ASASP | Association of Synthetic Amorphous Silica Producers

ASASP Policy paper on the ongoing Harmonised Classification and Labelling procedure (CLH) for Silicon Dioxide (CAS no: 112945-52-5/112926-00-8)

12 July 2024

The Association of Synthetic Amorphous Silica Producers (ASASP), a sector group of Cefic, and SASforREACH, the EU REACH consortium for Silicon Dioxide / Synthetic Amorphous Silica would like to share their joint position on the ongoing classification of Silicon Dioxide (also called Synthetic Amorphous Silica or SAS). Silicon Dioxide is currently being proposed for harmonized classification by the Dutch Competent Authority (RIVM) as STOT RE 1[1] by inhalation, (H372) (Registry of CLH intentions until outcome - ECHA (europa.eu). The public consultation was opened on 10th June and closes on 9th August 2024.

Executive summary

ASASP and SASforREACH are of the opinion that the proposed classification for Silicon Dioxide as STOT RE 1 is not warranted as it is not based on intrinsic properties of the substance and for the following reasons:

1. SAS is a substance with no intrinsic toxicity

Synthetic Amorphous Silica (SAS) is being proposed for classification based on adaptive, unspecific inflammatory effects, in rat repeated dose inhalation toxicity studies, which are generic to all particles regardless of the substance. Classifying a substance based only on its particle effects deviates from the legal scope of the CLP because the hazard identification process can only assess the intrinsic properties of substances to determine their potential to cause harm.

2. SAS is safe as placed on the market

The assumption made by the CLH Report Submitter that all untreated SAS forms are respirable is a fundamental error. More than 90% of SAS forms, as placed on the market (as per Article 8(6) CLP, as supported by recital 30) are not respirable. Any concerns regarding inhalation exposure are thus mitigated, if not eliminated.

3. What's tested in toxicity tests is different to what's on the market

Repeated dose inhalation studies according to OECD test guidelines require particles to be intentionally modified to be respirable for the test animals to investigate effects (OECD TG 413[2] with MMAD - mass median aerodynamic diameter ≤ 2 µm respectively ≤ 3 µm in the previous test guideline). Inhalation testing for regulatory purposes can therefore not be conducted on SAS forms as placed on the market, as required by Articles 8(6) and 9(5) of the CLP, recital 30.

[1] Specific Target Organ Toxicity by Repeated Exposure Category 1

[2] OECD (2018), *Test No. 413: Subchronic Inhalation Toxicity: 90-day Study*, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264070806-en.

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4. CLP is not fit for purpose to regulate particles

The proposed cut-off limit concentrations for STOT-RE classification by CLP (Annex I 3.9) are unrealistically high. Repeated dose inhalation studies show that inflammation is triggered by respirable particles at concentrations far below these limits. SAS shows reversible inflammation caused by physical conditions, not intrinsic properties of the substance itself.

5. Rats are more sensitive to particles than humans

Rats are more sensitive to particles than humans, as shown by inhalation studies on various materials, not just SAS. This is due to the anatomy of rat lungs, which are predisposed to more severe inflammation. Over 40 years of human health data supports this, showing no respiratory toxicity in humans.

6. The whole respiratory tract is not affected

The proposal by the CLH Report Submitter to classify the whole respiratory tract is made on a wrong interpretation of observations in the nasal cavities. These observations are not relevant for human health hazard assessment. The inflammatory effects observed in the studies are restricted to the lungs and its associated lymph nodes.

Based on the above ASASP and SASforREACH does not agree with the proposed classification of SAS as STOT RE 1. It contradicts the law as it stands. Should classification continue to be proposed, we acknowledge an alternative approach where - based on the data provided by industry - classification is limited to respirable particles of forms of SAS as placed on the market reaching the alveoli with the target organ being lung and not the respiratory tract.

The above messages are further outlined below.

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Scientific evidence demonstrates SAS particles do not pose a hazard or a risk for human health at intended or foreseeable conditions of use

1. SAS is a substance with no intrinsic toxicity

Synthetic Amorphous Silica (SAS) is being proposed for classification based on adaptive, unspecific inflammatory effects, in rat repeated dose inhalation toxicity studies, which are generic to all particles regardless of the substance. Classifying a substance based only on its particle effects deviates from the legal scope of the CLP because the hazard identification process can only assess the intrinsic properties of substances to determine their potential to cause harm.

SAS is one of the most rigorously tested substances regarding potential hazards and risks to humans or the environment. Toxicological and ecotoxicological tests as well as epidemiological data in combination with decades of experience in its manufacture and use have resulted in no indications of risks to health or the environment through SAS exposure when the substance is handled appropriately.

SAS is essentially non-toxic in humans via the oral, dermal/ocular or inhalation routes of exposure. No systemic toxicity in humans has been observed.[3]

SAS induces reversible inflammation in rat inhalation studies with artificially modified respirable particles. This is caused by physical conditions, not by the intrinsic properties of the substance itself. In a recent scientific re-assessment and re-evaluation of 14 repeated inhalation (90-d) toxicity studies in rats performed with different respirable particles which exhibit no or very low inherent toxicity (including SAS)[4] it was demonstrated that they can all induce a very similar response in the lung and lung-associated lymph nodes ("foreign material reaction"), which is the general biological response to particulate material deposition in the alveolar region of the lung and are not the effects associated to an intrinsic property of the substances.

2. SAS is safe as placed on the market

The assumption made by the CLH Report Submitter that all untreated SAS forms are respirable is a fundamental error. More than 90% of SAS forms, as placed on the market (as per Article 8(6) CLP, as supported by recital 30), are not respirable and therefore cannot cause any adverse effects to the lungs. Any concerns regarding inhalation exposure are thus mitigated, if not eliminated. This is demonstrated by data generated by ASASP and SASforREACH members based on EN 481 standard. The results confirmed that the respirable fraction is at a very low level.

SAS is a nanostructured material, i.e. it exhibits internal structures at the nanoscale which are irreversibly bound to aggregates. The aggregates are the smallest dispersible units, but they can only be found in liquid dispersions under harsh ultrasonic dispersion conditions. Their size can reach from

[3] ECETOC JACC Report 51, Synthetic Amorphous Silica

[4] Weber et al., *Regenerative and progressing lesions in lungs and lung-associated lymph nodes from fourteen 90-day inhalation studies with chemically different particulate materials*, Toxicology Letters, 29/12/2023, Regenerative and progressing lesions in lungs and lung-associated lymph nodes from fourteen 90-day inhalation studies with chemically different particulate materials - ScienceDirect

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the sub µm range to the range of a few µm. The aggregates interconnect further to form much bigger agglomerates. SAS materials as placed on the market are present in the form of agglomerates only. These agglomerates are generally not respirable.

3. What's tested in toxicity tests is different to what's on the market

Repeated dose inhalation studies according to OECD test guidelines require particles to be intentionally modified to be respirable for the test animals to investigate effects (OECD TG 413[5] with MMAD - mass median aerodynamic diameter ≤ 2 µm respectively ≤ 3 µm in the previous test guideline). Inhalation testing for regulatory purposes can therefore not be conducted on SAS forms as placed on the market, as required by Articles 8(6) and 9(5) of the CLP, recital 30[6].

Industry commissioned studies on aerosol generation[7] of low-density particles to demonstrate the high energy required to break agglomerates into small respirable aggregates and maintain them. For testing following revised OECD TG 413 (2018), agglomerated SAS needed to be broken down into even smaller airborne particles with MMAD ≤ 2 µm. Such small particle sizes can only be produced by applying significant shear stress (pressurized air) in a dedicated laboratory setting[8]. These tests show that under normal conditions of use, particles of respirable size are not easily generated.

4. CLP is not fit for the purpose of to regulate particles

The proposed cut-off limit concentrations for STOT-RE classification by CLP (Annex I 3.9) are unrealistically high. It is widely known that toxicity testing labs are reluctant to expose animals to concentrations up to 20 and 200 mg/m³[9]. For low-density particles, these concentrations are much too high and would cause animals to suffer unnecessarily. Repeated dose inhalation studies show that inflammation is triggered by respirable particles at concentrations far below these limits. Continuing to compare observed effects at these doses with CLP cut-off value for classification is not adequate. CLP guidance recognizes the need to carefully consider the applicability of those values, derived from acute toxicity limits, to particulate material in rat inhalation studies considering STOT RE classification[10].

5. Rats are more sensitive to particles than humans

In inhalation studies, rats have been the model of choice for many years. However, it is well recognized - also by ECHA - that humans and rodents differ significantly in their biokinetic functions so the effects of nanomaterials observed in rodents do not directly translate to humans.[11]

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[5] OECD (2018), *Test No. 413: Subchronic Inhalation Toxicity: 90-day Study*, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264070806-en.

[6] Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

[7] Wessely B et al. Experimental Study on the Transport and Alteration Behavior of Aerosols From Low Density Powders for Acute Inhalation Toxicology Studies .Front. Public Health 10:907202. doi: 10.3389/fpubh.2022.907202

[8] Wolfgang Dekant et al., Issues in the inhalation toxicity testing and hazard assessment for low density particulate materials such as synthetic amorphous silica (SAS) Toxicology Letters, 16/02/2023, https://doi.org/10.1016/j.toxlet.2023.02.002

[9] Statement Creutzenberg O. 2024. Study director at Fraunhofer-Institut für Toxikologie und Experimentelle Medizin (Fraunhofer ITEM), Hannover, Germany

[10] Guidance on the Application of the CLP Criteria Version 6.0, Jan 2024, page 472

[11] ECHA Guidance on information requirements and chemical safety assessment - Appendix R7-1 for nanomaterials applicable to Chapter R7a Endpoint specific guidance (December 2022), 1bef8a8a-6ffa-406a-88cd-fd800ab163ae (europa.eu)

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In fact, many inhalation toxicity studies on various materials, not only SAS, have proven that rats are more sensitive to particles exposure than humans. This is due to clear differences in anatomy of the nose and respiratory tract, but also to physiological differences (the rat can only breathe through the nose and is not able to cough and expectorate) which make the rat more sensitive than human to particles exposure.[12] Macrophages primarily involved in the rat lung clearance (alveoli) have a higher inflammatory potential than those in humans (interstitium).

In addition, over 40 years of human health data are supporting this fact, showing no respiratory toxicity in humans.[13] Considering those epidemiology data during the hazard assessment is key.

6. The whole respiratory tract is not affected

The proposal by the CLH Report Submitter to target the whole respiratory tract for classification is made on a wrong interpretation of observations in the nasal cavities. The observations are not relevant for human health hazard assessment. The inflammatory effects observed in the studies are restricted to the lungs and its associated lymph nodes.

Chitinase positive hyaline inclusion in epithelial cells are unspecific findings observed (age-related increase as a background finding and increasing incidence with any kind of test item by nose-only inhalation), which do not progress to any adverse effect or inflammation in rats and mice[14].
The hyperplasia observed in association with one specific precipitated SAS form is an artefact based on the aerosol generation for rat studies with high shear forces. Under real conditions where no shear forces are applied this specific morphology of the particles cannot occur during production and handling. These effects constitute an isolated case not observed in any other studies.

Conclusion

Based on the above ASASP and SASforREACH do not agree with the proposed classification of SAS as STOT RE 1. It contradicts the law as it stands. Should classification continue to be proposed, we acknowledge an alternative approach where - based on the data provided by industry - classification is limited to respirable particles of forms of SAS as placed on the market reaching the alveoli with the target organ being lung and not the respiratory tract.

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[12] Chamanza R, Wright JA. A Review of the Comparative Anatomy, Histology, Physiology and Pathology of the Nasal Cavity of Rats, Mice, Dogs and Nonhuman Primates. Relevance to Inhalation Toxicology and Human Health Risk Assessment. J Comp Pathol. 2015 Nov;153(4):287-314.

[13] Evangelia E. Antoniou, Jürgen Nolde, Bart Torensma, Wolfgang Dekant, Maurice P. Zeegers, Nine human epidemiological studies on synthetic amorphous silica and respiratory health, Toxicology Letters, 2023, https://doi.org/10.1016/j.toxlet.2023.08.005.

[14] Weber K, Warfving N, Bruer GG, Krueger N, Okazaki Y, Schoenauer R, Schaudien D. Eosinophilic globules, Toxicol Lett. 2024 Apr 30:S0378-4274(24)00083-3. doi: 10.1016/j.toxlet.2024.04.012

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About SAS

SAS is a highly versatile chemical substance providing multiple essential functions. It is used in various highly innovative applications in strategic sectors from the automotive industry to renewable energy (e.g., batteries), construction insulation, from cosmetics, food & pharmaceuticals to paints & coatings, adhesives & sealant, including plastics and rubber, paper and packaging and several other industries whose finished products are needed and used daily.

SAS has unique properties and uses e.g. as a purification agent in the manufacturing of COVID-19 vaccines' , in powder mixtures or even table salt as a flow additive, in toothpaste as abrasive agent helping with removal of plaque, in beer to reduce the level of haze forming, in animal feed for better digestibility of vitamins, in semiconductor manufacturing for chemical mechanical polishing (CMP), or in batteries used in electric vehicles (EV) and energy storage in general. SAS is being increasingly used in diagnostic and biomedical research such as cancer therapy, DNA delivery, and enzyme immobilization – all of these being essential for human well-being and enabling strategic autonomy of net zero and circular industries.

What are the consequences of a STOT RE classification

The silica industry is strategically important for the European market and vice versa the European market represents a considerable portion globally (20% of the world's production of SAS). The EU/EEA is one of the global leaders in the production of SAS (840 000 t/a) and is a net exporter of SAS products, especially precipitated and pyrogenic silicas. It is estimated that almost half of the EEA production (45%) is exported outside the EEA.

STOT RE 1 classification of SAS would not only undermine the confidence in the long-term performance of many formulations relying on SAS, but also significantly affect the ability for a wide range of products in state-of-the-art technologies and industries to compete against non-EEA manufacturers.

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