HAZARDS AND RISKS OF POORLY SOLUBLE LOW TOXICITY PARTICLES

OUTCOME OF THE EDINBURGH EXPERT WORKSHOP

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Some background…..

- Rats exposed chronically to high concentrations of respirable *poorly soluble low toxicity* (PSLT) materials develop lung cancer (e.g., titanium dioxide, carbon black).
  - ✓ Lung cancer only at doses which **overload** macrophage particle clearance.
  - ✓ Lung cancer is preceded by marked inflammation and epithelial proliferation.
  - ✓ Lung cancer after PSLT has not been demonstrated in mice and hamsters.
- Mechanism
  - ✓ PSLT materials are not directly genotoxic.
  - ✓ Lung cancer believed to be a consequence of persistent inflammation and epithelial cell proliferation.
- Human experience - Epidemiology studies have not demonstrated associations between PSLT exposure and lung cancer.

Decisions by authoritative & regulatory organizations regarding PSLT inhalation and cancer……

- IARC: Classified titanium dioxide and carbon black as **possibly carcinogenic to humans** based on the rat lung cancer data (and absence of increased lung cancer in epidemiology studies).

- ECHA: Committee for Risk Assessment (RAC) classified titanium dioxide as **suspected of causing lung cancer through the inhalation route** based on a rat data with titanium dioxide and supporting evidence from rat studies with other PSLTs, i.e., carbon black.

- NIOSH: Differentiated the cancer hazard of titanium dioxide based on particle size and the exposure level in rats causing cancer:
  - Ultrafine size (<0.1 μm dia) titanium dioxide - a **potential human carcinogen**
  - Larger size (≥0.1 μm dia) particles - **unclassifiable as to carcinogenic hazard**

The debate on PSLTs, rat lung cancer, lung overload and what it all means for human hazard…

- The rat lung cancer response should be considered relevant to human hazard. Precautionary principal
- The rat lung cancer response to PSLT exposures under condition of lung overload is not relevant to lower non-overloading exposures. Overload ≠ Non-Overload
- The rat lung cancer response to PSLT exposures causing lung overload is unique to this species and should not be used for human hazard assessment. Rat overload is not relevant to other species

Expert Workshop on the Hazards and Risks of Poorly Soluble Low Toxicity Particles

Purpose: Understand the state-of-the-science on lung overload, PSLT inhalation toxicology and hazard classification.

Approach: Convene a panel of highly experienced scientists and regulators expert on PSLT toxicology, debate the science and document their agreements and differences.

- Definition of PSLT.
- Lung particle overload: implications for study design and interpretation.
- Use of the rat as a model for PSLT inhalation toxicology.
- Implication of rat inhalation data for human health hazards and risks.

Details in: Driscoll, KE and Borm, PJA. *Inhal Toxicol.* 32 (2):1, 2020

Expert Workshop on the Hazards and Risks of Poorly Soluble Low Toxicity Particles

Experts (15)

- Substantial knowledge and experience with PSLT toxicology and/or related regulatory matters. (listed in: *Driscoll and Borm, Inh. Toxicol, 2020*)
- Provided their expert opinions and rationale and contributed to preparing summaries.
- Acted in an individual capacity

Observers (15)

- Participated in discussions and gave comments.
- Representation from ECHA, HSE, RIVM, EPA, ACGIH, MAK and others.
- Industry participation driven by sponsors.

Expert Workshop on the Hazards and Risks of Poorly Soluble Low Toxicity Particles

Workshop Format

- Topics and specific questions developed by the moderators, Paul Borm and Kevin Driscoll.
- Questions were reviewed beforehand with experts.
- During the workshop the questions were debated and discussed among the experts.
- Summaries of expert consensus, differences and comments were prepared, agreed at the meeting and published as written.

Consensus reached on the following:

What is a PSLT?

- Developed a functional definition of PSLT – solubility, toxicity, benchmarking.
- Materials should not grouped as PSLTs for hazard without supporting data.

Lung Particle Overload

- Defined particle overload
  - Can occur in all animal species including humans
  - Not relevant for materials with inherent toxicity (e.g., crystalline silica).
  - Species differences exist in the nature of the lung response to overload e.g., inflammation, hyperplasia, tumors.
- Study Design - Chronic inhalation studies should include a top exposure level which produces overload.

Consensus reached on the following:

Relevance of the Rat for Hazard and Risk of PSLT

- The rat exposed under particle lung overload is not a relevant model for human lung cancer hazard for exposures under non-overload conditions.
- The non-neoplastic lung responses of the rat to PSLT (inflammation, epithelial hyperplasia and fibrosis) should be considered for human hazard and risk.
- Inflammation is a critical endpoint for PSLT occupational exposure setting as inflammation occurs at lower exposures and precedes other adverse responses.

Consensus reached on the following:

Human Health Hazard and Risk

- The rat is a sensitive species for inhalation testing (nonneoplastic effects) and is the species for which most of the data on PSLT has been generated.
- PSLTs should not be considered as human lung carcinogens based on rat data (and no other supporting species data) alone.
- Research Need: Mechanistic studies are needed to better understand the differences between rats and humans, in order to enable improved extrapolations.

Topics for which consensus was not reached

- Has lung particle overload been demonstrated in humans?
  - A majority (10/15) believed findings for highly exposed coal miners support the occurrence of overload in humans.
  - A minority (5/15) believed the coal miner data, is suggestive, but not definitive.

- Is the rat lung response to PSLT (inflammation, hyperplasia, fibrosis, tumors) unique from other species?
  - A majority (10/15) believed the rat is more sensitive than other species but there is not sufficient information to say the rat cancer response to PSLT is unique.
  - A minority (5/15) believed the rat cancer response to PSLT was unique and not relevant to other species.

Summary

- An expert panel was convened and consensus and disagreements on PSLT inhalation toxicology **documented and published after peer review**

- Key outcomes

- Defined a process for characterizing a material as a PSLT and provided guidance on inhalation study design.
- Consensus on OEL Setting: the prevention of lung inflammation should be the driving principle in PSLT risk assessment and exposure setting.
- Consensus on relevance of PSLT exposure and rat lung cancer to humans:
  - The rat lung tumors occurring only under lung overload is not a relevant to human lung cancer hazard exposed under non-overload conditions.
  - PSLTs should not be considered as human lung carcinogens based on rat data alone and no additional supporting data (from other species, mechanisms).

Implications of the expert consensus?

1. Need clarity on what materials are PSLTs and which are not, including the importance of particle size in the definition.

2. Re-assess guidelines for evaluation and classification of inhaled particulate based on expert consensus opinions.

3. Revisit prior PSLT hazard classifications to determine if they remain appropriate. *Currently classification is based solely on lung cancer in rats under conditions of marked overload.*

Back Up

From RAC Documentation for Titanium Dioxide

"RAC refers to these PSLT particle carcinogenicity data as supporting evidence"

"the carcinogenicity profile described for TiO2 is not exclusively characteristic for TiO2 but applies to the whole group of chemicals referred to as "poorly soluble low toxicity particles""

RAC acknowledges that the carcinogenicity profile described for TiO2 is not exclusively characteristic for TiO2 but applies to a group of chemicals with similar toxicity profile addressed as "poorly soluble low toxicity particles"

From NIOSH Bulletin 63

"NIOSH questions the relevance of the 250 mg/m3 dose for classifying exposure to TiO2 as a carcinogenic hazard to workers and therefore, concludes that there are insufficient data at this time to classify fine TiO2 as a potential occupational carcinogen"

- Sponsors
  - Institute of Occupational Medicine (IOM),
  - University of Edinburgh, Lung and the Environment Group Initiative (ELEGI)
  - International Carbon Black Association (ICBA)
  - Titanium Dioxide Manufacturers Association (TDMA)
  - Eurometaux
  - International Antimony Association
  - Industrial Mineral Association (IMA)
  - Iron Platform

- Experts did not receive remuneration for their participation in the workshop (except travel costs and incidentals).

- Input on the Workshop structure, content, summary and publication were neither solicited nor provided by any Sponsors.

Experts

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