A proportionate approach to the regulation of the particles based on the latest science

The Particles Platform Workshop, titled "A Proportionate approach to the regulation of particles based on the latest science" was held on 2 October 2025 in Brussels and online.

The Workshop covered the latest scientific and regulatory developments concerning particles, with a particular focus on defining and categorising "poorly soluble low toxicity particles" (PSLTs) and their broader health and regulatory implications. Key topics included the need for a clear and holistic definition of PSLTs, the importance of understanding particle characteristics and their interactions with biological systems, and the importance for industry of harmonising regulatory approaches at both the European and international levels, particularly related to classification as Specific Target Organ Toxicity – Repeated Exposure (STOT RE). The discussion also explored the impact of recent legal decisions, such as the annulment of the harmonised classification and labelling (CLH) under the Classification and Labelling Regulation (CLP) of certain forms of titanium dioxide (TiO_2), and the complexity of the legal and scientific frameworks applicable to particles.

The way forward will require continuous scientific dialogue to refine the definitions and scope of key terms like PSLTs, and to ensure future regulations remain proportionate, transparent, and based on the latest science. The workshop highlighted the value of international harmonisation and further collaboration among regulators, scientists, and industry to close possible regulatory gaps and safeguard both workers and public health.

Morning session

Opening remarks

Andrew McIntyre, a lawyer at Brick Court Chambers, UK opened the Workshop and was the moderator; he introduced the key topics of the day. Andrew was supported for the scientific roundtables by Dr. Rainer Otter, toxicologist, who most recently served as a Vice President for Regulatory Affairs at BASF.

Introductory speech

Paul Speight, the Head of the Safe and Sustainable Chemicals Unit at the European Commission's DG Environment, welcomed the workshop and highlighted its importance in the context of ongoing scientific and regulatory developments. Speight also noted the historical background including the 2022 Workshop on particles and discussions in CARACAL.

Speight highlighted that the Commission is particularly interested in advancing the definition and scope of “poorly soluble low toxicity particles” (PSLTs), including clarifying whether fibres and nanoparticles should be included. Speight emphasised the need for a clear, holistic definition of PSLTs, the importance of understanding particle characteristics and their biological interactions, especially in the context of hazard classification and regulatory grouping. Speight encouraged discussions in which not only worker protection is considered, but also broader protection of citizens and suggested that harmonisation at the international United Nations' Globally Harmonized System of Classification and Labelling of Chemicals (UN GHS) level would be valuable for both industry and regulators.

Speight addressed the recent European Court of Justice decision in which the classification of certain forms of TiO_2 as a carcinogen was annulled, explaining that this creates a regulatory gap that the Commission must address. Speight also clarified that while the harmonised classification is annulled, manufacturers and importers are still required to self-classify TiO_2 based on available data. Speight cautioned against over-interpreting the court’s judgment, noting that some legal questions remain unresolved and emphasising that the decision is case-specific. The Commission plan to publish an explanatory notice on the Official Journal.

A follow-up question was raised if it would be better for the ECHA Board of Appeal to be the forum to challenge CLH decisions as it includes technically qualified member. There were a number of contributions to the answer, including that this has not been asked and that this would require a change to the recently updated CLP Regulation, as the ECHA Committee for Risk Assessment (RAC) issues scientific opinions for CLH (and not decisions).

The regulations today

Peter Sellar, a partner at Squire Patton Boggs (Brussels), specialising in EU regulatory law, addressed the EU regulatory context for inhalation toxicity with a legal perspective. Sellar highlighted that particles are primarily regulated in the workplace context, where the risk is most significant and key regulations include the Chemical Agents Directive (CAD) and the Carcinogens, Mutagens and Reprotoxic substances Directive (CMRD), both of which have a risk rather than a hazard focus and noted that globally, particles are generally regulated through risk regulations, not through the UN GHS framework.

Sellar highlighted the three principles relevant to particle regulation under CLP; (1) classification should be based on the substance as placed on the market and as reasonably expected to be used; (2) classification is based on the intrinsic hazardous properties of a substance as reaffirmed by the TiO_2 legal case which emphasised that the concept must be interpreted in a literal sense, thus “properties which a substance has in and of itself” and (3) that the CLP Regulation requires assessors to take into account all available evidence while expressly justifying their conclusions. Sellar also highlighted that a weight of evidence approach can include unreliable studies for long as that unreliability is noted.

Sellar concluded that the legal framework for regulating particles is complex, with overlapping risk- and hazard-based approaches and that the appropriateness of using EU CLP for particle regulation remains an open question, especially as science evolves.

The appropriateness of sample preparation for inhalation studies

Dr. Frank Babick is head of the Research Group for Mechanical Process Engineering at the Technical University of Dresden, specializing in particle characterisation, nanomaterials, and aerosol science. Babick explained that generating aerosols for inhalation studies, especially with shear-sensitive powders is technically challenging. A key requirement for aerosols in these studies is the specific particle size distribution, characterised by the mass median aerodynamic diameter (MMAD) together with the geometric standard deviation (GDS). However, the same substance in different forms can have dramatically different aerodynamic and geometric diameters, affecting inhalation exposure and the outcomes. Babick emphasised that the energy required to achieve the required particle size distribution in laboratories is much higher than what occurs in real-world applications and therefore there is a need for substance specific test guidelines or best practice guides, rather than a one-size-fits-all approach.

To be or not to be a PSLT

Professor Paul Borm is a consultant and academic with deep expertise in particle toxicology, especially regarding nanomaterials and occupational health. Borm began by highlighting the challenge of defining what constitutes a PSLT and why grouping is important for regulatory and scientific clarity. Borm referenced the seminal work of Paul Morrow, who grouped low toxicity particles based on the effect on the elimination rate constant in chronic inhalation studies.

Morrow's research showed that, in rats, as the lung particle burden increases, clearance slows down at 0.1 microlitre particle volume per lung and eventually stops at 10 microlitre particle volume per lung. This interval of 0.1 to 10 is denominated as lung overload and is associated in the rat lung by inflammation. Borm used the analogy of traffic congestion in Brussels to explain how clearance slows progressively, not suddenly. Borm also stressed that the overload-induced effects seen in rats are not observed in humans and other rodent species including mice and hamsters due to differences in lung structure, macrophage capacity, and clearance mechanisms. Therefore, the current EU hazard-based regulatory approach is not related at all to actual human risk.

Borm noted that the definition of low toxicity for PSLTs is still lacking and recommends the low toxicity component to be based on in vivo data showing absence of inflammation before overload occurs and called for more use of mechanistic, human-relevant data and to update guidelines to reflect scientific advances.

Mechanism of lung overload

Dr. Klaus Weber is a veterinarian and biologist who is the founder of Anapath Services GmbH and an expert in toxicologic pathology. Weber highlighted the role of alveolar macrophages which ingest inhaled particles as a normal, non-adverse response but when overloaded, they become senescent (aged, dysfunctional), rupture, and release their contents, triggering inflammation. The presence of granulocytes, and the formation of microgranulomas which are small inflammatory nodules are considered adverse effects. Weber illustrated these processes with histological images, showing the progression from normal clearance to chronic inflammation which irreversible scarring. The histopathological grading of the severity of these lung effects is essential for regulatory assessment.

Weber also highlighted anatomical and physiological differences between rats and humans and in particular, that the lung overload with macrophage dysfunction and lung burden occur at different thresholds in rats and humans which makes it problematic to use this data in rats for hazard assessment for humans.

Weber also presented a new Macrophage Research Project with the aim to establish clear, reproducible criteria for when macrophage overload has occurred, based on cell size, morphology, and marker expression with the ultimate goal to use these markers to improve the interpretation of inhalation studies, distinguishing between effects caused by mechanical overload and those due to toxicity of particles.

Weber also emphasised that the project will hopefully support animal welfare by reducing unnecessary animal testing, especially at unrealistically high concentration levels that always produce similar mechanical overload effects.

Rats are not small humans

Dr. Andreas Stucki is a biomedical scientist with expertise in *in vitro* inhalation toxicity testing and the development of advanced lung models. Stucki started with the historical context and described how animal testing became standard after a 1937 drug safety scandal in the US, leading to the requirement that drugs be tested on animals before market approval. Stucki emphasised that the rat became the default for animal studies due to the low cost and ease of breeding, not because it is biologically equivalent to humans.

The rat is not a small human, with significant differences including lung mass, alveolar number, and breathing rates as well as having a much more complex nasal structure affecting particle deposition. The rat also has a larger olfactory region (50% in rats vs. 3% in humans). The branching pattern of rat lungs is different, leading to less homogeneous particle distribution compared to humans. In addition, rats are obligate nose breathers resulting in risk of suffocation in rat inhalation studies, while humans can breathe through the mouth and/or nose, affecting exposure.

Human alveolar macrophages are larger and more numerous which allows humans to clear more particles from the lungs than rats. By simply multiplying the fold-differences in alveolar surface area, macrophage numbers per alveoli, and volume of macrophages, rats are estimated to be theoretically up to 20,000 times more sensitive to particle overload than humans. Therefore, due to differences in anatomy, physiology, and clearance mechanisms, the results from rat studies do not accurately predict human outcomes. The presentation called for critical evaluation of current guidelines and encouraged the adoption of new methods and models for better human hazard assessment.

Roundtable 1

The first roundtable included the presenters from the first sessions and a question-and-answer session with the audience. There was a broad consensus on the following points:

- It would be useful to have a solid and clear definition for PSLTs, especially for the low toxicity component
- Rat inhalation studies are problematic in case of particulate materials since they are technically difficult and can lead to false hazard identification
- Unnecessary animal testing should be avoided, especially at unrealistically high exposure levels that always produce the same mechanical overload effects
- The Organisation for Economic Co-operation and Development (OECD) test guidelines for 28 and 90-day inhalation studies, OECD TG 407 and 408 respectively, and in particular the test atmosphere generation, have limitations for particulate materials, and it is important to update the test guidelines
- Objective guidance is needed to distinguish mechanical lung overload from other effects in inhalation studies

For the criteria for low toxicity, an audience member advised that ISO 10993-1:2018 - Biological evaluation of medical devices has a criterion for toxicity and could be considered. Another suggested a tiered approach is required for the criteria for low toxicity.

It was debated whether the EU's hazard-based approach (CLP) is appropriate for particulate materials.

For CLH, ECHA highlighted that the CLH process is based on a review of all current available evidence and therefore issues with the guidance would relate to new commissioned studies such as under REACH processes.

The European Commission recognised that there are challenges in this area, but it is unlikely that they would consider it appropriate to pause on-going CLH proposals as allowed under Article 37 of the CLP Regulation.

Afternoon session

Setting OELs in the EU

Fabio Faraulo works in the Health and Safety at Work Unit of Directorate-General for Employment, Social Affairs and Inclusion which is responsible, among others, for developing and implementing policy initiatives in the area of occupational health and safety, including protection of workers from the risks arising from the exposure to chemicals which includes harmonising EU minimum requirements for OELs. The process involves selecting priority chemicals, mandating ECHA to conduct a scientific assessment, consulting social partners and the Advisory Committee on Safety and Health at Work (ACSH) as well as conducting an impact assessment and submitting a proposal to the European Parliament and Council for adoption.

PSLTs have been prioritized for OEL setting due to increasing concern about workplace exposure to dusts and widespread exposure to a variety of substances across many employment sectors. There is also a need for a clearer definition of PSLTs and for grouping them for hazard identification.

ECHA scoping exercise for PSLT OELs

Dr. Laurence Hoffstadt, Senior Scientific Officer from the Hazard Assessment Directorate explained that ECHA has been tasked with preparing a scoping study to clarify the definition of PSLT, compile a list of substances that may fit this definition and possibilities for grouping these substances. The work is under the Chemical Agents Directive (CAD), and currently, there are no

EU-wide OELs though some national limits exist. The process began with a public call for evidence. The first phase of the work will run until spring 2026, with the final report expected by May 2027. This report will be used to determine if RAC is mandated to derive a health-based OEL for PSLTs.

One challenge is that there are a lot of other definitions in this area including poorly soluble particles (PSP), particles not otherwise classified (PNOC), and dust; all these will be considered. In this study both human epidemiological and animal data will be reviewed, including any available and robust human data. It will also look at toxicokinetics and possible hazardous properties, not just lung effects. ECHA will not limit itself to OECD test guideline studies but will consider all available information using a weight-of-evidence approach. Hoffstadt also clarified that the scoping study does not serve the same purpose, as the scientific report drafted during the OEL derivation process, which is more formal and is subject to a consultation. However, in both cases, all relevant data, endpoints, and expert opinions are considered.

Quantifying a definition of poorly soluble particle (PSP)

Dr. Blanca Serrano, Secretary-General of ECETOC presented the ECETOC project aimed to gather and analyse both published and unpublished inhalation studies in rats conducted according to OECD test guidelines 412 and 413 with the aim to establish a quantitative threshold for defining the solubility of PSPs and to test whether the Morrow hypothesis regarding lung burden and overload holds across substances. Fifteen different particles were evaluated and most followed the Morrow hypothesis where effects in rats were only observed above a volumetric lung burden threshold of 1 µL/g lung. Effects for soluble particles such as zinc oxide were seen below this threshold which supports the distinction between poorly soluble and soluble particles.

The study shows the importance of considering aggregate density and dynamic dissolution rates, not just static tests, for regulatory relevance. A decision tree was proposed: if a particle's calculated lung burden at realistic workplace concentrations does not exceed the overload threshold, it can be classified as a PSP. In addition, OELs are preferred over CLP classification which link to OECD guidelines and their associated TG test conditions often force overload conditions and thus do not reflect real-world exposures.

The definition of low toxicity for a PSLT remains a challenge and therefore it is recommended to undertake further in vitro work on the mechanism including human macrophage models to better define and validate low toxicity. A manuscript of the study has been submitted for publication.

Roundtable 2

The second roundtable, held in the afternoon, included speakers from the session, joined by Professor Len Levy from Cranfield University, UK and Dr. Lan Ma-Hock, Head of the BASF Inhalation Toxicology Laboratory, and focused on scientific uncertainties in defining and assessing PSLTs. Key points of consensus included:

- A clear definition for PSLTs is still lacking, especially regarding the “low toxicity” component.
- Rat inhalation studies have limitations due to species differences between humans and rats in lung physiology and particle clearance.
- Greater use of human epidemiological data and biomonitoring is recommended, with a preference for high-quality human data when available.
- New approach methodologies (NAMs), such as *in vitro* macrophage models and in silico tools, offer promise for reducing animal testing and improving relevance to human health. However, challenges remain in validation and regulatory acceptance, and NAMs are unlikely to play a major role in the current ECHA PSLT OEL scoping study.
- Hazard identification is not the same as hazard classification and also not the same as hazard quantification.
- Care needs to be taken with the consideration of academic studies as they are research based and are often undertaken to a lower standard and lack key criteria such as positive and historical control data.

In addition, there was a discussion about assessment epidemiological studies, as well as the variability and reproducibility of academic research.

Wrap up

Andrew McIntyre wrapped up the Workshop by thanking all the participants and highlighting the key points of the day.

If you need any further information regarding this workshop, please contact the Particles Platform at smi@cefic.be.