



# Particles and inhalation toxicity: What is the way forward?

A scientific workshop on particles and inhalation toxicity

## Cefic's workshop on Particles and inhalation toxicity

### Summary

05 December 2022

Cefic's workshop on Particles and inhalation toxicity took place on the 5<sup>th</sup> December in Brussels. The Workshop has been the first opportunity to start a constructive and open dialogue on some important aspects on the topic of particles and inhalation toxicity, which merits further scientific attention. It was attended by academia and experts on the topic, regulators and industry representatives.

This scientific workshop focused on particles which exhibit no or very low inherent toxicity and affecting only the respiratory tract. What industry aimed at from this dialogue was a common way forward to deal with particles and inhalation toxicity. We believe that these exploratory discussions, alongside the recent research findings presented by the experts, could significantly help to prepare the ground for possible solutions for determining a fit-for-purpose respirable particle size fraction for testing and helping better to interpret some of the histopathological findings seen in rodent studies.

#### Presentations session

The Workshop opened with introductory presentations by the experts and after each presentation there was possibility to ask clarification questions.

In his introductory presentation, Prof. Dekant explained the process and analysis conducted on the inhalation toxicity of particulate materials. He explained what happens when particles have to be adapted to the requirements from OECD TG 413 ( $MMAD \leq 2 \mu m$ ) and for this reason, why they are no longer in the form(s) or physical state(s) in which the substance or mixture is placed on the market (as required by Article 8.6 CLP Regulation). In fact, testing according to OECD TG 413, 403 or 436 methods require the generation of artificially-made respirable particles size. In many cases, the original substance that is placed on the market consists of larger particles or particles that agglomerate and aggregate in larger bulks.

Dr. Weber presented the findings of a re-evaluation of lung and lung-associated lymph node sections from a number of previously performed inhalation studies. There were no criteria for selecting the studies/materials used in this investigation. It was simply the fact of being particles used in inhalation studies and the analysis was then conducted on all such materials in Fraunhofer institute's archive from 90 days studies.

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. 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. Based on the findings on day 1, all 14 dusts would be considered for STOT RE classification under the current interpretation of CLP.

Furthermore, it was shown that recovery periods increase the visibility of toxicity due to the impacts on BALT (Bronchiolar-Associated Lymphoid Tissue) and lymph nodes and also allow to differentiate between regenerative inflammation (*Restitutio ad integrum*) and progressive inflammation associated with irreversible adverse effects (e.g. Quarz DQ12). Against this background, the importance of analyzing animal recovery groups was highlighted.

Prof. Borm, in his presentation, explained how inflammation is the normal reaction to an inhaled foreign material in the lung and for this reason, why it should not be considered as a toxicological finding *per se*, particularly if reversible. Two important messages were emphasized: 1) More research on the reversibility of inflammation and its crucial checkpoints is needed; 2) The persistence/progression of inflammation in the recovery period after sub-chronic exposure may actually be a better descriptor of adversity.

Prof. Zeegers concluded the first session by presenting the importance of epidemiological studies, where available. Due to limitations of the rat models, which were highlighted, these studies need to be taken into consideration in any evaluation, including classification and labelling processes, as an important source of information. In fact, such human observational studies may have a far more relevant design than an experimental rodent study.

### **Discussion session**

A discussion session followed the presentations. The main points raised were the following:

- Aerosol generation is key for inhalation testing *in vivo* and the techniques used need to be well understood. This is a challenge as it requires specific equipment, plus a good knowledge of the material under test and how it behaves and alters in dynamic systems.
- Doses and outcomes are intimately linked most of the time.
- Why should we test particulates if, because of the current OECD TGs, one can predict the STOT RE results of the study at  $t = 90$  days in an OECD 413 for particulate materials?
- The inflammation visible after exposure to particles is the typical biological reaction activating cleaning mechanism. Inflammation may become irreversible and generate adverse effects, but is there a checkpoint up to which inflammation can be considered not to be adverse anymore?
- Animal lung tissue recovery is of prime importance to analyse the effects. A recovery group is not required in any sub-chronic test guideline and there was a suggestion, in discussion, to have it mandatory. The new version of the testing guidance recommends a post-exposure examination, but this is still not binding. However, requiring a recovery group would mean more animals to be sacrificed and this may be an issue with regard to animal welfare.
- Does the animal model represent the reality of the humans? The fundamental issue is that we are not able to test to humans, so we need to find a good animal model and a balanced Weight of Evidence approach using any occupational data that are available.
- The potential problem with human data is that they may be limited and poorly documented, for regulators. Thus, what can we do to improve and make human data more available and usable? Additional endpoints? Making better use of good quality routine occupational health surveillance data, where available?
- Regulators can only use the 'tools' (guidelines) that are currently available so, if they are inappropriate or could be improved, industry should come forward with suggestions for alternatives and solutions.

## Wrap up and conclusions

The moderator Prof. Levy wrapped up the session with the following key points:

- 1) Particles have to be adapted to the requirements from OECD guidelines and for this reason they are no longer in the form(s) or physical state(s) in which they are placed on the market.
- 2) The inflammatory response, visible after exposure to particles seen in rodent studies, is the typical biological reaction activating a cleaning mechanism.
- 3) A recovery period would be of help in inhalation testing guidance.
- 4) The relevance of the findings from epidemiological studies as well as health and medical surveillance in humans is important and should be taken into account in the overall evaluation.
- 5) Expert judgement is critical for the interpretation of the safety of particulate substances.

**In conclusion, it became clear that further discussion is needed on some key elements and industry was encouraged to come up with possible alternatives and solutions. The intention is to keep an ongoing dialogue between experts, industry and regulators with the aim of identifying a common way forward to deal with particles and inhalation toxicity.**

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