EUROPEAN CHEMICALS AGENCY

Helsinki, 11 September 2014

Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)

DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) of REGULATION (EC) NO 1907/2006

For octocrilene, CAS No 6197-30-4 (EC No 228-250-8)

Addressees: Registrant(s)[1] of octocrilene

This decision is addressed to all Registrant(s) of the above substance Registrant(s) with active registrations on the date on which the draft for the decision was first sent, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an annex to this decision.

Registrant(s) meeting the following criteria are *not* addressees of this decision: i) Registrant(s) who registered the above substance exclusively as an on-site isolated intermediate under strictly controlled conditions and ii) Registrant(s) who have ceased manufacture/import of the above substance in accordance with Article 50(3)of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by Anses[2] on behalf of the French Competent Authority (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of REACH Regulation.

This decision does not take into account any updates of the registrations of the Registrant(s) after 18 December 2013, the date upon which the draft decision was circulated to the other Competent Authorities of the Member States and ECHA pursuant to Article 52(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossiers of the Registrant(s) at a later stage, nor does it prevent the issuance of further substance evaluation decisions, be it in the present substance evaluation or future substance evaluations.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of France initiated substance evaluation for octocrilene, CAS No 6197-30-4 (EC No 228-250-8). On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to environment (suspected PBT/vPvB) and to exposure (wide dispersive use, high aggregated tonnage), octocrilene was included in the Community rolling action plan (CoRAP) for substance evaluation pursuant to Article 44(2) of the REACH Regulation to be evaluated in 2012. The CoRAP was published on the ECHA website on 29 February 2012.

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.
[2] The French Agency for Food, Environmental and Occupational Health & Safety (REACH Mandated National Institute on behalf of the French Competent Authority)

The Competent Authority of France was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA (eMSCA) noted additional concerns regarding human health (potential thyroid toxicity, suspected toxicity to reproduction) and the environment (suspected endocrine activity, exposure of the aquatic compartment).

Therefore the eMSCA considered that further information was required to clarify the abovementioned concerns. Consequently, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 28 February 2013.

On 4 April 2013 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

The Registrant(s) provided comments to ECHA on the draft decision by the deadline of 6 May 2013.

On 10 May 2013 ECHA notified the eMSCA of the comments received. The eMSCA considered the comments received from the Registrant(s). The information contained therein was reflected in the Statement of Reasons (section III) and an amendment to the Information Required (Section II) was made.

In accordance with Article 52(1) of the REACH Regulation, on 18 December 2013 the eMSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days.

Subsequently, ECHA and five MSCAs submitted proposals for amendment to the draft decision.

On 7 February 2014 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The eMSCA reviewed the proposals for amendment received and amended Sections II and III of the draft decision.

On 17 February 2014 ECHA referred the draft decision to the Member State Committee.

By 10 March 2014, the Registrants' comments were provided on the proposed amendments. The Member State Committee took these comments into account.

After discussion in the Member State Committee meeting on 8-10 April 2014, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 10 April 2014. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test methods/instructions and the registered substance subject to the present decision:

1. *In vivo* mechanistic study in rat (as further specified in Section III);

2. Extended One Generation Reproduction Toxicity Study in rats, oral route, with the DNT cohort and an extended pre-mating period of 10 weeks (test method: OECD 443);

3. Water solubility (test method: EU A.6 with an adequate analytical method able to quantify low levels of octocrilene and a validated limit of quantification (LOQ), as further specified in Section III);

4. Adsorption – Desorption Using a Batch Equilibrium Method (test method: OECD 106);

5. Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (test method: OECD 308) including the identification of the degradation products provided that the condition prescribed in Section III.5. is fulfilled;

6. *Daphnia magna* Reproduction Test (test method: OECD 211);

7. Bioaccumulation: recalculation of the BCF value from data of the already provided bioaccumulation test, or test to be conducted according to OECD guideline 305 in Zebra fish (dietary exposure) (as further specified in Section III);

8. Earthworm Reproduction Test (test method: OECD 222);

9. Androgenised Female Stickleback Screen (AFSS, test method: variant of OECD 230);

10. Information on direct emission scenario to the aquatic environment in the risk assessment;

11. Additional information on the environmental exposure assessment;

12. Estimation of the PEC_{soil} via sludge.

Furthermore, pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit full study reports for the information required under points 1 to 6 of this Section II. Indeed a complete rationale and an access to the whole available information (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation etc.) are needed to fully assess the provided information and to efficiently clarify the concerns.

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by 18 September 2016 an update of the registration dossiers containing the information required by this decision.

At any time, the Registrant(s) shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrant(s).

III. Statement of reasons

Based on the evaluation of all relevant information submitted on octocrilene and other relevant and available information and taking into account the comments of the

Registrant(s), proposals for amendment submitted by Member State Competent Authorities/ECHA and the deliberations of the Member State Committee, ECHA concludes that further information is required in order to enable the eMSCA to complete the evaluation of whether the substance constitutes a risk to human health or the environment.

The Registrant(s) are invited to consider the following for information requests numbers 3 to 9 below. From the data provided in the registration dossiers, octocrilene shows the following properties: very low solubility in water (< 0.1 $mg.L^{-1}$), high lipophilicity (log Kow > 6), low volatilisation from water (Henry law constant: $3.1*10^{-04}$ $Pa.m^3.mol^{-1}$), high potential of sorption into sewage sludge, sediment and soil compartments (log Koc: 5.61), stability in environmental compartments (from biodegradation studies). From the available scientific literature (Kameda *et al.*[3], 2011, Poiger *et al.*[4], 2004, Rodil *et al.*[5], 2009), octocrilene occurs in surface water and sediments. Due to these properties, octocrilene is considered as a "difficult substance" that requires to be tested following the OECD guideline n°23.

1. *In vivo* mechanistic study by oral route in rat in order to demonstrate specific thyroid toxicity mode of action via liver enzyme induction (sub acute repeated toxicity; no OECD guideline available).

Initial requirement

A carcinogenicity study is waived by the Registrant(s) on the following ground: "octocrilene was found to be non-genotoxic in bacterial and mammalian cell mutagenicity tests and no induction of chromosomal aberrations in mammalian cells *in vitro* or in mice *in vivo* was observed. Additionally, there is no evidence from repeated dose studies that the substance is able to induce hyperplasia and/or pre-neoplastic lesions. As a consequence, there is no indication for further testing octocrilene in a carcinogenicity study". Nevertheless, in the 90 days study, a treatment related slight or moderate hypertrophy of the follicular epithelium of the thyroid gland, associated with minimal or slight pale staining colloid is observed at the two highest doses (500 and 15000 ppm). An increased number of hypertrophic cells in the pituitary gland of males is also observed.

In order to explain the non-relevance in human of this thyroid hypertrophy, the Registrant(s) make the hypothesis of an induction of liver enzymes leading to the excretion of thyroid hormones (T4) and therefore to thyroid toxicity. This mechanism is considered to be rodent specific as this species is highly sensitive to the decrease of this hormone. However, the Registrant(s) did not provide any data to support this hypothesis. From additional and informal information provided by the Registrant(s), neither hormonal dosage nor enzymatic activity investigation has been performed. Moreover, the Registrants have not provided a sub-chronic study on a second species or long-term studies. Accordingly, the proposed Registrants' assumption cannot be validated on the basis of the current knowledge. Other mechanisms, like direct action on the thyroid could explain the effects and could be relevant to humans.

Summary of Registrants' comments and response to comments

In response to the original draft decision, the Registrant(s) extensively discuss an induction mechanism of liver biotransformation enzymes in order to underline the specific sensibility

[3] Kameda, Y., Kimura, K. and Miyazaki, M. 2011. Occurrence and profiles of organic sunblocking agents in surface waters and sediments in Japanese rivers and lakes. *Environmental Pollution* 159, 1570–1576.
[4] Poiger, T., Buser, HR., Balmer, ME., Bergqvist, PE. And Müller, MD. 2004. Occurrence of UV filter compounds from sunscreens in surface waters: regional mass balance in two Swiss lakes. *Chemosphere* 55 (7), pp. 951–963.
[5] Rodil, R. *et al.* 2009. Non-porous membrane-assisted liquid-liquid extraction of UV filter compounds from water samples. *Journal of Chromatography A* 1216, 4887–4894.

of rodents compared to humans and to conclude that the target organ is the liver. The Registrant(s) consider that the observed pituitary and thyroid abnormalities are a secondary effect to hepatic induction and therefore non relevant for humans which is a less sensible species than rodents to these effects. Although no measurements of T3, T4 and TSH has been perfomed in the 90 days study, the Registrant(s) state that the finding is of no relevance for humans and this proposed mechanism has been extensively investigated and represents a well known mode of action in toxicology. The Registrant(s) conclude that a further mechanistic *in vivo* study in rats is considered unnecessary.

The eMSCA considers too simplistic to justify the hypertrophy of the follicular epithelium by the sole hepatic induction of liver biotransformation enzymes without data to corroborate this hypothesis. As explained in the draft decision other mechanisms are also possible to explain the observed effect and the relevance of a thyroid hypertrophy to humans cannot be excluded so far with the available data. As no long-term study has been carried out on the substance, other modes of action, directs or indirects, should be further investigated. Whatever the involved mechanisms are (direct or indirect), they significantly lead to hyperplasia of follicular cells and hypertrophy *via* stimulation of TSH secretion by the pituitary gland responding to an insufficient rate of circulating hormones. In conclusion, the Registrants' argument stating that the induction of liver biotransformation enzymes explains the observed thyroid hyperthrophy caused by octocrilene shall be supported by measurement of thyroid hormones (serum T3, T4), TSH and hepatic hormone activity (i.e. UDPGT, EROD, PROD, etc.).

Summary of proposals for amendmant made by MSCAs, Registrants' comments on them and response to Registrants' comments

Proposals for amendment were submitted asking to add the dosage of thyroxine 5'-deiodinase (iodothyronine deiodinase Type = D1) in order to allow concluding on the hormonal activity in the liver enzyme induction and to include the investigations on the thyroid toxicity mode of action into the EOGRTS protocol (see requirement point 2). In response to these, the Registrant(s) highlighted that the inclusion of additional parameters (i.e. T3 measurements in pups due to the need of high amounts of blood for analysis) and dosage groups (thyroxine 5' deionidase) into an EOGRTS would result in logistical difficulties and is therefore technically not feasible.

Another proposal for amendmant was submitted rejecting the need to request a mechanistic study that would be intended to inform on the need for a carcinogenicity study or to refine the NOAEL; the eMSCA answered that the mechanistic study is not intended to assess the need of a carcinogenicity study that is already deemed unecessary to refine the NOAEL and concludes to not further consider this proposal.

A further proposal for amendmant was submitted asking to further detail the technical study content in order to allow the Registrant(s) to understand exactly the type of study that is requested and proposing several amendments in this way; the eMSCA agreed with this proposal.

There were also proposals for amendment submitted regarding a request in the draft decision for an Amphibian Metamorphosis Assay on *Xenopus laevis* (test method: OECD 231), which are relevant for the consideration of the present request: Two Member State Competent Authorities suggested that the confirmation of the thyroid effect should be awaited before deciding on whether to request the Amphibian Metamorphosis Assay. ECHA acknowledges that as the proposals for amendment suggest, the mechanistic study also contributes to the clarification of the concerns for other environmental species than rats. It agrees that a testing strategy should be followed, requiring the Registrant(s) at this stage

to perform the mechanistic study and to wait with the decision on any future testing requirements for clarifying the environmental concerns until the data resulting from this study is available. It is also for this reason that the request for the Amphibian Metamorphosis Assay was not included in the present decision.

In a general response to the proposals for amendments, the Registrant(s) reiterate their arguments already submitted before and considered by ECHA as outlined above.

Considering all the above, it is necessary to carry out an *in vivo* sub-acute mechanistic study in rat to demonstrate the mode of action of the thyroid toxicity thereby possibly confirm the Registrant(s) initial assumptions of a rodent specific mechanism that is not expected to occur in humans. The conditions and design of the study should be the same as that specified in the sub acute study (28 days) toxicity in rat exposed by oral route to three doses of substance (Test method: OECD 407) with the following additions/modifications in order to demonstrate the assumed mode-of-action of the thyroid toxicity:

- Venous blood should be taken in all animals after fasting (at least 12 hours) on the day: -3; 3; 7; 14; 21 and 28 of treatment for determination of thyroid hormones (total and free T3 and T4) and thyroid stimulating hormone (TSH);
- Clinical biochemistry is required for liver only and should be performed on blood samples obtained of all animals just prior to or as part of the procedure for killing animals;
- Liver, adrenal glands, pituitary gland, hypothalamus and thyroid weights should be recorded and samples of liver and thyroid should be subjected to microscopy.
- Liver microsomes should be isolated for assessment of the following enzyme amounts/activities using well-established analytical methods:
    - Cytochrome P450 (Cyt P450) total amount;
    - Ethoxyresorufin-O-deethylase (EORD);
    - Pentoxyresorufin-O-depentylase (PROD);
    - Benzoxyresorufin-O-debenzylase (BROD);
    - T4-specific UDP-glucuronosyltransferase (T4-UDP-GT);
    - 4-Methylumbeliferone-glucuronosyltransferase (MUF-GT);
    - Hydroxybiphenyl- glucuronosyltransferase (HOBI-GT);
    - Thyroxine 5'-deiodinase (iodothyronine deiodinase Type = D1).

Conclusion

The initial requirement in the draft decision is maintained:

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out an *in vivo* sub acute mechanistic study in rat by the oral route to measure thyroid hormones (serum T3/T4), TSH and hepatic enzymatic activity (i.e. UDPGT, EROD, PROD, etc.) in order to provide enough accurate information that explain the mode of action of the thyroid effects and potentially confirm the initial assumption of a rodent specific mechanism that is not expected to occur in humans.

Notes for consideration by the Registrant(s)*:*

ECHA notes that in their comments on the proposals for amendment suggesting incorporation of the additional parameters into the EOGRTS, the Registrant(s) suggested that possibly those parameters could be included in a range finding study prior to the

reproductive toxicity study in order to bypass the raised logistical difficulties. The Registrant(s) may use the mechanistic study as a range-finding dose study for the EOGRTS if they can ensure that it would fulfill the criteria to be used as a range-finding dose study and at the same time not affect the reliability of the mechanistic study.

2. Extended One Generation Reproduction Toxicity Study in rat, oral route, with a DNT cohort and an extended pre mating period of 10 weeks (test method: OECD 443).

Initial requirement

The endpoint on toxicity to reproduction is partly covered in the registration dossiers by two mechanistic studies (Hershberger assay[6] and uterotrophic assay). The Registrant(s) conclude in a weight of evidence approach that the repeated dose toxicity studies and gender specific endocrine toxicity studies, taken together, provide no evidence for adverse effects of octocrilene on fertility. Such conclusion is not agreed based on the following reasoning.

From the 90-days study in rat, significant effects are observed in two endocrine glands (pituitary and thyroid) and not sufficiently assessed (see previous request). In the Hershberger assay, effects are observed on male reproductive organs (statistically significant decrease of the absolute and relative weight of ventral prostate and weight of the muscle bulbocarvenosus/levator ani). However the other three tissues do not display any degree of growth reduction. If it can be concluded on the absence of androgen antagonist effect according to the OECD guideline 441 positive criteria (two positive responses over five studied tissues), these results are considered equivocal and further investigation is needed on this issue.

In the scientific literature estrogenic and anti-androgenic activities are reported *in vitro* for several UV filters including octocrilene (Kunz and Fent, 2006)[7].
According to Schlumpf *et al.*[8] (2010) a maternal transfer of several UV filters including octocrilene via breastfeeding is demonstrated as UV filters are found in 85.2% of human milk samples tested.

In conclusion from this overall weight of evidence on both reproductive organs effects and potential exposure of highly sensitive populations, the two provided mechanistic studies are considered not sufficient to properly cover the concern on potential reproductive effects. The fertility endpoint is not investigated by the Registrant(s) in the dossiers. Therefore the eMSCA originally considered at this step that a two-generation reproduction toxicity study, oral route (test method: EU B.35/OECD 416) was the most appropriate testing to answer this concern.

Summary of Registrants' comments and response to comments

In their comment, the Registrant(s) argue that octocrilene does not affect fertility and development based on a weight of evidence approach from the provided studies (oral subchronic repeated dose study, subchronic repeated dose study in rabbits, prenatal

[6] Note that the Hershberger essay has been carried out in 2003 whereas the guideline OECD 411 is dated September 2009 ; therefore the study is lowered to reliability 2.
[7] Kunz, P.Y. and Fent, K. 2006. Multiple hormonal activities of UV filters and comparison of in vivo and in vitro estrogenic activity of ethyl-4-aminobenzoate in fish. *Aquat Toxicol* 79:305-324
[8] Schlumpf, M., Kypke, K., Wittassek, M., Angerer, J., Mascher, H., Masher, D., Vökt, C., Birchler, M. and Lichtensteiger, W. 2010. Exposure patterns of UV filters, fragrances, parabens, phthalates, organochlor pesticides, PBDEs, and PCBs in human milk; correlation of UV filter with use of cosmetics. *Chemosphere 81*: 1171-1183.

developmental toxicity test). Based on this evidence the Registrant(s) consider a two-generation study as scientifically unnecessary. The Registrants' comment and answer extensively to the eMSCA statements from the literature provided in the initial draft decision. Based on the overall evidence, the Registrant(s) conclude that octocrilene is unlikely to interact with the estrogen or androgen receptors in *in vivo* situations and do not consider that a two-generation reproduction test is necessary; instead the Registrant(s) propose to carry out an OECD 421 study with adjustments to the given test protocol in order to cover the whole spermatogenic cycle by extending the premating dose period.

The eMSCA considered from the provided Hershberger essay that, even if an absence of androgen antagonist effect could be concluded by strictly applying the OECD guideline 441 positive criteria (i.e. two positive responses over five studied tissues), these results are considered equivocal and further investigation is needed on this issue. The Registrants' argument to explain weight reduction of the sexual organs due to an induction of the metabolism of testosterone propionate following a possible enzyme induction is denied by the fact that the serum testosterone measured at the end of treatment is equivalent between the groups treated with propionate testosterone (TP) and the group treated with TP and octocrilene. The OECD validation program of Hershberger / Phase 2 test has been performed on anti-androgens, some of which being liver enzyme inducers; the enzyme inducer status has not been mentioned as a test limitation in the technical guidance 441. Furthermore, the induction should be strong enough to interfere with the serum levels of testosterone in consecutive daily subcutaneous injections of testosterone. The eMSCA concludeed that results from the Hershberger test for a possible antiandrogenic potential are equivocal and arouse concerns that are not solved by the Registrants' weight of evidence. The concern on the developmental and reproductive toxicity of octocrilene can be answered by a two-generation reproduction toxicity study in rats that is considered appropriate to sufficiently clarify the concern by providing information on the integrity and performance of the male and female reproductive systems, and on the effect on neonatal and postnatal developmental toxicity.

Summary of proposals for amendmant made by MSCAs, Registrants' comments on them and response to Registrants' comments

Several proposals for amendmant were submitted asking to replace the two-generation reproduction toxicity study, oral route (test method: EU B.35/OECD 416) by an Extended One Generation Reproductive Toxicity Study in rats (oral route, according to the internationally adopted test method OECD TG 443) with cohort DIT, DNT and including the toxicological endpoints (hormonal dosage) referred above in the requirement point 1, in order to minimize animal testing. In its proposals for amendmant, another MSCA proposes to leave it up to the eMSCA to decide potential changes of the draft decision in relation to the specification of the EOGRTS with regard to length of the pre-mating period and inclusion of the F2 generation; existing knowledge on the chemical does not support the omission of the developmental neurotoxicity (DNT) and developmental immunotoxicity (DIT) cohorts (OECD 443, paragraph 2); in addition this proposal for amendmant specifies that as the concern is specifically related to thyroid and anti-androgenic effects, cohorts for developmental neurotoxicity (Cohort 2A and 2B) should be included to evaluate possible effects e.g. on the development of the brain which may be affected by thyroid disrupting substances. Similarly another MSCA underlined in its proposal for amendmant that by default the OECD TG 443 should be requested without F2 and with DNT/DIT cohorts but added that, based on the ongoing discussions at Competent Authorities for REACH and CLP (CARACAL) and MSC regarding the diverging views on the value of the F2 generation and the DNT and DIT cohorts, conducting the F2 could be considered relevant for a certain number of substances with significant exposure of relevant populations (consumers, professional users). Proposal for amendmant recommended, even if an information gap for

fertility is raised, not to assess the reproductive toxicity considering the low evidence for endocrine disruption based on the available data but, in another option, at least to replace the request for OECD 416 with OECD 443 EOGRTS.

In response to the proposals for amendment s, the Registrant(s) explained again with the same arguments, already submitted in response to the former draft decision, that the reasoning given by the eMSCA is considered not robust to scientifically justify the requirement for further tests on reproductive toxicity. Concerning the EOGRTS, the Registrant(s) did not see any sound scientific rationale for the proposal of this study including the cohorts DNT and DIT, supported by arguments that were already provided in response to the former draft decision and already taken into account by the eMSCA. In this way, the Registrant(s) agreed with the proposals for amendmant that recommended not to assess the reproductive toxicity considering the low evidence for endocrine disruption based on the available data and considering that no indication of an immunotoxic potential could be identified from the subchronic repeated dose toxicity study in rats. Those arguments had already been taken into account and formerly answered (see above).

ECHA has taken into account the proposals for amendment and the Registrants' comments thereon. There is no information available on fertility. However, such information is required to assess the concern that the substance may pose for professionals and consumers[9] (non-cosmetic uses) and also for workers. Due to this need for information on fertility and due to the concern for the potential of the substance for bioaccumulation and endocrine disruption, ECHA considers that the EOGRTS (OECD 443) addresses best the concerns in this specific case.

The thyroid effects shown in the 90-day study in rats as well as the potential bioaccumulation are arguments for extending cohort 1B to the F2 generation. Considering that on the one hand the main consumer use is covered by Regulation (EC) No 1223/2009 on cosmetic products (the "Cosmetics Regulation") but on the other hand the need to clarify the concern for other uses and for the environment, ECHA requests the EOGRTS without extending cohort 1B to the F2 generation. The Registrant(s) may prior to testing decide whether to extend cohort 1B to the F2 generation if they consider this appropriate. Specifically, if the Registrant(s) determine that uses of the substance by workers as well as non-cosmetic professional and consumer uses of the substance may lead to significant exposure of professionals, workers and consumers the extension of the cohort 1B to mate the F1 animals to produce the F2 generation should be considered by the Registrant(s).

The request for the DNT Cohort is justified by the observed effects on the thyroid in the existing repeated dose toxicity study and the equivocal findings in the Hershberger assay. In this case the mechanism responsible for the observed thyroid effect may be rodent specific but this has not yet been adequately documented by the Registrant(s). In addition it should be noted that, in contrast to effects caused by hypothyroidism in adult rodents, the effects in the developing organism are independent of TSH, and instead result from decreases in tissue levels of T4 and T3. This mechanism is likely to be relevant for humans (Crofton, 2008)[10]. Therefore, results from the DNT Cohort are likely to provide additional information that can be used in the evaluation of whether or not, the observed thyroid effect in rats is relevant for humans.

There were also proposals for amendment submitted regarding a request in the draft decision for an Amphibian Metamorphosis Assay on *Xenopus laevis* (test method: OECD 231), which are relevant for the consideration of the present request: Two Member State

[9] This terminology stems from the Cosmetics Regulation (EC) No 1223/2009 on cosmetic products.

[10] Crofton, K.M. 2008. Thyroid disrupting chemicals: mechanisms and mixtures. International Journal of Andrology 31: 209-223

Competent Authorities suggested that the confirmation of the thyroid effect should be awaited before deciding on whether to request the Amphibian Metamorphosis Assay. ECHA acknowledges that as the proposals for amendment suggest, the EOGRTS also contributes to the clarification of the concerns for other environmental species than rats. It agrees that a testing strategy should be followed, requiring the Registrant(s) at this stage to perform the EOGRTS and to wait with the decision on any future testing requirements for clarifying the environmental concerns until the data resulting from this study is available. It is also for this reason that the request for the Amphibian Metamorphosis Assay is not included in the present decision.

Therefore, ECHA considers necessary that an Extended One Generation Reproduction Toxicity Study in rat, by oral route (OECD 443), without F2 generation and with the assessment of the developmental neurotoxicity (DNT) cohort is performed in order to evaluate

- the integrity and performance of the male and female reproductive systems,
- the effect on neonatal and postnatal developmental toxicity.

Taking into account the bioaccumulation potential of the substance, a prolongation of the pre-mating period to 10 weeks is requested, as recommended in the OECD guidance document[11].

As indicated above the Registrant(s) should prior to testing decide whether there is a need to extend cohort 1B to the F2 generation due to significant exposure of the substance to workers, professionals and consumers.

Conclusion

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out an Extended One Generation Reproduction Toxicity Study in rat, oral route (test method: OECD 443), with a DNT cohort.

Raised regulatory issues between the REACH and the Cosmetic Regulation

ECHA notes that in their comments on the draft decision and their comments on the proposals for amendment suggesting a postponement of the decision, the Registrant(s) expressed their concerns and pointed out an alleged conflict between performing animal tests and the marketing ban stemming from the Cosmetics Regulation. ECHA highlights, that this issue is covered by the Communication from the Commission to the European Parliament and the Council on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics, dated 11 March 2013 (COM-2013, 135 final). This communication states the following in its chapter 3.1. "Ingredients used in cosmetics will generally also be subject to the horizontal REACH requirements and animal testing may be necessary as a last resort to complete the respective data packages. [...] The Commission considers that animal testing that has clearly been motivated by compliance with non-cosmetics related legislative frameworks should not be considered to have been carried out 'in order to meet the requirements of this Directive/Regulation'. The resulting animal testing data should not trigger the marketing ban and could subsequently be relied on in the cosmetics safety assessment. [...]". This means that the marketing ban does not apply to substances which have been subject to animal testing under the REACH Regulation in order to determine a human health concern for non-cosmetic uses of the substance. Furthermore, the marketing ban does not apply where animal testing is needed

[11] Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test, Series on testing and assessment n°151, july 2013.

for the purposes of assessing the risks arising from exposure to workers irrespective of whether the substance is solely used in a cosmetic product.

It should be further highlighted that the marketing ban in the Cosmetics Regulation does not apply where animal testing under the REACH Regulation is required to determine environmental concerns for substances used in cosmetic products (see recital 5 of the Cosmetics Regulation).

Regarding the case of octocrilene and as mentioned in the registration dossiers, the substance is not specifically developed for cosmetic purposes and is not exclusively used in cosmetic products. As also highlighted above the requests are motivated by exposure of consumers and professionals to the substance in non-cosmetic products, exposure of workers using the substance, and exposure of the environment to the substance. Therefore the considered animal testing under REACH is motivated by compliance with non-cosmetics related legislative framework.

On the basis of the considerations set out above ECHA does not consider in this context that there is any conflict between the REACH and the Cosmetic Regulation leading to a need to postpone the conduct of the requested studies.

3. Water solubility (test method: EU A.6) with an adequate analytical method able to quantify low levels of octocrilene and with a validated limit of quantification (LOQ).

Initial requirement

The provided key study for the water solubility gives an indicative value of <0,1mg/L at 20°C that is reliable but not accurate. A water solubility value of 3.8 µg/L at 25°C from the database SRC PhysProp (Physical Properties Database) is provided as supportive data but is not consistent with an additional water solubility value (55.056 µg/L) reported from QSAR calculations. In the frame of an informal discussion[12] with the Registrant(s), further information has been submitted: pre-experiments to long-term toxicity test to aquatic invertebrates provide water solubility values in the range of 4-4.5 µg/L. These values are however considered not reliable enough becausethey were obtained from a supersaturated micro emulsion which doesn't correspond to the standard conditions for the measurement of water solubility. The approximate value of 4 µg/L is thus deemed as a high limit for water solubility which is actually expected to be lower. As a conclusion, no accurate and reliable value of water solubility of octocrilene can be deduced from the available data. However an accurate and reliable value is necessary for the environmental risk assessment: the knowledge of the water solubility is indeed a prerequisite for setting up test conditions for range fate (e.g. biodegradation, bioaccumulation) and effects studies (REACH guidance R7.a, R.7.1.7).

Therefore it is considered necessary to determine the water solubility with the test method EU A.6 and with an adequate analytical method able to quantify low levels of octocrilene with a validated limit of quantification (LOQ). Note that from the literature, detection methods are implemented by several authors with a detection limit below 10 ng/L (Poiger *et al.*[3], 2004; Balmer *et al.*[13], 2005).

Summary of Registrants' comments and response to comments

[12] E-mail answer received from the lead registrant, dated 31 August 2012
[13] Balmer ME., Buser, HR., Müller, M. and Poiger T. 2005. Occurrence of some organic UV filters in wastewater, in Surface waters, and in fish from Swiss lakes. *Environ Sci Technol* 39:953-962

The Registrant(s) agreed to perform the required test and proposed a protocol to the eMSCA (OECD 105 column elution method, analysis of the eluted water phase, re-extraction by organic solvent or solid extraction in order to concentrate the substance; method accuracy expected within the nanogram range). ECHA agrees with the intended method of determination and specifies the expected information to be reported in the test conclusion.

Conclusion

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: water solubility (test method EU A.6) with an adequate analytical method able to quantify low levels of octocrilene with a validated limit of quantification (LOQ).

4. Adsorption – Desorption Using a Batch Equilibrium Method (test method: OECD 106)

Initial requirement

No requirement was initially provided on this issue.

Summary of Proposals for amendment made by MSCAs, Registrants' comments on them and response to Registrants' comments

Proposals for amendment were submitted asking to provide further analytical information on the adsorption/desorption behaviour of the substance from a test method OECD 106 (Adsorption – Desorption Using a Batch Equilibrium Method) and not a test method OECD 121 (estimation of the Adsorption Coefficient on Soil and on Sewage sludge using High Performance Liquid Chromatography), which is considered to deliver more precise analytical results. The reasoning is that the estimated log Koc (calculated with PCKocWin v1.66) provided by the Registrant(s) is only slightly below the upper end of the confidence interval of test method OECD 121 (defined by reference substance DDT, log Koc = 5.63). Moreover the proposals for amendment suggested that exposure assessment should be based on measured values in order to draw appropriate conclusions regarding possible further risk management options.

In response to the proposal for amendment, the Registrant(s) considered that the adsorption/desorption behaviour is sufficiently covered with the provided QSAR calculation. Thus they disagree with the necessity to conduct an experimental study according to OECD TG 106, also taking into account expected detection difficulties even when using radiolabelled test substance.

ECHA considers that the K_{OC} value is one of the key inputs for environmental fate modelling and exposure assessment and agrees that measured data are needed because more accurate, especially for a lipophilic substance. ECHA agrees to consider the test method OECD 106 more relevant than test method OECD 121.

Conclusion

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision and the following requirements: Adsorption – Desorption Using a Batch Equilibrium Method (test method: OECD 106).

5. Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (test method: OECD 308);

Initial requirement

No requirement was initially provided on this issue.

Summary of proposal for amendments made by MSCAs, Registrants' comments on them and response to Registrants' comments

A proposal for amendment was submitted asking to add a sediment simulation testing (test method; Aerobic and anaerobic transformation in aquatic sediment systems, EU C.24/OECD TG 308) in order to clarify the PBT concerns that have been identified. This is indeed a low solubility, potentially persistent, lipophilic and highly adsorbing organic substance. It already screens as potentially very bioaccumulative on the basis of its log Kow and further testing has been proposed to clarify bioaccumulation potential, aquatic and mammalian toxicity. If the results indicate that the substance meets the Annex XIII B (or vB) and T criteria, there will still be a data gap for P as no measured half-life is available for comparison with the formal criteria.

In response to the proposal for amendment, the Registrant(s) agreed that there is a data gap for P, if the substance meets the Annex XIII B and T (or vB) criteria but disagreed with the need of a sediment simulation test, pointing out that according to Annex VIII, IX and X, further biotic degradation testing shall only be proposed if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance and its degradation products. The Registrant(s) accepted the alternatively proposed stepwise approach, that a sediment simulation test has to be conducted if it is needed for PBT/vPvB clarification and to condition it to the results of the B and T assessment first.

The ECHA agrees, in part of a general PBT approach and in order to clarify the P concern (according to the available data, the P criterion is met based on screening criteria exclusively), that a test on the behaviour of the substance in aquatic/sediment systems (OECD TG 308), with the identification of the potential degradation products, is necessary. However ECHA decided to condition this simulation assay to the results of the bioaccumulation assessment reffered ti in point III.7 below (i.e. if the substance is not B or vB, a simulation test would be considered not necessary).

Conclusion

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision and the following requirements: Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (test method: OECD 308), provided that the substance is B/vB.

6. *Daphnia magna* Reproduction Test (test method: OECD 211).

Initial requirement

The substance's physico-chemical properties (low solubility, high lipophilicity, high potential of sorbing and stability in the environment compartments) and the results from the provided key acute toxicity studies on aquatic organisms indicate the need to investigate further the effects on aquatic organisms.

The registration dossiers provide only acute toxicity studies on aquatic organisms. No inhibitory or toxic effects are observed for two trophic levels (fish and daphnia). A slight toxic effect on growth rate is observed in algae at the highest tested concentration.

Except for the provided key daphnia test, no analytical result can be derived from the chemical control analysis of the tests media, when performed, due to the poor water solubility and the low sensitivity of the used analytical methods. The measurement of tested concentrations during the test is a requirement according to OECD guidelines in order to evaluate the reliability of *in vivo* data.

Therefore results from these acute key studies on aquatic organisms shall be interpreted cautiously. An absence of acute toxic effects at the saturation concentration cannot be used as the basis for predicting no chronic toxicity at saturation or at lower concentrations. A long-term aquatic toxicity study shall be considered and provided by the Registrant(s).

The results of fish bioaccumulation study carried out with ^{14}C- radiolabelled octocrilene showed no toxic effects or behavior abnormalities to zebrafish after 28d of exposure (uptake period).

Daphnia chronic toxicity testing is waived by the Registrant(s) on the ground that, because of the high viscosity of octocrilene, a physical effect on daphnids is likely to occur that prevents to perform a long term toxicity testing on daphnia.This theoretical argument is not supported by any provided study or data and is considered not relevant because aquatic organisms are not exposed to the viscous substance itself but to the fraction solubilized in water or to the adsorbed fraction. Moreover, the acute test on daphnia is carried out without any physical effect observed. Accordingly this argument is rejected.

In the frame of an informal discussion with the Registrant(s) on this concern, the Registrant(s) stated that it is not possible to maintain the substance concentration in a long-term test. However, the provided fish bioconcentration study shows that the substance concentration has been kept constant in a long-term study below the solubility limit. Accordingly this argument is also rejected.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision and the following requirements: Daphnia magna Reproduction Test (test method: OECD 211).

The Registrant(s) must apply the following operating requirements:

- The specific requirements for poorly water-soluble substances and adsorbing substances described in the OECD guidance N°23 must be followed in order to maintain exposure concentrations and to analyze exposure.
- Analytical methods with high-sensitivity detection (such as ^{14}C-radiolabeled test substance) shall be used to measure the substance concentration throughout the tests.
- The range of tested concentrations shall be around the updated water solubility limit in order to distinguish potential physical effects (put forward in the waiving) and potential ecotoxicological effects: the Registrant(s) will refer to results from the requested water solubility test.

Summary of Registrants' comments and response to comments

The Registrant(s) agreed to perform the required test.

Conclusion

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision and the following requirements: Daphnia magna Reproduction Test (test method: OECD 211).

7. Bioaccumulation in Fish (Zebra fish): aqueous and dietary exposure (test method: OECD 305): recalculation of the BCF value from data of the already provided bioaccumulation test, or test to be conducted according to OECD guideline 305.

Initial requirement

In the literature, concentrations of octocrilene are reported in fishes in a range from 40 to 2 400 $ng.g^{-1}$ lipids with an average of 630 $ng.g^{-1}$ lipids (Gago-Ferrero *et al.*[14], 2012; Buser *et al.*[15], 2006). These results, taken together with the high lipophilicity of octocrilene, indicate its bioaccumulation potential. Bioamplification could also be expected.
From the provided key bioconcentration study on Zebra fish, the proposed calculated BCF value is considered underestimated and accordingly invalid. The measurements of octocrilene in unfiltered water samples are indeed used to calculate the BCF value while measurements in filtered water samples are reported much lower in the report (raw data not provided). A relevant BCF should have been calculated based on filtered water samples in order to take into account the potential ad/absorption of octocrilene.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to recalculate the BCF value using the original data from filtered water and to provide the raw data. If such data are not available or not usable for the requested purpose, the Registrant(s) are required to carry out a new bioconcentration study in Zebra Fish (test method: OECD 305).

Summary of Registrants' comments and response to comments

The Registrant(s) agreed to recalculate the BCF values based on filtered samples (instead of the former values calculated on non filtered samples) but stressed the fact that this does not reflect the real exposure conditions. The eMSCA highlights that recent results of a scientific study (Gago-Ferrero *et al.*[16], 2013) indicate for the first time that octocrilene accumulates in liver of dolphins at high concentration levels (up to 782 $ng.g^{-1}_{lipid\ weight}$) similar to those of anthropogenic organic persistent pollutants. eMSCA invites the Registrant(s) to consider this new study in the hazard assessment of the substance.

Summary of proposals for amendments made by MSCAs, Registrants' comments on them and response to Registrants' comments

Proposals for amendments were submitted asking
- to recalculate BCF with growth-dilution correction and lipid normalization.
- to carry out of a new bioconcentration study in Zebra Fish depending on the BCF recalculation result: if the resulting BCF is below 2 000 L/kg, a repeated test will not be required.

[14] Gago-Ferrero, P., Diaz-Cruz, MS. and Barcelo, D. 2012. An overview of UV-absorbing compounds (organic UV filters) in aquatic biota. *Anal Bioanal Chem* 404, 2597-2610.
[15] Buser, HR., Balmer, M.E., Schmid, P. and Kohler, M. 2006. Occurrence of UV Filters 4-Methylbenzylidene Camphor and Octocrylene in Fish from Various Swiss Rivers with Inputs from Wastewater Treatment Plants. Environ. Sci. Technol. 40(5), pp 1427-1431.
[16] Gago-Ferrero *et al.*, 2013. First determination of UV filters in Marine Mammals. Octrocrilene levels in Franciscana Dolphins. . *Environ. Sci. Technol.* 47:5619-5625

- if a new testing is necessary, to perform it by a dietary method, since the data can provide additional useful perspectives on bioaccumulation potential for poorly soluble substances (such as assimilation efficiency and depuration rate).

During the commenting phase on the proposals for amendment, the Registrant(s) provided additional data indicating that a BCF can be recalculated but didn't comment on a specific proposal for amendment.

The eMSCA agrees with the provided proposal for amendment and considers that the kinetic BCF can be underestimated if it is not corrected for growth. Moreover and to reduce the variability of results for a substance with high lipophilicity, the bioconcentration should be expressed as normalised to a fish with a 5% lipid content (based on the whole body wet weight) in addition to the value derived directly from the study. The eMSCA agrees that due to the substance properties (very low solubility, potentially persistent, lipophilic and highly adsorbing) a dietary method should be implemented if a new test would be considered necessary. However the decision to require a new bioaccumulation test will be discussed lateron based on the results and the evaluation of this recalculation. Nonetheless, if the data needed to recalculate a robust BCF are not available, a dietary bioaccumulation test in fish is considered immediately necessary.

Conclusion

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to recalculate the BCF value using the original data from filtered water and to provide the raw data. A robust BCF value should be recalculated with growth-dilution correction and lipid normalisation, if data are available. If such data are not available or not usable for the requested purpose, the Registrant(s) are required to carry out a dietary bioaccumulation test in Fish (test method: OECD 305).

8. Earthworm Reproduction Test (test method: OECD 222);

Initial requirement

No requirement was initially provided on this issue.

Summary of proposal for amendment made by MSCAs, Registrants' comments on them and response to Registrants' comments

A proposal for amendment was submitted asking to add a long-term toxicity testing on terrestrial invertebrates (test method; Earthworm reproduction test, OECD TG 222). Indeed monitoring data show that this substance is present in the aquatic environment (fish, surface water and sediment), presumably as a result of releases from treated products some of which will be via waste water. This means that sewage sludge and soil are likely to be exposed.

In response to the proposal for amendment, the Registrant(s) agreed that the substance falls (due to its potential persistence and high adsorption potential) into the Soil Hazard Category 3 and accept the suggestion to conduct a chronic earthworm test (OECD 222) to satisfy this requirement.

The eMSCA agrees to the proposal for amendment and considers it relevant to assess soil exposure (via sewage sludge) for this substance that shows a high adsorption potential. A PNEC can be used in a screening soil risk assessment through the use of the equilibrium partitioning method (EPM). As indicated in the Table R.7.11-2 of the REACH guidance R7, and even if for the moment no conclusion about the toxicity of the substance to aquatic organisms is available, a confirmatory long-term soil toxicity testing is needed in the

screening assessment approach. Thus a long-term toxicity testing on terrestrial invertebrates is considered necessary.

Conclusion

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision and the following requirements: Earthworm Reproduction Test (test method: OECD 222)

9. Androgenised Female Stickleback Screen (AFSS, OECD TG 230 modified, Series on Testing and Assessment n°148)

Initial requirement

In the scientific literature, anti-estrogenic and anti-androgenic activities of octocrilene are reported *in vitro* amongst several other UV filters (Kunz and Fent[6], 2006). Estrogenic activity of octocrilene is reported by Matsumoto *et al.* [17], 2005. Accordingly a potential estrogen agonist/antagonist and a potential androgen antagonist effect of octocrilene are raised and more information is considered needed to clarify this concern.

Therefore, it has been considered necessary to carry out the following studies using the registered substance subject to this decision: Fish Short Term Reproduction Assay (test method: OECD 229) and Androgenised Female Stickleback Screen (AFSS, OECD TG 230 modified, Series on Testing and Assessment n°148).

Summary of Registrant(s) *comments and response to comments (the* Registrant(s) *grouped its comments on both the AFSS and the AMA testing requirements)*

In their comment, the Registrant(s) explained that no evidence exists that the substance is hormonally active *in vivo* in ecotoxicological related organisms, stating that *in vitro* testing showing an antagonist activity of octocrilene can not be extrapolated to fish and amphibians, or are not appropriate to show such effect; they state that *in vivo* testing on mammals (already available through the Hershberger test and uterotrophic test) are more appropriate to invalidate results from *in vitro* testing. The Registrant(s) stated that sediment is the only target compartment due to the physico-chemical properties of the substance; they concluded from the Kaiser *et al.* 2012[18] study that there is no chronic toxicity nor endocrine related effect in sediment-dwelling organisms. The Registrant(s) concluded that the effects observed *in vitro* can be disproved by the available mammalian toxicity studies and that there is no need to conduct any of the 3 requested studies (Fish Short Term Reproduction Assay (test method: OECD 229) and Androgenised Female Stickleback Screen (AFSS, OECD TG 230 modified, Series on Testing and Assessment n°148); Amphibian Metamorphosis Assay on Xenopus laevis (test method: OECD 231)).

The eMSCA first reminds the usual testing approach from *in vitro* screening to *in vivo* testings; eMSCA considers the anti-androgenic activity reported *in vitro* (that is not denied by the Registrant(s)) as a sufficient concern for triggering further *in vivo* assessment in species that are relevant for the environmental aquatic compartment. The Registrant(s) do not provide any in depth assessment / interpretation on the potential antiandrogenic activity of octocrilene apart from quoting the Hershberger assay as "negative"; however as

[17] Matsumoto, H., Adachi, S. and Suzuli, Y. 2005. Estrogenic activity of ultraviolet absorbers and the related compounds. *Yakugaku Zasshi*, 125(8) Journal of the Pharmaceutical Society of Japan, 643-652

[18] Kaiser, D., Sieratowicz, A., Zielke, H., Oetken, M., Hollert, H., Oehlmann, J. (2012) Ecotoxicological effect characterisation of widely used organic UV filters. Environ. Poll. 163: 84-90

previously discussed, even if the Hershberger assay may show no indication of anti-androgenic effects by strictly applying the guideline interpretation, results are considered equivocal and arouse concerns that are not solved by the provided Registrants' weight of evidence.

The eMSCA disagrees with the Registrants' opinion to consider the water compartment as non-relevant and, on the contrary, underlines that several studies report significant concentrations of octocrilene in the water column (from 5 ng l^{-1} in water samples from Swiss Lakes up to 4 461 ng l^{-1} in coastal areas). Therefore the eMSCA considers the water column compartment as relevant for further necessary testing in addition to the available data on the sediment-dwelling organisms. Results from the recent publication by Kaiser *et al.*, 2012 indicating absence of any chronic toxicity and endrocrine related effects for sediment-dwelling invertebrates are not transposable to water organisms (vertebrates and invertebrates).

Summary of proposals for amendment made by MSCAs, Registrants' comments on them and response to Registrants' comments

Proposals for amendment were submitted supporting the requirement of an Androgenised female stickleback endocrine screening assay and asking

- to delete Fish short term Assay (OECD 229) because it has low statistical power to detect anti-androgens,
- to add a statement on the strength of evidence currently available for anti-androgenicity effects,
- to add a clear explanation for the choice of the fish species proposed for the screening assay (with reference to the OECD ED test framework),
- to implement this testing in a step wise approach.

In response to a proposal for amendment, the Registrant(s) recommended to focus on the outcome of the upcoming toxicological studies in the first instance in order to address endocrine related effects in vertebrates, before drawing a conclusion on whether or not additional ecotoxicological studies in fish are required, i.e. a tiered testing approach is proposed.

The eMSCA agrees with the first proposal for amendment and thus deleted the Fish short term Assay (OECD 229) from the requirements. Anti-androgenicity effects observed *in vitro* combined with the equivocal results in the Hershberger assay (as already stated above) clearly raise the suspicion on an anti-androgenic mode of action that should properly be answered. In this case and in the conceptual framework[19] level 3, consideration must be given to conduct of a fish screen (androgenised female stickleback screen [AFSS, OECD TG 230 modified, Series on Testing and Assessment n°148]).The species proposed for the AFSS assay is the three-spined stickleback (*Gasterosteus aculeatus*). In the current requirements, this test is the only one specifically targeted on the anti-androgenic action and therefore is not conditioned to a stepwise approach.

Conclusion

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Androgenised Female Stickleback Screen on the three-spined stickleback (*Gasterosteus aculeatus*) species (AFSS, OECD TG 230 modified, Series on Testing and Assessment

[19] Guidance Document on standardised test guidelines for evaluating chemicals for endocrine disruption (N°150), OECD, ENV/JM/MONO(2012)22

n°148).

Risk assessment refinement: environmental exposure scenario in relation with the initial grounds of concern

10. Information on a direct emission scenario to the aquatic environment in the risk assessment

No direct exposure scenario of aquatic and sediment-organisms is provided in the environmental exposure assessment. However, the wide dispersive use of octocrilene as UV-filters in cosmetic products leads to a direct contamination of the aquatic environment through outdoor water activities. According to Amine, H. *et al.*[20] (2012) octocrilene occurs in the aquatic environment through two principal sources: direct inputs from recreational activities and indirect inputs from wastewater.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide a risk assessment considering a direct exposure scenario of aquatic and sediment organisms.

11. Provide additional information on the environmental exposure assessment

In order to clarify the submitted environmental emission scenarios and to make sure of their relevance, information, clarifications and justifications about the following parameters are required from the Registrant(s):

- Tonnage: provide a detailed argumentation on the choice of tonnage values for each life cycle step (formulation, industrial use, consumer and professional use, service life articles) and each use identified in the use mapping section.
- Release estimation: for each parameter listed below and used to determine releases in environmental compartments, provide the original value with supportive document if necessary and any detailed argumentation about the relevance of the used values. Justify the refined parameters based on risk management measures and operational conditions. Provide a detailed argumentation on the relevance of the OC and RMM used.
    - Number of release days (days/year),
    - Release fraction to air/wastewater/soil (%),
    - Fraction of main source (%),
    - Sewage treatment plant flow (m^3/d),
    - Flow of receiving water (m^3/d),
    - Dilution factor (-).
- PEC values at local and regional scale: indicate the software used to estimate local and regional PEC values (e.g. Euses, ECETOC, etc.).

12. Estimate the PEC_{soil} via sludge

No $PECs_{soil}$ via sludge application is provided in the environmental exposure assessment. Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide the estimation of PECsoil via sludge for each emission scenario. If a national/local regulation indicates the prohibition to spread sludge from municipal or industrial wastewater treatment plant, this information must also be provided.

Regarding endpoints 8, 9 and 10, the Registrant(s) provided the following common

[20] Amine, H., Gomez, E., Halwani, J., Casellas, C., Fenet H. 2012. UV filters, ethylhexyl methoxycinnamate, octocrylene and ethylhexyl dimethyl PABA from untreated wastewater in sediment from eastern Mediterranean river transition and coastal zones. *Mar. Pollut. Bull.*

comment that is answered by the eMSCA as follow.

The Registrant(s) suggested to postpone an update on exposure scenarios until after the hazard assessment is finalized.
ECHA stresses the fact that the entire chemical safety assessment (including exposure scenarios, etc.) shall be updated immediately once the revised hazard assessment is available, shall take into account all the provided comments and testing requirements and shall be included in the next dossier update.

IV. Adequate identification of the composition of the tested material

The substance identity information submitted in the registration dossiers has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation. In relation to the required tests, the sample of the substance to be used for the new studies shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested materials to be subjected to the tests subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the studies must be shared by the Registrant(s).

V. Avoidance of unnecessary testing by data- and cost- sharing

Avoidance of unnecessary testing and the duplication of tests is a general aim of the REACH Regulation (Article 25). The legal text foresees the sharing of information between registrants. Since several Registrants of the same substance are required to provide the same information, they are obliged to make every effort to reach an agreement for every endpoint as to who is to carry out the test on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation.

If ECHA is not informed of such agreement within 90 days, it shall designate one of the Registrant(s) to perform the tests on behalf of all of them. If a registrant performs a test on behalf of other Registrant(s), they shall share the cost of that study equally and the Registrant(s) performing the test shall provide each of the others with copies of the full study reports.

This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/datasharing_en.asp.

VI. General requirements regarding Good Laboratory Practice

ECHA always reminds Registrant(s) of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

VII. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]

Jukka Malm
Deputy Executive Director

Annex: List of registration numbers – This annex is confidential and not included in the public version of this decision