February 16, 2020

Comments to public consultation on the Committee for Risk Assessment (RAC) proposal for a harmonized classification and labelling on Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica

Statement for Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica , aka hexamethyldisilazane (HMDZ) -Treated Synthetic Amorphous Silica (SAS), reflecting the position of Cabot Corporation, one of the leading manufacturers of HMDZ-Treated SAS regarding the relevance of findings with specific treated SAS types in acute inhalation studies

1.0 Introduction

Acute inhalation toxicity studies on Cabot's treated SAS grades reported in ECETOC 2006 and Becker et al. 2013 are listed in the Confidential Appendix 1. Based on a weight of evidence as presented below, a classification of Acute Inhalation Toxicity Category 2 under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, and the Globally Harmonized System of Classification and Labelling of Chemicals (GHS, 2017) is not warranted for HMDZ-treated SAS.

2.0 Scientific arguments

The following scientific basis must be considered for the (non) classification/labelling of HMDZ-treated SAS.

2.1. High respirable particle concentrations result in suffocation and non-specific toxicity

Confidential Appendix 1 lists studies conducted on hexamethyldisilazane (HMDZ)-treated SAS, as well as dimethyldichlorosilane (DMD)-treated SAS and polydimethylsiloxane (PDMS)-treated SAS to which the RAC committee read-across to complement their hazard assessment. The surface-treated SAS used in the experimental studies had almost 100% of the particle size distribution with MMAD values less than 4 µm, and therefore was able to reach the alveolar portion of the lungs in experimental animals. As stated in ECETOC (2006), some of the studies reported that the surface-treated SAS had completely occluded some of the smaller bronchioles. These effects were seen as an indication of suffocation, and the adverse effects appeared to be primarily due to the physical presence of the surface-treated SAS rather than to a direct toxic effect of the substance. The effect of surface-treated SAS on the lungs is considered to be the result of very high particle concentrations, resulting in obstruction of the airways leading to mortality (ECETOC, 2006). Cabot studies on surface-treated SAS shown in confidential appendix 1 show clear evidence of suffocation.

Per the below note by the study director in the Cabot study report (TNO 2000) cited in Becker et al 2013: "It should be borne in mind that, although exposure at *1g/m³ seems a moderate loading, in fact because of the extremely low density, it should be compared with regard to an obstruction to a load of ~20g/m³ of a material with density close to 1), assuming that the obstruction is related to the volume of the particles rather than to the mass*."

It seems relevant to consider the real volume occupied by the particle in the airways during the classification assessment. Highly fluffy voluminous particles would severely impair the breathing function, by a physical effect – blockage of airways. The relevant question is therefore whether or not such a kind of study is relevant to be conducted on such a fluffy material. Referring to the above citation, comparing the test dose corrected for the density with the concentration triggering the classification, would allow to conclude that the material is out of the classification threshold.

Cabot commissioned an expert review to determine whether the acute inhalation toxicity results on DMD-treated SAS (TNO 2000) should lead to a classification (Illing, 2000). A summary of the expert statement is provided below:

> *"The normal response to exposure to levels of insoluble particulates that exceed the capacity of the lung clearance mechanisms, including amorphous silicas, is alveolar macrophage release, phagocytosis of dust particles, lysis of the overloaded macrophages and damage to epithelial cells, leading to high levels of phospholipids (which have detergent-like activity). Blood vessels may also be damaged. The process has been identified using both in vitro and in vivo studies. Animals showing these effects can survive for considerable periods of time. (see Adamis et al., 2000, Anonymous, 1999; Donaldson and Borm, 1998; Fubini, 1998 and references therein).*
>
> *In the test reports the pathologist suggests that there may be some chemical involvement in the toxicity*
> *of DMD-treated SAS. In my opinion, this is no more than the normal inflammatory response to this type of insoluble particulate. Animals in high dose groups probably suffocated because they were exposed to excessive levels of a low-density insoluble dust. The necropsy findings and the limited histological information are consistent with an overloading of the dust clearance mechanisms as a consequence of very high loading with an insoluble particulate. Providing that animals survive the exposure period; the continuing effects are not necessarily life threatening within the time scale of an acute toxicity study.*
>
> *Overall, the findings support the suggestion that the lung dust clearance mechanisms were grossly overloaded."*

In addition, the histopathology report for one of the PDMS-treated SAS study listed in ECECTOC 2006 (Confidential Appendix 4), clearly states that the observed deaths were the results of foreign body reaction in the lung.

A careful review of the varying methodologies and results seen in the available acute toxicology studies highlights the need for a clearer understanding of the behavior of treated SAS travelling to and within the animal lung. Open questions around the actual particle size and dose delivered into the respiratory tract of the animals, as well as the behavior of the particles within the lung, are critical to understand how treated SAS impacts the animal, and whether the effects seen are due to toxicology or simply physical effects (suffocation) that would be seen from any particle of similar size, loading, and physico-chemical properties. To enable this level of understanding the SASforREACH consortium (of which Cabot Corporation is a member) has commissioned a mechanistic study in conjunction with TU Dresden, and the Fraunhofer Institute in Hanover, to help answer these questions, including:

- Allow acute toxicity inhalation testing in accordance with OECD 403/436 achieved for a range of cohesive powders with difficult flow mechanics while generating aerosols of the powders in the range of 1-4um with concentration up to 5000mg/l
- Understand re-agglomeration behavior between aerosol generation and the point of inhalation
- Accurately measure actual particle size and concentration delivered to the animal through the use of an “artificial rat nose” sampling system
- Pathological examination of the breathing tract and lungs of the rats to determine the loading and in case of death, the reasons for death

The testing system should be complete in June, with the corresponding animal studies ready before the end of the year.

2.2. Particle size distribution of the tested material is different from the commercial product

The relevant particle sizes for both untreated and treated SAS, as produced and marketed, are the sizes of their agglomerates. Typically, the mean size of the agglomerates is in the order of several hundred microns (Stintz and Heinemann, 2001). However, the experimental design of the acute inhalation toxicity test calls for the application of high shear stress resulting in a significant reduction of the agglomerate size, so that nearly 100% of the particle fraction has a Mass Median Aerodynamic Diameter (MMAD) below 4 µm to allow for exposure of all relevant regions of the respiratory tract.

Thus, in the experimental studies, nearly 100% of the particle size distribution in air is below 4 µm and therefore able to migrate to the alveolar region of the lung. In contrast, some studies have shown that only a minor fraction (less than 1%) of commercially available untreated and treated SAS types has been measured to be respirable (thoracic + alveolar fraction) (Stintz and Heinemann, 2001). The size of the particles (agglomerates) measured by Laser Diffraction either by

- A free flow technique (i.e. treated SAS material flows directly into the laserbeam without the agglomerates to be broken by any external shear forces) or,
- a sedimentation shaft GRADIS/L dry dispersion unit, representative of weak dispersion forces, that was developed for measuring particle size in combination with the laser diffraction spectrometer HELOS KR;

is very much representative of the size of the material as placed on the market.

This is supported by recent Cabot studies conducted on representative samples of treated SAS (Confidential Appendix 2). These studies show that a very low amount (1.77% for HMDZ-treated SAS; 1.15% for DMD-treated SAS; 0.57% for PDMS-treated SAS) of the particles as placed on the market would fall in the respirable range. Under normal foreeable handling and use conditions, the treated SAS will only reach the upper airways or not be inhaled at all. Therefore, the available acute inhalation toxicity tests are not representative of the commercial surface-treated SAS products and are not relevant for hazard assessment (ECETOC, 2006). Section 1.3.2.4.9.4 of GHS (2017) states:

> "Route of exposure, mechanistic information, and metabolism studies are pertinent to determining the relevance of an effect in humans. When such information raises doubt about relevance in humans, a lower classification may be warranted. When there is scientific evidence demonstrating that the mechanism or mode of action is not relevant to humans, the chemical should not be classified."

Because the test material for acute inhalation studies have a much higher respirable fraction than is present in commercial SAS grades, 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.*"

In addition, OECD Guidance 39 (2018) paragraph 8 states that: "As a rule, testing should be done unless there are compelling reasons for not testing, such as: There is little or no significant human exposure to a test chemical by the inhalation route as it is produced, marketed or used".

This is also claimed in the CLP Guidance on classification on page 241/242: "*Article 9(5) When evaluating the available information for the purposes of classification, the manufacturers, importers and downstream users shall consider the forms or physical states in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used.*"

> Workers and end users of the substance are unlikely to be exposed to particles in the inhalable or respirable ranges. Typically, the users pour the bags of silica into loading stations. This is a low-shear process; thus, the substance will remain in agglomerated form. As high energy blending (and transport) is carried out in closed mixers and blenders, this will not lead to worker exposure to the de-agglomerated substance. (Interservice memorandum R Nick to C Bramante dated 10 March 2000-Confidential Appendix 3). Suitable precautions are undertaken before maintenance staff are permitted to carry out work that might lead to exposure to de-agglomerated treated silica. Accidental exposure to the product through bag splitting or mis-pouring (both low shear processes) is unlikely to result in de-agglomeration of treated silica. Exposure due to uncontained failures of blenders, mixers and associated pipework is unlikely as these are rare events.

Given the nature of the material (a low bulk density, low solubility particulate material), the physicochemical characteristics (including particle size) and exposure patterns are critical to assess the relevance of the test results for the purpose of a classification.

To conclude, the process of preparing treated SAS for acute inhalation studies results in a test material that is substantially different from the commercial product; thus the ability of the surface-treated SAS product to reach the alveolar region is not relevant to humans for an acute exposure situation, and surface-treated SAS should not be classified for Acute Inhalation Toxicity.

3.0 Conclusion

As discussed above, acute inhalation toxicity studies with surface-treated SAS use a form of test material with a much higher respirable fraction than is present in commercial surface-treated SAS products. The non-specific toxicity observed in acute inhalation animal studies, including obstruction of the airways, is a result of the high respirable fractions. The observed respiratory failure accompanied by a complete or partial obstruction of the respiratory tree, labored breathing, histopathology findings highlighting pulmonary tissue congestion, edema and lung hemorrhage are consistent with suffocation symptoms due to the presence of foreign material in the respiratory tree. Therefore, the acute inhalation studies do not represent a unique toxicological behavior of the commercial surface-treated SAS products, especially the HMDZ-treated silica and no classification for Acute Inhalation Toxicity is warranted on the basis of these studies.

4.0 Appendixes:

Appendixes are considered Cabot confidential information and are submitted as Confidential Appendixes.

- Appendix 1 List of Cabot acute inhalation toxicity studies and summary of observations.
- Appendix 2. Dustiness testing reports for DMD-, HMDZ- and PDMS-treated SAS representative samples.
- Appendix 3. Interservice memorandum R Nick to C Bramante dated 10 March 2000
- Appendix 4. Addendum summary of histopathologic observations of lung tissue for Toxicogenics Study 420-0689 [PDMS-treated SAS]

5.0 References

Becker et al. (2013). Safety assessment of silylates and surface-syloxysilicates, International Journal of Toxicology 32(Supplement 1) 5S-24S

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OECD TG403. OECD Guideline for the Testing of Chemicals – Acute Inhalation Toxicity. Adopted September 7, 2009. http://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd-tg403.pdf

OECD TG463. OECD Guideline for the Testing of Chemicals – Acute Inhalation Toxicity/ acute toxic class method. Adopted September 7, 2009. https://read.oecd.org/10.1787/9789264076037-en.

OECD 2018. Guidance document on inhalation toxicity studies. Series on Testing and Assessment No. 39. https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)28/rev1&doclanguage=en

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