Helsinki, 15 November 2018

Addressee: [redacted]

Decision number: CCH-D-2114450985-37-01/F
Substance name: Sulphur hexafluoride
EC number: 219-854-2
CAS number: 2551-62-4
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 28 February 2018

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision CCH-D-21 14290519-38-01/F of 5 February 2015 ("the original decision") ECHA requested you to submit information by 12 August 2016 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified above, and concludes that

Your registration still does not comply with the following information requirement:

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in rats or rabbits, inhalation route

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

The respective Member State competent authority (MSCA) and national enforcement authority (NEA) will be informed of this decision.[1] They may consider enforcement actions to secure the implementation of the original decision.

[1] Only the final decision will be sent to the National enforcement authority so they can consider enforcement actions.

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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, 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[2] by Kevin Pollard, Head of Unit E1

[2] 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

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

You were requested to submit information using the registered substance according to test guideline EU B.31 / OECD 414 for pre-natal developmental toxicity endpoint.

In the updated registration subject to follow-up evaluation, you have adapted the corresponding information requirement with a weight-of-evidence approach according to Annex XI, Section 1.2 by providing

1. a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test according to OECD 422 test guideline ([redacted] 2009)
2. a study report according to The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline for Detection of Toxicity to Reproduction for Medicinal Products. The study is performed in the rat. In the study the test material was administered *i.v.* (intravenous) as a suspension of microbubbles at 0.2, 1.0 and 5.0 ml/kg/day of the medicinal product. You have not provided any conversion of the administered dose to mg/kg bw/d, however, according to publicly available information[3] available at the website of the European Medicals Agency, *"Each ml of the dispersion contains 8 microliter of the registered substance microbubbles, equivalent to 45 micrograms."* No adverse effects for maternal or developmental toxicity, or embryotoxicity were observed in the study. NOAEL was set at 5.0 ml/kg/day (which corresponds to 225 microg/kg bw/day according to the publicly available information[3]).
3. a study report according to ICH Harmonised Tripartite Guideline for Detection of Toxicity to Reproduction for Medicinal Products. Study is performed in the rabbit. The same doses and administration route were used as in the rat study, and no adverse effects were observed. NOAEL was set at 5.0 ml/kg/day.

In the original decision, ECHA already rejected the use of the OECD 422 ([redacted] 2009) alone to fulfil the information requirement for this endpoint. The argument was that this study does not cover the key parameters required for a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations.

Regarding the two ICH studies, ECHA considers that the ICH test guideline is in some ways comparable to OECD 414 although gravid uterus weight and placental weight are not addressed in the ICH guideline. However, the designs of the provided studies according to the ICH guidelines have the following two major additional deficiencies: (a) very low doses were used in the studies (b) inhalation exposure is not covered because administration in the form of *i.v.* bolus of stabilized sulphur hexafluoride microspheres is not comparable to inhalation exposure lasting several hours.. Thus the provided studies are not adequate for hazard and risk assessment in the context of dossier evaluation.

ECHA considers that the ICH studies do not provide sufficient evidence to conclude that the registered substance has or has not potential for developmental toxicity.

Further, the toxicokinetic data (Pashin, 1987) in the dossier indicates that the registered substance is systemically available in perirenal fatty tissue as well as in blood and other tissues for several hours after inhalation exposure. On the other hand, according to other

[3] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000303/WC500055380.pdf

toxicokinetics studies in the registration dossier ([redacted] 1994 and [redacted] 2009) the registered substance is rapidly removed from the blood via the pulmonary route (80-90% eliminated after 11 minutes) after *i.v.* administration of microbubbles. Therefore *i.v.* administration of microbubbles is not comparable to inhalation exposure and therefore it cannot provide sufficient information on the effects of the registered substance in the body.

Finally, estimated exposure concentration for workers is [redacted] mg/m^3 with inhalation volume of 10 m^3 / 8 hours leading to daily exposure of [redacted] mg. For 70 kg body weight this corresponds to an approximate exposure dose of [redacted] mg/kg bw/d. The highest *i.v.* dose tested in the ICH study is 225 micrograms/kg bw/d in rat and the human equivalent dose is only 36.5 micrograms/kg bw/d, which is significantly lower than the daily exposure dose estimated for a 70 kg person.

You stated in your comments that you regarded ECHA's reminder to adapt the information requirement to be a restriction for conducting new animal studies with the registered substance despite ECHA's request to do so. This reminder is by no means a restriction to perform an experimental study as requested in a decision. It only reminds the the registrants of the possibility to adapt, if the information requirement can be fulfilled with an adaptation. If you decide to adapt, ECHA notes that any such adaptation needs to a have scientific justification conforming to the appropriate rules in the respective Annex. For the reasons already explained in the decision and in the following paragraphs, ECHA considers the adaptation is not in compliance with the respective information requirement as there is not sufficient weight of evidence to conclude whether the substance has or has not a particular hazardous property.

With regards to the missing information on the placental weights and abnormalities, you commented that placental weights and placental abnormalities had been investigated in the ICH studies. However, ECHA observes that no results on placental weights or other relevant information such as overview of result per dose group were available in the registration dossier when this draft decision was notified to you.

With regards to the conversion of the administered dose in ml/kg/day to mg/kg bw/d, you explained in your comment that the information was not available under endpoint study records of the ICH studies, but in the endpoint summary on reproduction toxicity (IUCLID section 7.8 - Toxicity to Reproduction – Endpoint Summary - Additional information). The doses were according to you 7.3, 37 and 183 µg/kg/day in the rat study, and 6.3, 31 and 157 µg/kg/day in the rabbit study. ECHA observes that those doses are even lower than the dose 225 µg/kg/day calculated by ECHA based on the publicly available information about the pharmaceutical product tested in the ICH studies. In ECHA's view, this renders the studies even less adequate for a robust hazard identification and risk assessment based on the weight of evidence. As the doses do not produce any systemic toxicity or reach the limit dose, it cannot be concluded whether the substance has or has not hazardous properties related to prenatal developmental toxicity. Furthermore, the OECD TG 422 does not address the morphological malformations similarly to investigations in a prenatal developmental toxicity study.

You have noted that the scientific approach may not be always unambiguously presented to ECHA for the assessment. Indeed, ECHA observes that in the IUCLID section 7.8 - Toxicity to Reproduction – Endpoint Summary, you have mentioned that the pharmaceutical product used as the test item in the ICH studies had a form of stabilized sulfur hexafluoride microbubbles. ECHA confirms that regarding the unambiguos presentation of the weight of evidence, the information about stabilization of the test item in the form of phospholipid

microspheres is not available in test material description under the endpoint study records of the ICH studies and thus, ECHA did not take it in account . Moreover, you have specified neither the nature of the stabilization, i.e. phospolid microspheresthe, nor the pharmaceutical excipients used for stabilization of the test item.

ECHA also observes that the summary of product charactristics (SPC) is publicly available for the pharmaceutical product tested in the ICH studies. Based on that ECHA understands that the test item contains excipients (macrogol 4000, distearoylphosphatidylcholine, dipalmitoylphosphatidylglycerol sodium, palmitic acid) to form sulfur hexafluoride phospholipid-stabilized microspheres. Further, the SPC states that chemical and physical stability of the lipid microspheres dispersion has been demonstrated for 6 hours.

As already explained in the decision, the differences in the toxicokinetic profiles appears to be confirmed by the toxicokinetic studies (Pashin 1987 vs [redacted] 1994 and [redacted] 2009). You have questioned reliability of the 1987 study, however, currently this is the only evidence about distribution of the registered substance upon inhalation exposure. In ECHA's view, it is well known that (phospho)lipid microspheres are used to control release of the active ingredient and to modify its absorption, distribution, metabolism and excretion. Additionally, with respect to the different routes of administration, you stated that the blood concentrations obtained after intravenous bolus application are in the same range as the blood concentrations measured after 28-day of repeated inhalation exposure. However, ECHA is of the opinion that the concentrations cannot be compared as the sulphur hexafluoride is enclosed in the microspheres after the instravenous administration of the pharmaceutical product and thus, not available in the same form as the registered substance upon inhalation. Thus, it cannot be assumed that the toxicokinetic profile and systemic availability of the registered substance upon repeated inhalation exposure differs from the toxicokinetic profile and systemic availability of the stabilized pharmaceutical product after bolus intra venous administration. In conclusion, the dose levels used in the studies seem to be too low for hazard identification for prenatal developmental toxicity as systemically toxic dose levels (or limit dose levels) have not been reached in respective studies. Furthermore there is no justification why higher dose levels can not be used. A credible explanation is lacking on why the toxicokinetics and toxicity should be considered similar via inhalation and intravenous microsphere.

ECHA acknowledges your comments on human exposure. However, the Weight of Evidence approach in REACH Annex XI, section 1.2., focuses purely on the possible hazardous properties of the substance and not on the likelihood of exposure or the estimated level of exposure.

The available information indicates that elimination of the substance from the body may be rapid, however, there is evidence on systemic availability and you have not provided evidence allowing to conclude that the registered substance was toxicologically inert.

ECHA notes that you consider that exposure to workers is only considered likely as part of incidental events and continuous worker exposure is largely unrealistic. However, an acceptable adaptation based on Annex XI, 3 is not available to justify omission of animal testing. Daily inhalation exposure in inhalation studies is considered adequate to address the potential exposure conditions.

Based on the above reasons, ECHA reiterates that the studies alone or in the weight of evidence approach do not provide sufficient information to conclude whether the registered substance has hazardous properties related to prenatal developmental toxcity to adapt

information requirement for pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) and therefore, they cannot be used to fulfil the information requirement addressed in the original decision.

Based on the above, ECHA concludes that the provided information alone or in a weight-of-evidence approach does not provide sufficient information for this endpoint and therefore, it cannot be used to fulfil the information requirement addressed in the original decision.

As detailed above, the request in the original decision was not met, and you are still required to provide a pre-natal developmental toxicity study according to test guideline EU B.31 / OECD 414.

Appendix 2: Procedural history

This decision is necessary after the follow-up evaluation according to Article 42(1) of the REACH Regulation, because in your updated registration you have provided new experimental information, which was not available to you or ECHA at the time when your registration was examined for the original decision.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft of this decision was notified to the Member States Competent Authorities according to Article 51(1) of the REACH Regulation.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and did not amend the request(s).

You updated your registration on 28 February 2018. ECHA took the information in the updated registration into account, and did not amend the draft decision, as only dossier header has been modified.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. The Article 42(2) notification for the original decision is on hold until all information requested in the original decision has been received.