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Evonik comment on classification of synthetic amorphous silica treated with hexamethylsilazane (CAS no. 68909-20-6; "Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica") as Acute toxicity Category 2 (H330) via the inhalation route with an ATE of 0.45 mg/L (dusts and mists)

Introduction

1. Evonik Resource Efficiency GmbH welcomes the opportunity to comment on the CLH recommendation made by the Risk Assessment Committee (RAC), extending the classification and labeling proposal of synthetic amorphous silica (SAS) treated with hexamethylsilazane (CAS nr 68909-20-6) to Acute Inhalation Toxicity Category 2 (Fatal if inhaled). As explained below, Evonik as the original notifier under BPD considers that the substance is subject to an unfair and unlawful process because of the lack of fair notice (and infringement of their right of defence and right to be heard), the failure by ECHA to take into account the latest scientific developments and relevant factors, the lack of reliability of the studies used by ECHA for the proposed classification and the failure to take into account ongoing studies (which would require ECHA to wait for the outcome of that study in order to proceed with the proposed classification proposal). These arguments are further detailed and developed in the specific sections below.

Specific Comments

(a) Lack of Fair Notice

2. We would like to highlight that we were very surprised when ECHA announced the adoption by RAC by simple majority of the proposal of the harmonised classification. We were not aware of this due to the fact that synthetic amorphous silica treated with hexamethylsilazane (HMDZ) was not on the agenda with the correct name. By not providing full notice of the fact that the substance was on the agenda meant that we had a chance to request participation in the RAC meeting to make our views known to you properly and effectively. The adequate correct substance identifiers (EINECS No., CAS No. and IUPAC chemical name) were not provided on the RAC agenda inviting to the review meeting.

3. We would like your views on how this overall context is consistent with ensuring our rights of defence and our right to be heard in a procedure which ultimately could culminate in a decision adverse to our interests.[1]

[1] In an administrative process leading to a decision which is potentially adverse to the interests of a party, that party must be able to make its views known effectively and properly: C-269/90, *Technische Universität München v Hauptzollamt München-Mitte*, ECLI:EU:C:1991:438, paragraph 14.

4. As a general comment, it should be noted that a targeted consultation with a deadline for commenting of two weeks (i.e. from 3 February 2020 until 17 February 2020) is not appropriate to enable all interested parties to provide appropriate comments on this significant classification change of the substance in concern.[2]

(b) Failure to take into account the latest scientific developments.[3]

5. According to the CLPR (REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL, Annex VI, Part 2): *"For all dossiers any relevant information from registration dossiers shall be considered and other available information may be used "*) and ECHA's "*Guidance on the preparation of dossiers for Harmonised Classification and Labelling*"[4], when preparing a CLH dossier, all relevant and reliable information should be considered in order to determine the classification for each substance.

6. As part of the SAS REACH dossier update activities, a thorough scientific review of the existing available studies (submitted separately by Prof. Wolfgang Dekant and Dr. Axel Bosch) on the possible acute inhalation toxicity of surface treated SAS was undertaken by highly qualified and independent toxicologists leading to the conclusion that no final interpretation can be derived from the available data for this toxicological endpoint for all SAS treated forms.

7. According to those experts, most of the existing studies are insufficient for an adequate assessment of this endpoint. The majority of the studies were conducted *before* the release of OECD Guideline 403 (September 2009). As a result, the methodology used does not exactly follow current standards for assessing acute inhalation toxicity in general.

8. All of the inhalation testing was conducted with a substance that differs significantly from commercial product based on particle size. In inhalation studies using rats, the atmospheric concentration required by the experimental design can only be achieved by reducing the particle size using a high-energy cascade impactor. In the resulting product for OECD 403 testing, nearly 100% of the particle fraction the MMAD range of 1 to 3 µm, and capable of entering the deep lung (alveolar particle fraction) of the test animal. By comparison, only minor amounts (less than 1%) of the commercially available surface treated SAS substances has been measured as respirable for humans (Stintz and Heinemann, 2001[5]). Using the same test method (sieving), >99% of the particle fraction of the commercial products is in excess of 90 µm and can only reach the upper airways of humans (nasal passages and throat) or

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[2] See ECHA's webpage at https://echa.europa.eu/harmonised-classification-and-labelling-consultation

[3] In adopting the Contested Act, the Defendant is legally obliged to take into account all relevant factors. Conversely, it is legally obliged to avoid taking into account any irrelevant factors: Case T-689/13, *Bilbaina de Alquitranes and Others v Commission*, ECLI:EU:T:2015:767, paragraph 24 and the case law cited; Case T-456/11, *ICdA and Others v Commission*, ECLI:EU:T:2013:594, paragraphs 70-71.

[4] See ECHA's webpage at https://echa.europa.eu/regulations/clp/harmonised-classification-and-labelling : ECHA Guidance on the preparation of dossiers for harmonised classification and labelling, version 2.0, August 2014, pages 25, 28-29.

[5] Stintz, M., Heinemann, M. 2001. Technical report "Particle analysis of pyrogenic (fumed) silica at technical concentrations and under technical handling and use conditions". Technische Universität Dresden, Institut für Verfahrenstechnik, 20.09.2001

cannot be inhaled at all. Therefore, the tests do not represent the toxicological behavior of the commercial product and cannot be considered relevant for inclusion in the hazard definition/hazard assessment of the substance.

(c) Lack of reliability of the studies

9. According to Article 5.2 of the CLP Regulation and the ECHA Guidance[6], the information taken into account for a proposed classification should be relevant, adequate, reliable and scientifically valid.

10. Based on Klimisch criteria, the surface treated SAS studies present major methodological deficiencies and were attributed recently by the reviewing independent experts a KL score of 3 (unreliable). This is justified by non-comparable test parameters, such as test concentrations, particle size control and measurement, exposure time, equipment type and whole-body study versus nose only designs. Also, the maximum dose recommended in OECD Guideline 403 was not achieved, mainly because of material properties.

11. The state of the art for particle size measurement under exposure conditions in animal experiments as well as the understanding of the particle size related deposition in the respiratory tract has improved significantly since that time. This has been reflected by a new evaluation of the study reliability. Today, it is unclear how RAC was able to derive conclusions from the data summaries presented in ECETOC and EPA HPV, therefore we invite RAC to request the full reports under confidentiality terms to verify the quality of studies and data.

12. SAS producers organized in the SASforREACH consortium requested independent toxicologists with a recognized expertise in inhalation toxicity to compile an expert statement (see the separately submitted expert statement from Prof. Dekant and Dr. Bosch). This expert statement concludes that acute inhalation toxicity of surface treated SAS is complex, and all study results need to be interpreted with caution due to issues of particle generation, particle size measurements and stability of respirable particles in the test atmospheres. None of the studies did a qualified review of the particle re-agglomeration and the impact of shear forces on the atmosphere generation. All studies needed to apply very high particle loads for testing. SAS is known to readily form agglomerates under low shear stress environments, such as when deposited in the lung. This behavior is seen in some studies as suffocation-type effects (obstruction of the airways) that cause lethality. Those effects are not an intrinsic property of the HDMZ surface treated SAS, but a result of the extreme particle load of the rodent lung with particulate material. This hypothesis will be further investigated within the mechanistic study, including HDMZ surface treated silica. Moreover, the huge differences in the respiratory tract structure makes it impossible to extrapolate such effects from rat to human because the particle size to cross section ratio for the rat is an extreme worst case for these kinds of effects. Besides, suffocation due to airway obstruction, toxic effects to other organs besides the respiratory tract after surface treated SAS-inhalation were not seen in the acute toxicity studies and did also not occur in repeated dose studies with surface treated SAS after oral administration. Furthermore, it has to be considered that, the acute inhalation toxicity studies with surface treated SAS

[6] ECHA Guidance on the preparation of dossiers for harmonised classification and labelling, version 2.0, August 2014, page 30.

intentionally generates a test material with a much higher respirable fraction than is present in commercial SAS grades. Therefore, the acute inhalation studies do not reflect an intrinsic toxicological effect of the commercial SAS grades. This is recognized in OECD Guidance 39 (2018) paragraph 69 which states:

> "*At very high concentrations, dry powder aerosols and chemically reactive liquid aerosols (e.g., polymers) tend to form conglomerates in the proximal nose causing physical obstruction of the animals' airways (e.g., dust loading) and impaired respiration which may be misdiagnosed as a toxic effect*."

13. As a consequence, classification of HMDZ treated SAS for Acute Inhalation Toxicity Cat 2 is not warranted. The higher potential of surface treated hydrophobic SAS for acute lethality is most likely due to reduced agglomeration forces as compared to hydrophilic SAS. This results in slower agglomeration and a larger particle doses can reach the lung as inhalable particles will be present for a longer time in the chamber atmosphere. But again, the present particle size distribution generated by high shear forces to fulfil the guideline requirements do not reflect the situation at the workplace or during known applications.

14. It should also be noted that harmonized classification under the CLP Regulation should be based on the intrinsic properties of the specific substance. Particle effects are not related to intrinsic properties and are not substance specific effects and it would be more appropriate to regulate those effects through other regulatory measures such as the setting of OELs.

(d) Information ongoing studies not yet taken into account

15. Based on the above facts, the experts Prof. Wolfgang Dekant and Dr. Axel Bosch recommend in their statement to perform an acute mechanistic inhalation toxicity study which meanwhile was launched with different forms of SAS and surface treated SAS (including HDMZ surface treated SAS) which incorporates detailed exposure monitoring in particular the optimized determination of particle sizes, a detailed pathological assessment of all exposed animals including determination of particle deposition in the airways and of oxygen or oxygenhemoglobin concentrations in blood after the exposure or in animals that died during the exposures. Detailed histopathological examination of heart and thymus will clarify any secondary sign of asphyxiation.

16. SASforREACH initiated a mechanistic study on acute inhalation of SAS in cooperation with Fraunhofer Institute Hannover/ITEM (animal experiments), University of Dresden (exposure/ particle characterization) and AnaPath (Pathology). The formalities incl. contracts are finalized. Work on exposure /particle generation is started at the University of Dresden in close cooperation with Fraunhofer. Results and Final Report are expected by the end of this year.

17. Within the framework of the substance evaluation, both ECHA and the evaluating member state the Netherlands have been informed of the initiating of this study and of its potential impact on the classification of the substance. Specifically, ECHA was informed in October 2019 and did not make any objection. Since there was no objection to the conducting of this

study, there is a legitimate expectation that this study should indeed be conducted and that it will be a relevant factor for the authorities to take into account.[7]

18. Additionally, according to the ECHA Guidance, if a substance is undergoing testing and if this testing is considered to be of potential relevance for the proposed harmonized classification, "*it must be carefully considered whether to proceed with the CLH dossier or to await the result of the testing*".[8]

Conclusion

Evonik considers the substance is subject to an unfair and unlawful process because of the lack of fair notice (and infringement of their right of defence and right to be heard). Synthetic amorphous silica treated with hexamethylsilazane was not on the agenda with the correct EC inventory name and CAS and EC number. By not providing full notice of the fact that the substance was on the agenda meant that we were not fully prepared to make our views known to you properly and effectively.

Furthermore, Evonik would like to emphasize that it is important to consider for the evaluation of acute inhalative toxicity of hexamethyldisilazane surface treated SAS the actual running mechanistic study performed in cooperation with Fraunhofer Institute Hannover/ITEM, University of Dresden and AnaPath. We are convinced that especially the comparative mechanistic study is of scientific importance. Based on the weakness of the current data on acute inhalative toxicity (Klimisch 3) this study was contracted out already in November last year by the SASforREACH consortium. It is the first acute inhalation study with silica comparing representative SAS forms (incl. HMDZ surface treated SAS) under standardized testing conditions. Special attention is paid to exposure characterization incl. particle size determination. A detailed pathological assessment of all exposed animals including determination of particle deposition in the airways and of oxygen or oxygenhemoglobin concentrations in blood after the exposure will be performed. A thorough histopathological examination of heart and thymus will clarify any secondary sign of asphyxiation. The superior target of this mechanistic study is to reduce the number of future animal experiments with substances such as SAS showing particle related effects only and no substance specific effects.

It is the first acute inhalation study with SAS comparing representative SAS forms (incl. surface treated SAS) under standardized testing conditions. Special attention is paid to exposure characterization incl. particle size determination.

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[7] In adopting the Contested Act, the Defendant is legally obliged to take into account all relevant factors. Conversely, it is legally obliged to avoid taking into account any irrelevant factors: Case T-689/13, *Bilbaina de Alquitranes and Others v Commission*, ECLI:EU:T:2015:767, paragraph 24 and the case law cited; Case T-456/11, *ICdA and Others v Commission*, ECLI:EU:T:2013:594, paragraphs 70-71.

[8] ECHA Guidance on the preparation of dossiers for harmonised classification and labelling, version 2.0, August 2014, section 5.2.7, page 29.

It is unclear how RAC was able to derive conclusions from the data summaries presented in ECETOC and EPA HPV without requesting the full reports, not verifying the quality of studies and data. Before deciding to extend an acute toxicity classification to SAS we would urge RAC to wait for the complete data set including the old studies (with reevaluation of reliability) and the results of the mechanistic study which will be available by the end of this year.