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A decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping)

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ABSTRACT

The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) 'Nano Task Force' proposes a *Decision-making framework for the grouping and testing of nanomaterials* (DF4nanoGrouping) that consists of 3 tiers to assign nanomaterials to 4 main groups, to perform sub-grouping within the main groups and to determine and refine specific information needs. The DF4nanoGrouping covers all relevant aspects of a nanomaterial's life cycle and biological pathways, i.e. intrinsic material and system-dependent properties, biopersistence, uptake and biodistribution, cellular and apical toxic effects. Use (including manufacture), release and route of exposure are applied as 'qualifiers' within the DF4nanoGrouping to determine if, e.g. nanomaterials cannot be released from a product matrix, which may justify the waiving of testing. The four main groups encompass (1) soluble nanomaterials, (2) biopersistent high aspect ratio nanomaterials, (3) passive nanomaterials, and (4) active nanomaterials. The DF4nanoGrouping aims to group nanomaterials by their specific mode-of-action that results in an apical toxic effect. This is eventually directed by a nanomaterial's intrinsic properties. However, since the exact correlation of intrinsic material properties and apical toxic effect is not yet established, the DF4nanoGrouping uses the 'functionality' of nanomaterials for grouping rather than relying on intrinsic material properties alone. Such functionalities include system-dependent material properties (such as dissolution rate in biologically relevant media), bio-physical interactions, *in vitro* effects and release and exposure. The DF4nanoGrouping is a hazard

Abbreviations: AOP, adverse outcome pathway; APPIE, Association of Powder Process Industry; ASTM, American Society for Testing and Materials; ATP, adenosine triphosphate; BAM, *German Federal Institute for Materials Research and Testing*; BAuA, *German Federal Institute for Occupational Safety and Health*; BET, (Method of) Brunauer, Emmett and Teller; BSAI, biological surface adsorption index; BSF, biological simulation fluid; BSI, British Standards Institute; bw, body weight; CEN, *European Standardization Organization*; CNT, carbon nanotube; DLS, dynamic light scattering; DNEL, derived-no-effect-level; DMEL, derived-minimal-effect-level; ECETOC, European Centre for the Ecotoxicology and Toxicology of Chemicals; ECHA, European Chemicals Authority; EFSA, European Food Safety Authority; EPA, Environmental Protection Agency; DF4nanoGrouping, Decision-making framework for the grouping and testing of nanomaterials; FP7, 7th Research Framework Programme; FRAS, ferric reducing ability of serum; GBP, respirable granular biodurable particles; HA, hazard assessment; HAR NM (alternatively HARN), high aspect ratio nanomaterial; IRMM, Institute for Reference Materials and Measurements; ISO (TC), International Standardization Organization (Technical Committee); JRC, Joint Research Centre; LDH, lactate dehydrogenase; MPS, mononuclear phagocyte system; MoA, mode-of-action; MNT, micronucleus test; MWCNT, multi-walled carbon nanotube; NC, negative control; NIOSH, National Institute for Occupational Safety and Health; NIST, National Institute of Standards and Technology; NOAEC, no observed adverse effect concentration; OECD, Organization for Economic Co-operation and Development; OEL, occupational exposure limit; PC, positive control; PPS, primary particle size; PSF, phagolysosomal simulation fluid; (Q)SAR, (quantitative) structure activity relationship; RA, risk assessment; REACH, Registration, Evaluation, Authorisation (and Restriction) of Chemicals; ROS, reactive oxygen species; SCCS, Scientific Committee on Consumer Safety; SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks; SEM, scanning electron microscope; SSA, specific surface area; STIS, short-term inhalation study; STOS, short-term oral study; TEM, transmission electron microscope; TG, test guideline; TNF-α, tumor necrosis factor alpha; UBA, *German Federal Environmental Agency*; VSSA, volume-specific surface area; WHO, World Health Organization.

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and risk assessment tool that applies modern toxicology and contributes to the sustainable development of nanotechnological products. It ensures that no studies are performed that do not provide crucial data and therefore saves animals and resources.

Information box: definitions of terms used in the present article

Benchmark material: A (nano-)material, which has been tested and evaluated according to standard criteria and to which new materials may reliably be compared for grouping purposes (Kuempel et al., 2012).

(Certified) reference material: A material that has undergone a process for validation or round robin assessment as 'reference material', thereby having fulfilled specific predefined requirements for, e.g., its homogeneity and stability (Stefaniak et al., 2013).

Intrinsic material properties: Characteristics of the material that are determined independently of the biological environment or test system. Accordingly, intrinsic material properties include chemical composition and impurities, primary particle size (PPS), surface area, water solubility and shape or aspect ratio.

Mode-of-action (MoA): Mechanisms by which substances may elicit cellular or apical toxic effects. To date, only a limited number of such mechanisms have been discerned for nanomaterials (cf. Chapters 3.5 and 3.6 'Grouping of nanomaterials by cellular and apical toxic effects' for further information on different MoAs).

Nanoform: As defined by the EU Commission's NANO SUPPORT Project (2012), the term 'nanoform' is used for REACH registration dossiers that (seem to) also address other forms (e.g. bulk). Thus, a nanoform registered 'alone' (not along with non-nanoforms) would be a nanomaterial.

Nanomaterial: In line with the EU definition (EU Commission, 2011), 'nanomaterial' is an overarching term to describe materials containing particles with external dimensions in the size range 1–100 nm.

Nanoparticle: A specific nanosized 'pieces of matter' (EU Commission, 2011).

Substance: The EU Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH; EP and Council of the EU, 2006) defines a substance a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition. Accordingly, in the present article, 'substance' is used as an overarching term encompassing nanosized and non-nanosized substances in all forms regardless of their state of dissolution.

System-dependent properties: Characteristics that are linked to the material's functionality in its environment, such as surface reactivity, dissolution rate, and dispersibility. The outcome of measurements of system-dependent properties is affected by the given surroundings, i.e. the choice of the test system (culture media, supplements, dispersing agents, etc.) or of the product application. System-dependent properties constitute bio-physical interactions of the particles with their environment. Accordingly, 'systems' may be, e.g., matrices in which a nanomaterial is embedded in a product, exposure media (aerosols, suspensions, etc.), or biological systems that the nanomaterial comes into contact with.

1. Introduction

Given the vast number of nanotechnological products entering the market and the multitude of different nanomaterials already available, hazard and risk assessments of each and every single variant of nanomaterial are impracticable and undesirable for economic reasons and stand in contradiction to the legal requirement to reduce animal testing (EP and Council of the EU, 2006, 2010). The 'grouping' concept aims at making substance hazard assessment more efficient. In its guidance documents, the European Chemicals Agency (ECHA, 2013) describes grouping as the process of uniting substances into a common group *if they are structurally similar with physico-chemical, toxicological, ecotoxicological and/or environmental fate properties that are likely to be similar or to follow a regular pattern*. Such similarities may be due to common functional groups, common precursors, or likely common breakdown products. Within a group, 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 further substances within the group. 'Read-across' is the application of the grouping concept to fill a data gap within a group of substances by using data from the same endpoint from another substance or other substances (ECHA, 2013; *cf.* Information box – for the definitions of terms as they are used in the present article).

For substances in general, technical guidance documents on grouping are available, e.g. from the Organization for Economic Cooperation and Development (OECD) or the ECHA (ECHA, 2008, 2012a,b, 2013, 2014; OECD, 2014a). By contrast, to date there are no specific regulatory frameworks for the grouping of nanomaterials. However, this topic is addressed in different publications, and preliminary guidance is provided in the context of substance-related legislation or the occupational setting. In an extensive review, the *European Centre for Ecotoxicology and Toxicology of Chemicals Task Force on Nanomaterials* (ECETOC Nano TF) assessed such available concepts for the grouping of nanomaterials for human health risk assessment (Arts et al., 2014). Based upon this review, in the present article, the ECETOC Nano TF proposes a functionality-driven *Decision-making framework for the grouping and testing of nanomaterials* (DF4nanoGrouping) that aims to group nanomaterials by their specific mode-of-action (MoA; *cf.* Information box) that results in an apical toxic effect.

In its review (Arts et al., 2014), the ECETOC Nano TF came to the conclusion that nearly all of the currently available approaches involve some form of grouping by intrinsic (material) properties or system-dependent properties that constitute bio-physical interactions. Of note, whereas the term 'physico-chemical characterization' is widely used in the literature, for the purpose of grouping, the ECETOC Nano TF distinguishes between 'intrinsic material properties' ('material properties') on the one hand and 'system-dependent properties' constituting bio-physical interactions on the other hand (Wiesner, 2014; *cf.* Information box for the definitions of these terms).

The grouping of non-nanosized substances is often based on (quantitative) structure–activity relationships ((Q)SARs) alone, and also the above-mentioned ECHA guidance only allows for grouping based upon structural similarities (ECHA, 2013). By

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