this approach enabled evaluation of latency periods between exposure and clinical onset of the disease. For most cancers this is difficult to evaluate using standard epidemiological study designs, but this work showed that this latency period is at least 11−12 years, but probably more than 20 years.

These results showed that readily available ecological data may be underused, particularly for the study of risk factors for rare diseases and those with long latencies.

Because these analyses were done using a systematic, a priori set out statistical approach, it can be extended to other combinations of diseases and exogenous risk factors. In addition to demonstrating the methodology for cancers of the brain and central nervous system, we will show results evaluating associations between the incidence of other (rare) cancers and potential risk factors from the World Bank list of Development Indicators.

184 HANDLING MISSING PARTICIPANT DATA IN META-ANALYSIS OF DICHOTOMOUS OUTCOMES: PROPOSED GUIDELINES FOR SYSTEMATIC REVIEWS OF RANDOMISED TRIALS

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10.1136/oemed-2013-101717.184

Objectives Systematic reviewers including all randomised participants in their meta-analyses need to make assumptions about the outcomes of those with missing data.

Our objective is to provide systematic review authors with guidance on dealing with participants with missing data for dichotomous outcomes.

Methods The authors conducted a systematic survey of the methodological literature regarding 'intention to treat' analysis and used an iterative process of suggesting guidance and obtaining feedback to arrive at a proposed approach.

Results We consider here participants excluded from the trial analysis for "non-adherence" but for whom data are available, and participants with missing data. Non-adherent participants excluded from the trial analysis but for whom data are available should in most instances be included in the meta-analysis, and in the arm to which they were randomised. For participants with missing data, systematic reviewers can use a range of plausible assumptions in the intervention and control arms. Extreme assumptions include 'all' or 'none' of the participants had an event, but these assumptions are not plausible. Less extreme assumptions may draw on the incidence rates within the trial (e.g., same incidence in the trial control arm) or in all trials included in the meta-analysis (e.g., highest incidence among control arms of all included trials). The primary meta-analysis may use either a complete case analysis or a plausible assumption. Sensitivity meta-analyses to test the robustness of the primary meta-analysis results should include extreme plausible assumptions. When the meta-analysis results are robust to extreme plausible assumptions, inferences are strengthened. Vulnerability to extreme plausible assumptions suggests rating down confidence in estimates of effect for risk of bias.

Conclusions This guide proposes an approach to establishing confidence in estimates of effect when systematic reviewers are faced with missing participant data in randomised trials.

Session: Mini sympsoium I: Nanomaterials and health: Sponsored by Nanonext-NL

185 FOUR-YEAR FOLLOW-UP STUDY OF HEALTH HAZARDS AMONG WORKERS HANDLING ENGINEERED NANOMATERIALS

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10.1136/oemed-2013-101717.185

Objectives The aim of this study was to investigate the health hazards in workers exposed to nanoparticles during manufacturing and application of nanomaterials.

Methods For this 4-year longitudinal study, we recruited 283 nanomaterial-handling workers and 213 non-exposed control workers from 15 manufacturing plants in Taiwan. Follow-up measurements were done at 6, 12, 24, 36, and 48 months. Among them, 206 nanomaterial-handling workers and 140 unexposed workers were followed up for more than twice. For each participant, a self-administered questionnaire was distributed to collect work history and personal habits after informed consent. Since there was a lack of equipment for personal sampling and summary index for mixed exposure, we adopted the control banding nanotool risk level matrix to categorise the risk level for each participant. Blood, urine and exhaled breath condensate (EBC) were collected to examine markers of cardiopulmonary injuries, lung and systemic inflammation, oxidative stress, and genotoxicity. Generalised Estimating Equation (GEE) model was applied to analyse these repeated measurements.

Results There were 108 workers in risk level 1, and 91 workers in risk level 2, and 7 in risk level 3. Although depression of antioxidant enzymes and increase of cardiovascular markers were found in the cross-sectional and early follow-up study, no significant difference was revealed between exposed workers and controls in the changes of biomarkers in this 4-year longitudinal study. The non-significant markers included lung injuries markers, cardiovascular disease markers, heart rate variability (HRV), inflammation markers, oxidative stress and lipid peroxidation markers, comet assay, pulmonary function test, and neurobehavioral function test.

Conclusions This longitudinal study suggests that there was no evidence of health hazards among nanomaterials handling workers. The preliminary survey of nanoparticle exposure level in the workplace was quite low. Such exposure level was not high enough to induce systemic health effects in nanoworkers.

186 IMPROVING THE IMPACT: NEEDS FOR AND PROGRESS IN GLOBALLY HARMONISED EPIDEMIOLOGIC STUDIES OF NANOMATERIALS WORKERS

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10.1136/oemed-2013-101717.186

Epidemiological occupational health studies in the carbon black and amorphous silica industries, two classic examples of nanomaterials, were carried out in the late 1980s/mid 1990s.

These days, some initial studies started to address the health of workers exposed to novel types of manufactured nanomaterials. These studies face three main challenges: exposure assessment, identification of suitable effect markers and size of populations. The relatively small current workforces in individual countries will probably necessitate the pooling of cohorts internationally. However, at the moment, the necessary conditions for such a pooling are not in place: namely agreements on design, exposure and effect characterisation are not in place. To bridge this gap and to provide a coherent approach in view of future epidemiological research, we recently proposed a roadmap [1] to reach global consensus on need a well defined, globally harmonised framework for the careful choice of materials, exposure characterisation, identification of study populations, definition of health endpoints, evaluation of appropriateness of study designs, data collection and analysis, and interpretation of the results. The proposed strategy should ensure that the costs of action are not disproportionate to the potential benefits, and importantly, that the approach is pragmatic and practical. Moreover, we should aim to go beyond the collection of health complaints, illness statistics or even counts of deaths: the manifestation of such clear endpoints would indicate a failure of preventive measures. Instead, we should agree on a minimum set of biomarkers and metrics of early effects for acute and chronic diseases while evaluating how concepts of systems biology, gene activation and epigenetics can inform such studies on outcomes and related biomarkers of potential interest.

187 MONITORING AND MODELLING OF EXPOSURE TO MANUFACTURED NANO OBJECTS, AGGLOMERATES & AGGREGATES (NOAA) FOR EPIDEMIOLOGIC STUDIES

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10.1136/oemed-2013-101717.187

Introduction A major challenge for setting up human field studies is the identification of sufficiently large number of workers with exposure to NOAAs. Pooling of data is necessary but requires harmonisation of methods. A multi-metric exposure approach is proposed, which may be better correlated to health effects, however, an appropriate exposure estimate has not been developed yet. Currently, workers' activities/tasks related to NOAA are time wise highly variable resulting in considerable within-worker, between-day variances. No validated models exist to predict exposure to NOAA, however, the concepts of such a source-receptor model have been presented, and for specific activities (i.e. powder handling or spraying) more detailed models are being developed. Meanwhile larger datasets on (mostly task-based) occupational (estimates of) exposure to NOAA are available, e.g. the NANOSH study, or will be built. Database structures are actively developed, e.g. the PEROSH -NECID database, and harmonised workplace exposure studies generating data will populate the NECID database in near future.

Methods and Results The challenges for exposure assessment for epidemiologic studies can be addressed by developing task-based exposure matrices profiles covering scenario's across the product chain of NOAA. Building blocks for such task-based exposure matrices will be existing models and those that are under development, e.g. Stoffenmanager nano, NanoSafer, further analysis of existing datasets to demonstrate task-specific exposures and tailored task-based measurements. Combined with worker specific information on type of NOAA, and frequency, duration etc. of activities/tasks per job title, estimates for exposure can be derived. In addition, co-exposures from process or combustion derived ultrafine particles will be taken into account. A multi-pathway approach is used, however, the focus will be on the inhalation route. Currently, the feasibility of such an approach is explored in a pilot study, which is supported by an extensive measurement campaign in the facility.

188 FROM THE VERY SMALL TO THE VERY LARGE: CHALLENGES IN CONDUCTING EPIDEMIOLOGIC STUDIES OF US WORKERS EXPOSED TO CARBON NANOTUBES

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10.1136/oemed-2013-101717.188

Presentation Time: 11:00 - 11:30

Objectives Carbon nanotubes (CNT) and carbon nanofibers (CNF) are among the first nanomaterials to reach commercial use in the US and are also showing evidence of serious health effects at occupationally relevant levels in toxicology studies. The objective of our work was to design an epidemiologic study of early possible health effects among US workers exposed to CNT and CNF, taking into account small workforce sizes, a global manufacturing and distribution system, uncertainty about which exposure metrics may best correlate with health effects, and short available latency.

Methods Initial exposure characterisation was conducted at 15 US manufacturers and users of CNT and CNF to determine the most specific and useful exposure metrics. Possible markers of early pulmonary, cardiovascular, and malignant health effects were identified from animal toxicology studies and epidemiologic research among populations exposed to ambient ultrafine particles. Power analyses were conducted to determine appropriate sample sizes.

Results A cross-sectional exposure assessment and epidemiology study was designed; it will include 100 workers from at least 10 US facilities making or using CNT or CNF. This study, now in progress, evaluates elemental mass and electron microscopy-based exposure metrics for each worker, along with early health outcomes including spirometry measures, blood pressure, and approximately 40 biomarkers of inflammation, oxidative stress, pulmonary fibrosis, cardiovascular disease, and cancer. The study will account for ambient ultrafine exposure using a combination of background sampling and non-specific direct-reading instruments that operate in the nanoscale range.

Conclusions Cross-sectional epidemiologic designs for nanomaterial exposures are feasible, but small workforce sizes and generally short latency limit power; cohort studies for outcomes such as malignant and nonmalignant respiratory and other disease may require international pooling. Researchers should collaborate to identify the most suitable exposure metrics and early health outcomes.

189 MEDICAL SURVEILLANCE AND EPIDEMIOLOGIC STUDIES OF ENGINEERED NANOMATERIALS (ENM) WORKERS IN FRANCE

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10.1136/oemed-2013-101717.189