ASASP | Association of Synthetic Amorphous Silica Producers

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Analysis of ECHA RAC Opinion on the Proposed Harmonised Classification of Synthetic Amorphous Silica (SAS)
- Summary -

1. Introduction

ASASP has conducted a detailed review of the RAC Opinion on Synthetic Amorphous Silica (SAS) and has identified major scientific shortcomings. The analysis highlights a number of issues that warrant further consideration, including aspects related to substance identity and scope, the interpretation of animal data in the context of human relevance under CLP, as well as mechanistic assumptions concerning surface reactivity.

2. Unclear Substance identity and Classification Scope

In the current RAC Opinion on SAS, aspects of the substance description contains inconsistencies and ambiguities that introduce uncertainty into the classification rationale.

2.1. Inconsistent use of “nano” and Ambiguous Substance Boundaries

The RAC Opinion designates the substance name with the term "nano” in the proposed Annex VI entry but concurrently states that the proposed classification is applicable to both nanoforms and non-nanoforms. This inconsistency creates considerable confusion, as "nano" in the chemical name suggests a limited scope to nanoscale materials, while the accompanying text implies a broader range that includes all non-surface-treated SAS forms.

2.2. Conflation of Distinct Types of Amorphous Silica

The RAC Opinion consolidates pyrogenic silica, precipitated silica and silica gel—which are in powder form and chemically equivalent—as well as colloidal silica, which exists exclusively as an aqueous dispersion. The particle morphology of the SAS types is not sufficiently considered when interpreting their physical–chemical properties and agglomeration behaviour.

This conflation introduces uncertainty regarding the interpretation of study results, thereby compromising accurate classification.

2.3. Misinterpretation of SAS material characteristics

The RAC Opinion does not accurately interpret particle size data generated from SEM/TEM measurements and aerosol generation methods. Variations in aerosolisation energy, aggregate structure, and surface morphology significantly impact particle toxicological outcomes. General OECD protocols cannot be universally applied to low density powder materials. The use of mixed datasets without accounting for these differences results in an oversimplified and scientifically unsound representation of SAS behaviour.

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3. Rats vs. Humans: A Detailed Examination of the Differences and Translational Limitations

3.1. Alveolar Architecture Differences

Human alveoli are about three times wider and hold twenty times more volume than those of rats, allowing much larger macrophage populations without blockage. Rats experience alveolar obstruction through particle buildup at lower exposure levels (Stucki et al. (2024), AnaPath (2026)).

3.2. Macrophage Biology and Immune Function

In rats, reactive macrophages may reach diameters ranging from 40 to 80 µm, sufficiently large to completely obstruct alveoli. In contrast, humans typically do not generate such disproportionately sized macrophages under comparable conditions, and human macrophages preserve their mobility even when subjected to particle loading. Furthermore, human alveolar macrophages demonstrate wider pathogen recognition and exhibit reduced reactivity to particulates relative to rats, thereby minimizing the probability of inflammatory escalation (AnaPath (2026)).

3.3. The Rat Lung Overload Phenomenon as a Species-Specific Failure Mode

Recent research by Weber et al. (2024) indicates that pulmonary alveolar macrophage overload in rats is characterised by a sequence of events—including macrophage immobilisation, cellular senescence, rupture, and lymphatic transport of cell debris—not observed in humans. The study demonstrates that rat alveolar macrophages experience a dose-dependent reduction in motility alongside increased expression of senescence markers, which collectively contribute to granulomatous inflammation. In contrast, humans do not possess the anatomical features that give rise to this pathological mechanism, rendering rat overload pathology unsuitable as a model for human risk assessment.

3.4. Species-Specific Deposition and Clearance Mechanisms

In rats, particles accumulate within the alveolar lumen, leading to macrophage immobilisation, rupture, and subsequent release of mediators that perpetuate inflammation. In contrast, humans primarily deposit particles interstitially. Human clearance mechanisms depend on mucociliary transport and macrophage migration toward the bronchioles, thereby preventing the elevated luminal particle concentrations observed in rats.

Toxicological and Regulatory Implications

Given the significant differences between species, high-dose inhalation studies in rats—especially those that reveal foamy macrophages, persistent granulomas, or lymph node fibrosis—should not be taken as evidence of human hazard. Regulatory guidelines require careful consideration of species differences, using a weight of evidence approach. Extensive research shows that rat-specific pathological findings should not be used to predict human effects for SAS.

Extensive and comprehensive epidemiological research, reviewed by Antoniou (2023, 2024) and the German Committee on Hazardous Substances (AGS*) (TRGS 900 (2024)), provides consistent evidence that no adverse human health effects have been identified among workers exposed to SAS over several decades. Therefore, dismissing these epidemiological studies is not justified in this context.

* AGS = Ausschuss für Gefahrstoffe. Advisory body of the German Federal Ministry of Labour and Social Affairs (BMAS)

4. Silanol Groups and ROS*: A Detailed Mechanistic Explanation

4.1. Silanol Groups: Chemical Stability and Ubiquity

Hydroxyl groups are common on metalloid oxide surfaces like silica, alumina, and clays. Dehydroxylation of SAS surface only occurs above 190 °C, consequently these groups do not react in the lungs to produce ROS. Their presence on SAS surfaces does not indicate toxicity.

4.2. ROS as a Biological Response, not a Chemical One

Activation of macrophages via NADPH (Nicotinamide Adenine Dinucleotide Phosphate) oxidase represents the principal source of ROS observed in vitro. Studies indicate that ROS production stimulated by SAS is moderate, dose-dependent, and significantly lower than levels caused by natural immune activators (Wiemann (2026)). These findings support the conclusion that ROS generation constitutes a physiological response rather than an SAS-specific risk (Nolde (2026)).

4.3. Protein Corona Effects in Realistic Exposure Environments

When SAS particles interact with proteins, such as those present in lung lining fluid, a protein corona develops, inhibiting the detection of extracellular reactive oxygen species (ROS). Consequently, serum-free in vitro assays tend to overstate ROS signals and fail to accurately represent in vivo conditions.

4.4. Evidence from High-Dose In Vivo Studies

Animal models exposed to high levels of amorphous silica by inhalation do not experience oxidative damage, in contrast to those exposed to crystalline silica. If silanol chemistry were responsible for ROS formation, such differences would not occur, casting significant doubt on the hypothesis that silanol-driven intrinsic reactivity is at play. There is no substantial evidence that silanol groups on SAS surfaces inherently cause oxidative stress. ROS production is caused by macrophage immune responses, not by SAS particle surface chemistry.

Moreover, the pathological pattern does not correlate with SAS but instead reflects a response to foreign materials or particles. This phenomenon is non-substance-specific and has been observed and documented with all non-toxic particles (Weber et al. (2024)).

5. Conclusion

The RAC Opinion on Synthetic Amorphous Silica (SAS) exhibits significant inconsistencies that compromise its scientific and regulatory integrity. Accurate substance identity is a prerequisite for hazard classification under CLP. Additionally, scientific evidence shows that rats are unsuitable models for assessing human inhalation risks, and that ROS formation is driven by macrophage physiology rather than silanol chemistry.

The challenges highlighted in this assessment illustrate the broader complexities inherent in evaluating particulate materials within the CLP framework. Existing data requirements for substances may not consistently provide a robust basis for assessing particulate materials. This underlines the necessity of initiating a comprehensive methodological review to ensure that assessments of particulate materials are conducted using scientifically rigorous criteria tailored to their distinct properties. It is essential to address these key concerns prior to advancing any classification efforts.

6. References

See dossier *ECHA RAC Opinion on SAS- Analyses & Expert Statements* - for reference details.

* ROS : Reactive Oxygen Species