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Response to letter to editor "Pulmonary toxicity in rats following inhalation exposure to poorly soluble particles of low toxicity: Testing at excessive concentrations overwhelming lung clearance"?

Dear editor

We thank Arts et al. (2020) for their interest in our paper in which we discuss the relevance of testing pulmonary toxicity of poorly soluble particles (PSPs) after inhalation (Bos et al., 2019). Their points have compelled us to clarify our statements for your readers as we believe there are flaws in the logic of the arguments in their points.

The authors agree with us that rat pulmonary toxicity data including lung inflammation need to be considered in the process of human hazard and risk assessment for poorly soluble particles and can be used to set a No-Observed-Adverse-Effect Concentration (NOAEC) and subsequently an Occupational Exposure Limit (OEL). However, although we addressed several topics related to the complex issue of impaired clearance, the letter is focusing very much on only two aspects of our paper. First, Arts et al. (2020) state that our paper is focused on inhalation experiments for the purpose of classification. The second aspect is the reference to synthetic amorphous silica (SAS).

As to the first aspect, we clearly state in our paper (section 3.2) that toxicity testing can be performed to meet 4 different regulatory needs that are listed in our paper: (1) prioritization, (2) classification (3) derivation of health-based guidance values and (4) risk assessment of exposure situations of concern. The purpose of classification is just one of these. It is further reasoned by us, that because of animal welfare principles, it is preferable that a toxicity study should be designed such that multiple of these regulatory needs will be met, preferably all. We therefore also extensively focused on the use of such data in risk assessment. Therefore, we respectfully disagree that our mere interest was to focus on classification.

Arts et al. (2020) find it remarkable to see that we have used consistently the term Poorly Soluble Particles and not what Borm and Driscoll (2019) have used, i.e. Poorly Soluble particles of Low Toxicity (PSLT) thereby ignoring the low toxicity component. Irrespective the fact that 'low toxicity' is a rather subjective undefined term, we have left out the low toxicity component on purpose. The purpose of toxicity testing is to establish the toxic potential of a material and if we have the means to accurately predict the hazard, testing would not be needed at all. Also, for existing chemicals like TiO_2 there are differences in the intrinsic hazard depending on crystal phase as well as related to the particle size, shape and surface characteristics. It is likely that when assessing health effects, a part of the hazard is caused by the general response of the immune system to foreign particles and part is driven by chemical specific aspects such a surface reactivity. The outcome of the toxicity test can be that the material under investigation can be 'classified' as PSLT.

Referring to REACH Guidance (R7A – 7.5.4.1), Arts et al. (2020) also suggest that testing at concentrations that overwhelm any normal clearance processes are of limited value. The argument brought forward apparently refers to the use of a kinetically-derived maximum dose (KMD) as the highest concentration to be tested in an animal experiment. As mentioned in our paper (section 3.3), Borm and Driscoll (2019) introduced the maximum functionally tolerated dose (MFTD) for PSLTs analogous to the KMD. The argument brought forward by Arts et al. (2020) touches upon several aspects discussed in our paper. For instance, when testing new PSPs no information is available yet about their clearance kinetics. Further, there is also no information beforehand on the mode of action and thus not on the appropriate dose metric to be considered for determining the most appropriate levels of exposure. In addition, it can generally not be determined if and how pulmonary effects in rats are related to a specific level of clearance impairment. And finally, as is also acknowledged by Borm and Driscoll (2019), there is no consensus that PSPs can be considered as one group with similar behavior and toxicity. For these reasons, it is not possible to derive a maximum exposure level for PSP testing in rats beforehand.

It seems to us that the authors have misunderstood our reasoning about derivation of a Benchmark Concentration (BMC) and reference to the paper by Slob (2014). What we wrote is that, starting from the basic principle that a BMC is a more accurate point of departure than a No-Observed Adverse Effect Concentration (NOAEC) for derivation of a Health-Based Guidance Value (HBGV), the top concentration should be high enough to induce sufficient toxicity to enable determination of a BMC with sufficient precision. At present, an OECD Expert group is working on the optimization of study designs to derive a BMD or BMC.

We also provided an example that workers can be exposed to synthetic amorphous silica (SAS) at conditions that have shown to be hazardous in rats (Choudat et al., 1990; Reuzel et al., 1991). This example is merely used as a supplementary illustration and has no impact on our line of reasoning or on our conclusions. However, Arts et al. (2020) are concerned that our arguments fail and they provide six arguments to support their statement.

As a first argument, Arts et al. (2020) state that the fibrosis observed by Reuzel et al. (1991) should not be seen as an adverse effect as it was later described by Weber et al. (2018) as fibrogenesis which is reversible. It is common knowledge that any induction of fibrosis should be seen as a serious adverse effect, irrespective of the fact that the tissue might be restored to its original morphology without any remaining signs of fibrosis. In addition, even in the case that fibrosis disappeared after termination of the exposure, human can be exposed continuously for very long times to SAS, which can result in a continuous

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development of fibrosis and no opportunity for reversibility.

In this context it is noteworthy that recently within the EU, a classification for specific target organ toxicity-repeated exposure (STOT-RE) to surface-coated SAS was among others based on the fibrosis observed in rats exposed to surface-coated SAS (Aerosil 974) in the Reuzel et al. (1991) study.[1] The observations made by Reuzel et al. (1991) were considered relevant and sufficient for classification, despite the re-evaluation by Weber et al. (2018). The re-evaluation by Weber et al. (2018) still appears to be subject of discussion.

Secondly, Arts et al. (2020) state that "It should be questioned whether SAS can be considered PSP or PSLT". This is a confusing statement as the authors do not provide a definition of 'poorly soluble' but at the same time acknowledge that exposure to SAS can result in impaired clearance.

Arguments 3–5 are descriptions on how exposures were assessed in the Choudat et al. (1990) study and do neither provide arguments against our statements nor against the probability that pulmonary effects in rats may occur at concentrations that are comparable with those at the workplace.

The last argument reads as if the authors claim that there is big difference in the Mass Median Aerodynamic Diameter as measured in occupational exposure scenario's compared to the expected smaller size ranges used in rat inhalation studies (Reuzel et al., 1991; Arts et al., 2007). It should be mentioned that for good reasons OECD has adapted the required size distributions in repeated dose studies (OECD TG412 and TG 413) to make these even smaller without a lower cut off to make the pulmonary deposition patterns more representable compared to what occurs in humans as rats have a higher filtration capacity of the upper respiratory tract. In addition, as Reuzel et al. (1991) did not provide size distributions at the time where cascade impactors where already in use for many years, it could also be argued that the aerodynamic particle size distributions were significantly larger than at the workplace.

The authors also refer to a workshop that partially dealt with this topic and at which one of the authors of Bos et al. (2019) participated but none of the authors of the letter to the editor. In this context, reference to a commentary by Borm and Driscoll (2019) does not seem relevant as this was merely an announcement of the workshop for which (at present) the final report is under review. Moreover, in a commentary by Saber et al. (2019), arguments are provided that carbon black and TiO_2 caused lung cancer in rats at air concentrations below the air concentrations that inhibit particle clearance in rats suggesting that carcinogenic classification of PSP is not only observed at impaired clearance typically noted in rats. In fact, chronic inhalation exposure to diesel exhaust particles in rats are less sensitive in terms of detecting lung cancer in comparison with epidemiological studies.

In summary, we very much appreciate the critical feedback from your readers, and here expressed by Arts et al. (2020). We believe that nobody can guarantee that people would not be exposed to (high) levels of respirable PSPs that may result in adverse health effects. We also believe that we carefully separated hazard, risk and classification issues in our paper.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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[1] https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e18195912e