EUROPEAN CHEMICALS AGENCY

Helsinki, 30 June 2016

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

For climbazole, CAS No 38083-17-9 (EC No 253-775-4)

Addressees: Registrant(s)[1] of climbazole (Registrant(s))

This decision is addressed to the Registrant(s) of the above substance with active registration pursuant to Article 6 of the REACH Regulation on the date on which the draft for the decision was first sent for comments. If Registrant(s) ceased manufacture upon receipt of the draft decision pursuant to Article 50(3) of the REACH Regulation, they did not become addressee(s) of the decision. A list of all the relevant registration numbers of the Registrant(s) that are addressees of the present decision is provided as an Annex to this decision.

Based on an evaluation by the Health and Safety Executive as the Competent Authority of the United Kingdom (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 Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 6 May 2015 i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(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 dossier(s) of the Registrant(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.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of the United Kingdom has initiated substance evaluation for climbazole, CAS No 38083-17-9 (EC No 253-775-4) based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and owing to initial grounds for concern relating to human health / suspected CMR (reproductive toxicity, with unusual and severe general toxicity noted) and human exposure (wide dispersive use, consumer use), climbazole was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2014.

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.

The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of the United Kingdom was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding worker exposure and, for the environment, the risk assessment and endocrine disruption.

The evaluating MSCA considered that further information was required to clarify the above-mentioned concerns. Therefore, 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 24 March 2015.

On 6 May 2015 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.

Registrant commenting phase

By 18 June 2015 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay.

The evaluating MSCA considered the comments received from the Registrant(s). On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

The draft decision as submitted to the Registrant(s) for commenting included the information requirement for the chronic fish toxicity end point. This has been removed at this time while the aquatic PNEC and PEC are refined with additional information. A further reason for postponement is that further fish testing might possibly be necessary to investigate endocrine disruption potential in due course. For animal welfare reasons, it may be preferable to consider a chronic test that can assess both apical and endocrine effects, if fewer animals are needed. However, this is subject to the outcome of the proposed *in vitro* assays.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 22 January 2016 the evaluating MSCA 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 of the receipt of the notification.

Subsequently, two Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 26 February 2016 ECHA notified the Registrant 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 those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and amended the draft decision.

Referral to Member State Committee

On 7 March 2016 ECHA referred the draft decision to the Member State Committee.

By 29 March 2016, the Registrant(s) did not provide comments on the proposals for amendment, in accordance to Article 51(5) and on the draft decision.

After discussion in the Member State Committee meeting on 25-29 April 2016, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 29 April 2016. ECHA took the decision pursuant to Article 52(2) and 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 (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

1. **Extended one-generation reproductive toxicity study (test method: OECD TG 443) in rats, oral route, with the registered substance, specified as follows:**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity); and**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

   and

2. **Simulation test – aerobic sludge treatment, A: activated sludge units, B: biofilms (test method OECD 303A or B);**

   The Registrant shall select, with justification, the most appropriate test methodology (OECD 303A or B).

3. ***In vitro* endocrine disruption screening studies;**

   H295R Steroidogenesis assay (test method OECD 456) with additional measurement of progesterone

   and either

   Stably Transfected Human Androgen Receptor Transcriptional Activation Assay for Detection of Androgenic Agonist and Antagonist Activity of Chemicals (Draft OECD Test Guideline due for finalisation in 2016), if adopted by time of testing

   Or

   Androgen Receptor Binding Assay (test method US EPA OPPTS 890.1150).

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall also submit the following information regarding the registered substance subject to the present decision:

4. Further information on worker exposure addressing the following aspects:

a. Descriptive text for each process/task within each exposure scenario shall be provided. This shall include: an explanation of the processes that are covered by each scenario and PROC code; the form in which the substance is present at each stage of the process; a justification for the choice of modelling parameters, including the choice of a non-default refinement factor applied to PROC 5 in exposure scenario 2; and

b. For those scenarios where climbazole is used as a solid dissolved in a liquid, the Registrant shall re-calculate the exposures with a tool that has the ability to model this condition of use or, alternatively, provide measured data. For modelled exposure estimates, a copy of the model output reports and a justification for each of the parameters selected shall be provided.

Deadline for submitting the required information

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **09 July 2018** an update of the registration(s) containing the information required by this decision[2], including robust study summaries and, where relevant, an update of the Chemical Safety Report.

The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

1. Extended one-generation reproductive toxicity study (Annex IX/X, Section 8.7.3; test method: OECD TG 443) in rats, oral route, with the registered substance

This request is relevant to a concern about the reproductive toxicity of climbazole and the nature of the unusual and severe general toxicity.

There was some evidence that climbazole had a specific effect on reproduction (sexual function and fertility; specifically, parturition and pregnancy outcomes) in the rat, although this interpretation was associated with a number of uncertainties in terms of the information available in the study reports.

Two studies provided information on these parameters: a one-generation reproduction study and a developmental toxicity study that was continued until lactation day 21. Both were conducted in the same strain of rat, at the same time (1979) and in the same test facility. A specific link to increased duration of gestation, maternal deaths and pup deaths was not made in the study reports. At 100 mg/kg/d, severe general toxicity was likely to have been a factor, but the situation is less clear at the mid-dose of 36 mg/kg/d, when toxicity in the parents was reported to be less severe and to decrease as the study progressed.

The systemic toxicity in adult animals was generally not well recorded in the study reports. Incidences, severity and individual animal data for clinical signs were not available, nor was information on systemic effects provided. The absence of detailed information on general toxicity makes it difficult to interpret the adverse effects on parturition, pregnancy outcome and female fertility. It is also not known if the dams with delayed onset of parturition

[2] The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).

exhibited maternal toxicity.

Other uncertainties in the interpretation of these studies were identified. For example, the purity of the test material was not stated in the reports. In the one-generation study, small numbers of dams were allowed to either deliver (maximum 9; 7 or 8 in the mid- and high-dose groups, respectively) or were available for *in utero* examination on GD 13. Group sizes were larger in the developmental toxicity study, but as a result of the excessive maternal toxicity at 100 mg/kg/d, which included the deaths of 16/20 dams during gestation, only two dams of this dose group delivered; consequently, the information on parturition and pregnancy outcomes in the high-dose group is limited in this study. Maternal toxicity was also reported in the mid-dose group and comprised hyperactivity, red ocular/nasal discharge, alopecia and self-mutilation (abdomen and extremities); the incidence of these effects was not reported. In this group, the duration of gestation was prolonged in 5/18 dams, although it is noted that gestation was also prolonged in some control animals. Full information on the pregnancy outcomes for all dams was not available in the study report or was inconsistent. Other than the gestation duration being increased, there was no information on the effect of climbazole administration on parturition; for example, if the onset of parturition was delayed but then proceeded normally, or if the labour was prolonged and difficult.

Therefore, the initial concern for reproductive toxicity has not been clarified and further information is requested to justify the existing concerns. The available information in the dossier indicates concerns relating to possible effects on parturition, pregnancy outcome and female fertility and the relationship of systemic toxicity in the adult animals to these. One of the manifestations of toxicity in the dams was reported as 'self-mutilation'. However, there was no detail on what this effect comprised.

In the initial draft decision sent to the Registrant(s) for commenting they were requested to conduct a combined repeated-dose toxicity study with the reproduction / developmental toxicity screening test (OECD 422) in rats by the oral route. The standard protocol was modified to better address the concerns identified (specifically effects on partrurition).

In their comments on the draft decision the Registrant(s) agreed to perform the modified OECD422 study because of the abovementioned concerns and uncertainties.

Proposals for amendment (PfAs) were received from 2 Member States. One proposed only changes to the study as requested, the other proposed two options; changes to the requested study OECD 422 or alternatively to perform a different study; the extended one-generation reproductive toxicity study (EOGRTS; OECD 443) (without the F2 but with the developmental neurotoxicity (DNT) and developmental immunotoxicity (DIT) cohorts) be requested instead of the OECD 422 study. In incorporating the suggested PfAs into the modified OECD 422 as requested, the final version of the study protocol was broadly comparable to the basic design OECD 443. The Registrant(s) made no comment on the proposals for amendment.

The relative merits of the modified OECD 422 and the basic design OECD 443 were discussed at the Member State Committee's 47th meeting and it was concluded that in using a similar number of animals, the OECD 443 would provide more information on endpoints leading to a more comprehensive assessment of reproductive toxicity which can contribute to regulatory risk management. This was highlighted as being important due to the severe reproductive hazard identified in a close structural analogue, triadimenol (EC [redacted]).

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study on the registered substance subject to this decision:
Extended one-generation reproductive toxicity study (test method: OECD TG 443) in rats, oral route, with the registered substance, specified as follows:

Dose level setting shall aim to induce some toxicity at the highest dose level;

- **Cohort 1A (Reproductive toxicity); and**
- **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

2. Simulation tests

This request is relevant to a concern about the environmental risk assessment and exposure assessment of climbazole.

ECHA is concerned that there may be aquatic risks based on an updated aquatic PNEC. This PNEC is based on the results of a study not originally used by the Registrants to derive the PNEC. The results of a published study using *Lemna minor* (Richter *et al*, 2013) are included in the registration dossier(s). However, as the full study protocol and results of this test were not available, the Registrant(s) gave this study a reliability score of 4 (not assignable) and did not use it to derive PNECs. The evaluating MSCA obtained additional information directly from the study authors. From this, it was concluded that the mean measured endpoints from the study were reliable and valid for PNEC derivation. Given this new information, the evaluating MSCA updated aquatic and sediment PNECs. A comparison of these PNECs to the PECs (derived in the CSR by the Registrant(s)) results in updated RCRs >1 and <10 for the aquatic environment for scenarios that include consumer use and regional background.

Very limited river monitoring using a semi-quantitative liquid chromatography mass spectrometry (LCMS) screening method detected climbazole at approximate concentrations in the range 0.009 µg/l – 0.01 µg/l, in three rural watercourses in England near sewage treatment plants (Environment Agency UK, 2014). These data confirm the presence of climbazole in the aquatic environment, suggesting PECs are realistic and the risks modelled by the evaluating MSCA using the updated PNEC may also be realistic. However, it is considered that the scope and coverage of the data are insufficient to refine the risk assessment.

To clarify the environmental risks of climbazole ECHA considers that information on the degradation of climbazole in a sewage treatment plant (STP) is required to refine environmental emissions and the PECs. Given the wide dispersive use including private (consumer) use exposure scenarios, STP fate information is required to update default risk assessment inputs.

The OECD 303 method assesses partitioning (to sludge and water) and degradation in an STP, thus providing further useful information to refine aquatic PECs. Overall, this study could be used to consider what percentage of climbazole reaching a STP is subsequently found in the effluent discharged to the river.

If risks remain following the provision of new fate data, further information on chronic fish toxicity may be required to refine the aquatic PNEC (depending also on conclusions about endocrine disruption potential – see Information Requirement 3 and section I).

In their comments on the draft decision the Registrant(s) said that the evaluating MSCA had not disclosed the additional data from the Richter *et al*. study and therefore it was not possible for them to comment on its validity or the updated aquatic PNEC. Consequently, the Registrant(s) rejected the requirement for simulation testing.

In response ECHA notes that the Richter *et al.* (2013) study is publically available. While the Registrant(s) gave the study a reliability score of 4 (unassignable) based on the absence of some study details, they did not attempt to clarify the information gaps with the study authors. ECHA also highlights that climbazole is a de-methylation inhibitor (DMI) fungicide. This class of fungicides is known to be particularly toxic to primary producers. ECHA therefore considers that the algal and *Lemna minor* ecotoxicity endpoints are crucial to PNEC derivation. This is why, the lead study author was contacted to request additional study details and mean measured endpoints for *Lemna minor*. This additional information was provided to the Registrant(s) by the evaluating MSCA during the commenting period.

Therefore, pursuant to Article 46(1) of the REACH Regulation and conditional upon risks remaining after consideration of the Richter *et al.* (2013) study, the Registrant(s) are required to carry out the following study on the registered substance subject to this decision: simulation test – aerobic sludge treatment, A: activated sludge units, B: biofilms (test method OECD 303A or B).

The Registrant(s) shall select, with justification, the most appropriate test methodology (OECD 303A or B).

3. *In vitro* endocrine disruption screening studies

This request is relevant to a concern about the environmental endocrine disruption potential of climbazole.

No data on endocrine disruption potential for the environment are available in the registration dossier(s).

Climbazole is an imidazole compound. A recent review (Matthiessen and Weltje, 2015) published in late March 2015 highlighted the endocrine disruption potential of some azoles, including imidazoles, in fish. There is experimental evidence that under laboratory conditions some azoles cause masculinisation or defeminisation in fish by inhibition of the cytochrome P450 enzyme aromatase (CYP19). This aromatase inhibition appears to the dominant mode of endocrine action in fish and spans a range of potencies for different azoles. In addition, there is evidence that some azoles (e.g. the imidazole compounds ketaconazole and prochloraz) interact with endocrine systems to inhibit testosterone production in fish or block the fish androgen receptor. For example, the endocrine disruption potential of prochloraz is well documented and used as a test example in OECD Guidance Document 181. ECHA concludes that climbazole belongs to a class of chemicals that have the potential to interfere with the endocrine system in fish, but direct read across between substances is not currently possible given the range of potencies.

Climbazole is supplied at a relatively low tonnage. However, it is not readily or inherently biodegradable. Given climabazole's wide dispersive use pattern and apparent persistence, aquatic exposure is likely, and this is confirmed by a very limited survey of English rivers using a semi-quantitative screening analytical method (Environment Agency UK, 2014). ECHA therefore considers that clarifying endocrine disruption potential in fish is a relevant consideration for this substance evaluation.

A literature search did not identify any information on the endocrine-disrupting potential of climbazole. *In vitro* screening tests provide results quickly and do not involve the use of vertebrates. Therefore in the original draft decision, the Registrant(s) were asked to conduct *in vitro* screening studies, taking into account OECD (2012) Series 150 (section C.2) and potential modes of action of climbazole (based on evidence from other azole-containing substances).

It was highlighted that further information requests would be considered on the basis of the results of these tests. The choice of testing was left open to the Registrant(s).

In their comments, the Registrant(s) considered that it was too premature to conduct endocrine disruption screening studies due to: 1) a lack of regulatory definition of endocrine disruption, and 2) a lack of validated methods. They did not propose any appropriate tests. The Registrant(s) did indicate that they potentially agree to run additional tests, if appropriate rationale is provided, as soon as there are validated methods, a clear testing strategy and the process and interpretation established.

In response, ECHA notes that a regulatory definition of endocrine disruption is not essential to begin the task of clarifying whether a substance may have potential to interfere with the endocrine system. ECHA has already requested *in vivo* tests to address concerns for environmental endocrine disruption for several substances under Substance Evaluation. In addition, three substances have been added to the Candidate List on the basis of environmental endocrine disruption potential. On this basis, it is not premature to conduct further studies for this purpose. ECHA notes that the *in vitro* methods proposed in the draft decision are validated international methods.

Since the Registrant(s) did not respond positively to the suggestion that they should identify relevant tests, ECHA has considered which *in vitro* assays are most appropriate to assess androgen receptor activity and aromatase inhibition. These are the modes of action most commonly highlighted for this class of substance, as outlined by Matthiessen and Weltje (2015). The following validated international test methods are relevant based on potential modes of action:

- OECD Test Guideline 456 (2011) H295R Steroidogenesis assay
- Stably Transfected Human Androgen Receptor Transcriptional Activation Assay for Detection of Androgenic Agonist and Antagonist Activity of Chemicals OECD draft Test Guideline due for finalisation in 2016)
- US EPA (2009) OPPTS 890.1150 Androgen Receptor Binding assay

At ECHA's Endocrine Disrupter Expert Group (EDEG) in September 2015 (at which the Registrant(s) were present), the evaluating MSCA was alerted about the outputs of *in vitro* screening. The Tox21 Program carried out in the United States (US EPA, 2015a) includes *in vitro* screening assays for both climbazole and a potential analogue chemical, triadimenol CAS no. 55219-65-3 (National Center for Biotechnology Information, 2015a and 2015b).

The evaluating MSCA has reviewed the Tox21 database for climbazole. The results were as follows:
- Two Aromatase Inhibition (AI) assays were positive. In a further assay a negative response was obtained;
- All Estrogen Receptor (ER) assays were inactive;
- Eight Androgen Receptor (AR) assays are available - all were inconclusive or inactive;ECHA notes that the Tox21 AR assays for prochloraz were also generally inconclusive or inactive. This suggests that human cell-based assays may not be appropriate for assessing AR ecotoxicological effects which are well documented for prochloraz (see Matthiessen and Weltje, 2015);
- All Aryl hydrocarbon Receptor (AhR) assays for climbazole were active.

The Tox21 *in vitro* data reflect a rapid screening, high throughput set of assays. While one ER assay protocol has been validated (although not for high throughput), the remainder are not validated or internationally recognised assays.

Therefore, ECHA considers that the Tox21 data described above are of limited reliability and are not sufficient to support *in vivo* testing in place of internationally validated *in vitro* tests at this time. In addition, ECHA considers that further mechanistic information, such as that generated by the OECD TG 456, would be useful before any further *in vivo* data are generated (should it be necessary).
At the EDEG-meeting the Registrant(s) highlighted that the substance triadimenol has been considered by the US Environmental Protection Agency (US EPA) Endocrine Disrupter Screening Program (EDSP). In that programme it was not considered a priority (US EPA, 2015b), which the Registrant(s) argued was supported by a Tox21 ER assay which was inactive.

ECHA notes that the EDSP program is based on estrogen receptor (ER) bioactivity using the ToxCast™ Endocrine Receptor Model and that the concern in this case is related to androgen receptor activity and aromatase inhibition, not estrogen receptor activity.

However, ecotoxicity data for triadimenol were considered by ECHA's Risk Assessment Committee (RAC) for the purpose of environmental hazard classification in December 2015. The available fish studies do show changes in vitellogenin formation in male fish, which suggests endocrine activity (ECHA, 2015). This supports ECHA's view that the Tox21 assays may not be consistent with *in vivo* data. In addition, triadimenol was active in two out of three Tox21 AI assays supporting AI potential concern.

A recent academic study (Chen *et al*, 2015) considered AI potential by screening positive AI results from the Tox21 database through an AroER tri-screen assay. This process screens in the presence of testosterone and 17β-estradiol to distinguish between AIs and ERβ (Estrogen Receptor beta) antagonists. The study identified climbazole as a potential Aromatse Inhibitor. It also noted that structural activity was not only linked to the 1,2,4-triazole class and other similar and novel structures exhibited AI potential. This further confirms a concern for climbazole that needs to be followed up.

Therefore, on the basis of the available information described above and given the lack of standard test guideline information specifically on climbazole, the concern regarding the endocrine disruption potential of climbazole needs to be addressed.

In a PfA, it was suggested that measurement of progesterone should be included in the OECD TG 456 steroidgenesis assay. This is due to some azole fungicides affecting progesterone production which may be related to increased gestation length and dystocia in pregnant animals. Such effects have been observed after exposure to other azole fungicides like epoxiconazole, prochloraz and tebuconazole (Danish EPA, 2007). One hypothesis is that the prolonged gestation length could be caused by the increased maternal serum level of progesterone, which is observed after exposure to these substances (Vinggaard *et al.*, 2005).

In the rat one-generation study and rodent developmental toxicity studies with climbazole, there was some evidence of increased gestation length and dystocia at a dose not inducing significant systemic toxicity. However, due to study limitations, a relationship between climbazole and dystocia was unclear. Measurement of progesterone in the OECD TG 456 assay will help clarify this concern for climbazole along with Information Requirement 1.

The evaluating MSCA will assess the results of the new *in vitro* data and Information Requirement 1 to consider whether the weight of evidence analysis indicates a potential for endocrine disruption that needs to be followed up with *in vivo* testing to clarify the concern further. This will also take account of the needs of the risk assessment but might include for example OECD Guidance Document 148 – Androgenised Female Stickleback Screen or OECD TG 234 (Fish Sexual Development Test).

The Registrant(s) made no comment on the proposals for amendment.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following studies on the registered substance subject to this decision: -

OECD TG 456 (2011) H295R Steroidogenesis assay with measurement of progesterone

and either

Stably Transfected Human Androgen Receptor Transcriptional Activation Assay for Detection of Androgenic Agonist and Antagonist Activity of Chemicals (Draft OECD TG due for finalisation in 2016), if adopted by time of testing

or

US EPA (2009) OPPTS 890.1150 Androgen Receptor Binding Assay.

4. Further information on worker exposure

The Registrant(s) have conducted a human exposure assessment in accordance with Article 14 and Annex I of the REACH regulation. However, the information provided is somewhat limited and no description of the tasks involved in the two professional exposure scenarios is given. Whilst it is acknowledged that the Registrant(s) have generally followed industry (Colipa) guidance on use mapping to select PROC codes for the second industrial scenario (formulation of end-products), the lack of descriptive texts means that it is not possible properly to understand the processes or determine if the appropriate process (PROC) codes have been selected for the two professional uses. For example, it is not stated if the substance is imported as a solid or dissolved; how it is transferred to the factory; if it is transported in bags, how the bags are transferred into the re-crystallisation vessels (manual tipping or automation); if the re-crystallisation process requires a drying stage, how this is performed.

The Registrant(s) have used ECETOC TRA version 3.0 to estimate exposures for the individual contributing scenarios within each exposure scenario. The modifiers applied have been clearly stated for each contributing scenario, and the evaluating MSCA has been able to reproduce the exposure estimates. However, in the exposure scenario for the formulation end-products, contributing scenario for mixing operations (open system) in batch process including filling of equipment and sample collection (section 9.2.10. of the CSR) (PROC 5), the Registrant(s) have applied a less conservative refinement factor of 0.5 rather than the default factor of 0.6 that is used by ECETOC TRA for a duration of activity < 4 hours. The Registrant(s)' justification for doing this is the 'shorter duration of activity of < 4 hours.' Overall, therefore, the initial exposure estimate was multiplied by the refinement factor of 1/0.6*0.5. The Registrant(s) should fully justify with data why the default modification factor of the ECETOC TRA tool has not been used.

Some of the conditions of use in the exposure scenario that covers formulation of end-products provide contradictory information; specifically, some contributing scenarios refer to the substance being dissolved in a liquid formulation but present as a solid in a solid mixture. These contributing scenarios are:

- material transfers from/to vessel container at non-dedicated facility, equipment cleaning and maintenance (PROC 8a);
- material transfer from/to vessel/container at dedicated facility (PROC 8b);

- transfer into small containers (PROC 9).

The Registrant(s) should clarify in what form the substance is present in each of these scenarios.

In the CSR, it is stated that for some contributing scenarios climbazole is used as a solid dissolved in a liquid; for these scenarios, ECETOC TRA has been used to model the exposures. However, the estimation of exposure to solids suspended or dissolved in liquids is outside the applicability domain of ECETOC TRA (ECETOC Technical Report 114, section 2.2.7). For these scenarios, an alternative suitable exposure modelling tool should be used, such as the Advanced REACH Tool (ART) or, for dermal exposures, RISKOFDERM. A copy of the model output reports and a justification for each of the parameters selected shall be provided. Measured data could be provided as an alternative to re-calculation of the exposures with models.

In their comments the Registrant(s) suggested waiting for the results of the requested studies before updating their dossier and CSR. This is noted by ECHA and the deadline has been amended accordingly to allow time for this.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) shall submit the following information regarding the registered substance subject to the present decision:

Further information on worker exposure addressing the following aspects:

a. Descriptive text for each process/task within each exposure scenario shall be provided. This shall include: an explanation of the processes that are covered by each scenario and PROC code; the form in which the substance is present at each stage of the process; a justification for the choice of modelling parameters, including the choice of a non-default refinement factor applied to PROC 5 in exposure scenario 2; and

b. For those scenarios where climbazole is used as a solid dissolved in a liquid, the Registrant(s) shall re-calculate the exposures with a tool that has the ability to model this condition of use or, alternatively, provide measured data. For modelled exposure estimates, a copy of the model output reports and a justification for each of the parameters selected shall be provided.

Deadline for submitting the required information

In the draft decision communicated to the Registrant(s) the time indicated to provide the requested information was 24 months (independent of study design) from the date of adoption of the decision. That timeline is maintained in this decision.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental studies, the sample of the substance to be used 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 material to be subjected to the test(s) 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 test(s) must be shared by the Registrant(s).

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

In relation to the experimental studies the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to 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

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.

VI. 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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[3] by Leena Ylä-Mononen, Director of Evaluation

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

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

References

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