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Towards a nanospecific approach for risk assessment

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ABSTRACT

In the current paper, a new strategy for risk assessment of nanomaterials is described, which builds upon previous project outcomes and is developed within the FP7 NANoREG project. NANoREG has the aim to develop, for the long term, new testing strategies adapted to a high number of nanomaterials where many factors can affect their environmental and health impact. In the proposed risk assessment strategy, approaches for (Quantitative) Structure Activity Relationships ((Q)SARs), grouping and read-across are integrated and expanded to guide the user how to prioritise those nanomaterial applications that may lead to high risks for human health. Furthermore, those aspects of exposure, kinetics and hazard assessment that are most likely to be influenced by the nanospecific properties of the material under assessment are identified. These aspects are summarised in six elements, which play a key role in the strategy: exposure potential, dissolution, nanomaterial transformation, accumulation, genotoxicity and immunotoxicity.

With the current approach it is possible to identify those situations where the use of nanospecific grouping, read-across and (Q)SAR tools is likely to become feasible in the future, and to point towards the generation of the type of data that is needed for scientific justification, which may lead to regulatory acceptance of nanospecific applications of these tools.

1. Introduction

It is generally accepted that the recent and upcoming large variety in nanomaterials provides a challenge for assessing their risk. Because nanomaterials of the same chemical composition can have many different physicochemical properties (e.g. size, shape, charge, etc.), the variation of different nanoforms is much larger compared to non-nanomaterials (Maynard et al., 2006). Whereas it has been indicated that – for now – the risks of nanomaterials should be assessed on a case-by-case basis for each individual nanoform with its specific size, shape, surface chemistry, etc. (e.g. SCENIHR, 2009; EFSA Scientific Committee, 2011), it is also recognized that it will require a lot of experimental animals as well as time, effort, and money to obtain for each case the necessary physicochemical, exposure and hazard data for all relevant exposure scenarios and endpoints. For a

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more sustainable situation, many initiatives have been taken to explore ways that enable a risk assessment of nanomaterials without the need to subject each individual nanoform to a full battery of experimental tests. Important aspects of these new approaches include amending tools like (Q)SARs, grouping, read-across and high-throughput screening/testing for nanomaterials. For successful applicability of such new approaches it is crucial that sufficient good quality nanospecific information becomes available (OECD, 2014a,b; Tantra et al., 2015).

In this paper, we describe a new strategy for risk assessment of nanomaterials in which we integrate and expand aforementioned approaches to guide the user how to prioritise those nanomaterial applications that may lead to high exposure or high toxic potential and ultimately high risks for human health. Additionally, we identify those aspects of the exposure, kinetics or hazard assessment that are most likely to be influenced by the specific properties of the nanomaterial(s) under assessment. It is to be noted that the focus is on human health; the potential risks for environment are also of importance, though beyond the scope of this paper and therefore remain to be further investigated in a future dedicated document. Further, the scientific knowledge on nanomaterials is not sufficient yet for defining benchmarks, cut-off values, validation and subsequent regulatory acceptance of nanospecific applications of (Q)SARs, grouping and read-across tools. In this paper the current knowledge will be integrated to identify those situations where the use of such nanospecific tools is likely to become feasible and regulatory acceptable in the near future, and to point towards the generation of the type of data that is needed for regulatory acceptance.

Currently, there is no indication that nanomaterials will lead to other toxicological endpoints than those known for non-nanomaterials (Nel et al., 2014; Donaldson and Poland, 2013; Gebel et al., 2014). For this reason, current regulatory frameworks on the safe use of chemicals, such as the regulatory framework for chemicals REACH (Registration, Evaluation, Authorisation and restriction of Chemicals; EU2006), are generally considered suitable to address the risks of nanomaterials (EC, 2012a,b; OECD, 2013). Within Europe REACH Guidance is being modified or developed to explain this (ECHA, 2012), while there is also a call to adapt the legal text, especially with regard to the information requirements on physicochemical properties (DG Growth, 2016; Roberts, 2016). Some (European) legislation has recently been adapted to set rules for the identification of nano-enabled applications (e.g. Cosmetics Regulation EC No 1223/2009 (EU, 2009) and Biocidal Product Regulation 528/2012 (EU, 2012)). The approach proposed in this paper is developed within the NANoREG project, which mainly focusses on REACH. However, in a later stage, it can be made applicable within other regulatory frameworks as well.

In parallel to the regulatory discussion, there is a scientific challenge to provide further insights in the specific properties that are crucial in the behaviour and toxicity of nanomaterials. These insights can aid in performing a proper and efficient risk assessment for nanomaterials in the future, preferably in a way that accelerates the rate at which the information needed for risk assessment can be generated. The proposed approach described below, facilitates further development of such insights by identifying:

a) those applications of nanomaterials that have the highest potential to cause adverse human health effects (due to high exposure and/or toxicity)
b) those aspects of exposure, kinetics or hazard that are most important to address in the human health risk assessment of nanomaterials,
c) those situations where the use of nanospecific grouping, read-across and (Q)SARS is likely to become feasible and potentially regulatory acceptable in the near future, and
d) the type of information needed for this regulatory acceptance.

The proposed approach is developed to be applicable to nanomaterials that are already on the market. However, elements of this approach, such as use of grouping and read-across methods and aspects most important to address the nanospecific issues within the risk assessment, will also be applicable to safe innovation approaches during the development of new nanomaterials in the research and development phase (Sips et al., 2015).

Nanomaterials are prone to many possible changes during their life cycle, like (partial) dissolution or degradation, complexation, aggregation, agglomeration, etc. Because these changes may differ from the changes of non-nanomaterials, the influence of these changes on the exposure and hazard of the nanomaterial should be assessed throughout its whole life cycle, from the manufacturing of the nanomaterial, through the different stages of the life cycle, including various uses, disposal and waste treatment.

The proposed approach is built on the extensive knowledge already developed in other European research projects or by other international organisations and committees. The most important sources of knowledge used are given in Table 1. The existing knowledge is subdivided in knowledge on newly developed risk assessment strategies (column 2), read-across and grouping approaches (column 3) and other supporting information (column 4). The most recent and relevant publications used in this paper, are mentioned.

1.1. Current knowledge on the nanospecific behaviour and toxicity

There is still a lot of debate on the terms nanospecific behaviour and toxicity, because differences in the behaviour and toxicity between nanomaterials and non-nanomaterials are not related to a nanospecific threshold below 100 nm, but more likely to be a gradual magnification of the intrinsic hazard by decreasing size (Donaldson and Poland, 2013). Nevertheless, in this paper the terms nanospecific behaviour and toxicity are still used to indicate changes in the response, interaction, behaviour and toxicity associated with the decreasing geometrical size of the (nano)materials.

The most distinctive feature of our approach is its focus on nanospecific issues in not only the hazard, but also the exposure assessment and kinetic behaviour. In other words, it makes use of the specific physicochemical properties that determine the nanospecific behaviour that influences to what extent and in which way nanomaterials come into contact and interact with the human body. Examples of such properties are dissolution rate and reactivity. These properties may change during the life cycle of a nanomaterial and are partly depending on interactions with the surrounding environment, which may lead to a different behaviour of nanomaterials in different situations.

The nanospecific behaviour is especially relevant for: a) exposure (deposition and agglomeration), b) absorption and distribution (transport across biological barriers like gut epithelium, blood-brain barrier, or skin), c) accumulation, and d) toxic potency (dose-response relationships).

Based on epidemiological and experimental research on the effects of (ultra)fine particles, it is known that small particles can cause inflammation, fibrosis, lung cancer, cardiovascular effects, neurodegenerative effects and teratogenic effects (Chen et al., 2016; Oberdorster et al., 2009). These health effects can also be caused by non-nanomaterials and are therefore not only restrictive or specific for nanomaterials. However, the nanospecific behaviour can lead to