aSASp | Association of Synthetic Amorphous Silica Producers

3rd February 2023

Subject: Comments to the Targeted Public Consultation for substance Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl), hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide (CAS # 68909-20-6) (HMDZ-treated SAS)

The Association of Synthetic Amorphous Silica Producers (ASASP), a sector group of Cefic, would like to share its comments to the Targeted Public Consultation for substance HMDZ-treated synthetic amorphous silica (SAS). As it is stated in the ECHA Note to RAC, "*the new study by the inhalation route, which provides additional mechanistic examinations, appears relevant for the assessment of acute toxicity by inhalation and complements the information assessed by RAC*".

In fact, the results of SASforREACH Consortium's new mechanistic study submitted by ASASP to RAC demonstrate that HMDZ-treated SAS **is not an acute toxicant by inhalation via a relevant mode of action.** The study confirms a physical blockage of the rat upper respiratory tract by agglomerated HMDZ-treated SAS as cause of **death by suffocation, and not due to intrinsic toxicity of the particle.** In addition, such a physical blockage is not relevant for humans due to anatomical differences between rat and human respiratory tracts[1]. For these reasons, ASASP concludes that HMDZ-treated SAS does not warrant a classification as acute toxicant and therefore the current RAC opinion on the classification for acute inhalation toxicity of this substance as Acute Tox. 2; H330 should be revised.

Background

In its final opinion on 5th December 2019, RAC proposed to classify HMDZ-treated SAS as **STOT RE 2**[2] (H373: "may cause damage to organs") and as **Acute Tox 2** (H330: "fatal if inhaled"). ASASP still firmly believes that the substance HMDZ-treated SAS does not warrant to be classified at all.

[1] JACC Report 51, page 99, 8.1.4, first paragraph (https://www.ecetoc.org/publication/jacc-report-51-synthetic-amorphous-silica/ .

[2] In 18th ATP, the European Commission states the following: "*the classification of this substance as STOT RE 2, recommended in the RAC opinion of 5 December 2019, should be included in Annex VI to Regulation (EC) No 1272/2008, since no new information has been received that would require further assessment for that classification".* ASASP still believes that the STOT RE classification is not warranted, and further research program is ongoing to demonstrate that the effects are not SAS-specific but particle-specific. For the first time, histopathological examinations of tissue slides from lung and lung associated lymph nodes from fourteen 90-day studies with 12 chemically different particles were directly compared by a team of pathologists in autumn 2022 and will be soon published in a peer review journal called "Toxicological Letters" (Impact factor from 2022-2023 4.372 up by 22%). The objective was to get a more comparative and holistic approach on the similarity of particle effects from a scientific perspective. It is of interest that on day 1 after 90 day exposure, all 14 particulate substances caused similar lesions with similar outcomes in the lung and lung associated lymph nodes, which is a particle effect.

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The Silica industry (SASforREACH Consortium) informed the European Commission and RAC that the group commissioned a mechanistic study in September 2019, to evaluate the cause of death in older studies due to signs of suffocation.

During CARACAL 41 meeting, the European Commission recognised that this is a non-standard case in which the role of physico-chemical effects should be analysed in more details. Therefore, it was concluded that the proposed classification for acute toxicity by inhalation Cat. 2 should be re-assessed by RAC, including the new information[3].

Unique study design – differences from previous studies

The intention of this study is to clarify **whether lethality in connection with low density hydrophobic particles is caused by physical obstruction or an intrinsic effect (such as systemic toxicity or disturbance of function or the physiology of the alveoli by interaction with the surfactant or membranes)**. As the guidelines for acute inhalation toxicity assessment (OECD 403 and 436) only require counting dead animals and a macroscopic examination of the surfaces of the organs in the abdominal and thoracal cavity, causes for lethality were not assessed in previous studies.

This new study differs from previous studies conducted following standard OECD protocols as additional physical, biological and histopathological parameters have been included to clarify the above question. The mechanistic study comprises:

- **physico-chemical characterisation of the generated aerosol** and the exposure atmospheres in the test system (stability, particle concentration, change in the particle size distribution over time). The aerosol generation is crucial for the correct execution of acute inhalation toxicity testing and to determine the highest technical feasible aerosol concentration with no or maximum acceptable altering;
- **examination of the entire respiratory tract pathology including proximal nose and nasal cavities** (for this purpose a new preparation and examination method was developed)
- **thorough histopathological examination of organs that are known to be sensitive to suffocation**
- **blood oxygen monitoring**

The aim was to clarify the origin of the effects described in former acute inhalation studies. Furthermore, “bottlenecks” for particles in the rat upper respiratory tract (e.g. nasal cavities) were not examined in the existing studies, while in this study, for **the first time the entire respiratory tract including proximal nose and nasal cavities were examined.**

Animal vs Humans

In the Annexes cited below, experts have investigated the human relevance of the observed lethality of HMDZ-treated SAS in acute toxicity testing using inhalation exposure in rats.

The result of the investigation is that suffocation effects on rats cannot be transferred to humans, because the anatomy of the rat respiratory tract differs from the human: mainly monopodial branching of airways, smaller ventilatory unit volume, smaller alveolar size and lower average number of cells per alveolus (Miller, Mercer and Crapo, 1993). The new mechanistic study shows that the OECD 403 and

[3] CA_13_2022_CARACAL 41_DSR_18th ATP

436 Guideline limit test concentrations (5000 mg/m^3) for acute toxicity studies for CLP classifications are too high for hydrophobic low-density particles. In fact, much lower technical feasible aerosol concentrations can lead to physical obstruction effects in rats, but are not reflective of what could happen in humans. Contrary to humans, the rat is an obligatory nose breather; while fixed in a tube for four hours during acute inhalation studies, the rat can neither protect its nose by fur nor can it physically clean it.

Conclusion

A complete physical obstruction of the proximal nose (nasal cavities) has been proven by histopathology as cause of mortality, due to suffocation. Clinical signs such as preterminal gasping and macroscopical findings in the lung (i.e. congestion, edema, acute emphysema and petechiae) are secondary effects resulting from obstruction of the nasal cavity at 500mg/m³. This should not be misdiagnosed as a toxic effect, as stated in OECD Guidance 39 (2018) para 51: "*At very high concentrations, dry powder aerosols …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"*.

The final results of the study have confirmed that the cause of animal death is suffocation, a physical effect due to the presence of foreign materials and not due to an intrinsic (i.e. substance-specific) toxic effect. For this reason, HMDZ-treated SAS does not warrant a classification as acute toxicant and we ask that the current RAC opinion on the classification for acute inhalation toxicity of this substance as Acute Tox. 2; H330 should be revised.

About ASASP

The Association of Synthetic Amorphous Silica Producers is a sector group of the European Chemical Industry Council (Cefic) and represents the major producers of synthetic amorphous silica (SAS) in Europe. ASASP is a non-profit organisation established in 1992 dedicated to promoting the safe use and benefits of SAS to society.

The health and safety of employees, consumers and the wider community are of the upmost importance to ASASP members. ASASP continues to be convinced that based on the available information, the use of SAS in consumer products is considered safe.

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Annex 1

EXPERT STATEMENT

The human relevance of the observed lethality of Silanamine, 1,1,1-trimethyl-N-

(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide (called Silanamine by RAC) (CAS # 68909-20-6) in acute toxicity testing using inhalation exposure in rats

Annex 2

ANNEX TO EXPERT STATEMENT

The human relevance of the observed lethality of Silanamine, 1,1,1-trimethyl-N-

(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide (called Silanamine by RAC) (CAS # 68909-20-6) in acute toxicity testing using inhalation exposure in rats

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