Regulatory Toxicology and Pharmacology 70 (2014) 492–506

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

A critical appraisal of existing concepts for the grouping of nanomaterials

Josje H.E. Arts [a], Mackenzie Hadi [b], Athena M. Keene [c], Reinhard Kreiling [d], Delina Lyon [e], Monika Maier [f], Karin Michel [g], Thomas Petry [h], Ursula G. Sauer [i], David Warheit [j], Karin Wiench [k], Robert Landsiedel [k,*]

[a] AkzoNobel, Technology and Engineering, Arnhem, Netherlands
[b] Shell Health, Shell International B.V., The Hague, Netherlands
[c] Afton Chemical, Richmond, VA, USA
[d] Clariant Produkte GmbH, Sulzbach, Germany
[e] Shell Health, Shell Oil Company, Houston, TX, USA
[f] Evonik Degussa GmbH, Hanau, Germany
[g] Henkel AG & Co. KGaA, Düsseldorf, Germany
[h] Toxminds BVBA, Brussels, Belgium
[i] Scientific Consultancy – Animal Welfare, Neubiberg, Germany
[j] DuPont Haskell Global Centers For HES, Newark, DE, USA
[k] BASF SE, Ludwigshafen, Germany

ARTICLE INFO

Article history:
Received 28 July 2014
Available online 7 August 2014

Keywords:
Nanomaterials
Risk assessment
REACH
Toxic Substances Control Act
Grouping of substances
Physico-chemical characterization
Exposure assessment
Hazard assessment
Biokinetics
Characterization

ABSTRACT

The grouping of substances serves to streamline testing for regulatory purposes. General grouping approaches for chemicals have been implemented in, e.g., the EU chemicals regulation. While specific regulatory frameworks for the grouping of nanomaterials are unavailable, this topic is addressed in different publications, and preliminary guidance is provided in the context of substance-related legislation or the occupational setting. The European Centre for Ecotoxicology and Toxicology of Chemicals Task Force on the Grouping of Nanomaterials reviewed available concepts for the grouping of nanomaterials for human health risk assessment. In their broad conceptual design, the evaluated approaches are consistent or complement each other. All go beyond the determination of mere structure–activity relationships and are founded on different aspects of the nanomaterial life cycle. These include the NM's material properties and biophysical interactions, specific types of use and exposure, uptake and kinetics, and possible early and apical biological effects. None of the evaluated grouping concepts fully take into account all of these aspects. Subsequent work of the Task Force will aim at combining the available concepts into a comprehensive 'multiple perspective' framework for the grouping of nanomaterials that will address all of the mentioned aspects of their life cycles.

Abbreviations: BAuA, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German NIOSH); BSI, British Standards Institution; CARACAL, Competent Authorities for REACH and CLP (EU); CEIN, Center for the Environmental Implications of Nanotechnology (University of California, USA); CLP, classification, labeling and packaging (EU); CMAR, carcinogenic, mutagenic, asthmagenic, or reproductive toxin; ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals; ECHA, European Chemicals Agency; EP, European Parliament; EPA, Environmental Protection Agency (e.g. USA); EU, European Union; FP7, 7th Research Framework Programme (EU); GAARN, Group Assessing Already Registered Nanomaterials (EU, ECHA); HPV, High Production Volume; HTS, high throughput screening; IATA, integrated approaches for testing and assessment; ICCR, International Cooperation on Cosmetics Regulation; LDH, lactate dehydrogenase; MARINA, managing risks of nanomaterials (FP7 project); MoA, mode of action; NanoMILE, engineered nanomaterial mechanisms of interactions with living systems and the environment: a universal framework for safe nanotechnology (FP7 project); NIA, Nanotechnology Industries Association (EU); NIOSH, National Institute for Occupational Safety and Health; NM, nanomaterial; OECD, Organization for Economic Co-operation and Development; OEL, occupational exposure limit; OSHA, Occupational Safety and Health Administration (USA); PCA, principal component analysis; QSAR, quantitative structure activity relationship; RCC (-NI), Regulatory Cooperation Council (-Nanotechnology Initiative) (USA-Canada); REACH, registration, evaluation, authorization [and restriction] of chemicals (EU); ROS, reactive oxygen species; SI, Supplementary Information; TF, Task Force; UBA, Umweltbundesamt (German EPA).

* Corresponding author. Address: Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany.
E-mail address: robert.landsiedel@basf.com (R. Landsiedel).

http://dx.doi.org/10.1016/j.yrtph.2014.07.025
0273-2300/

1. Scope and background: the need to assess nanomaterials by criteria related to conceivable risks

As more and more nanotechnological products enter the market, the importance of adequately assessing nanomaterial (NM) exposure, biokinetics, hazard and risk is now widely recognized. Worldwide, different governments, authorities, international organizations and other institutions are developing policy frameworks and guidance documents relating to nanotechnology, as such, and, specifically, to the safe development, handling and use of NMs. Generally, the following aspects are addressed as potentially influencing NM hazard: The properties and biophysical interactions of NMs, their specific types of use and exposure, uptake and kinetics, and possible early and apical biological effects (Fig. 1; Oomen et al., 2014a,b). However, the specific alignments and contents of guidance documents for the hazard and risk assessment of NMs differ from country to country or jurisdiction to jurisdiction.

It is expected that the safety of a substantial number of NMs will have to be assessed. This is mainly a consequence of the very broad definitions for 'nanomaterial' as they have been laid down, e.g., by the EU Commission (2011) or the United States – Canadian Regulatory Cooperation Council (RCC-NI, 2013a). Further taking into account the abundance of NM modifications in regard to particle size, shape, or surface properties, the need to perform separate or additional safety assessments of NMs as compared to their respective bulk material counterparts could result in full-blown testing programs for each individual NM. In terms of testing capacities, their realization would not be accomplishable within a reasonable timeframe. Additionally, 'tick-box' testing schemes are not justifiable on scientific grounds since they inevitably lead to the collection of large amounts of unnecessary data instead of focusing on relevant studies. Such testing schemes also contravene the need to restrict animal testing in line with the 3Rs principle to replace, reduce, and refine animal testing (Russell and Burch, 1959) that has been implemented in European legislation (EP and Council of the EU, 2010). Concordantly, the provisions of the EU REACH regulation on the registration, evaluation, authorization and restriction of chemicals prescribe that animal testing may only be undertaken as a last resort (EP and Council of the EU, 2006).

The so-called 'grouping of substances' (or category approach) has been recognized as an important means to avoid unnecessary new testing: In this approach, closely related chemicals are considered *as a group, or category, rather than as individual chemicals*. . . [so that] *not every chemical needs to be tested for every endpoint. Instead, the overall data for that category should prove adequate to support a hazard assessment*. . . [and] *must enable an estimate of hazard for the untested endpoints* (OECD, 2014). For chemicals in general, technical guidance documents on grouping are available, e.g. from the Organization for Economic Cooperation and Development (OECD) or the European Chemicals Agency (ECHA, 2008, 2012a, 2013a, 2014; OECD, 2014). This grouping concept implies that some, if not all, information on the hazard of a NM can be derived from the respective bulk material, from molecules or ions of its constituents, or from similar NMs.

By contrast, to date, there is little experience with the specific grouping of NMs. Whereas molecules in solutions or vapors are usually distinct definable species, NMs and particles generally do not exist as distinct species. Instead, they are a population of primary particles and, preponderantly, aggregates and agglomerates of various sizes and different surface coatings. The composition of the NM surface and of the molecules adsorbed onto it influences the biokinetic and toxicological properties of the respective NM,

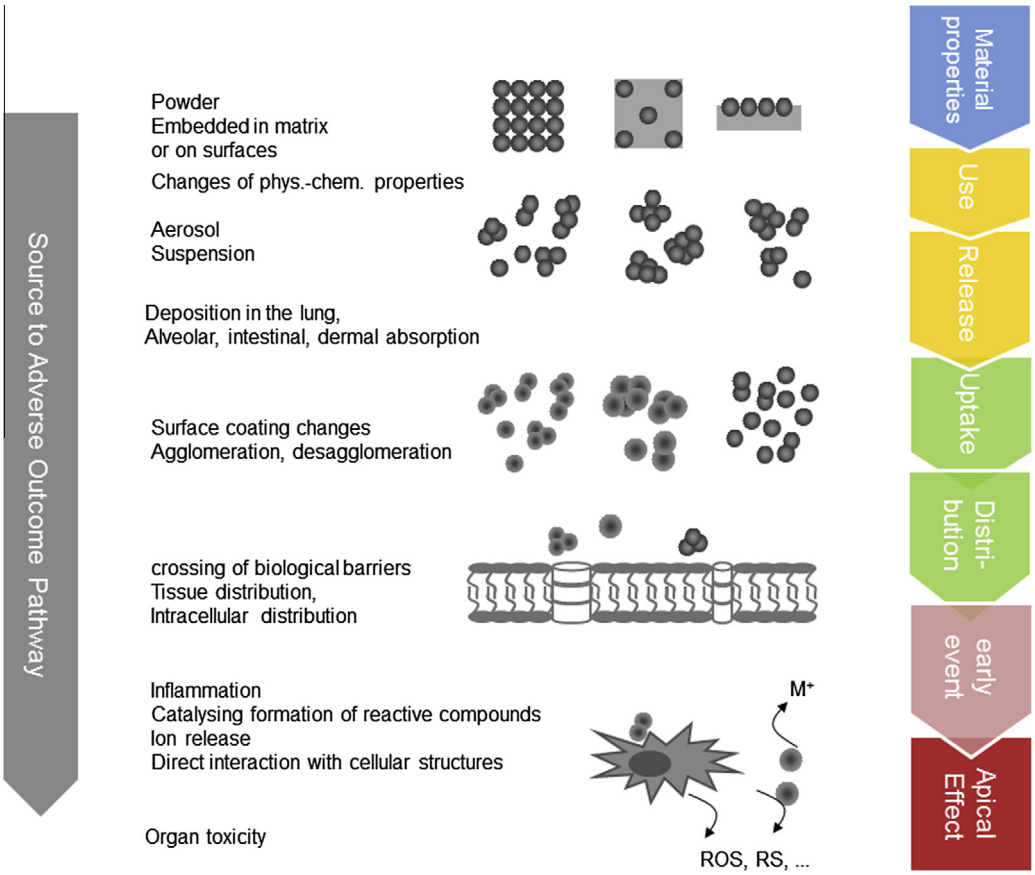

Fig. 1. Source-to-adverse-outcome pathway to derive the relevant physico-chemical (blue), exposure (yellow), biokinetics (green) and hazard (red) endpoints (from: Oomen et al., 2014b; reprinted with the permission of the authors).