ACGIH 2020 Herbert E. Stockinger Award Lecture

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Is there such thing as innocuous dust?
Results of a long-term inhalation study and consequences for the toxicological assessment and grouping of particles.

Inhalation of dusts has been a concern for human health for centuries, from both occupational and generally ambient air exposures. For granular, non-fibrous particles, terms such as “biologically inert", “Inertstaub”, innocuous or nuisance dust or "particulates not otherwise classified" or “… specified (PNOS)” have been used to distinguish dusts with a low potency of toxic effects from those which are more potent or induce specific adverse effects. The term “nuisance dust” already indicates that even these dusts may have some unwanted effects. Adverse effects have been linked to “overload” conditions during which the lung burdens, due to inhalation of high aerosol concentrations, overwhelm lung clearance leading to inflammatory responses. Any particle would trigger lung effects at overload conditions, but some particles would also have effects at lower lung burdens. Hence, more particularized terms are used for particles without specific toxicity: poorly soluble, low-toxicity (PSLT) particles or granular, biopersistent dust (GBS). For these allegedly “unspectacular” particles common health-based threshold level value (TLV and other OELs) have been established. However, a specific definition of this group of particles is missing.

Few of these particles have been tested for long-term effects by inhalation. Two presumed PSLT particles, titaniumdioxide and carbon black, caused lung tumors upon long-term inhalation of high aerosol concentrations in rats. These tumors were regarded as consequences of chronic inflammation by lung overload conditions.

Recently, a long-term inhalation study with ceriumdioxide (NM212) and bariumsulfate (NM220) nanoparticles was finished. It was performed according to OECD test guideline no. 453; additions were made to the standard protocol to find evidence of inflammation and potential lung tumors with high sensitivity. Aerosol concentrations were 0.1, 0.3, 1 and 3 mg/m^3 and 50 mg/m^3, respectively. Levels of cerium measured in the organs increased with higher exposure concentrations and over time. However, the accumulation only reached a very low level. Lung burdens of Barium were unexpectedly low during the first three months of exposure, due to fast clearance most probably by dissolution in vivo. Barium lung burdens increased thereafter. Animals in all exposure groups showed chronic inflammation of the lungs, with stronger inflammation at higher exposure concentrations. The nature of the inflammation varied between the two particles. Ceriumdioxide triggered a chronic inflammation already at the lowest dose, but no lung tumors were found which could be attributed to ceriumdioxide exposure. With bariumsulfate one malignant tumor in one hundred animals was detected which may be exposure-related. In extrapulmonary organs, accumulation was at low-levels and did not lead to any pathological changes.

Obviously, both particles were not PSLT: Bariumsulfate was soluble *in vivo* and ceriumdioxide was toxic at low lung burdens. Moreover, ceriumdoxide caused inflammation without volumetric overload, and chronic inflammation did not lead to tumor formation. Apparently, there is no strict link between overload, inflammation and tumor formation. And it seems to be difficult to find particles which are strictly PSLT. This is pointing to a need for a definition of PSLT and this is indeed currently being discussed.

There is an even wider need for defining groups of similar particles: While there is a TLV for PSLT, such a grouping does not suffice data requirements of other regulations such as European REACH. At the same time, it is impossible to perform full toxicological testing on each particulate material. Hence, grouping (and subsequently read-across of toxicological properties) is necessary. Different schemes on grouping particles are currently being discussed. At the heart of this are three questions (i) which properties are relevant to decide on similar toxicology, (ii) how similar is similar enough (in terms of numeric cut-offs or overlap of continuous property ranges) and (iii) how (by which methods) do we generate data to serve these decision criteria? Obviously, identical sets of comprehensive toxicological data of two particles would proof sufficient similarity. But grouping needs to do with less and hence more uncertain information. This is according to the principle of economy “*Frustra fit per plura quod potest fieri per pauciora*” which is attributed to William of Ockham and later formulations are given by *inter alia* Isaac Newton and Ernst Mach as well as William Russel, the doyen of the 3R principle. Here we propose a tiered grouping scheme, which relies on few material properties in tier one (composition, size, surface area, morphology) and material functionalities (dissolution, dispersion stability, dustiness, reactivity, *in vitro* toxicity) in tier 2; only in exceptions animal studies are required in tier 3.

Two particles being similar does not imply they are identical. Likewise, probably no particle is truly PSLT; it is, however, almost or more or less like PSLT. Whether the boundaries defining similarity are claimed narrow and the associated uncertainty is low enough, needs to be discussed and eventually agreed upon the scientific and regulatory communities.