Helsinki, 31 July 2017

Substance name: 1,2,4-triazole
EC number: 206-022-9
CAS number: 288-88-0
Date of Latest submission(s) considered[1]: 22/07/2015
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressees: Registrant(s)[2] of 1,2,4-triazole (Registrant(s))

DECISION ON SUBSTANCE EVALUATION

1. Requested information

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

- H295R Steroidogenesis Assay *in vitro*; test method: OECD 456.

You shall provide an update of the registration dossier(s) containing the requested information, including robust study summary and, where relevant, an update of the Chemical Safety Report by **7 February 2018**. Within this time frame, the Registrant(s) shall also provide the full study report of the requested study. The deadline takes into account the time that you, the Registrant(s), may need to agree on who is to perform any required tests.

The reasons of this decision 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.

2. Who performs the testing

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study on behalf of all Registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

[1] This decision is based on the registration dossier(s) at the end of the 12 month evaluation period.

[2] The terms Registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

3. Appeal

You can appeal this decision to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals

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

[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.

Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on 1,2,4-triazole and other relevant available information, ECHA concludes that further information is required in order to enable the evaluating Member State Competent Authority (evaluating MSCA) to complete the evaluation of whether the substance constitutes a risk to human health. The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in order to clarify the concern for endocrine disruption, reproductive toxicity and neurotoxicity.

1.1 H295R Steroidogenesis Assay *in vitro* (OECD 456)

The Concern(s) Identified

***In vitro* data**

1,2,4-triazole is a common metabolite from triazole-containing fungicides of which several data show that azole fungicides do not only have an impact on the ergosterol biosynthesis in fungi and yeast, but can also have an impact on the sex steroid biosynthesis in mammals and in humans (Zarn *et al.*, 2003; Menegola *et al*., 2006).

The antifungal activity of azole fungicides relies on the inhibition of the sterol 14α-demethylase-enzyme (CYP51) to prevent the demethylation at the C14-position of lanosterol by competitive reversible binding to the haem moiety of the enzyme (the heterocyclic nitrogen atom -N4 of triazole- binds to the haem central iron). As a result, the synthesis of ergosterol, an essential membrane component in fungi and yeast, is blocked (Zarn *et al.*, 2003; Marotta and Tiboni, 2010). Triazole is therefore the moiety responsible for the action on the enzyme but the affinity for the enzyme will depend on the substitution on the triazole ring. Furthermore, it was demonstrated that the inhibition of CPY51 depends on the azole derivative and lesser on the source of CPY51 (Zarn *et al.*, 2003).

Sterol 14α-demethylase is also found in mammals and is expressed in many different tissues (Zarn *et al.*, 2003).

The amino acid sequence of Sterol 14α-demethylase is highly genetically conserved between phyla. The homology of the amino acid sequence between rats and humans is 93% and is 40% between fungi and humans (Zarn *et al.*, 2003).

In mammals, the enzyme sterol 14α-demethylase either converts lanosterol directly to follicle fluid meiosis-activating sterol (FF-MAS), which is further metabolized to the testis meiosis-activating sterols (T-MAS) or after preceding reduction by sterol Δ24-reductase into MAS-412, which is further metabolized into MAS-414. The MAS play an important role in the development of testis and spermatids and possibly also have an impact on the oocyte development (Zarn *et al.*, 2003).

It was shown that some azole compounds also inhibit many other CYP450 enzymes. Azole compounds also affect aromatase (CYP19, member of CYP450), the enzyme responsible for the conversion of androgens to estrogens, by demethylation of

androstendione and testosterone at the C-10 position. This takes place by competitive reversible binding and hereby affecting the conversion to estrone and estradiol, respectively. A good balance of sex steroid hormones is crucial for development, maintenance and function of the reproductive system and differentiation of the sexual phenotype during ontogeny (Zarn *et al.*, 2003).

Although on the molecular level there were no profound differences between species, distinct differences may occur in respect to resulting ED related toxicological effects (e.g. histopathological changes in the testis in dogs whereas no observed effects in rats) are observed in laboratory animals after exposure to azole derivatives (Zarn *et al.*, 2003).

A non-guideline *in vitro* study on estrogen biosynthesis indicated that 1,2,4-triazole showed minimal (<15%, steroid accumulation in culture medium is expressed as a percentage of the accumulation in control cultures treated with hFSH-human Follicle Stimulating Hormone and testosterone without the substance) inhibitory effects on oestradiol formation when exposed to a single dose of 10^{-5} M and it was concluded that the substance has no suppressive effect on aromatase activity (Wickings *et al.*, 1987). Yet, it should be underlined that this study was only performed with a single dose and that it only covers aromatase, which is a part of the steroidogenesis pathway.

Additionally, in accordance with test guideline OPPTS 890.1200: Aromatase (Human Recombinant), an OECD Conceptual Framework level 2 test method, the aromatase activity is to be measured in the presence of eight concentrations of the test chemical (OECD Guidance document N°150). The lowest concentration to be tested is generally 10^{-10} M, the highest 10^{-3} M. Hence, the conclusions of the above mentioned study of Wickings *et al.* (1987) cannot be considered as decisive.

Originally in 2015, only one *in vitro* assay on the inhibition of aromatase (CYP 19) was available in the ToxCast/Tox21 program and according to this limited information 1,2,4-triazole was considered in-active.

By the end of 2016, data on the ToxCast high-throughput H295R steroidogenesis assay became available in the iCSS ToxCast Dashboard (https://actor.epa.gov/dashboard/) and the effects (stimulation and inhibition) on the 10 measured hormones were negative. However, no univocal conclusion can be drawn on the possible endocrine mode of action (steroidogenesis) of 1,2,4-triazole because uncertainty exists on the exact applied concentration in this study (see 'Consideration of Registrant's comments').

***In vivo* data**

Different toxicological studies with 1,2,4-triazole show several adverse effects on fertility and development in rodents, which could be related to the endocrine system. These observed adverse effects are shortly described below.

The incidence of cryptorchism was above the historical values at the treated dose groups (100 and 200 mg/kg bw/d) in a developmental toxicity study in rats (Renhof, 1988) and an increase of pre- and post-implantation losses was observed.

Statistically significant decrease in epididymal sperm counts in P0 at 3000 ppm (188.6 mg/kg bw/d), decrease in testicular sperm at all doses in P0 and statistically significant decrease of the percentage of normal sperm morphology at 500 ppm (30.9 mg/kg bw/d) and 3000 ppm (188.6 mg/kg bw/d) in P0 were noted in the two-generation reproductive toxicity study in rats (Young and Sheets, 2005). A delay in sexual maturation in female F1 pups at 250 ppm (17.4-19.3 mg/kg bw/d) and 500 ppm (36.2-38.7 mg/kg bw/d) was also seen.

In the 90-day toxicity study in mice (Wahle, 2004), a statistically significant increase in the number of apoptic-like bodies (at 487 and 988 mg/kg bw/d), disturbances in spermatid development and focal tubular atrophy in the testes (at 988 mg/kg bw/d) were observed.

Statistically significant decrease in the number of recent-cycle and total corpora lutea at 500 ppm (34.4-37.5 mg/kg bw/d) in F1 and a statistically significant increase in total corpora lutea at 3000 ppm (217.9-231.7 mg/kg bw/d) in P0 was found in the 2-generation study in rats (Young and Sheets, 2005). A similar trend of increase in the number of total and recent-cycle corpora lutea was also observed in the combined subchronic toxicity/neurotoxicity screening study in rats (Wahle and Sheets, 2004) at the two highest doses (3000 ppm (234 mg/kg bw/d) and 1000/4000 ppm (275 mg/kg bw/d)), but the difference was not statistically significant.

Moreover, on basis of the results obtained in the 2-generation study in rats (Young and Sheets, 2005), it is not possible to conclude whether exposure to 1,2,4-triazole above 500 ppm would have caused impaired fertility of the F1 generation as no pups were produced at the highest dose (3000 ppm).

The mode of action of the above mentioned adverse effects is unknown and it cannot be excluded that it is endocrine mediated. Inhibition of steroidogenesis may be a possible mode of action to explain these findings.

Taking into account wide dispersive use (use as fertilizer), high tonnage and the environmental exposure of 1,2,4-triazole and its derivatives (azole fungicides) which are metabolized mainly to 1,2,4-triazole, the potential risk for human health and environment cannot be excluded.

Why new information is needed

Taking into consideration that inhibition of steroidogenesis is a well-known mode of action of azole fungicides (i.e. through binding of the N4-atom of the triazole to the haem moiety of CYP51), as well as the shortcomings of the study from Wickings *et al.* (1987) (single dose, examination of aromatase only and lack of measurement of the androgens) and the uncertainty regarding the exact concentration tested in the ToxCast high-throughput steroidogenesis assay, it can be concluded that currently available data are not decisive on a possible endocrine mechanism, more specifically steroidogenesis.

The requested steroidogenesis study may provide information about endocrine disruptive mechanism/mode of action. In that case this mode of action can be linked to adverse

effects seen in the available studies on endocrine relevant endpoints. This may lead to the identification of 1,2,4-triazole as Substance of Very High Concern according to article 57(f) of REACH and can therefore improve risk management measures for 1,2,4-triazole, keeping in mind its wide dispersive use, high tonnage and the environmental exposure.

Considerations on the test method and testing strategy

H295R Steroidogenesis assay (OECD 456) is an *in vitro* screening assay (OECD CF level 2) providing mechanistic data concerning the interaction of xenobiotics with the endocrine system, more specifically with the production of 17β-estradiol (E2) and testosterone. This assay will allow examination whether 1,2,4-triazole effectively inhibits some enzymes involved in the steroidogenesis pathway and thus affects the sex steroid hormones.

The Registrant(s) shall submit the full study report for the information required. Indeed a complete rational and access to the whole available information (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.) are needed to fully assess the provided information and to efficiently clarify the concerns.

The evaluating MSCA will review the new information submitted by the Registrant(s) and will determine whether the submitted information is sufficient for appropriate risk management measures.

Alternative approaches and Proportionality of the request

Several adverse effects on fertility and development were observed in different *in vivo* toxicological studies in rodents.

In order to identify a substance as an endocrine disruptor it should be demonstrated that it alters the function(s) of the endocrine system (mode of action), causes an adverse effect in an intact organism or (sub)population and that there is a biologically plausible link between the mode of action and the adverse effect.

The H295R Steroidogenesis Assay (OECD 456) is an *in vitro* test which provides information about one particular group of mechanisms of action (Molecular Initiating Events) by examining the ability of 1,2,4-triazole (parent compound) to directly interfere with the synthesis of estrogen and/or testosterone via perturbation of the system of enzymes required for steroid biosynthesis.

The H295R Steroidogenesis Assay (OECD 456) is currently the only validated *in vitro* screening assay included in the OECD conceptual framework for the detection of steroidogenesis interference beginning with the sequence of reactions from cholesterol to the production of 17β-estradiol (E2) and/or testosterone, thus including aromatase.

Therefore the request for a Steroidogenesis Assay is suitable and necessary to obtain information that will allow to determine the potential ED mode of action of 1,2,4-triazole, as there is no equally suitable alternative way available of obtaining this information.

Consideration of Registrants' comments

The Registrant(s) in their comments agreed that the results of the stereoidogenesis test will provide information on the potential of 1,2,4-triazole to modulate the endocrine system in mammals.

They also stated that while initially only one *in vitro* assay on the inhibition of aromatase (CYP19) of 1,2,4-triazole was performed within the ToxCast/Tox 21 program, additional data covering steroidogenesis assay have been made available as part of the ToxCast/Tox21 program. These results show an 'inactive' (no effect on the level of hormones) result for all of 10 measured hormones, including estradiol and testosterone (Karmaus *et al.*, 2016). According to the Registrant(s), this study met all of the key technical criteria of the OECD 456 guideline, hence a full dataset on 1,2,4-triazole is now available to assess an endocrine mechanism. Therefore the request for H295R steroidogenesis assay (OECD 456) is not relevant and should be removed from the decision.

ECHA has thoroughly evaluated the information available in the ToxCast/Tox21 program (iCSS ToxCast Dashboard), as well as the reliability of the high-throughput screening test applied in the Karmaus *et al.* study (2016).

The ToxCast high-throughput steroidogenesis screening assay, which is a modified OECD 456 *in vitro* H295R steroidogenesis assay, is in several aspects not of equal value or directly comparable to the results produced by the OECD test guideline:

- all test samples are evaluated in duplicate rather than triplicate;
- 70% cell viability is accepted instead of 80%;
- concentration-dependent effects were evaluated using the ToxCast Data Analysis Pipeline rather than the OECD guideline recommended Dunnett's Test to identify significant effects in consecutive chemical concentration groups;
- pre-stimulation of the cells with forskolin (strong inducer) to induce steroidogenesis prior to chemical treatment;
- no validation process performed as described in OECD Guidance Document n°34.

The pre-stimulation of the cells with forskolin makes it difficult to find or measure effects of chemicals causing only a weak or moderate increase in hormone levels. This could explain why in Karmaus *et al.* (2016) only very few cases of increased hormone levels were found. For 1,2,4-triazole rather an inhibitory effect is to be expected. In view of ECHA, the ToxCast steroidogenesis assay can be used to evaluate effects on the inhibition of hormone production, but it will be difficult to measure weak or moderate increase in hormone levels as the cells were already pre-stimulated before the addition of test chemical.

The ToxCast steroidogenesis assay with 1,2,4-triazole was performed with a single high nominal concentration (99.9µM) at which no cytotoxicity has been estimated (estimated cytotoxicity threshold is 161.93µM). Other response concentrations were not further determined as no significant effects on hormone levels were seen at the maximum tolerated concentration (100µM) using a cut-off ≥1.5 fold change over DMSO controls on a per plate basis.

However in the OECD 456 guideline, the initial run is to be performed with spaced log 10 intervals with 1000 µM being the maximum concentration (i.e.: 0.001, 0.01, 0.1, 1, 10, 100 and 1000 µM), 10 fold higher than the single tested nominal concentration of 100µM in the ToxCast steroidogenesis assays.

Furthermore, in an OECD 456 study, when the substance is soluble, not cytotoxic and the initial run is negative, a second run should be performed to confirm these results. This was not the case in the high-throughput screening for 1,2,4-triazole.

Moreover, the delivery of exact volumes of solutions and samples into the wells during dosing is critical because these volumes determine the concentrations used in the calculations of assay results.

As part of the ToxCast program, periodic quality control (QC) checks of the stock solutions of test compounds are performed. A notation for a QC check (T0) of a 20 mM stock solution of 1,2,4-triazole indicated a caution, that the measured concentration was lower than the expected value (5 – 30%). It was confirmed by US EPA that only one stock solution was used to prepare the samples of 1,2,4-triazole used for the ToxCast assays and that during analytical quality control for the ^{1}H-NMR sample only a concentration of 1.3 mM was measured, whereas the expected concentration was 3 mM. This caution flag according to US EPA is thus also applicable for the concentration used in the steroidogenesis assay performed in the ToxCast/Tox 21 program.

Moreover ECHA would like to point out that ^{1}H-NMR is not the most appropriate method for quantification analysis, but rather other techniques such as GC-MS and LC-MS/HPLC-MS should be used (see also US EPA, 2014). The suppression of the C-H proton resonances in the method used for ^{1}H-NMR analysis of 1,2,4-triazole using presaturation pulses (to suppress the interfering resonances of water and DMSO) indicates the somewhat low measured concentration (43% of theoretical). Although this suppression is likely to have occurred, it is unclear to which extent the signal may have been suppressed, leading to continued uncertainity regarding the concentration of 1,2,4-triazole that was present in the sample used for ToxCast screening. This has been also confirmed by US EPA. Based on these ^{1}H-NMR results of diluted 1,2,4-triazole stock solution (measured concentration 1.3 mM/3 mM = 43% of the nominal expected concentration) the caution '10 – 50% of expected quantity' seems to be more appropriate rather than the "5 – 30% of expected value' flag as mentioned in the ToxCast database.

ECHA would like to underline that currently no conclusion can be drawn on the stability of the stock solution based on the available data.

Taking the above into consideration, ECHA is of the opinion that this uncertainty on the exact concentration used for the ToxCast steroidogenesis assay with 1,2,4-triazole is crucial, because it suggests that the negative results obtained for this substance are the outcomes of a measurement with a much lower than expected single concentration (100 µM). Therefore, ECHA concludes that it is not unequivocally proven that 1,2,4-triazole does not demonstrate an effect on steroidogenesis in the 10-50 µM to 1000 µM range

and considers it still appropriate to request an *in vitro* steroidogenesis study according to OECD 456 guideline. The results from this requested study will allow to conclude on the concern that 1,2,4 triazole demonstrates a possible impact on steroidogenesis and thus acts via an endocrine mechanism.

Consideration of proposals for amendment (PfA) and registrant's comments

One MSCA proposed either to remove the requested *in vitro* assay as further information will not improve risk management of the substance, or, in case the request for the in vitro assay is upheld, to specify in the decision that in case of a negative result, no further testing is to be carried out and in case of a positive result, the registrant should consider the next steps carefully.

The registrants in their comments agreed that further information will not improve risk management for 1,2,4-triazole.

ECHA disagrees with this and considers it still appropriate to request further testing. The study will allow to determine the potential ED Mode of Action of 1,2,4-triazole and there is no other equally suitable alternative way available to obtain this information.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the registered substance, substance subject to this decision: Steroidogenesis *in vitro*; test method: OECD 456.

Deadline

In the original draft decision the time indicated to provide the requested information was 27 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested an extended one generation reproduction toxicity study. ECHA considers that a reasonable time period for providing the currently required information in the form of an updated registration is 6 months from the date of the adoption of the decision.

References

ECHA Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7a: Endpoint specific guidance).

Karmaus A.L., Toole C.M., Filer D.L., Lewis K.C. and Martin M.T. (2016), High-throughput screening of chemical effects on steroidogenesis using H295R human adrenocortical carcinoma cells, ToxSci Advance Access

Marotta F. and Tiboni GM. (2010) Molecular aspects of azoles-induced teratogenesis., Expert Opin Drug Metab Toxicol. 2010 Apr,6(4): 461-82. Review.

Menegola E. , Broccia M.L., Di Renzo F., Massa V. and Giavini E (2006) Postulated pathogenic pathway in triazole fungicide induced dysmorphogenic effects, Reproductive Toxicology 22, 186-195.

Renhof, M. (1988) 1, 2, 4-triazole: investigations into embryotoxic effects on rats after oral administration. Unpublished report No. 17402, dated 21 November 1988, from Bayer CropScience AG, Wuppertal, Germany. Submitted to WHO by Bayer CropScience, Germany, on behalf of TD*MG*.

US EPA (2014) ToxCast Chemical Inventory: Data Management & Data Quality Considerations, 1-38.

Wahle, B.S. (2004) A subchronic toxicity testing study in the CD-1 mouse with 1, 2, 4-triazole. Unpublished report No. 201052, dated 13 December 2004, from Bayer CropScience LP, Stilwell, Kansas, USA. Submitted to WHO by Bayer CropScience, Germany, on behalf of TDMG.

Wahle, B.S. & Sheets, L.P. (2004) A combined subchronic toxicity/neurotoxicity screening study in the Wistar rat with 1, 2, 4-triazole. Unpublished report No. 201024, dated 13 December 2004, from Bayer Crop-Science LP, Stilwell, Kansas, USA. Submitted to WHO by Bayer CropScience, Germany, on behalf of TDMG.

Wickings, E.J. Middleton, M.C. & Hillier, S.G. (1987) Non-steroidal inhibition of granulosa cell aromatase activity *in vitro*. *Journal of Steroid. Biochemistry* 26, 641□646. Submitted to WHO by Bayer CropScience, Germany, on behalf of TDMG.

Young, A.D. & Sheets, L.P. (2005) A two-generation reproductive toxicity study in Wistar rat with 1,2,4-triazole. Unpublished report No. 201220, dated 14 January 2005, from Bayer CropScience LP, Stilwell, Kansas, USA. Submitted to WHO by Bayer CropScience, Germany, on behalf of TDMG.

Zarn J.A., Brüschweiler J.B. and Schlatter J.R. (2003) Azole fungicides affect mammalian steroidogenesis by inhibiting sterol 14α-demethylase and aromatase, Environmental Health Perspectives 111 n°3, 255-261.

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 human health endpoints (reproductive toxicity, neurotoxicity, carcinogenicity and endocrine disruption), wide dispersive use, high (aggregated) tonnage and exposure to environment and consumers, 1,2,4-triazole CAS No 288-88-0 (EC No 206-022-9) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2015. The updated CoRAP was published on the ECHA website on 17 March 2015. The Competent Authority of Belgium (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

Pursuant to 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.

In the course of the evaluation, the evaluating MSCA has found enough evidence to remove carcinogenicity from the list of concerns for 1,2,4-triazole, hence this has not been further elaborated in this decision.

The evaluating MSCA considered that further information was required to clarify the following concerns: endocrine disruption, reproductive toxicty and neurotoxicity. 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 11 March 2016.

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

ECHA notified you of the draft decision and invited you and the other Registrant(s) 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 into account the comments from you, which were sent within the commenting period, and they are reflected in the Reasons (Appendix 1).

Commenting by other MSCAs and ECHA

On 9 March 2017, 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. They are reflected in the Reasons (Appendix 1).

Referral to Member State Committee

On 25 April 2017, ECHA referred the draft decision, together with your comments, to the Member State Committee.

On 12 April 2017, ECHA invited you to comment on the proposed amendment(s) by 12 May 2017. Any comments on the proposal(s) for amendment were taken into account by the Member State Committee and are reflected in the Reasons (Appendix 1).

Pursuant to Article 51(6) of the REACH Regulation the ECHA Member States Committee unanimously agreed that no further information needs to be requested on 1,2,4-triazole regarding its reproductive toxicity and developmental neurotoxicity concern at this stage. The Committee deemed it more appropriate to follow the indication of the evaluating MSCA to prepare a proposal for a harmonized classification dossier under Regulation (EC No. 1272/2008) in due course. Based on the outcome of this harmonized classification proposal, the evaluating MSCA will re-evaluate the most appropriate way forward on how to address any remaining concerns.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-54 meeting and ECHA took the decision according to Article 52(2) and 51(6) of the REACH Regulation.

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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 fulfil otherwise 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 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.

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 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.