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Criteria for grouping of manufactured nanomaterials to facilitate hazard and risk assessment, a systematic review of expert opinions

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ABSTRACT

With the emergence of nanotechnology the number of manufactured nanomaterials (MNM) in production and use is constantly increasing. Exposure of workers to MNM is of concern, because still much is unknown about health effects. MNM may have different properties, testing of each material is time consuming and costly. Experts have proposed various approaches to categorize MNM to facilitate risk assessment of human health effects based on shared properties of various materials. A systematic literature survey was undertaken to identify expert opinions on grouping of MNM published between the years 2000 and 2015. We summarized and synthesized the opinions according to a systematic review of text and opinion. We identified 22 articles that fulfilled our inclusion criteria reporting 17 proposals with three proposals for groups and 14 proposals for criteria for grouping. Five proposals suggested one or more of the following groups of concern: fibrous, biopersistent, high solubility with high toxicity, chemically active. Criteria proposed in multiple studies were: viable testing options, mode of action, physicochemical properties predicting toxicity. We conclude that a limited number of groups have been proposed to categorize MNM according to human health concern. Further research should be conducted to underpin the proposed groups with empirical evidence.

1. Introduction

Nanomaterials are especially developed for their useful technological properties and they are used in an ever increasing number of commercial products. In addition to useful properties the change to the nanoscale may also have effects that are harmful to health. The rapid increase in development and production of manufactured nanomaterials (MNM) and the potential harmful health effects different from those of their larger counterparts makes it urgent to find reliable risk assessment methods (Alshehri et al., 2016; Jain et al., 2018; Piccinno et al., 2012). Occupational exposure of workers to MNM is of particular concern because they may be exposed for longer time periods and the exposure levels may be higher compared to consumers of nanomaterial containing products. With the large number of new materials to be produced in the future, there is a need to prioritize the most relevant for risk management. **Proper material characterization has been pointed out as a key element in hazard identification and the subsequent risk assessment of MNM (Krug, 2014). Many of the published articles in the literature have inadequately dealt with physicochemical characterization or have poor quality material characterization and therefore most of the scientific journals have set up a minimum list of material characterization to be performed** (Hussain et al., 2015).

In the approach used by the European Chemical Agency (ECHA) chemical substances that have similar properties may be placed in groups for the purpose of risk evaluation. ECHA uses the following definition of a group: “Substances that are structurally similar with physicochemical, (eco)toxicological, and/or environmental fate properties that are likely to be similar or follow a regular pattern” (ECHA, 2013). Such similarities may be due to common functional groups, common precursors, or likely common breakdown products. Within a group of substances, each individual substance may not need to be tested. Instead, endpoint specific effects of an unknown substance may be derived from the endpoint-specific effects of the other substances within the group. This approach is known as ‘Read-across’ which is the application of the grouping concept to fill the knowledge gap for one substance in a group of MNM by using data from the same endpoint from another MNM. Oomen et al., among others, have defined grouping or categorization of MNM along similar lines (Oomen et al., 2014, 2015). They state that the term “group” or “category” represents a number of MNM, which share commonalities relevant for risk, i.e. one or more common properties in a physical, chemical, exposure,

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toxicological endpoints, toxicokinetics or fate. It is assumed that the knowledge of MNM similarities and their subsequent categorization into groups with similar biological endpoints will facilitate hazard identification and the risk evaluation processes. However, given the complexity of MNM and the limited knowledge on how they may affect human health, various grouping approaches have been proposed. As part of the WHO project to develop guidelines for protecting workers from potential risks of manufactured nanomaterials the following question was formulated: 'which specific MNM and groups of MNM are most relevant with respect to reducing risks to workers and which should this guideline now focus on, taking into account toxicological considerations and quantities produced and used.' To find answers to this question we wanted to identify the various approaches for grouping MNM.

Therefore, the aim of this review is to give an overview of the published opinions **(in the timeframe 2000–2015)** of experts that propose strategies for grouping and categorization of MNM and to identify similarities and differences in the criteria that they use for grouping. **A distinction between this review and other published reviews is that our approach was to identify only reviews and opinions and to impartially present the views of the authors. Furthermore, we focused only on the grouping approaches relevant for hazard assessment of MNM in occupational settings.**

2. Methods

We followed a systematic review approach with the inclusion criteria defined by an adapted PICO approach P for Participants, I for Intervention, C for Control and O for Outcomes (Morgan et al., 2016). We adapted our specific PICO question following methods proposed for systematic reviews of text and opinion (https://joannabriggs.org/assets/docs/sumari/ReviewersManual-2014.pdf). Our specific PICO question was as follows: For workers exposed to MNM, which criteria are proposed by experts to group MNM into categories with similar toxicological properties. To be included the scientist or group of scientists had to propose explicit criteria for grouping based on a specific theory or toxicological **arguments including those taken from published studies. We did not however, ourselves include empirical studies on toxicological properties of specific MNM such as animal (*in vivo*) or *in vitro* studies. Information on nanomaterials metrics was included whenever addressed by the experts, but was not a primarily aim in this review.** In addition, the criteria had to be used specifically for MNM. The toxicological properties of MNM were to be taken into account and inhalation was regarded as the most likely exposure route.

We defined MNM according to the definition adopted by the European Commission from 2011 which defines a nanomaterial "a natural, incidental or manufactured material containing particles in an unbound state or as an aggregate and where for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%. By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials." MNM hold specific properties due to their small particle size, however, research has shown that this may not always be the case for toxicological properties since other characteristics than particle size may be drivers of toxicity. Specific properties due to other characteristics rather than the small size for example chemical composition and other physical characteristics may be associated with adverse health effects (Dusinska et al., 2013; Kroll et al., 2011).

This literature review includes manufactured nano-objects (nanoparticles, nanofibers, and nanoplates), agglomerates and aggregates form of these materials as well as nanostructured materials. The form of the MNM refers to the physical form of the MNM such as being a powder, liquid, paste or solid form. The terminology for grouping of MNM is adopted from Oomen et al., (2014, 2015) where the term "group" or "category" represents a number of MNM that share commonalities relevant for risk, identified as one or more common properties in a physical, chemical, exposure, toxicological endpoints, toxicokinetics or fate. A MNM may belong to more than one group or category. This definition of group/category is well in line with the definition published by the OECD in 2014 in a regulatory context (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en) as well as the definition given by ECHA. As this definition was developed before MNM were considered in regulations, the term grouping also refers to data sharing between MNM and/or non-MNM of the same substance, for example from one specific (nano) form of titanium dioxide to another specific (nano) form of titanium dioxide or ultrafine particles (UFP) to nanoparticles (NP).

Inclusion criteria: We included only review or expert opinion articles which i) describe grouping/categorization strategies for MNM assessing the MNM for specific properties associated with adverse health effects and ii) taking the toxicological properties of MNM into account and inhalation as the most important exposure route.

Exclusion criteria: individual publications describing original *in vitro* and *in vivo* toxicity studies were not included.

The literature search strategy and information sources: Based on the concepts of nanomaterials and expert opinion we developed a search profile including search words and terms appropriate for the different databases (Supplementary Material 1). We limited the search by excluding diagnostic procedures, nanomedicine and ecotoxicology. We searched Medline through PubMed, Embase, OSH Update from 2000 to 2015. Fig. 1 depicts the screening and selection process. The studies were identified using the PICO criteria described above. First, two assessors (SZ and VS) independently screened the abstracts for possible inclusion, according to the inclusion/exclusion criteria. The two assessors discussed any differences in the assessment and if no agreement was reached, the paper was included for further assessment. The

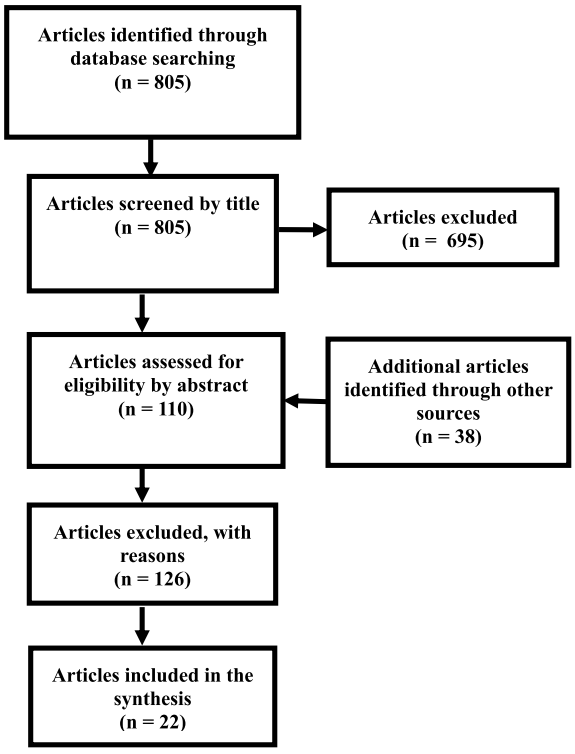

Fig. 1. The literature search flow diagram.