Topical Scientific Workshop
Regulatory Challenges in Risk Assessment of Nanomaterials
23-24 October 2014

Background paper for the five topics

Contents

Introduction

Topical scientific workshops of the European Chemicals Agency aim to foster discussions among academia, regulators, industry and other stakeholders on the possible regulatory impacts that the latest scientific developments may have. An anticipated outcome of these workshops is the emergence of new or improved approaches, which may be applied in the implementation of the REACH, CLP and Biocidal Products Regulations.

As a background paper to the Topical Scientific Workshop on Regulatory Challenges in Risk Assessment of Nanomaterials, this document aims to frame the discussions and preparations for the event. In addition, this document is also written to stimulate discussions among academia, regulators and stakeholders on the possible regulatory impacts that the latest scientific developments may have and will be made publically available prior to the workshop.

Discussions will be reinforced by information on recent scientific developments related to the risk assessment methodologies currently being applied in chemicals management in a regulatory context. The workshop strives to provide a platform for academia, regulators and stakeholders to address how the main long-term regulatory challenges, as further outlined in this paper, can be reflected and employed in the current and future research initiatives.

The workshop will be structured into five sessions, each mirroring a prioritised area where further discussion is needed and where science and frontline research may offer solutions to be applied in a regulatory context.

1. Challenges in the regulatory risk assessment of nanomaterials
2. Measurements and characterisation of nanomaterials
3. Metrology and dose metrics for hazard and exposure assessment throughout the life cycle
4. Environmental fate, persistence and bioaccumulation throughout the life cycle
5. Read-across and categories of nanomaterials

This document gives a background to the individual sessions but also highlights where the main challenges are by pinpointing issues for further discussion.

An anticipated outcome of the workshop is the realisation of new or improved approaches which may be applied in the implementation of the REACH, CLP and Biocidal Products Regulations. In practice, this means we strive to identify recommendations, rules of thumb or generic strategies that should support the implementation of chemical regulations for nanomaterials (NM) by authorities.

1. Challenges in the regulatory risk assessment of nanomaterials

1.1 Background

There are currently no provisions in REACH that explicitly refer to nanomaterials[10]. However, nanomaterials are considered to be covered by the substance definition under REACH. The basic principle stated in Article 1(3) 'This Regulation is based on the principle that it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment' applies to nanomaterials. Moreover, the Commission's second regulatory review on nanomaterials reminded that 'REACH applies equally to substances for which all or some forms are nanomaterials'.

Safe use claims under REACH should be based on explicit and transparent documentation supporting the hazard, exposure and risk assessment of nanomaterials and the existing risk assessment paradigm developed for traditional chemicals should – in principle – also be applied to nanomaterials. However, in line with scientific developments, there are specific considerations that registrants should report in specific endpoint sections, as this information will aid the evaluation of the adequacy of the tests performed and data obtained with regard to the safety assessment of nanomaterials (e.g. sample preparation, solubility/dispersion, use of stabilisers etc.)[9].

Together with industry, stakeholder groups, Member States and the Commission, ECHA has given more clarity to registrants on how to demonstrate the safe use of their substances in all forms under REACH. This work has generated best practice, clarified policy lines and improved the existing guidance for nanomaterials[4-7].

ECHA was actively involved in REACH implementation projects on substance identity, information requirements and exposure assessment (RIP-oNs 1-3[1]) and in NANOSUPPORT[2] with DG JRC. ECHA also initiated a Nanomaterial Working Group (NMWG) as an advisory group consisting of experts form Member States, the European Commission, ECHA and accredited stakeholder organisations and coordinated the GAARN project (Group Assessment of Already Registered Nanomaterials) to assess current registrations for representative nanomaterials with their respective registrants[4-7].

1.2 Issues to be addressed

It is recognised that some issues still need to be further clarified when the conventional risk assessment paradigm is applied to nanomaterials. Currently, a key issue in regulatory risk assessment of nanomaterials is to identify, if and when, revisions and amendments in e.g. guidance, are needed to make sure that the risk of nanomaterials can be appropriately assessed and documented.

This session aims to give an overview of the current challenges in the regulatory risk assessment of nanomaterials. Uncertainties on the applicability of the conventional risk assessment paradigm should be identified and more importantly how these knowledge gaps can be filled. Furthermore, the aim of the session is to develop proposals on how current methodologies for assessing potential risks of nanomaterials can be improved.

<u>ECHA recognises the following key issues in regulatory risk assessment:</u>

- Identification of the relevant key characteristics or properties affecting the release, exposure behaviour (fate and kinetics), effects (hazards) and the subsequent risks of nanomaterials (including their different nanoforms)

- Lack of available and validated data on the hazard properties of nanomaterials (including their different nanoforms)
- Lack of common understanding on how to distinguish between different nanoforms and what criteria should be used to make such assessment
- Lack of scientific justification for extrapolations between nanomaterials and 'standard' ("bulk") chemicals, including the categorisation of different nanoforms
- Selection of appropriate risk assessment approaches and methodologies for the most relevant hazard endpoints related to the risks of nanomaterials
- Uncertainty associated with reaching conclusions about the fate and distribution of the nanomaterials in the environment

ECHA recognises the following key issues in risk management:

- Knowledge of use profiles of nanomaterials
- Methods to mitigate exposure
- Validation of exposure models (e.g. computational modelling tools such) for nanomaterials

1.3 References

[1] http://ec.europa.eu/environment/chemicals/nanotech/reach-clp/ripon_en.htm
REACH Implementation Project on Nanomaterials (RIPoN) final reports

[2] http://ec.europa.eu/environment/chemicals/nanotech/reach-clp/nano-support_en.htm
Nano Support Project final reports

[3] http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
ECHA Guidance on Information Requirements and Chemical Safety Assessment

[4] http://echa.europa.eu/regulations/nanomaterials
ECHA nanomaterials web page

[5] http://echa.europa.eu/documents/10162/5399565/best_practices_physiochem_subst_id_nano_en.pdf
Best practice on physicochemical and substance identity information for nanomaterials - Report from first GAARN meeting

[6] http://echa.europa.eu/documents/10162/5399565/best_practices_human_health_environment_nano_en.pdf
Assessing human health and environmental hazards of nanomaterials - Best practice for REACH Registrants - Report from second GAARN meeting

[7] http://echa.europa.eu/documents/10162/5399565/best_practices_human_health_environment_nano_3rd_en.pdf

Human health and environmental exposure assessment and risk characterisation of nanomaterials – Best practice for REACH Registrants - Report from third GAARN meeting

[8] http://echa.europa.eu/documents/10162/13643/appendix_r14_05-2012_en.pdf
ECHA Guidance, Appendix to Chapter R.14, 2012

[9] http://search.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2012)40&docLanguage=En
GUIDANCE ON SAMPLE PREPARATION AND DOSIMETRY FOR THE SAFETY TESTING OF MANUFACTURED NANOMATERIALS Series on the Safety of Manufactured Nanomaterials No. 36 JT03332780

[10] http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/nanomaterials_en.pdf
Follow-up to the sixth meeting of the REACH competent authorities for the implementation of Regulation (EC) 1907/2006 (REACH) on 15-16 December 2008

2. Measurement and characterisation of nanomaterials

2.1 Background

The measurement and characterisation of nanomaterials is one of the key pre-requisites for a proper hazard and risk characterisation of substances and even more so for nanomaterials. Far from being straightforward, this is a multi-faceted challenge that requires knowledge on a number of key elements, including at a minimum the following:

1) an enforceable definition for nanomaterials,
2) agreed physico-chemical properties necessary for a characterisation of nanomaterials (e.g. size, surface area, etc.),
3) standardised methods for the quantification of these parameters.

The EC has adopted a recommendation for a regulatory definition of "nanomaterial" to be implemented in all EU regulations in Oct 2011[1]. Although there are other definitions available[2] and although this definition may undergo changes[3], the EU recommended definition is the one currently being implemented for regulatory purposes across the EU legal frameworks. The Biocidal Products Regulation[4] and the Regulation of Medical Devices[5] are the first EU regulations to include reference to the recommendation in the legal text followed by Cosmetics[6] and Biocides[7]. It is foreseen that modifications of the REACH annexes for nanomaterials will explicitly include the recommendation.[8]

[1] Commission Recommendation of 18th October 2011 on the definition of nanomaterial available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF
[2] reports EUR 24403 and EUR 26567, ISO/TS 80004-1:2010; Nanotechnologies -- Vocabulary -- Part 1: Core terms
[3] Commission Recommendation of 18th October 2011 on the definition of nanomaterial available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF
[4] http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1400573994565&uri=CELEX:52012AP0010
[5] REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on medical devices COM(2012)542
[6] EU Regulation 1223/2009 available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2009R1223:20130711:en:PDF
[7] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:167:FULL:EN:PDF
[8]COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE Second Regulatory Review on Nanomaterials available at http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:52012DC0572

ECHA is already implementing the recommendation where nanomaterials are seen as substances in their own right or as forms of a substance.[9] This was discussed in detail at the first GAARN (Group Assessing Already Registered Nanomaterials) project[10] meeting where it was stressed that the use of several analytical techniques for characterising nanoforms (multi-method approach) was favoured as no single currently available method can provide sufficient information on all the physicochemical parameters necessary to characterise nanoforms; a reasoning that, to some extent, holds true for any substance.

2.2 Issues to be addressed

The term "measurement and characterisation" itself can refer to a wide variety of regulatory and scientific problems that need to be addressed to ensure the safe use of nanomaterials. There is a need to address the characterisation of nanomaterials in different stages of the lifecycle and for different purposes, namely characterisation of nanomaterials:

1) for the purpose of identification,
2) during (hazard) testing, and
3) for the purpose of exposure assessment.

For the purpose of identifying nanomaterials, the EC recommendation for the definition of nanomaterials serves as the reference point. However, implementation of the recommendation is not trivial due to a variety of challenges. These include the absence of standard methods, the absence of reference materials, and the diversity in what is covered by the EU recommendation for nanomaterials. The JRC report [1] has highlighted the need for standard methods and the complexities of applying existing non-standard methods to determine particle size on a number basis (as required by the EU recommendation) and the challenges with agglomerates and aggregates. Many on-going FP7 projects are addressing this challenge (NANOREG, NanoDefine etc.)[2] with regards to measurement of nanomaterials. Furthermore, CEN TC 352 has accepted a mandate (M461) from the EU Commission to develop standards relevant for nanotechnologies that will also address this.[3]

The characterisation of nanomaterials within hazard testing is also critical. To ensure adequacy and comparability of test data, a minimum set of physico-chemical characteristics, as well as careful sample preparation are necessary. The relevance of particle size measurements, as well as other parameters for sample characterisation for

[9] GAARN meeting best practices report available at https://echa.europa.eu/documents/10162/5399565/best_practices_physiochem_subst_id_nano_en.pdf.
[10] Established in January 2012 by DG Environment from the European Commission and chaired by ECHA, the purpose of GAARN was to build a consensus in an informal setting on best practices for assessing and managing the safety of nanomaterials under the REACH Regulation.
[1] Requirements on measurements for the implementation of the European Commission definition of the term "nanomaterial" available at http://ec.europa.eu/dgs/jrc/index.cfm?id=2540
[2] http://www.nanosafetycluster.eu/eu-nanosafety-cluster-projects/seventh-framework-programme-projects/enanomapper.html
[3] M/461 MANDATE ADDRESSED TO CEN, CENELEC AND ETSI FOR STANDARDIZATION ACTIVITIES REGARDING NANOTECHNOLOGIES AND NANOMATERIALS available at http://ec.europa.eu/enterprise/standards_policy/mandates/database/index.cfm?fuseaction=search.detail&id=443#

testing has been addressed by the OECD WPMN in its draft guidance on sample preparation and dosimetry.[4]

Finally, the characterisation of nanomaterials during their use, and the potential exposure of people and the environment to nanomaterials are important. It is recognised that nanomaterials may be incorporated into a variety of matrices during their use.

Furthermore, nanomaterials have a tendency to aggregate/agglomerate, however, the stability of such aggregates/agglomerates within the use, and the potential release of smaller particles is not clear. Therefore, it is relevant to consider a) how to measure and characterise the release of nanomaterials from such matrices during their life cycle, and b) how to measure the stability of aggregated/agglomerated particles and their potential for releasing smaller particles during the entire life cycle of the substance.

Focus should be given to the current status of the field and getting a perspective on future research directions, potential obstacles and how they could be overcome – ideally updates from cutting edge methods relevant for regulatory needs from the FP7 projects and/or national/international initiatives. Additional attention will be paid to integrated or tiered approaches that allow the best characterisation of mono- and polydispersed materials helping authorities to address nanomaterials in an effective manner.

3. Metrology and dose metrics for hazard and exposure assessment throughout the life cycle

3.1 Background

The agreement of the most appropriate metrics for each type of nanomaterial within each specific route of exposure and (eco)toxicological endpoint is one of the most important gaps regarding the regulatory testing of nanomaterials.

The most optimal dose metrics to be used for nanomaterials are still under discussion. Dose-response relationships have been reported in several studies, especially *in vitro* studies, using nanomaterials such as single- and multiple carbon nanotubes and various forms of nanometals (Hansen and Baun, 2012).

In general in these studies, dose refers to "dose by mass". However, for nanomaterials this may not sufficiently describe the dose that determines a particular response in a biological system. A specific mass of a variety of nanomaterial consisting of the same chemical substance but with different properties such as particle size may have completely different toxicity profiles (Park et al 2012). Oberdörster *et al.* (2005) suggested that the biological activity of nanoparticles might not be mass-dependent, but dependent on physical and chemical properties not routinely considered in toxicity studies. For example several studies (Oberdörster (1996), Oberdörster *et al.* (2007), Stoeger *et al.* (2006, 2007) found that the surface area of the nanoparticles is a better descriptor of the toxicity of low-soluble, low toxicity particles. For inhaled insoluble sphaerical particulate matter, it was suggested that the particle displacement volume

[4] Guidance on Sample Preparation and Dosimetry for the Safety Testing of of Manufactured Nanomaterials available at ENV/JM/MONO/(2012)40

rather than surface area appears to be the most critical metric for these types of nanomaterials (Pauluhn (2011)). Other studies (Wittmaack (2007a, b) found that the particle number was the best dose metric while others (Warheit *et al.* (2007a, b)) found that the number of functional groups in the surface of nanoparticles influenced their toxicity.

The dose metrics that are most appropriate to compare the risks of nanomaterials are probably variable, but seem to depend on the type of nanomaterial, the route of exposure, the kinetics and/or the (eco)toxicological endpoint studied.

More data from toxicokinetics and *in vivo* toxicity studies would aid further progress on establishing the most appropriate dose metrics for nanomaterials. For example, for multi walled carbon nanotubes (MWCNT) attempts were made to identify common mechanistic denominators between higher and lower density, biopersistent nanosized and submicronsized insoluble particles. It appears that the potency of these particles to induce inflammation-related sustained lung injury is solely dependent on biokinetics rather than the particles inherent properties (Pauluhn (2011)).

Furthermore, nanomaterials interact strongly with their surroundings during the life cycle of manufacture as well as during their preparation, sample collection or during contact with cellular media and biological fluids and may see their physical, chemical and biological properties evolving. When nanomaterials aggregate, it may become even more difficult to assign a single physical qualifier for unequivocal characterisation.

3.2 Issues to be addressed

This session will discuss the state of art regarding the most appropriate metrology and dose metrics that should be used in the context of the risk assessment of nanomaterials.

From the current knowledge several important challenges emerged:

- The best choice of metrics or measurements heavily depends on (eco)toxicological considerations.
- A single metric is generally not sufficient to characterise and quantify nanomaterial exposure for all types of nanomaterials.
- Exposure is best characterised by multiple parameters and thus should be described by a set of information.
- Size distribution is important for understanding the likelihood of deposition of particles in certain parts of the airways.
- Particle size and surface area concentration are associated with the potential toxicity of a nanomaterial.
- Particle (or fibre) number concentration is important as, in some cases, this metric may be more relevant than the mass metric in determining potential risk from exposure to nanomaterials. Furthermore, the mass of airborne nanoparticles will usually be very small and therefore can be much more difficult to measure than the particle number.

- The mass concentration is important because there is already a large body of research on exposure to and (eco)toxicity of particles in the mass-based metric.
- Since the mass-based metric is currently a fundamental cornerstone in all chemical regulations, any change will also require further thoughts on how existing legal thresholds can be applied and harmonised.

A common understanding and harmonisation of the most appropriate metrics used to describe exposure and hazard characterisation for nanomaterials is needed. To design and perform the studies using appropriate dosing, it is important to take into account the likelihood and degree of human and environmental exposure in terms of the physicochemical nature, aggregation state, and concentration (number, mass, surface area) of manufactured nanomaterial.

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4. Environmental fate, persistence and bioaccumulation throughout the life cycle

4.1 Background

In the REACH Regulation, the assessment of environmental fate is primarily based on a number of standard information requirements; among others, physicochemical characteristics of the substance, biotic and abiotic degradation, and bioaccumulation. Due to the wide range of nanomaterials and their variety of different forms, sizes, shapes and surface characteristics, their environmental fate assessment can become very complex. REACH testing strategies and standard test guidelines are in principle applicable for assessing the fate of nanomaterials (Hankin et al. 2011, Kűhnel and Nickel, 2014) nevertheless there seems to be a clear need for adaptation and development of test guidelines and discussion on the necessity of introducing nano-specific information into the environmental fate assessment.

The unique properties of nanomaterials bring new challenges to the applicability of harmonised test guidelines for chemicals. A preliminary review of OECD test guidelines outlines that the majority of the OECD TGs for chemicals are generally applicable for nanomaterials (OECD 2009). However, the applicability of individual test methods depends on the physical and chemical properties of nanomaterials in different environmental media. In 2013 at the OECD meeting on "Ecotoxicology and environmental fate", further recommendations on the development needs regarding the OECD TGs for assessing the environmental fate and behaviour of nanomaterials were given by experts (OECD 2014). For example, there is a need for the development of new test guidelines for specifying dissolution behaviour and adsorption-desorption properties of nanomaterials and guidance on the determination of dispersion behaviour and transformation processes in environmental media. Furthermore, limitations in aquatic bioaccumulation tests predicting the bioaccumulation of nanomaterials were observed. In addition, lack of harmonised methods in sample preparation, characterisation of the test substance and its different forms may reduce the reliability of the environmental fate assessment of nanomaterials in general.

Due to the complex interactions of nanomaterials with their environment and potentially changing physical-chemical characteristics during their life cycle, many uncertainties in understanding their behaviour in the environment remain. Especially extrapolation of fate data across media, biological species and across nanomaterials with different properties is challenging. Based on these identified challenges and development needs, it

has been stated that the environmental fate of nanomaterials cannot be reliably assessed with the currently available standards (Schwirn et al. 2014). Therefore, updates in guidance for environmental fate assessment to fulfil the information requirements set in REACH and harmonisation of the regulatory risk assessment approaches will have to be foreseen.

4.1.1 Degradation assessment

Degradation is an important process that may result in the reduction or transformation of a chemical substance in the environment. Pre-requisite for biodegradation is that the test material is based on organic carbon chemistry. As a result, fully inorganic nanomaterials will not require testing in the biotic degradation tests. The OECD TGs for biodegradability that are recommended in the ECHA Guidance on information requirements and chemical safety assessment (R.7b, November 2012) measuring carbon dioxide production or oxygen uptake are, in principle, applicable for nanomaterials to the same extent as for bulk materials. These OECD TGs have been developed and validated for the assessment of organic compounds whereas many nanomaterials are primarily inorganic and even carbon-based nanomaterials arguably tend to be of an inorganic nature. However, there is evidence on single-walled carbon nanotubes (SWCNT), multi-walled carbon nanotubes (MWCNT) and fullerene (C60) degradation by oxidative enzymes (Allen et al. 2008, Schreiner et al. 2009). Degradation of organic coatings or functional groups of some inorganic nanomaterials may be assessed by these traditional biodegradation tests, but this still needs to be validated.

Simulation tests for biological degradation in various environmental compartments are applicable in principle, but again the detection and quantification of the nanomaterial is the challenge. The possible degradation to carbon dioxide, integration into biomass or other partitioning can be followed e.g. using labelled test materials. In addition to the biodegradation; hydrolysis, photo-degradation, oxidation and reduction plays an important role in environmental fate assessment. For hydrolysis testing, the chemical structure of the material and whether it contains groups that could be subject to hydrolysis dictate whether this test is necessary or appropriate. It has been suggested that degradation of nanomaterials may also be identified as changes at the nanomaterial surfaces (e.g. by oxidation processes or changes of coatings) and transformation as basic changes in composition or form (e.g. dissolution or hetero-aggregation) (Kűhnel and Nickel, 2014).

4.1.2 Bioaccumulation assessment

To determine if and under which circumstances nanomaterials accumulate in the environment and environmental species, more knowledge on the key characteristics that influence the fate, behaviour and kinetics of nanomaterials and implementation of this knowledge within the risk assessment approaches and regulatory frameworks is needed.

For organic substances, there is an established relationship between octanol/water partition coefficient (Kow) and bioaccumulation or bioconcentration factor (BCF). With regard to nanomaterials, it is not possible to make log Kow or solubility estimations, since they are dispersed and not in solution. Therefore, estimation based on log Kow for assessing potential for bioaccumulation of nanomaterials is not acceptable. Furthermore, current possibilities for using non-testing approach (e.g. QSAR) are limited while no generally accepted approached are available for nanomaterials (Appendix R7-2

Recommendations for nanomaterials applicable to Chapter R7c Endpoint specific guidance).

Bioaccumulation testing in aquatic organisms according to OECD TG 305 (bioaccumulation in fish OECD, 2012b) is generally considered to be applicable, but the calculation of the BCF has been critically discussed with regard to nanomaterials. Recommendations from the OECD expert meeting were to examine dietary exposure for nanomaterials and to amend the TG 305 with specifications for the testing of nanomaterials (OECD 2014). Nanomaterials have a tendency to aggregate, and thus their likelihood to end up associated with sediment is high (Klaine et al. 2008).

Bioaccumulation in sediment-dwelling organisms according to OECD TG 315 is generally considered an applicable approach for nanomaterials as well as OECD TG 317 for terrestrial bioaccumulation. There may still be a need for development of new standard approaches, application of new nano-relevant endpoints (uptake rate, internalisation rate, and attachment efficiency) and general agreement of the bioaccumulation testing strategies for nanomaterials (Kűhnel and Nickel, 2014). One of the main challenges in testing the bioaccumulation of nanoparticles is their detection, quantification and characterisation in the various test guidelines that exist.

4.2 Issues to be addressed

Within the regulatory frameworks, assessment of the environmental fate of the nanomaterials should be based on the generally accepted and scientifically valid techniques. It has been commented that the REACH Guidance does not fully cover the specific environmental fate of nanomaterials (alterations, dissolution and partitioning) and adjustments have been recommended by Meesters et al. (2013). Is there a need for further information on environmental fate of nanomaterials to address the existing uncertainties that go beyond those requirements laid down in REACH to date (Schwirn et al. 2014)?

This session aims to provide an overview of the environmental fate assessment of nanomaterials and facilitate discussion on the testing strategies to assess the environmental fate of nanomaterials in a regulatory context.

The key scientific issues related to the fate of nanomaterials in the environment to be covered under this session include:

- Implementation of the testing strategies for environmental fate, (bio)degradation and bio-accumulation from regulatory point of view.
- Identification of the critical data gaps in relation to information requirements and in the methodologies to measure release, fate and behaviour.
- Identification of key characteristics or properties of the nanomaterial that influence the environmental fate assessment in the environment e.g. particle size, surface area, crystallinity, shape, coatings, aggregation and agglomeration behaviour.
- Identification of soil or sediment parameters affecting the fate and behaviour of nanomaterials.

- Nano-specific issues related to transformation, persistence and bioaccumulation regulatory assessment e.g. development of 'nano-relevant' endpoints replacing Kow, BMF or BCF.
- Needs for and advances in method development to ensure the reliable assessment of the fate of nanomaterials in a regulatory context.
- How to extrapolate fate data across media, biological species, and across the physico-chemical properties of nanomaterials?
- Level of acceptable uncertainty in environmental fate assessment.
- Role of interaction of particles with biological systems.
- Based on the scientific evidence, are the current standards information requirements in REACH Regulation on environmental fate adequate to assess the fate of nanomaterials in the environment?

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5. Read-across and categories of nanomaterials

5.1 Background

Read-across and categories of nanomaterials are valuable approaches used to predict specific properties of substances for which there is insufficient experimental data. In a read-across approach, endpoint information from one or many chemicals is used to predict the same endpoint, either qualitatively or quantitatively, for one or many other chemicals. In a category approach, a group of substances whose properties are likely to be similar or follow a regular pattern is constructed.

Within the group, a property can be estimated through, for example, read-across or trend analysis. For predictions of nanomaterial properties using read-across or categories, three main possible scopes of prediction are foreseen: (1) from bulk to all nano-forms, (2) from bulk to specific nano-forms, (3) from one or many nano-forms to one or many nano-forms (nano-forms of different chemical identity, of the same chemical identity but with differences in physicochemical characteristics, and coated vs. uncoated nano-forms).

Read-across is recognised as one of the key issues in finding a pragmatic way to bridge existing data gaps in the hazard characterisation of nanomaterials. Therefore, there is a push from both academia and policy makers, to find a way forward in agreeing on e.g. criteria for when and how read-across may be acceptable. Currently in several FP7 projects, read-across is an identified deliverable but the issue is also discussed at a global level in an OECD context.

Any read-across and category approach applied for nanomaterials in a regulatory context must not compromise the insurance of the safe use of the substance and thus must be based on a robust scientific justification. The approach should identify and consider the properties or parameters that drive the endpoint in question.

For the toxicological effects of nanomaterials, it has been shown that the drivers include parameters such as nanoparticle charge, solubility, composition (including the presence of impurities, coatings and surface treatment), shape and the ability to translocate over biological barriers [Donaldson and Poland, 2013]. The importance of shape has, for example, been shown in experiments on carbon nano tubes and titanium oxide fibres. Non-curled carbon nano tubes with a length of more than 10 um were shown to persist in the peritoneal and pleural cavity of mice leading to substantial inflammation and fibrosis, while tightly curled carbon nano tubes were rapidly cleared and did not cause inflammation or fibrosis [Poland et al., 2008; Murphy et al., 2011].

Similarly, in experiments on mouse macrophages exposed to titanium oxide nanoparticles, both spherical particles (60-200 nm) and short fibres (0.8-4 um) were completely phagocytosed while long fibres (15-30 um) caused distortion of the macrophages [Hamilton et al. 2009]. In addition to the above, parameters such as solubility, biological persistence, dispersability and biological effects have also been suggested to serve as a possible basis for read-across and grouping.

5.2 Issues to be addressed

In the regulatory context, the main challenge is how to use the available hazard information in acceptable read-across and categories of nanomaterials for prediction of the hazard endpoints related to, for example, fate, ecotoxicity and toxicity. At this point in time, establishing the criteria and validation approaches with a high enough certainty to not jeopardise safe use is crucial. The combination of key criteria and possible cut-off points that determine whether read-across and/or categories can be used without making underestimations of hazards, and for which purpose, are still to be defined.

Further clarification is also needed on how to best evaluate and to appropriately take into account uncertainties associated with read-across and categories, and if any uncertainty would be different from that associated with conventional substances.

This workshop session aims to explore the possibilities, limitations and pre-requisites of read-across and categories of nanomaterials in a regulatory context. Key questions include:

- Which common approaches for read-across and categories of conventional chemicals can also be considered applicable to nanomaterials?
- What parameters need to be assessed (as a default or case-by-case) in support of read-across for the purpose of predicting fate, ecotoxicological and toxicological endpoints? Can any parameter be used in isolation? Can default sets of properties be defined?
- How far does the mode of action have to be known? What techniques elucidating mode of action can be helpful (e.g. –omics based)?
- How can parameters such as bio-accessibility, effect of corona formation, impurities, coating and surface treatment, toxicokinetics and translocation potential be addressed or accounted for?

- What are the factors giving rise to uncertainty in these approaches? Are there nanomaterial-specific factors and how are these best addressed? What is the level of uncertainty in using read-across and grouping for specific endpoints or groups of endpoints? How can underestimation of critical parameters be avoided?
- To what extent can QSAR models be used to support read-across and categories of nanomaterials?
- What are the benefits and limitations of 'pre-defined' categories or families of nanomaterials by international organisations such as the OECD or WHO?

5.3 References

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