

Fresh debate over rodent tests for lung cancer with PSLTs

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More data needed on mechanisms, some parties say

Europe

Classification

Nanomaterials

Chemical industry

CLP Regulation

A



fresh debate on the suitability of rodent test data for determining the potential carcinogenicity of particulate substances has emerged in an academic journal.

So-called poorly soluble, low toxicity particulate substances (PSLTs) have risen up the regulatory agenda, following the European Commission's decision to [classify](#) titanium dioxide as a category 2 carcinogen by inhalation, under CLP.

The Titanium Dioxide Manufacturers Association ([TDMA](#)) strongly disagrees with the classification, which it claims is based on "a precautionary interpretation of old studies". It would prefer to see a binding harmonised occupational exposure limit (OEL).

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Industry now fears a similar outcome for another PSLT, carbon black, which France is set to evaluate in 2022 under the community rolling action plan. The chemical has a wide range of uses, including in tyres, rubber, plastics, and pigments for inks and paints. The Corap justification document points to rodent inhalation studies showing carcinogenicity but "inadequate evidence in humans".

Lung overload

Historically, the debate has focused on lung overload, which occurs when the rate of particle accumulation exceeds the rate of particle clearance. Much of the evidence that PSLTs cause lung cancer is from studies in which the rodents experienced this. Some parties argue that lung cancer arising in rats when the lungs are overloaded is not necessarily relevant to humans not experiencing overload.

In February 2019, Paul Borm from Dutch firm Nanoconsult and Kevin Driscoll from Rutgers University in New Jersey, US, consulted a panel of experts from industry and academia. Many reportedly agreed that results are "highly questionable" when lung cancer is only observed following exposures at overload levels.

They published a commentary article in the journal *Particle and Fibre Toxicology*, hoping to "reactivate the public debate" over PSLTs.

A team from the National Research Centre for the Working Environment (NRCWE) in Copenhagen, Denmark, published a response suggesting that the chronic inhalation study in rats "may be better than its reputation" for assessing lung cancer risk.

The researchers said there are studies showing that diesel exhaust particles, carbon black nanoparticles and titanium dioxide can induce lung cancer in rats at particle concentrations below overload. "Data from chronic inhalation studies with rats can, and should, be used in risk assessment of nanomaterials when epidemiological data are not available," they concluded.

In July, Drs Driscoll and Borm got together with other authors to question the Danish team's interpretation of results. After a final response from the NRCWE team, the journal's editor closed the discussion, stating that "it is clear there are different views

on how to assess and interpret adverse effects seen in experimental animals at impaired particle clearance conditions ... in light of human health risk assessment."

"From the present debate, it is obvious that the available data can be interpreted in different ways," Ulla Vogel and Søs Poulsen from the NRCWE told Chemical Watch.

The way forward is "more research and more data, especially on particle clearance", they said. The scientists would also like to see more work done to understand the mechanisms of particle-induced carcinogenicity. "Better mechanistic knowledge allows for smarter testing," they said.

Dr Borm, however, doubts that new test methods would help. "More testing will not change the issue," he told Chemical Watch.

But he does see a need to develop a deeper understanding of particle-induced inflammation. "We need to understand which type of inflammation is beneficial and to what extent inflammation becomes an adverse event," he said.

Drs Driscoll and Borm were part of an expert workshop on PSLTs in Edinburgh in 2019. Amongst other topics, lung particle overload and the relevance of the rat as a model for PSLT inhalation toxicology were discussed.

In their [report on the workshop](#), Drs Driscoll and Borm recommended that guidelines for evaluating and classifying PSLTs should be "reassessed" and that "prior decisions on PSLT hazard classification be revisited to determine if they remain appropriate".

Meanwhile, Dr Borm would like to see a total "rethink" of what he sees as Europe's "hazard-based approach".

"We haven't seen the end of the PSLT discussion," he told Chemical Watch.

Labelling for titanium dioxide will be required from autumn 2021 for mixtures in powder form, containing at least 1% of particles with a diameter of 10 micrometres or less.

In February, some titanium dioxide manufacturers spoke of [possible legal action](#) against the EU executive.

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