: for the read-across approach; to undertake some additional experimental data; to consider currently running studies with analogous substances; and to include a deadline of at least 18 months for the 90-day toxicity study based on a current lack of capacity at [redacted] due to the REACH 2018 registration deadline.

ECHA requested you to submit documentary evidence from the selected test laboratory(ies) indicating the scheduling timelines for the study(ies) in question of the laboratory facility(ies). ECHA notes that you did not provide documentary evidence and failed to justify why a deadline of 54 months is required. Therefore, ECHA has not modified the deadline of the decision. Additionally, ECHA notes that the timeline has been set to allow for sequential testing.

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 2 November 2016.

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

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

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

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-57 meeting and ECHA took the decision according to Article 51(6) 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.