ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 13 March 2018

Addressee: [redacted]

Decision number: CCH-D-2114387555-36-01/F
Substance name: 2-ethylhexyl salicylate
EC number: 204-263-4
CAS number: 118-60-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 20.05.2016
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. **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;**

2. **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).**

3. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20./OECD TG 211) with the registered substance;**

4. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish sexual developmental test (OECD TG 234)) 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 **20 September 2021**. 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 Claudio Carlon, Head of Unit, Evaluation E2

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

Appendix 1: Reasons

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally similar substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met". According to Annex XI, section 1.5. there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for the reference substance(s), and the data should be adequate for the purpose of classification and labelling and/or risk assessment.

0.1 Description of the grouping and read-across approach proposed in your dossier

You have sought to adapt the information requirement for pre-natal developmental toxicity study (Annex IX, Section 8.7.2) and extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.) by applying a read-across approach according to Annex XI, Section 1.5.

You have proposed read-across between methyl salicylate, (CAS RN 119-36-8) as the source substance and the substance subject to this decision, 2-ethylhexyl salicylate (EC 204-263-4) (CAS RN 118-60-5) as the target substance.

Your dossier contains a read-across justification as a separate attachment in Section 13 of the IUCLID dossier. This justification also cross-references a document attached in Section 7.1 of the IUCLID dossier (toxicokinetics, metabolism, and distribution). This second document analyses the toxicokinetics of the source and target substances. You use the following arguments to support your proposed read-across:

- You expect that the source and target substances, as well as other salicylate esters, all being esters of salicylic acid, will hydrolyse rapidly to form salicylic acid and the corresponding alcohol. In the case of the source substance the corresponding alcohol is methanol, whereas in the case of the target substance it is 2-ethylhexanol.
- You consider that the rapid metabolism justifies the use of information from the source substance, as they are expected to lead to the same metabolite (salicylic acid).
- You have provided a number of toxicity studies on the source substance, including sub-chronic and chronic toxicity studies, as well as a 3-generation reproductive toxicity study. You consider that the available toxicity studies on the source and target substance show consistent results, justifying the read-across
- ECHA further notes that your justification mentions the existence of data on developmental toxicity of acetylsalicylic acid, salicylic and other salicylates. However you have not provided the studies on these substances in the dossier for the endpoints in question.

Based on this, you consider that the source and registered substances have similar properties for the above-mentioned information requirements.

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

ECHA considers that your read-across hypothesis is based on hydrolysis of the target and source substances to a common product, which mediates the properties of the substance, as well as the similarity in toxicity of the source and target substances, as summarised above. However, ECHA considers that there is insufficient information to support your read-across hypothesis in the registration dossier for the following reasons:

1) To support this hypothesis you have included an analysis of the toxicokinetics of the source and target substances. While the structure of these substances suggests that hydrolysis can be expected, ECHA considers that it is necessary to provide experimental evidence demonstrating that the hydrolysis of the target (registered) substance actually occurs, and to give information on the rate of the hydrolysis. While some of the references do indicate that the source substance is hydrolysed, the analysis does not provide any experimental evidence of the hydrolysis of the target substance. Therefore, it is not possible to conclude that any hydrolysis would occur and that it would be rapid. Finally it is not possible to exclude effects from the parent substance prior to the hydrolysis.

2) Even if the hydrolysis occurs rapidly, it is necessary to provide information on the toxicity of the hydrolysis products. The dossier contains information from the source substance, methyl salicylate, for the endpoints above. However, this information is not sufficient to address the toxicity of all hydrolysis products of the target substance. Even assuming rapid hydrolysis, the studies on the source substance would provide information only on the toxicity of the common metabolite salicylic acid. However, these studies provide no information on the toxicity of 2-ethylhexanol, the second metabolite.

In fact, the only analysis on the potential toxicity of this particular metabolite can be found in the toxicokinetic analysis ("[redacted]", attached to section 7.1 of your registration dossier), which states the following (p 6-7): "*Only very high dose levels of 2-ethylhexanol (≥500 mg/kg body weight) are considered to lead to a saturation of metabolism, exceeding this detoxifying pathway and resulting in increased levels of 2-ethylhexanoic acid (Hellwig et al. 1997; Deisinger et al. 1994). Such high levels of bioavailable 2-ethylhexanol cannot be reached from the uses of ethylhexyl salicylate and therefore the formation of relevant levels of 2-ethylhexanoic acid can be excluded.*"

Although you did not provide the two studies (Hellwig *et al.* and Deisinger *et al.*), they are nevertheless publically available, and provide relevant information. ECHA considers that the study by Hellwig *et al.* demonstrates that 2-ethylhexanol can cause teratogenicity at sufficiently high dose levels. In addition, the Deisinger paper shows evidence of metabolic saturation at the high dose of 500 mg/kg.

Assuming the hydrolysis occurs rapidly, ECHA considers that you have not completely addressed the potential toxicity of the metabolites. The available publication (Hellwig *et al.*) indicates that the 2-ethylhexanol may cause some concern for developmental toxicity, and that the toxicity of the source and target substances may be different at least with respect to this endpoint. Second, complete and rapid hydrolysis of the 1 mmol of the target substance would yield 1 mmol of 2-ethylhexanol and 1 mmol of salicylic acid. Assuming the limit dose of 1000 mg/kg/bw is used, and 100% oral absorption occurs as is indicated in your assessment of the toxicokinetics, this would result in the generation of approximately 519 mg/kg/bw of 2-ethylhexanol and 550 mg/kg/bw of salicylic acid. Based on the available information, such doses may result in the saturation of the detoxifying pathway for 2-ethylhexanol. This is contradicting your hypothesis, the complete hydrolysis of the registered substance may cause sufficiently high doses of 2-ethylhexanol to cause metabolic saturation and possible developmental toxicity.

In order to justify your read-across, you would at a minimum need to 1) demonstrate that complete and rapid hydrolysis does occur for both the source and target substances, and 2) take into account the potential toxicity of all metabolites. If the hydrolysis is not rapid, and animals are exposed to the parent substance prior to its hydrolysis, you should also address the potential toxicity of the parent substance, as well as any potential interaction caused by the presence of the parent and metabolites.

ECHA notes that although your read-across justification does not take into account the potential toxicity of all metabolites of the substance, such information on the toxicity of the metabolites salicylic acid as well as 2-ethylhexanol is available, though it has not been included in your dossier. The information available on 2-ethylhexanol indicates that it can cause teratogenicity at higher doses. Information on sub-chronic toxicity of 2-ethylhexanol is available (e.g. in REACH registration database), but not included in your dossier. ECHA notes that you may be able to use this information (subject to any copyright that may be applicable) to complete your read-across hypothesis, if you can demonstrate rapid hydrolysis.

For the reasons presented above and on the basis of the information provided in your registration dossier, your hypothesis is not a reliable basis whereby the properties of the registered substance may be predicted from data for the source substance.

In your comments, 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 2-ethylhexyl salicylate than does methyl salicylate. As such the registrants 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].

0.3 Conclusion on the grouping and read-across approach

For the reasons 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

[2] https://echa.europa.eu/support/grouping-of-substances-and-read-across

rules of adaptation as set out in Annex XI, 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.

Consideration on uses of the substance in relation to the tests requested in the decision

In your comments to the proposal for amendment for an extended one-generation reproductive toxicity study 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 imply worker exposure since thereis 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. 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 not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

You have sought to adapt this information requirement according to Annex XI, Section 1.2. You provided the following justification for the adaptation: "*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 421 screening study with 2-ethylhexyl salicylate, 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.*"

3 Please see https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2 for of the following reasons:

- In the technical dossier you have provided a study record for a "reproduction/ developmental toxicity screening test" (test method: OECD TG 421). However, this study does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations. Therefore, your adaptation of the information requirement is rejected.

- In addition, although ECHA notes that your adaptation mentions a number of additional developmental toxicity studies available for several substances (acetylsalicylic acid, salicylic acid and other salicylates) and performed in several animals species and in humans, your technical dossier does not contain any study summaries of those studies.

- Finally as explained above in Appendix 1, section 0 of this decision, your read-across adaptation on the basis of Annex XI, Section 1.5 , for this information requirement is rejected.

Consequently, ECHA considers that there is insufficient weight of evidence from the available information to conclude that the substance does not cause developmental toxicity in a pre-natal developmental toxicity study, and your adaptation based on a weight of evidence approach is rejected.

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, 2-ethylhexyl salicylate 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 reponsibility to justify your choice based on available information.

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, you consider that dermal exposure is more relevant for workers, and that you should be able to choose the route of administration on a case by case basis. Based on the information provided in the technical dossier, ECHA considers that there is no

information on the registered substance itself, demonstrating effects following dermal route exposure. The information you provided relates to the analogue, methyl salicylate about which ECHA has not accepted your read-across approach and which, in any case, does not demonstrate higher or higher/ different systemic toxicity than the one observed in oral studies. Hence despite the possible exposure to workers, ECHA still considers that the oral route is the most appropriate route of administration.

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.

2. 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 concerns in relation to reproductive toxicity are observed in the reproduction/developmental toxicity screening test conducted with the registered substance according to OECD TG 421. More specifically, gestation length was prolonged in the mid- and high dose groups (80 and 250 mg/kg bw/day, respectively). This finding was not statistically significant but "*it was dose dependent and the values were beyond the biological background*" and thus considered to be test item-related. In addition, higher post-implantation loss resulted in lower litter size (80 and 250 mg/kg bw/day), mean number of living pups was reduced (statistically significant at 250 mg/kg bw/day), and birth index, i.e. number of pups born alive as a percentage of implantations, was reduced (statistically significant at 80 and 250 mg/kg bw/day). There was also a statistically significant reduction in body weights of pups in the 250 mg/kg bw/day group.

Based on the findings, you conclude that "*the adverse effects on reduced viability of offspring represent developmental toxicity rather than reduction of the fertility of either male or female animals. It can therefore be concluded that 2-ethylhexyl salicylate is not likely to have any significant adverse effect on fertility.*" By 'reduced viability', you refer to

"*decreases in litter size, number of live-born progeny, number of survivors to PND4 and PND5 and number of survivors to weaning*".

ECHA notes that in addition to developmental toxicity, a reduction of fertility may also have an impact in the post-implantation loss, decreased number of living pups, and reduced birth index. ECHA also notes that gestation length and post-natal development of offspring are not examined in a pre-natal developmental toxicity study, and therefore it is not possible to conclude that these effects are due to developmental toxicity, rather than due to reproductive toxicity.

Pursuant to Annex IX, Section 8.7.3., column 1, an extended one-generation reproductive toxicity study is thus an information requirement for registrations of the registered substance.

In your comments, you claim that the request is not triggered at this tonnage band, since "*based on the information in the current registration dossier, there is not sufficient evidence to trigger the study at Annex IX*", specifying additionally that the test-item related effects on fertility are not justified; you also consider that "*the [OECD TG 421] study may have been biased by maternal toxicity effects. […]; maternal toxicity in rats leading to secondary reproductive and developmental findings is not excluded in this study.*"

ECHA considers that the EOGRTs 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. The absence of effects seen in the 90-day study cannot remove the triggers seen in pregnant animals.

b) Information provided

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

You have provided the following justification for the adaptation: "*Weight of Evidence was applied based on the an oral OECD 421 reproduction toxicity screening study with 2-ethylhexyl salicylate and a 3-generation oral reproduction toxicity study with the read-across substance methyl salicylate. The two studies gave consistent results with NOAEL of 386 mg/kg bw/day in the 3-generation study and no evidence of fertility effects at 250 mg/kg bw/day in the OECD 421 study, respectively.*

Additionally, for 2-ethylhexyl salicylate, an uterotrophic assay in rats revealed no estrogenic activity and no specific binding was observed in vitro to the androgen and estrogen receptors. Data with inhalative or dermal exposure are not available. The assessment of the potential of ethylhexyl salicylate to impair fertility has been completed with read-across data from studies on Methyl salicylate (MeS) and Acetylsalicylic acid (ASA). A read-across justification is provided as attachment to IUCLID section 13 respectively as appendix to the CSR."

To support your weight of evidence adaptation you have provided the following sources of information:

1. Reproduction/developmental toxicity screening test in rats, oral route, (OECD TG 421; GLP), with the registered substance
2. Three-generation reproductive toxicity study in rats, oral route (OECD TG 416; "*several deficiencies in relation to OECD Guideline 416 in terms of parameters studied*", non-GLP)

performed with the proposed analogue substance methyl salicylate (CAS RN 119-36-8) (Collins *et al.*, 1971)
3. "OECD validation work on *in-vivo* uterotrophic screening assay" (GLP) with the registered substance
4. Non-guideline *in vitro* androgen receptor binding study with the registered substance
5. Non-guideline *in vitro* estrogen receptor binding study with the registered substance

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 with respect to an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that this study provides relevant information on two aspects, namely on sexual function and fertility in P1 and F1 generations (further referred to as 'sexual function and fertility') and on development and toxicity of the offspring from birth until adulthood due to prenatal, postnatal and adult exposure in the F1 generation (further referred to as 'effects on offspring').

Relevant elements for 'sexual function and fertility' are in particular functional fertility (oestrous cycle, sperm parameters, mating behaviour, conception, pregnancy, parturition, and lactation) in the P0 parental generations after sufficient pre-mating exposure and histopathological examinations of reproductive organs in both P and F1 generations. Relevant elements for 'effects on offspring' are in particular peri- and post-natal investigations of the F1 generation up to adulthood including investigations to detect endocrine disruptive properties, investigations on developmental neurotoxicity, investigations on developmental immunotoxicity, and postnatal development of F2 generation. Also the sensitivity and depth of investigations to detect effects on 'sexual function and fertility' and 'effects on offspring' needs to be considered.
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.

Evaluation of the provided information

You have provided a three-generation reproductive toxicity study performed with the proposed analogue substance methyl salicylate (CAS RN 119-36-8). However, as explained above in section 0 of the decision '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, 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" or "effects on offspring". Thus, this piece of information is only of low value in the weighing the evidence.

You also provided an *in vivo* uterotrophic screening assay, *in vitro* androgen receptor binding study and *in vitro* oestrogen receptor binding study which do not directly provide information on 'sexual function and fertility' nor 'effects on offspring'.

For the acetylsalicylic acid mentioned in the weight of evidence justification, no evidence was provided to support the justification, thus this does not support the weight of evidence justification.

With respect to 'sexual function and fertility' of P and F1 generations, you have provided an OECD TG 421 screening study with the registered substance that provides information on histopathological changes in major reproductive organs and on reproductive performance of the P generation. The study provided does not contain any information on oestrus cycle or sperm parameters and no information on 'sexual function and fertility' of F1 generation. ECHA further notes that the statistical power of this study is low and that 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'.

With respect to the 'effects on offspring', you have provided only very limited information for the registered substance. More specifically, the OECD TG 421 screening study investigates offspring toxicity only until postnatal day 4. However, peri- and post-natal investigations of the F1 generation up to adulthood, including information on sexual maturation, investigations on developmental neurotoxicity and investigations on developmental immunotoxicity are not addressed at all.

Thus information from OECD TG 421 is valid but limited for both 'sexual function and fertility' and 'effects on offspring' as indicated above.
Taken together, the results from the OECD TG 421 are the only useful *in vivo* source of information on 'sexual function and fertility' and 'effects on offspring' but provide only limited evidence due to limited investigations and statistical power (sensitivity and depth of investigations to detect effects). Some support on low hormonal agonist activity is provided, but together with the results from the OECD TG 421 they do not adequately address the reproductive toxicity to the extent required at this tonnage level so that a conclusion can be drawn on the hazardous properties of the registered substance.

Conclusion

Hence, the sources of information you provided do not, individually or combined, allow to conclude on the dangerous (hazardous) property of the registered substance with respect to the information requirement for Annex IX, 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.

In your comments, you claim that the effects seen in the OECD TG 421 study were slight, and only indications, and that these should over-ride the indications from the analogue substances. Nonetheless, ECHA considers that it is not possible to draw conclusions on the results of the OECD TG 421 study, because of the very limited investigations that are performed on the dams. Therefore, ECHA concludes that the sub-chronic (90-day) or the OECD TG 421 studies on the registered substance do not provide information which contradicts information from the studies on the analogue substance. Therefore, ECHA considers that the weight of evidence for triggering these studies remains valid.

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 K_{ow} >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 triggered 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 request for extension of Cohort 1B 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 Annex IX, Section 8.7.3. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted, as they provide complementary information.

ECHA notes the existence of information derived from available *in vivo* studies, on the registered substance itself and on a substance structurally analogous to the registered substance, showing evidence of neurotoxicity.

More specifically, the available repeated dose 90-day oral toxicity study (OECD TG 408; IRDC, 1994) conducted with the registered substance showed a slight increase in absolute brain weight, and a slight decrease in absolute and relative thyroid/parathyroid weights in males from the treated groups (50 to 250 mg/kg bw/day), while no significanct variation was observed in body weights of the treated groups.

In addition, in the combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test (OECD TG 422) conducted with a structural analogue (3,3,5-Trimethylcyclohexyl salicylate, EC number 204-260-8), the thyroid glands showed "*a greater incidence and/or severity of diffuse hypertrophy of the follicular epithelium in females given 300 mg/kg bw/day and in both sexes given 750 mg/kg bw/day*". ECHA notes that the lack of these findings in the repeated dose study for the registered substance could be due to lower dosing of the test substance.

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 *in vivo* studies on the registered substance itself and a substance structurally analogous to the registered substance.

In your comments, you argue that the neurotoxicity is not triggered, because (a) the effects seen are not consistent or of toxicological significance or related to test item; (b) the effects seen with the analogue substance, homosalate, on thyroid were limited to females at doses up to 300 mg/kg/day; (c) 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 (a) although the information from study 1 above (90-day) does not fulfil the Annex IX, section 8.6.2 requirements, the information it provided (suggesting "effects or mechanisms/ modes of action") can be used in the assessment of triggers for the EOGRT study. The effects seen in one sex only, or not dose-related, or lacking histopathological correlates, are a sufficient basis to raise a concern for triggering. There was a slight increase in the absolute brain weights in males and absolute and relative decrease of thyroid and parathyroid weights in males from the treated groups (50 to 250 mg/kg bw/day).; (b) In addition to the effects at the top 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; (c) 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 Annex IX, Section 8.7.3.

ECHA notes that existing information on a substance structurally analogous to the registered substance (3,3,5-Trimethylcyclohexyl salicylate; EC number 204-260-8) derived from the available *in vivo* study (OECD TG 422) shows evidence of immunotoxicity. More specifically, there was a lower globulin level in males at the high dose (750 mg/kg bw/day) and a reduction in thymus weight (absolute, relative to the brain and/or body weight) in both sexes at the high dose (statistically significant for males). In addition, histopathological examination showed a greater incidence and severity of decreased cortical lymphocytes of thymus in males at the mid- and high dose (300 and 750 mg/kg bw/day, respectively), and in females at the high dose level. ECHA notes that the lack of these findings in the repeated dose study for the registered substance could be due to lower dosing of the test substance.

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 on substance structurally analogous to the registered substance.

In your comments, you argue that the immunotoxicity 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, you describe reasons why the test could not correctly interpreted, (thyroid stimulation and prostaglandin synthesis inhibition) which may render the EOGRTS test technically impossible. However ECHA does not consider this to be a valid reasoning as to why the test is technically impossible, as foreseen in the Article XI, section 2. Furthermore the data the statement relies on is not provided in the dossier and ECAH can therefore not assess it.

d) 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).

Note for your consideration

As indicated on page 18 of the Appendix of this decision, the highest dose level of the extended one-generation reproductive toxicity study shall be set with the aim to induce some toxicity to allow comparison of 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.

ECHA notes that in a 14-day dose range finding study on the registered substance via the oral route using gavage dosing,mortality was observed at 1000 mg/kg bw/day, as well as reduction in food consumption and body weight gain at 300 mg/kg bw/day. On the other hand, ECHA notes that in the dietary 90-day repeated dose toxicity study on the registered substance, conducted up to doses of 250 mg/kg bw/day, no similar adverse effects were observedDietary administration and gavage administration can have markedly different effects at the same daily dose.

Taken together, this information indicates that a study involving repeated dose exposure can be performed at higher doses via dietary administration compared to gavage administration, and that it may be possible to achieve a dose between 250 mg/kg bw/day and the limit dose of 1000 mg/kg bw/day using dietary administration.

ECHA further notes that in your comments to the draft decision, you indicated that the dietary route would be preferrable for a variety of reasons, including animal welfare (as acids resulting from the hydrolysis are expected to be irritating to the stomach via gavage dosing), and practical reasons (difficulty in gavage dosing of small animals). ECHA agrees with your comments in this case, and considers that the study should be performed via the oral route, using dietary exposure.

Finally, according to the ECHA guidance on information requirements and chemicals safety assessment (Chapter R.7a Version 6.0, July 2017), the extended one-generation reproductive toxicity study may provide useful information on repeated dose toxicity after exposure over a prolonged period of time (about 90 days for parental animals), even though it is not aiming at investigating repeated dose toxicity *per se*. Given the lack of information on the repeated dose toxicity of the substance at doses higher than 250 mg/kg bw/day via dietary exposure, you should use the information generated through the requests in this decision to (re)evaluate the general toxicity of the substance following repeated exposure, including the need for performing any additional investigations.

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

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.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. 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 1.1.2, by selecting under 'data waiving' the option "study scientifically not necessary/other information available". You also provided the following justification for the adaptation:

"As the substance has a very low water solubility and a high log Kow the substance is expected to bind primarily to sludge and sediments. Therein it is expected to be rapidly degraded as it was proved to be readily biodegradable. Furthermore, no aquatic toxicity was observed in acute tests with algae, daphnia and fish. Thus, there is no need for further investigation of long-term toxicity to invertebrates".

ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.1.2., where data from experiments not carried out according to GLP or according to test methods referred to in Article 13(3) can be used. These would need to be considered equivalent to test methods referred in Article 13(3). ECHA notes that the information you have provided in your justification for the adaptation is not considered equivalent to test methods referred in Article 13(3). Therefore, your adaptation according to Annex XI, Section 1.1.2. cannot be accepted.

Notwithstanding the above, ECHA understands, that you suggest that the test can be waived as there is no exposure to the substance in the water compartment and that there is no concern observed in acute tests. ECHA notes that you have not performed an exposure assessment and that consumer uses are foreseen under the uses of the registered substance; therefore, exposure to the aquatic compartment cannot be excluded. Secondly, the substance has a low water solubility and the results obtained in acute toxicity test are questionable to detect any toxic effect. According to Annex VII, Section 9.1.1, column 2, the registrant shall consider long-term testing if the substance is poorly water soluble.

Therefore, ECHA considers that there is a need to investigate the effects on aquatic organisms further, and your adaptation of the information requirement cannot be accepted.

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

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 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.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on long-term toxicity to fish 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 1.1.2, by selecting under 'data waiving' the option "study scientifically not necessary/other information available". You also provided the following justification for the adaptation:

"As the substance has a very low water solubility and a high log Kow the substance is expected to bind primarily to sludge and sediments. Therein it is expected to be rapidly degraded as it was proved to be readily biodegradable. Furthermore, no aquatic toxicity was observed in acute tests with algae, daphnia and fish. Thus, there is no need for further investigation of long-term toxicity to fish".

ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.1.2., where data from experiments not carried out according to GLP or according to test methods referred to in Article 13(3) can be used. These would need to be considered equivalent to test methods referred in Article 13(3). ECHA notes that the information you have provided in your justification for the adaptation is not considered equivalent to test methods reffered in Article 13(3). Therefore, your adaptation according to Annex XI, Section 1.1.2. cannot be accepted.

Notwithstanding the above, ECHA understands that you suggest that the test can be waived as there is no exposure to the substance in the water compartment and that there is no concern observed in acute tests. ECHA notes that you have not performed an exposure assessment and that consumer uses are foreseen under the uses of the registered substance; therefore, exposure to the aquatic compartment cannot be excluded. Secondly, the substance has a low water solubility and the results obtained in acute toxicity test are questionable to detect any toxic effect. According to Annex VIII, Section 9.1.3, column 2, the registrant shall consider long-term testing if the substance is poorly water soluble. ECHA notes that poorly water soluble and/or hydrophobic substances require longer time to be significantly taken up by the test organisms and so steady state conditions are likely not to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for hydrophobic/poorly water soluble substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. Still, long-term toxicity cannot be excluded and should be investigated. Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble.

ECHA further notes that due to lack of effects in short-term studies it is not possible to determine the sensitivity of species. Therefore, the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), is not

applicable in this case and the long-term studies on both invertebrates and fish are requested to be conducted.

Therefore, long-term aquatic toxicity studies are indicated and your adaptation of the information requirement cannot be accepted.
Consequently, there is an information gap and it is necessary to provide information for this endpoint.

You provided comments on this request asking to modify the decision to a conditional long-term toxicity testing depending on the outcome of the Daphnia chronic toxicity test results. For the purpose of the Chemical Safety Assessment (CSA), the information under REACH should at least cover species from three trophic levels: algae/aquatic plants, invertebrates (Daphnia preferred), and fish (as mentioned in Guidance Chapter R7b, version 2017). As explained above, there is no adequate fish toxicity data, which is necessary for CSA purposes.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) can be performed to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth (see ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b, Figure R.7.8-4).

ECHA notes that Column 2 of Annex IX section 9.1. specifies that the choice of an appropriate test to be used to fulfill the information requirements for long-term aquatic toxicity depends on the results of the chemical safety assessment (CSA), while Annex I indicates that the CSA should cover all hazards.

On the basis of the information reported in the toxicological endpoints in the technical dossier, your substance may have endocrine disruptor effects or may be part of a category where endocrine disruptor effects such as anti-estrogenic and anti-androgenic or steroidogenesis effects are observed.

Publications of Morohoshi *et al.*, 2005[4] and Miller *et al.*, 2001[5], indicate that *in vitro* studies on the registered substance show weak anti-estrogenic effects. Additionally, the publication of Kunz and Fent 2006[6], indicate that the substance exhibits weak anti-estrogenic and androgenic effects, as well as anti-androgenic effects in *in vitro* assay.

Furthermore, in an *in vivo* test, the screening study (OECD 421) for reproductive/developmental toxicity conducted on the registered substance, increased gestational length, indicating that the registered substance may cause endocrine disrupting

[4] K. Morohoshi, H. Yamamoto, R. Kamata, F. Shiraishi, T. Koda, M. Morita. Estrogenic activity of 37 components of commercial scunscreen lotions evaluated by in vitro assays. Toxicology in Vitro 19 (2005) 457-469.

[5] D. Miller, B.B. Wheals, N. Beresford, J.P. Sumpter. Estrogenic activity of phenolic additives determined by an in vitro test yeast bioassay. Environmental Helath Perspectives 109 (2001) 133-138.

[6] P. Kunz and K. Fent, Multiple Hormonal activities of UV filters and comparison of *in vivo* and *in vitro* estrogenic activity of ethyl-4-aminobenzoate in fish. Aq. To. 79 (2006) 305-324.

effects. In addition, the effects observed in the *in vitro* androgen binding assay submitted in the technical dossier, indicate further concern on the potential endocrine disrupting effects of the registered substance.

Based on the afore mentioned arguments, ECHA considers that in this specific case, it is more appropriate to conduct an *in vivo* assay that also provides data on adverse effects on endocrine relevant effects.

ECHA notes that the Fish Sexual Development Test (FSDT) (OECD TG 234) is an appropriate test to cover the information requirement of Annex IX, Section 9.1.6. The FSDT study provides further information on ED potential in terms of androgenic, anti-estrogenic or anti-androgenic effects. ECHA hence considers it appropriate to assess the endocrine disrupting properties of the registered substance. According to OECD test guideline 234, this test can be considered "*an enhancement of TG 210: Fish, Early Life Stage Toxicity Test, where the exposure is continued until the fish are sexually differentiated,* [...]*, and endocrine-sensitive endpoints are added*". As such the FSDT covers both the standard information normally requested and the mode of action(s) that has been identified, as mentioned above, *i.e* ED properties.

ECHA notes that in the initial draft decision, you were given the choice to fulfil this standard information requirement by performing either: the fish early-life stage (FELS) toxicity test (test method OECD TG 210) or the Fish Sexual Development Test (test method OECD TG 234). A Member State Competent Authority submitted a Proposal for Amendment (PfA) to request the Fish Sexual Development Test (FSDT) (OECD TG 234) only.

ECHA considers that in this specific case, the Fish Sexual Development Test (OECD TG 234) is the most appropriate long-term fish toxicity test to generate information necessary for hazard and risk assessment.

In your comments submitted in response to Member State Competent Authority (MSCA) Proposals for Amendment (PfAs), you reiterated that you considered long-term fish testing only necessary if based on the long-term daphnia toxicity test and the CSA, a need for further studies is shown. However, you still considered that if a study was needed it should be the OECD TG 210 as you do not agree with the request for the OECD TG 234 due to the the following:

1) disagree that there is an ED concern, and
2) note that there is no guidance on ED criteria and test systems and
3) such request goes beyond the scope of a Compliance Check (CCH),

1) As mentioned above, ECHA considers the information available suggests the substance may have potential ED properties.

2) ECHA notes that while ED specific guidance is under preparation, the OECD GD 150, provide guidance for testing and for clarifying ED concern.

As discussed above, the OECD TG 234 falls under the standard information requirement of long-term toxicity testing on fish (Annex IX, section 9.1.6.1) since it is an appropriate test to address the identified issue and data-gap. ECHA also notes that the draft of OECD TG 234 is described in ECHA Guidance on information requirements and chemical safety assessment (Chapter R7b), however, as the section on Fish toxicity section has not been updated since 2008, as can be seen on the document history (p4 and 5 of Guidance Chapter R7b, version 4 June 2017), full description of the guideline is not included. However, as stated in the

guidance itself it "*aims to assist users in complying with their obligations under the REACH Regulation. However, users are reminded that the text of the REACH Regulation is the only authentic legal reference and that the information in this document does not constitute legal advice.*"

ECHA also notes that, in the ECHA Guidance on information requirements and chemical safety assessment (Chapter R7b, version 4.0, June 2017), it is given that "*other OECD TGs should be considered for endocrine disrupting chemicals or when other effects not covered by early fish development are expected to be of particular relevance*". Therefore, according to ECHA Guidance on information requirements and chemical safety assessment (Chapter R7b, version 4.0, June 2017), other OECD TGs than the ones addressed in the Guidance alone should be considered for endocrine disrupting chemicals.

3) ECHA considers that the request for the FSDT does not go beyond the scope of CCH as it covers the standard information requirement of long-term toxicity testing on fish (Annex IX, section 9.1.6.1) and it may reduce animal testing while it covers the information for hazard and risk assessment, including the potential effects caused by endocrine disrupting properties of the substance.

ECHA acknowledges that conducting the OECD TG 234 study is more expensive and uses more animals than the other long-term fish studies, given as alternatives for long-term fish testing in ECHA Guidance R7b. However, ECHA considers that conducting the OECD TG 234 at this stage, instead of OECD TG 210 could prevent additionnal animal testing in future. ECHA notes that the substance is on draft CoRAP (https://echa.europa.eu/documents/10162/13628/corap_list_2018-2020_en.pdf/3be44b84-5d72-01fe-f8d7-3a5a9c27951e) with "potential ED" identified as the initial ground for concern.

In conclusion, due to the reasons given above, ECHA considers that the Fish Sexual Development Test (FSDT) (OECD TG 234) is the most appropriate test to cover the standard information requirement of long-term toxicity testing on fish of Annex IX, 9.1.6.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:
Fish Sexual Development Test (test method: OECD TG 234)

Notes for your consideration

Due to the low solubility of the substance in water, you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

In order to proceed with a test design that will allow both to provide information on Androgenic, Estrogenic or anti- and Steroidogenesis effects and to be used for risk assessment, you are advised to choose as indicated in the OECD TG 234 protocol, five concentrations (paragraph 30.).

Deadline to submit the requested information

In the draft decision communicated to you the time indicated to provide the requested information was 30 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. ECHA notes that the draft decision sent to you for commenting set a deadline of 30 months for performing the requested studies. Normally, the deadline for the combination of studies requested in this decision is 42 months. ECHA has therefore amended the deadline from 30 months to 42 months.

In your comments to the Member States' proposals for amendment (PfAs) you requested a deadline extension 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 CROs 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.

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 8 December 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 amended the deadline.

ECHA received proposal(s) for amendment and did not modify the draft decision.

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

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed 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.