1601d HAZARD DETERMINANTS OF CARBON NANOTUBES (CNTS) DRIVING MOLECULAR INITIATING EVENTS (MIES) IN ADVERSE OUTCOME PATHWAYS (AOPS) OF AIRWAYS DISEASES

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Introduction Because of their unique physico-chemical properties, CNTs have attracted a great deal of research interest and have many promising industrial applications. However, this also increases the exposure potential for workers, raising the need to understand their hazard for an effective occupational health and safety management. CNTs can induce lung inflammation, granuloma formation, fibrosis and cancer in rodents; in particular, MWCNTs are known to induce *in vitro* markers of remodelling and fibrosis. CNTs greatly vary in length, thickness, rigidity, aspect ratio, surface defects and reactivity, with a remarkable contribution of synthesis methods and post-treatments. Thus, CNTs are not a single substance, but a heterogeneous family of materials that elicit different biological responses and, thus, are associated with different hazard levels not simply ascribable to the fibre paradigm.
Methods Cell models representative of the airway barrier were challenged with MWCNT preparations endowed with different physico-chemical properties, evaluating endpoints such as viability, expression of pro-inflammatory markers, nitric oxide production, epithelial barrier competence, clonogenic activity, genotoxicity. Epithelial-mesenchymal transition (EMT) was also assessed as an early event leading to fibrosis and, possibly, involved in neoplastic transformation.
Results Only long MWCNTs promoted EMT and caused frustrated phagocytosis. On the other hand, MWCNT agglomeration led to contact-mediated focal epithelial damage and impaired barrier functionality *in vitro*. Functionalization with carboxyl or amino groups modified the quantity and type of proteins adsorbed and, hence, the interaction with cells.
Discussion These findings may contribute to safe-by design manufacturing of MWCNT. Importantly, all the endpoints evaluated represent MIEs than can be combined to construct putative AOPs, associated with disease onset and progression. It is therefore concluded that the knowledge of the physico-chemical properties associated to the MIEs of different adverse outcomes is a pre-requisite for the toxicological profile of a MWCNT preparation.

1601e A NEW RISK GROUPING CONCEPT FOR HIGH ASPECT RATIO MATERIALS – ADDING FIBRE RIGIDITY TO THE PICTURE

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Introduction Identification and management of risks related to both established and innovative materials are central aims of occupational safety and health. Therefore, we propose a new grouping scheme to evaluate the risk of High Aspect Ratio Materials (HARM) according to hazard and exposure aspects.
Methods Our approach to measure the fibre rigidity (discussion) is based on frequency measurements at resonance conditions of single vibrating fibres by means of radio-frequency engineering and scanning electron microscopy; using Euler-Bernoulli's beam theory to determine the young modulus.
Results The new scheme considers both intrinsic material and handling process-related properties such as bio-durability, toxicity, respirability, HARM morphology/dimensions as well as grade of agglomeration and dust release propensity during/after processing. It is based on the results of extensive research regarding those properties and their scalability for risk assessment, most notably the dustiness. Its utilisation requires data for the mentioned intrinsic and process related properties. Especially with respect to aspects of dustiness, this requires data on HARM release propensities for different handling conditions. However this talk will focus in the fibre rigidity as new parameter.
Discussion We propose to include the aspect of rigidity, more precisely the fibre flexural rigidity, as an extension to the fibre-toxicological paradigm as a new parameter for HARM toxicity assessment. Critical fibre rigidity is most probably the key to frustrated phagocytosis or HARM translocation and distinguishes HARM toxicology from that of granular biodurable particle materials. The potential toxicity of HARMs is widely known and was also shown for CNTs/CNF in many recent studies. We believe that the toxicity should not be evaluated solely by the fibre dimensions in context with systematic animal testing, but propose to combine a fibre's composition and diameter into the property flexural rigidity. For bio-durable HARM, rigidity has the potential to become an overarching, material independent assessment parameter.

1601f A NEW RISK GROUPING CONCEPT FOR HIGH ASPECT RATIO MATERIALS – THE SHAKER DUSTINESS TEST

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Introduction High aspect ratio materials (HARM) like carbon nanotubes (CNT) exhibit material properties that enable innovative applications but also raised concerns about potentially harmful effects to humans due to their asbestos-like morphology. Control banding by grouping of HARM by hazard- and exposure-related properties is a promising approach to risk assessment and risk mitigation for a large family of materials. Limit values enabling a differentiation of HARM with low, moderate or high dustiness as well as information about the dust morphology are necessary for control banding.
Methods We have developed a dustiness test for powdery HARM, in particular for CNTs. In the Shaker method, a laminar low volume air flow passes through a vertically vibrating powder column resulting in powder fluidization. Vibration is required to overcome adhesive forces between powder grains that would otherwise hinder fluidization. The Shaker method combines aerosol monitoring over the dust generation process to determine the emission intensities with simultaneous dust sampling. Subsequent sample analysis by means of scanning electron microscopy (SEM) obtains information about dust morphology.
Results and discussion Using a standard operation procedure, we performed dustiness tests on 20 CNTs. The results lead to material rankings based on the emission intensity and the

definition of limit values for low, moderate and high dustiness. The SEM-aided morphological analysis allowed us to rank the materials for the propensity to emit individual fibres and their grade of agglomeration. We also measured the diameter and length distributions to identify potential rigid fibres and those matching the WHO-criteria for hazardous fibres. These results are the basis of our proposed new grouping strategy for control banding, which classifies HARM using a risk matrix that considers both intrinsic material and process-related properties such as bio-durability, toxicity as well as dustiness, grade of agglomeration and presence of hazardous WHO-fibres.

1601g OCCUPATIONAL EXPOSURE TO CARBON NANOTUBES: THE STATE OF KNOWLEDGE

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Introduction In an emerging field of nanotechnologies, assessment of exposure is an integral component of occupational and environmental epidemiology, risk assessment and management, as well as regulatory actions. This review focuses occupational exposure to carbon nanotubes (CNT).
Methods PubMed and Scopus databases were searched for period 2000–2017 using all keywords combinations based on the following structure: 'assessment' and 'exposure' and 'carbon nanotube'. The words 'assessment' and 'exposure' were alternatively replaced by 'measurement' and by 'human' and 'occupational', respectively. The word 'carbon nanotube' was alternatively replaced by 'single-walled carbon nanotube', 'double-walled carbon nanotube', 'multi-walled carbon nanotube', and their abbreviations. Only field-studies conducted in occupational settings were included. The quality of the exposure measurement protocol and results reporting were reviewed. The results were compared with the current NIOSH recommended exposure limit (REL) of 1 $\mu g/m^3$ respirable elemental carbon (EC) mass-concentration as an 8 hour time-weighted average.
Result Twenty-five studies conducted in R and D laboratories, small-scale pilot-production facilities, and, more rarely, large-scale primary or secondary manufacturer/user facilities in the USA (eleven), the Republic of Korea (four), Japan (four), Russia (one) and Europe (four) were reviewed. Open handling of CNT powder during the sieving, mechanical work-up, packaging, and clean-up work-tasks was classified at highest likelihood of exposure. Fourteen most recent studies measured EC concentration, although using different methods and aerosol fractions. All but one studies observed EC values exceeding the REL. The quantification of CNT agglomerates and/or CNT-contained particles lacks methodological standardisation and precluded any comparison of results.
Discussion Currently available occupational-exposure data are limited, because production and use of CNT are relatively recent and workforce sizes remain small. Due to high variability of methods and instruments used for exposure sampling and analysis and of criteria used for interpreting their results, results are difficult to compare. Further effort of methodological standardisation is warranted.

1601h CHALLENGING ISSUES IN CARBON NANOTUBE OCCUPATIONAL RISK ASSESSMENT AND MANAGEMENT STRATEGIES

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Introduction High aspect ratio nanoparticles (HARNs) represent a growth area in nanotechnology. Best known of all HARNs are carbon nanotubes (CNTs). These nanomaterials have found applications in several production fields with subsequent potential for occupational exposure during industrial manufacture, use and disposal. Concerns regarding possible adverse health effects on workers who are routinely exposed to CNTs have been motivated by their resemblance to asbestos fibres, as well as by the International Agency for Research on Cancer classification of one type of multi-walled, CNTs-7, as 'possibly carcinogenic to humans'. Therefore, aim of this work is to point out critical topics that should be addressed in industrial hygiene contexts for a suitable CNT risk assessment and precautionary management.
Methods Available literature was analysed to extrapolate priorities of research concerning toxicological issues, risk assessment and management strategies for CNT exposed workers.
Results Toxicological *in vitro* and *in vivo* research may be helpful in identifying and characterising CNT hazards, particularly in defining what are the properties that may dictate fibre pathogenicity including carcinogenicity, i.e. width, length, biopersistence. Additionally, environmental monitoring strategies should be developed to assess not only airborne CNT concentrations, but also other metric parameters, i.e. fibre number and surface area, which may better represent the effective dose for adverse health effects. In this scenario, innovative field-portable, near real-time instruments, and personal samplers can meaningfully provide more timely and accurate aerosol characterisation.
Discussion The extrapolation of definite evidence for CNT risk characterisation seem a challenging issue due to great heterogeneity of these materials. Suitable toxicity models able to predict fiber-type pathogenic effects according to specific physico-chemical characteristics and doses of exposure should be pursued for a suitable risk assessment process. These may be important also for the definition of appropriate occupational exposure limits to manage the exposure and protect workers' health.

Neurotoxicology and Psychophysiology

1713 ADVERSE NEUROLOGIC HEALTH EFFECTS OF OCCUPATIONAL SOLVENT EXPOSURE– FROM RECOGNITION TO PREVENTION

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Aim of the special session The typical adverse neurological effect of long-term occupational solvent exposure is called