

Helsinki, 06 April 2018

Substance name: Isopentyl p-methoxycinnamate (IPMC)  
EC number: 275-702-5  
CAS number: 71617-10-2  
Date of latest submission(s) considered<sup>1</sup>: 17/5/2017  
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)  
Addressee(s): Registrant(s)<sup>2</sup> of Isopentyl p-methoxycinnamate (Registrant(s))

### DECISION ON SUBSTANCE EVALUATION

Based on Article 46(1) of the REACH Regulation (Regulation (EC) No 1907/2006), you are requested to submit the following information on the registered substance:

1. Either an Amphibian Metamorphosis Assay, test method OECD 231, **or** a Larval Amphibian Growth and Development Assay, test method OECD 241
2. Fish Sexual Development Test, test method OECD 234, using either Japanese Medaka (*Oryzias latipes*) or Zebrafish (*Danio rerio*)
3. Provide information and justification for parameters in the environmental exposure assessment within the Chemical Safety Report as further specified in Appendix 1.

You shall provide an update of the registration dossier(s) containing the information requests of 1 and 2 by **13 April 2020** from the date of the decision, and the information request 3 by **13 October 2020** from the date of the decision, including robust study summaries and, where relevant, an update of the chemical safety report. The full study report(s) have to be submitted for requests 1 and 2. The deadlines take into account the time that you, the Registrant(s), may need to agree on who is to perform any required tests. They have been set to allow for sequential testing.

The reasons of this decision and any further test specifications are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision.

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<sup>1</sup> This decision is based on the registration dossier(s) on the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

<sup>2</sup> The terms registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.



### **Who performs the testing?**

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the studies on behalf of all registrant(s) within 90 days. Instructions on how to do this 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 a suspensive effect and is subject to a fee. Further details are described under: <http://echa.europa.eu/regulations/appeals>.

Authorised<sup>3</sup> by Leena Ylä-Mononen, Director of Evaluation

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<sup>3</sup> 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

Based on the evaluation of all relevant information submitted on Isopentyl p-methoxycinnamate (IPMC) and other relevant available information, ECHA concludes that further information is required to enable the evaluating Member State Competent Authority (evaluating MSCA) to complete the evaluation of whether the substance constitutes a hazard or risk to the environment.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested to clarify the concern for endocrine disruption.

### 1. **Amphibian Metamorphosis Assay (OECD TG 231), or a Larval Amphibian Growth and Development Assay (OECD TG 241)**

#### The concern(s) identified

The concern is related to the potential for environmental endocrine disruption in non-mammalian (amphibian) species. The endocrine activity of the substance in amphibians should be clarified in order to determine whether it poses a hazard and/or risk to the environment.

#### Why new information is needed

Information is available from *in vitro* systems and *in vivo* studies on mammalian species which indicates that 2-ethylhexyl trans-4-methoxycinnamate (OMC, CAS no. 83834-59-7), a structural analogue of IPMC, has some limited anti-thyroid activity. In your chemical safety assessment you have claimed it is possible to use these data on OMC to also determine the endocrine disrupting (ED) potential of IPMC and it is the initial view of ECHA that the data does indicate a potential interaction of both substances with the hypothalamic-pituitary-thyroid (HPT) axis of the endocrine system.

In an *in vitro* thyroid receptor transactivation study on OMC by Hofmann *et al.* (2009), HepG2 cells (hepatoma derived liver cell line) were stably transfected with a T3 (triiodothyronine) responsive plasmid with a luciferase reporter. OMC tested positive at a concentration of 1  $\mu$ M (effects 1.5x over vehicle control). In contrast, the endogenous ligand, T3 gave a much more marked positive response at 0.1 nM (122x over vehicle control) using the same assay system. It is concluded that OMC has some limited transactivational capacity *in vitro* at the T3 receptor, but it is significantly less potent than T3.

The information on OMC from OECD Conceptual Framework (CF) Level 3 mammalian *in vivo* testing (Schmutzler *et al.*, 2004 and Klammer *et al.*, 2007) also points towards some perturbations of enzymes and hormones relevant to the HPT axis but in ovariectomised animals only. In the study by Schmutzler *et al.* (2004), where rats were exposed at 270 and 1450 mg OMC/kg/day in a soya-free diet for 12 weeks, serum thyroid hormone (thyroxine -T4) levels were decreased at the low dose only and Type 1-deiodinase (DI) was decreased at both dose levels. No consistent changes in T3 levels were observed at any dose suggesting that the decrease in Type 1 DI activity was insufficient to impact circulating T3 levels. OMC had no reported effects on TPO (thyroid peroxidase) activity. It is also noted that there was no consistent changes in T4 or TSH (thyroid stimulating hormone) and reverse T3 (rT3) was not measured. There is no information available to indicate when blood samples were taken for hormone measurements making it difficult to determine whether there was any influence of

circadian rhythms on thyroid hormone changes.

In the study by Klammer *et al.* (2007), where rats were dosed at 10, 33, 100, 333 and 1000 mg OMC/kg/day for 5-days, serum TSH was statistically significantly decreased at 333 and 1000 mg/kg/day, T3 levels were significantly lowered to 63% of control at 1000 mg/kg/day and T4 was statistically significantly decreased by 75% and 59% at 333 and 1000 mg/kg/day. TSH receptor protein increased in the thyroid by 144% at the top dose - and in the liver, Type 1 deiodinase was statistically significant decrease by 38% and 46% at 333 mg/kg and 1000 mg/kg/day compared to controls. Inconsistent or no effects were observed on these parameters when exposed to the positive control E2. No effect was found on type 2 DI activity and there was also no effect of E2 in this assay. Hypothalamic TRH mRNA (messenger RNA) levels were unaffected. In agreement with the study by Schmutzer *et al.* (2004), OMC did inhibit hepatic type 1 DI activity. However, it would normally be expected that inhibition of hepatic type 1 DI activity would cause decreased T3 levels, and elevated TSH levels as the pituitary responds to the decrease in T3. It is unclear why TSH levels were decreased in this study, although the TRH (thyroid releasing hormone) mRNA data suggest the hypothalamic signal is not perturbed. Also, the TPO data from the studies by Klammer (2007) and Schmutzer *et al.* (2004) appear to exclude inhibition of TPO activity.

Although the precise mode of action is unclear, it can be concluded from the *in vivo* mechanistic studies that OMC (and by inference IPMC) can perturb the rat HPT axis. This is consistent with the T4 data from a further developmental neurotoxicity study in rats (Axelstad *et al.*, 2011). However, no adverse effects have been observed in the available mammalian *in vivo* studies on OMC, which can be plausibly linked to a thyroid disrupting mode of action. Currently, the need for further investigations for thyroid disruption in mammals is uncertain due to the lack of clear thyroid related behavioural effects in the developmental neurotoxicity study (Axelstad *et al.*, 2011), the lack of agreement about which other endpoints are regarded as adverse and the lack of standardised methods to investigate such endpoints.

However, amphibians are sensitive to thyroid hormone perturbation and it is not possible to conclude from the limited ecotoxicological information available on OMC or IPMC that adverse effects in amphibian species would not occur. A study is therefore required to determine whether the mechanistic interactions observed with OMC, could lead to adverse effects in amphibian (sub)populations at relevant environmental concentrations of the registered substance. Based on the results of a limit or range-finding test, it may be possible to conduct an Amphibian Metamorphosis Assay (OECD TG 231) as an initial screening step at Level 3 in the OECD CF. However, if effects in this are anticipated (or indicated), it would be more appropriate to conduct a Larval Amphibian Growth and Development Assay (OECD TG 241) at Level 4 in the OECD CF. The decision on the final choice concerning which of the above mentioned two test(s) to conduct in order to fully address this concern rests with you as the Registrants. The results may provide further information on thyroid disruption which could be used in conjunction with the current database and any new scientific or test method developments to evaluate whether additional testing may be necessary.

#### What is the possible regulatory outcome

Possible regulatory outcomes are that further information may be required to address the potential environmental hazard or risk, or that the registered substance may, or may not, be considered to be an environmental endocrine disruptor according to the current World Health Organisation/International Programme on Chemical Safety working definition (WHO/IPCS, 2002). This may trigger its consideration as a possible substance

of very high concern (SVHC) under REACH Article 57(f) along with further subsequent regulatory risk management activity.

#### Considerations on the test method and testing strategy

The test is required to be conducted on the registered substance according to either OECD Test Guideline 231 (Amphibian Metamorphosis Assay) or OECD Test Guideline 241 (Larval Amphibian Growth and Development Assay). It should investigate potential endocrine-mediated effects resulting from exposure to the test substance according to recommendations in the test guideline. The test should identify whether the registered substance can interfere with the normal function of the HPT axis during the metamorphosis of amphibian tadpoles or on their growth and development, normally from the species *Xenopus laevis*. The study should be conducted up to the limit of solubility of the registered substance in the test medium and close attention should be paid to the analysis and presentation of actual measured concentrations of the substance. Reference should be made to OECD Guidance document (No. 23) on aquatic toxicity testing of difficult substances and mixtures. Based on pre- or range-finding tests, it may be possible to conduct this as a limit test, but if any potential ED-related effects are seen, then it would be desirable to determine a no observed effect concentration (NOEC) value for these effects.

The full study report should be submitted to allow consideration of the raw data and their statistical analysis. If it is first decided to conduct a screening study at Level 3 in the OECD CF, i.e. an Amphibian Metamorphosis Assay (AMA), OECD TG 231, then, depending on the results from this and other studies requested in this decision, further testing according to Level 4 in the OECD CF may be required at a later stage (i.e. the Larval Amphibian Growth and Development Assay (LAGDA), OECD TG 241). Alternatively the LAGDA test may be conducted in the first instance.

#### Consideration of alternative approaches

No other approaches have been presented in the registration dossier regarding effects of IPMC or OMC on the HPT endocrine axis of fish or amphibians, but ECHA has assessed whether alternative approaches could be used to address the concern expressed in this Decision. ECHA considers that there are sufficient reliable *in vitro* and *in vivo* mammalian data on OMC already at Levels 2 and 3 in the OECD CF to indicate a plausible endocrine mode of action of OMC and IPMC on thyroid hormones or pathways. Therefore non-mammalian *in vitro* testing just focussed on determining this mode of action is not justified as the concern would remain.

It may also be possible for the test to be conducted on the structural analogue substance OMC, for which Substance Evaluation on similar issues has also been undertaken. However, a scientifically reasoned case justifying read-across of results from a study on OMC to the registered substance would be necessary (according to ECHA's Read Across Assessment Framework (RAAF), 2015 or later version). This would need to present evidence to allow conclusions to be drawn about relative potencies and bioavailability of the two substances in aquatic test systems.

#### Consideration of your comments on the draft decision and PfAs and of the PfAs

In your comments you agreed to perform the study, but will consider testing OMC and reading across the result, as offered above. You consider ecotoxicological read-across is appropriate based on structural similarity, however more information is needed to assess the similarity of bioavailability. You indicate that the latter is currently compromised by

the lack of comparability of water solubility and n-octanol-water partition coefficient values for the two substances. To address this, you propose new studies for these two endpoints using the same test methods and laboratory. You agreed that if read-across is then used, you will document this in your registration dossier according to the ECHA RAAF. ECHA acknowledges your proposal to perform new physico-chemical studies to support the read-across. At present the read-across can only be evaluated using the available data. ECHA highlights the RAAF sets out various elements to justify read-across, not just physico-chemical similarity.

You made several suggestions for the AMA test design. Firstly you suggested to determine the water solubility of the substance under relevant test conditions. ECHA agrees that this would be useful to ensure the study can be performed at or up to the limit of solubility. ECHA highlights that the measurements should be made without the addition of test organisms.

You also proposed to conduct the study as a limit test at the limit of water solubility under relevant test conditions. If adverse effects occur, you would then conduct a full study. The option for this test design was already offered in the draft decision and it is in principle reasonable and in the interests of animal welfare. If you do use this approach you will need to ensure that there are no statistically significant effects to allow a conclusion of "no effects" from the limit test, and provide justification for the statistical approach used. You will also need to ensure that the test is not performed at concentrations causing lethality. If read-across is being used, you will need to show that the acute ecotoxicity values for IPMC do not contradict any NOEC in the new study for OMC.

You noted that the test is designed to provide a NOEC, rather than EC<sub>x</sub>, and the Decision has been amended accordingly.

Finally you also suggested sharing the draft study protocol and relevant pre-test results with the evaluating MSCA for approval of the protocol. The evaluating MSCA is ready to comment on the draft study protocol, although it will not be in a position to provide "approval" as final responsibility for the test and assessment lies with you as the Registrants.

Two Member State Competent Authorities (MSCAs) made proposals for amendment (PfAs) on this request, and in response this decision has been amended to offer a choice of whether you (or the Registrants for OMC) conduct either the AMA (OECD TG 231) or LAGDA (OECD TG 241) test. However, the suggestions for designing and conducting the test can equally be applied whichever test guideline is chosen.

In your subsequent comments on the PfAs made by MSCAs, you disagreed with the suggestion from one MSCA that 'there is a high likelihood for adverse effects in amphibians' so requiring the performance of a LAGDA instead of an AMA test. You have indicated that you still consider it appropriate to first conduct the AMA test along with some initial screening and range-finding studies to determine any acute toxicological threshold. If there was a positive outcome in the AMA test it is likely that you would, in any case, need to further address this concern using a LAGDA study.

Additionally one MSCA proposed revisions to the text relating to the summary of the mammalian data used to justify this request. Taking your comments on this PfA into account the suggested text on the uncertainties in the current mammalian database has been revised.

With respect to the deadline in the draft decision, you requested that this is extended to be the same as OMC. You argued that this is necessary as the data required to support the read-across may not be available within the deadline for IPMC. If the timescales were the same you indicate that the dossier updates could be prepared together.

The evaluating MSCA considered this request. Originally the deadline of 21 months for IPMC was the sum of 15 months for the amphibian and fish studies performed in parallel, and 6 months for the environmental exposure update. The same calculation was used for OMC, but that deadline also included other requests making a total of 33 months. These other requested studies, if performed on OMC, have no impact on the IPMC testing. If you decide to use read-across as described above, the preparation of the amphibian and fish Robust Study Summaries for IPMC could occur in parallel with OMC, and would be straightforward as the text could then be copied across from OMC. As above, the amphibian and fish tests were allocated 15 months for both substances, and previously there was no reason to extend this. For consistency with the timing of the OMC amphibian and fish tests, the deadline for IPMC was extended to 24 months. It was considered that the additional time could be used by you to assess the validity of the read-across which would need to be done prior to conducting the AMA and FSDT tests. This could include any new physico-chemical testing.

In a PfA it was subsequently suggested to split the revised deadline of 24 months into a deadline of 18 months for the AMA/LAGDA study and the Fish Sexual Development Test OECD 234, with a further 6 months for the exposure assessment information. In your comments on this proposal you anticipated 18 months for the endocrine disruption testing would be insufficient, citing your comments made on the draft decision requesting ED information on OMC (the results of which you plan to read-across to IPMC). Specifically you cited the need for extensive preliminary testing due to the poor water solubility and high log Kow of the substance, together with your proposal for a non-GLP Fish Early Life Stage (FELS) test (OECD 210) and acute amphibian testing for range-finding purposes. While ECHA considers the original test time scale would allow for preliminary testing, the need for the FELS test could result in more time being required than normal for the FSDT. As the test deadlines for the AMA/LAGDA and FSDT were increased by 6 months as specified in the Decision for OMC, for consistency the same deadlines are applied in this Decision.

### Conclusion

Therefore, based on the substance evaluation and in accordance with Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the registered substance subject to this decision:

A study conducted according to either an Amphibian Metamorphosis Assay, OECD Test Guideline 231, **or** a Larval Amphibian Growth and Development Assay, OECD Test Guideline 241.

### **2. Fish Sexual Development Test OECD 234**

#### The concern(s) identified

The concern is related to the potential for environmental endocrine disruption in non-mammalian (fish) species. The endocrine activity of the substance in fish should be clarified in order to determine whether it poses a hazard and/or risk to the environment.

### Why new information is needed

Information is available from *in vitro* and *in vivo* studies on mammalian and non-mammalian species which indicates that the registered substance and a structurally similar one (OMC) could interact with the hypothalamic-pituitary-gonadal (HPG) axis of the endocrine system in fish. In your chemical safety assessment you have claimed it is possible to use the data on OMC to also determine the ED potential of IPMC and it is the opinion of ECHA that the data does indicate a potential interaction of both substances with the HPG axis. The *in vitro* studies on the registered substance (for example Kunz and Fent, 2006) suggest that IPMC could both act as an androgen receptor agonist and antagonist, and an oestrogen antagonist, but it shows low potency.

Studies on OMC at Level 3 in the OECD CF for Testing and Assessment of Endocrine Disruptors (OECD, 2012) also indicate potential HPG effects, in particular those by Christen *et al.* (2011), Inui *et al.* (2003) and Zucchi (2011). In the study by Christen *et al.* (2011), adult male and female fathead minnow (*Pimephales promelas*) were exposed to mean measured concentrations of 5.4, 37.5, 245 and 394 µg OMC/L for 14 days. There was statistically significant down-regulation of the oestrogen receptor gene (ER $\alpha$ ) at 394 µg/L OMC, the androgen receptor (AR) at 37.5, 244.5 and 394 µg/L OMC and 3 $\beta$ -hydroxysteroiddehydrogenase (3 $\beta$ -HSD) at 244.5 and 394 µg/L OMC in the liver of female fish (all by more than 1.5x compared with controls). This indicated potential anti-oestrogenic and anti-androgenic activity following exposure to OMC. Activity of 3 $\beta$ -HSD was also down-regulated in the liver of male fish, indicating some oestrogenic activity. Changes in gene expression were organ specific as there was no significant effect on ER $\alpha$ , AR or 3 $\beta$ -HSD in the brain or ovary of female fish and there was no effect of ER $\alpha$  or AR in male fish (any organ). Plasma VTG levels were significantly increased in male fish exposed at 244.5 µg OMC/L but this was not dose-dependent as no significant effects were seen at the highest test concentration. There was no significant effect of OMC on gonadosomatic index (GSI) or on the number or score of nuptial tubercles, but there were significant effects reported on the histology of male and female fish gonads at the highest test concentration of 394 µg/L OMC, these effects were interpreted by the authors as consistent with an oestrogenic or anti-androgenic effect.

In the study by Inui *et al.* (2003), the potential oestrogenic effects of OMC on adult male Japanese Medaka (*Oryzias latipes*) were investigated. The fish were exposed to nominal concentrations of 0.034, 0.34, 3.4 and 34 mM OMC for seven days, but maintenance of these concentrations was not analytically verified. There were indications that plasma VTG levels were slightly elevated in a dose-dependent manner, but no level of statistical significance was given. There were, however, significant effects reported in a dose-dependent manner at all concentrations on mRNA expression of oestrogen mediated genes for VTG and also in choriogenin (CHG) proteins and for the oestrogen receptor (ER $\alpha$ ). These effects could be consistent with positive autoregulation of this receptor following exposure to oestrogenic compounds.

In the study by Zucchi *et al.* (2011), adult male zebrafish (*Danio rerio*) were exposed to median measured concentrations of 2.2 and 840 µg/L OMC for 14 days. OMC caused slight but statistically significant up- and down- regulation of key genes associated with hormonal pathways with some evidence for oestrogenic activity (ER $\alpha$  in the whole body; ER $\beta$  in the whole body and liver; VTG-1 in the liver) and anti-androgenic activity in the liver and whole body of fish. Conversely, there was down-regulation of VTG-1 in all other tissues except the liver. The authors concluded that OMC weakly affects genes involved in hormone pathways, but they also reflected that it is difficult to link the results of this study to a specific mode of action. OMC may act through several mechanisms/modes of action involved in the sex hormonal pathways, and this may explain the varied changes



in gene expression observed. However, owing to the varied and inconsistent gene expression levels found in the whole body and specific tissue analysis, it is felt that the results of this study are not conclusive in determining a potential for apical, population-relevant endocrine disrupting (ED) effects in fish.

Considered altogether, the above information points towards alterations in gene expression of various (anti-) oestrogenic and androgenic pathways and in VTG levels in fish consistent with some evidence of endocrine activity. This is sufficient to lead to a concern also with the registered substance, IPMC.

However, the information is also inconclusive due to inconsistencies in whether effects were up- or down-regulated, whether they were all statistically significant and uncertainties over the exposure concentrations in the studies. All were non-standard guideline, public domain studies and many effects were observed above the reported limit of solubility of OMC (0.22-0.75 mg/L). Not all of the data were supported by clear and direct measurement of relevant physiological endpoints. A further reliable (Klimisch 2) Level 3 study on fish by Kunz *et al.* (2006) did not show in any VTG induction in fathead minnow following a 14-day exposure to OMC.

Although the precise mode of action is unclear, it can be concluded from the *in vitro* and *in vivo* studies that OMC and IPMC can perturb the rat HPG axis. The substance may affect several mechanisms/modes of action involved in the sex hormonal pathways, examples of mechanistic/mode of action observations are decreased GnRH release *ex vivo* and increased luteinising hormone (LH) levels *in vivo*, decreased sex hormone levels *in vivo*, estrogenic activity *in vivo* and progesterone receptor antagonism *in vitro*. A decrease in sperm counts was observed in two *in vivo* rodent studies and a decrease in relative prostate weights was observed by Axelstad *et al.* (2011). However, no clear adverse effects were observed on sexual function and fertility, and development in standard studies in experimental animals (OECD CF 4/5) for OMC.

Establishing a link between these changes and one specific endocrine mode of action is challenging since OMC may act through several modes of action at the same time. The uncertainty about which mode of action to investigate and the lack of effects in standard fertility and developmental toxicity studies makes further investigations for sex hormone disruption in mammals difficult to justify.

For fish, no relevant data are available from standard *in vivo* studies falling in OECD CF Levels 4 or 5 which would provide adequate information on apical effects in fish, such as fecundity, reproduction and development - alongside mechanistic effects to confirm cause and effect. In order to clarify the relevance of the reported interactions with the HPG axis in fish, a Level 4 Fish Sexual Development Study (FSDT) OECD TG 234 is therefore required to confirm these observations from the public domain data and determine whether such interactions could lead to actual adverse effects on fish (sub)populations at relevant environmental concentrations. It is possible that the requested fish study will provide additional information which can be used in conjunction with the current database and any new scientific or test method developments to evaluate whether additional testing may be necessary.

#### What is the possible regulatory outcome

Possible regulatory outcomes are that further information may be required to address the potential environmental hazard or risk, or that the registered substance may, or may not, be considered to be an environmental endocrine disruptor according to the current World Health Organisation/International Programme on Chemical Safety working

definition (WHO/IPCS, 2002). This may trigger its consideration as a possible SVHC under REACH Article 57(f) along with further subsequent regulatory risk management activity.

#### Considerations on the test method and testing strategy

The test is required to be conducted according to OECD Test Guideline 234 (Fish Sexual Development Test). It should investigate potential endocrine-mediated (anti-) oestrogenic or androgenic effects resulting from exposure to the test substance according to recommendations in the test guideline. These effects should include (but not necessarily be restricted to) investigation of blood VTG levels, sex ratio, gonad histopathology (according to OECD Guidance document No. 123), including genetic sex determination. Because of the possibility for genetic sex determination, it may be preferable to conduct the study on Japanese Medaka (*Oryzias latipes*), however the test guideline is also validated for Zebrafish (*Danio rerio*) and this species could be used instead since there are currently no clear indications of significant differences in species sensitivity. Histopathological examination of both liver and kidney should also be performed. The study should be conducted up to the limit of solubility of the substance in the test medium and close attention should be paid to the analysis and presentation of actual measured concentrations of the substance. Reference should be made to OECD Guidance document (No. 23) on aquatic toxicity testing of difficult substances and mixtures. Based on pre- or range-finding tests, it may be possible to conduct this as a limit test, but if any potential ED-related effects are seen, then it would be desirable to determine a NOEC and/or EC<sub>10</sub> value for these effects. If the full test is required, it should be performed using five test concentrations together with controls.

The full study report should be submitted to allow consideration of the raw data and their statistical analysis. Depending on the results of this and other studies requested in this decision, further testing according to Level 5 in the OECD CF may be required (e.g. a Medaka Extended One Generation Reproduction Test (to OECD TG 240) or Full Fish Life-Cycle Test).

#### Consideration of alternative approaches

No other approaches have been presented in the registration dossier regarding effects of IMPC or OMC on the fish HPG endocrine axis, but ECHA has assessed whether alternative approaches could be used to address the concern expressed in this Decision.

One approach would be to undertake testing first using a Level 3, 21-day Fish Screening Assay (OECD TG 230) or a Fish Short Term Reproduction Assay (OECD TG 229). However, if positive endocrine disruption results were seen in this alternative test, then the Fish Sexual Development Test would still be required and this would not be in the interests of animal welfare. A further Level 3 test would not investigate the range of mechanistic and apical endpoints of a Level 4 test, nor show how these are linked. ECHA also considers that there are sufficient reliable *in vitro* and *in vivo* mammalian and non-mammalian data already at Levels 2 and 3 in the OECD CF to indicate a plausible mechanistic endocrine mode of action of OMC (and by inference IPMC) on oestrogenic or androgenic hormones or pathways. Therefore further testing at these lower Levels is not justified as the concern would remain.

It may also be possible for the test to be conducted on the structurally similar substance OMC, for which Substance Evaluation on similar issues has also been undertaken. However, a scientifically reasoned case justifying read-across of results from a study on

OMC to the registered substance would be necessary (according to ECHA's Read Across Assessment Framework, 2015 or later version). This would need to present evidence to allow conclusions to be drawn about relative potencies and bioavailability of the two substances in aquatic test systems.

ECHA has also considered whether to request the two ED tests in this decision in parallel or sequentially. Two different modes of action are investigated, and for any required risk management, this would need to be specifically protective of the adverse effects resulting from each mode of action. This means the outcome of both tests will be required as the sensitivity of each mode of action needs to be understood. If only one test was conducted, even if this indicated the substance was an SVHC, it would not be known if the second test indicated greater sensitivity (and hence require more stringent risk management). Therefore, as both tests are required, there is no reason to request these sequentially.

#### Consideration of your comments on the draft decision and PfAs and of the PfAs

In your comments you agreed to perform the study, but will consider testing OMC and reading across the result, as offered above. You consider ecotoxicological read-across is appropriate based on structural similarity, however more information is needed to assess the similarity of bioavailability. You indicate that the latter is currently compromised by the lack of comparability of water solubility and partition coefficient values for the two substances. To address this you propose new studies for these two endpoints using the same test methods and laboratory. You agreed that if read-across is then used, you will document this in your registration dossier according to the ECHA RAAF. ECHA acknowledges your proposal to perform new physico-chemical studies to support the read-across. At present the read-across can only be evaluated using the available data. ECHA highlights the RAAF sets out various elements to justify read-across, not just physico-chemical similarity.

You made several suggestions for the test design. Firstly you suggested to determine the water solubility of the substance under relevant test conditions. ECHA agrees that this would be useful to ensure the study can be performed at or up to the limit of solubility. ECHA highlights that the measurements should be made without the addition of test organisms.

You proposed to conduct a non-GLP OECD TG 210 Fish Early Life Stage (FELS) study at the limit of water solubility under relevant test conditions as a pre-test to evaluate chronic toxicity endpoints. Depending on the results the FSDT will be carried out either as a limit test or as a full test with at least five test concentrations and an appropriate control group. ECHA agrees that in the absence of chronic fish data for IPMC, performing the non-GLP FELS test as proposed is a reasonable approach. The possibility of a limit test FSDT was already offered in the Decision, and in principle reasonable and in the interests of animal welfare. If you do use this approach you will need to ensure that there are no statistically significant effects to allow a conclusion of "no effects" from the limit test, and provide justification for the statistical approach used. ECHA agrees that if the full test is performed this should be using at least five test concentrations and an appropriate control group. If read-across is being used, you will need to show that the acute ecotoxicity values for IPMC do not contradict any NOEC in the new study for OMC.

You stated that the diagnosis of endocrine-related histopathology will be done according to the corresponding OECD guidance document. ECHA confirms this should be OECD GD 123, and the reference has been added to the test specification above.

You suggested to additionally include histopathological examination of both liver and kidney, highlighting that this will aid interpretation of general toxicity when assessing ED-related endpoints. ECHA agrees that this is a useful additional analysis, and have added this to the test specification above.

You suggested (also in your subsequent comments to the PfAs) that the test is designed to provide a NOEC, rather than ECx. While the decision was initially amended to reflect this comment, in a PfA made by a MSCA, it was highlighted that the OECD 234 test guideline can also be used to determine an ECx in relation to certain endpoints (e.g. for VTG measurements). Therefore, the decision has not been amended. The most appropriate response variables (ECx and/or NOEC) to include in the final study report are ultimately for you and the conducting laboratory to determine.

Finally, you suggested sharing the draft study protocol and relevant pre-test results with the evaluating MSCA for approval of the protocol. The evaluating MSCA is ready to comment on the draft study protocol, although it will not be in a position to provide "approval" as final responsibility for the test and assessment lies with you as the Registrant(s).

Three MSCAs made PfAs that the species to be used in the test should include Zebrafish as well as Japanese medaka. These cited a lack of current evidence that Zebrafish (despite the lack of a single genetic sex marker) are less sensitive than Japanese medaka, as well as the possibility for you to consider contract laboratory experience with the different species. Consequently the decision was amended to offer the option of either Japanese medaka or Zebrafish. In your subsequent comments, you agreed with these PfAs.

Additionally one MSCA proposed revisions to the text relating to the summary of the mammalian data used to justify this request. Taking your comments on this PfA into account the suggested text on the uncertainties in the current mammalian database has been revised.

### Conclusion

Therefore, based on the substance evaluation and in accordance with Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the registered substance subject to this decision:

A Fish Sexual Development Test using either Japanese Medaka (*Oryzias latipes*) or Zebrafish (*Danio rerio*) according to OECD Test Guideline 234.

### **3. Environmental exposure assessment**

Provide information and justification for parameters in the environmental exposure assessment within the Chemical Safety Report (CSR), specifically:

- Justify the split of supply tonnage for consumer use (consumer and professional) for the exposure scenario "end-use of cosmetics";
- Justify the choice of Fraction Main Local Source (FMLS) and tonnage allocation to the region;
- Justify how the direct emission is modelled;
- Provide information on the per cent weight/weight (w/w) concentration of IPMC used in consumer products (including typical mean concentrations in specific product types, if there is significant variation, and the range).

### The concern(s) identified

ECHA is concerned that IPMC may pose a risk to the environment, but there are insufficient data available to allow a reliable conclusion to be drawn. Risk characterisation ratios (RCRs) for consumer use are close to one (█), but there are aspects of the methodology using non-default data which lack justification. Using default values suggest that RCRs could be above 1.

IPMC is a chemical supplied with all professional and consumer applications stated to be wide dispersive use in the CSRs. It is also used in consumer products that are either "down-the-drain" applications or result in direct environmental exposure. It is therefore very important to clarify any environmental risk that IPMC might pose, and ensure any risk management is adequate.

A second concern relates to whether IPMC is an environmental ED substance as described above. If the substance is determined to meet the REACH Article 57(f) criteria (equivalent level of concern) a decision will be needed on the most appropriate risk management. In making this decision, it is important for ECHA to understand the use pattern and be certain about the environmental exposure. This is required to ensure the effectiveness of any new risk management proposed.

### Why new information is needed

At present ECHA considers that the available data are insufficient to allow an accurate assessment of environmental exposure to be made. A number of aspects require additional information, justification or explanation to provide confidence in the assessment, and therefore the environmental exposure. The specific issues are listed below.

#### *Justify split of supply tonnage for consumer use (consumer and professional) end-use of cosmetics*

In the environmental exposure assessment, you provide two consumer use scenarios: one models use with discharge to a wastewater treatment plant (WWTP) and the other models direct release to the aquatic environment (without WWTP) for IPMC used in sunscreens outdoors.

You allocate more than 90%<sup>4</sup> of the supply volume to discharge via a WWTP, with the remainder assumed to be directly released to the environment. The amount for direct release is justified in the CSR as being *based on the assumption that [this] percentage of the EU tonnage was released directly to the aquatic environment through outdoor activities*. It is not clear what the source of the original percentage value is. In correspondence with the evaluating MSCA, you indicated that the value is considered to effectively be a "worst case", although you did not have any data to support your assumption. Prior to any risk management decisions, it is important to have more accurate data on use pattern and emissions to ensure that control measures are suitably targeted. The justification for the chosen value is also important because the RCRs in the CSR for the current exposure scenarios are very close to one (for example, the summed wide dispersive use local aquatic RCR is █). Small changes in the assumptions about release could lead to risks, which would need to be addressed.

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<sup>4</sup> The actual tonnage information is confidential and not included in this Decision.

*Justify choice of Fraction Main Local Source (FMLS) and tonnage allocation to the region*

For the consumer use involving discharge via a WWTP, you use a *percentage of tonnage used at a regional scale* of 5.3% and a FMLS of 0.00075. These are smaller values than the default values (appropriate for the supply volume and use of IPMC) in the ECHA Guidance R16 on Environmental Exposure assessment. As a consequence the PECs are also smaller than would be calculated using default values.

The parameters are two of the key values that determine the chemical load estimated to reach the "standard WWTP" serving 10000 people. The default values are intended to reflect average per capita usage, but account for causes of variation such as seasonality (for example for anti-freeze chemicals), and country-specific consumption.

The values for regional tonnage and FMLS used by the registrant are stated in the CSR to be based on refined consumption pattern information in Roche *et al.* (2010). This paper builds on the previous Human and Environmental Risk Assessment (HERA). The HERA approach aimed to refine the default release scenario values in the environmental risk assessment for chemicals used in domestic washing and cleaning products: the "HERA detergents scenario". This was principally designed for High Production Volume (HPV, >1000 t/y) chemicals. Roche *et al.* (2010) extends the HERA scenario to HPV household and cosmetic products. This is important as chemicals in these products may not be HPV substances. The paper summarises product usage data for nine types of household and cosmetic products, i.e. laundry, surface care, toilet care, dishwashing, hair care, oral care, deodorant, body care and bleach. The paper does not recommend a specific value for the regional tonnage fraction, but provides several statistics for each product category. The closest to the value used for IPMC (5.3 %) is the maximum value for hair care (5.36 %). Roche *et al.* (2010) does not discuss FMLS. In the HERA assessment, the default FMLS of 0.002 (for cleaning/washing agents and cosmetics) is refined for HPV chemicals but remains unchanged for Low Production Volume (LPV) chemicals.

For a LPV such as IPMC, it is much less clear whether the kind of averaging performed by HERA or Roche *et al.* (2010) is appropriate. This is principally because some applications of IPMC, for example in sun screen, will be seasonal in use, and may well also vary more latitudinally, for example within a "region". In addition, the categories (and sub-categories) used by Roche *et al.* (2010) do not appear to include sun screen, or the other uses (mentioned in the CSR formulation lifecycle stage) described in the CSR. This means it is unclear which, if any, of the values provided by Roche *et al.* (2010) can be used to allow an estimation of likely usage of cosmetics containing IPMC at a country level across the EU, and thus by extrapolation allow the default regional tonnage value to be refined.

In correspondence with the evaluating MSCA, you indicated that the values used are from the Cosmetics Europe specific environmental release category (spERC) for wide dispersive use of down the drain products (hair and skin care products). ECHA has reviewed the spERC, but there is no supporting information to justify the values or their origin, so the concern described above remains about the applicability to IPMC.

Therefore, you need to provide justification for the values chosen for the regional tonnage fraction and FMLS. Any values different to the default need to be supported by use-specific information for IPMC.

*Provide more information and justify how the direct emission is modelled*

The CSR describes this use as “outdoor activity”, and ECHA appreciates that direct emission to the aquatic environment is most likely to be result from bathers in freshwater (e.g. rivers, lakes) or in the sea. However, it is not clear what modelling steps you use to calculate a local aquatic PEC from the initial input tonnage allocated to direct emission. The CSR only indicates the regional tonnage fraction and does not mention the FMLS value in this scenario. ECHA can calculate a similar RCR value to you by applying the same regional tonnage assumption and FMLS as for the indirect emission modelling. However, as described above ECHA is not convinced by the reasoning for the choice of those refined values.

It is also unclear exactly what the local aquatic PEC from this scenario is intended to protect. Generally, it is expected that the PEC would provide a “reasonable worst case” environmental concentration. However, by its nature, direct emission will vary depending on the number of people on, for example, a beach. While clearly it is not possible to model every possibility, it needs to be clear what standard scenario you have modelled to ensure safe use. You should also include a sensitivity analysis to indicate the effect of the assumptions used.

*Concentration used in consumer products*

The maximum concentration of IPMC permitted by the Cosmetic products regulations (EC No 1223/2009) is 10% w/w. However, the actual concentrations used in cosmetic products may be lower. For any future risk management consideration, it is important to understand the typical concentration (and range) for relevant product types, because this will affect the distribution of the substance (e.g. if it is used at lower concentrations, there will be more formulated product and environmental emissions may then be more diffuse).

What is the possible regulatory outcome

These data will be used to confirm whether there are environmental risks. If there are, these will need to be addressed through additional data gathering. For example further ecotoxicological testing may be required, such as a 21-day Daphnia magna reproduction toxicity study, as part of a follow-up decision. If it is not possible to refine the risk assessment with further data, risk management will be needed, for example by limiting the amounts of substance that can be used in final products.

Secondly, the environmental exposure assessment will inform any future risk management decisions if the substance is determined to be SVHC due to endocrine disrupting properties. Refined information on the use pattern and environmental exposure at different lifecycle stages will ensure the most appropriate risk management measure is chosen.

Consideration of alternative approaches

This request has been tiered in a sequential order so that the hazard data (requests 1 and 2) are produced first.

No obvious alternatives are available: the request to justify parameters in your environmental exposure assessment is suitable and necessary to obtain information that

will allow to clarify whether there is an environmental risk. More explicitly, there is no equally suitable alternative way available of obtaining this information.

You could rely on default estimates for the purpose of the current CSR, and address any risks by refining other aspects of the risk assessment. However there is a limit to such an approach, for example the assessment factor used to derive the PNEC can only reduce to 10 using standard ecotoxicity data of fish, Daphnia and algae, and exposure refinement will be necessary.

In addition, if risk management is necessary as a result of future SVHC identification (e.g. due to the confirmation of endocrine disrupting properties that are considered to be an equivalent level of concern under REACH Article 57(f)), ECHA requires a more reliable environmental exposure assessment.

#### Consideration of registrants' comments on the draft decision

In your comments you acknowledge that there are deficiencies in your current environmental exposure assessment for the "end-use of cosmetics" modelling. You also indicate that together with the evaluating MSCA, you are going to work towards the development of a SpERC for the direct release of UV filters into the environment.

ECHA notes your acknowledgement, and that the evaluating MSCA agreed to work with the registrants on the spERC development as a general initiative resulting from the industry/ECHA workshop on UV filters on 7 March 2017.

You ask that if the evaluating MSCA has information on emission patterns of UV-filters this is shared with you. The evaluating MSCA has no specific information. The request to update this aspect is because the current proposed emissions in the CSR lack sufficient justification, particularly when the sources you have used are reviewed. Any references cited in the Decision are publically available and based on either references in your CSR or sources within those references.

#### Conclusion

Therefore, based on the substance evaluation and in accordance with Article 46(1) of the REACH Regulation, ECHA concludes that you are required to provide the following information for the registered substance subject to this decision:

- Provide information and justification for parameters in the environmental exposure assessment within the Chemical Safety Report as further specified above in this Appendix.



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## **Appendix 2: Procedural history**

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to potential endocrine disruption, wide dispersive use/consumer use, Isopentyl p-methoxycinnamate (IPMC) CAS No 71617-10-2 (EC No 275-702-5) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2016. The updated CoRAP was published on the ECHA website on 22 March 2016. The competent authority of the United Kingdom (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

In accordance with Article 45(4) of the REACH Regulation, the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision under Article 46(1) of the REACH Regulation to request further information. It subsequently submitted the draft decision to ECHA on 21 March 2017.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation as described below.

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

### **Registrant(s)' commenting phase**

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took the comments from you, which were sent within the commenting period, into account and they are reflected in the reasons (Appendix 1). The deadline was amended.

### **Proposals for amendment by other MSCAs and ECHA and referral to the Member State Committee**

The evaluating MSCA notified the draft decision to the competent authorities of the other Member States and ECHA for proposal(s) for amendment.

Subsequently, the evaluating MSCA received proposal(s) for amendment to the draft decision and modified the draft decision. They are reflected in the reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

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

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



### **MSC agreement seeking stage**

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-58 meeting and ECHA took the decision according to Article 52(2) and 51(6) of the REACH Regulation.

### **Appendix 3: Further information, observations and technical guidance**

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.
2. Failure to comply with the request(s) in this decision, or to otherwise fulfil the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.
3. In relation to the required experimental study/ies, the sample of the substance to be used ('test material') has to 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 material to be subjected to the test(s) subject to this decision and to document the necessary information on the 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.
4. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who will carry out the study 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. 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](https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx)

Further advice can be found at <http://echa.europa.eu/regulations/reach/registration/data-sharing>. If ECHA is not informed of such agreement within 90 days, it will designate one of the registrants to perform the stud(y/ies) on behalf of all of them.