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Information Requirements for nanomaterials - IRNANO

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Information Requirements for nanomaterials - IRNANO

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Preface

The project on Information Requirements for nanomaterials (IRNANO) was carried out during the period September 2012 to January 2013.

During the project, a proposal for regulatory information requirements for nanomaterials was developed and discussed in relation to existing knowledge and legislation in the area of regulating nanomaterials. The results of the project can be seen as a stimulus for discussion or as a technical contribution to the current discussions in the field on both national and EU-levels.

Focusing on technical/scientific aspects, the reader is assumed to have some background knowledge on regulation of chemicals and nanomaterials.

The project was carried out by COWI A/S with DHI as subcontractor. Frans M. Christensen (COWI A/S) and Poul Bo Larsen (DHI) acted as the main authors.

As a part of the project, three half-day advisory group meetings were organised. Furthermore, the advisory group provided extensive written input to the project. The advisory group consisted of the following members:

- Anders Baun, Chem. Eng, Professor, DTU Environment, Technical University of Denmark,
- Lars Toräng, Chem. Eng., Ph.D., Sun Chemical, Køge, Denmark.
- Keld Alstrup Jensen, Senior Researcher, National Research Centre for the Working Environment
- Anne-Mette Boisen, Cand. Scient., Ph.D., Danish Environmental Protection Agency
- Gregory Moore, Cand. Scient., Ph.D., Danish Environmental Protection Agency
- Sandi Muncrief, Legal Advisor, Danish Environmental Protection Agency
- Flemming Ingerslev, Chem. Eng., Ph.D., Danish Environmental Protection Agency.

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Danish EPA, January 2013

Sammenfatning og konklusioner

Formål og afgrænsning
Det overordnede formål med projektet er at udarbejde et forslag til informationskrav for nanomaterialer (stofidentifikation, karakterisering, fysisk-kemiske egenskaber, toksicitet, skæbne og effekter i miljøet), som på et senere tidspunkt vil kunne indarbejdes i lovgivning vedrørende informationskrav for nanomaterialer. Det udarbejdede forslag er baseret på en gennemgang af eksisterende videnskabelige projekter/rapporter (referencer) forfattet af en række ekspertgrupper, organisationer og myndigheder.

Den måde REACH stiller informationskrav til kemiske stoffer (REACH Annex VI-XI) er blevet anvendt som struktur for det udarbejdede forslag for nanomaterialer, samt til analyse af informationskrav foreslået i de gennemgåede referencer. Det har været uden for projektets rammer at udarbejde konkrete og mere detaljerede vejledninger for de enkelte informationskrav og test af nanomaterialer.

Trods anvendelsen af REACH-strukturen skal det udarbejdede forslag til informationskrav for nanomaterialer ikke ses som et isoleret forslag til opdatering af REACH. Det skal ses som et forslag, som også kunne blive implementeret enten som en specifik nano-lovgivning, i relation til EU sektor-specifik lovgivning eller som national lovgivning. Det er således uden for projektets rammer at vurdere og foreslå, hvordan forslaget konkret kan implementeres i lovgivningen.

Følgegruppe
I forbindelse med projektets igangsættelse har Miljøstyrelsen nedsat en følgegruppe af eksperter, som løbende er blevet kontaktet i projektetforløbet (se også preface). Gruppen har gennem tre møder haft grundige diskussioner af projektets forslag og bidraget med skriftlige kommentarer fire gange gennem projektforløbet.

Metode og resultat af gennemgangen
Ved projektstart blev 26 relevante rapporter, som berører informationskrav for nanomaterialer, udpeget. Disse referencer er anført i Appendix A.

Hver reference blev indledningsvist gennemgået og summeret kort (Appendix 2). De mest relevante referencer ("key references") blev derefter gennemgået mere detaljeret med henblik på at bestemme:

- hvilke forskellige, mulige informationskrav der blev adresseret i rapporterne,
- hvorvidt testmetoder blev diskuteret, og
- om regler for generering af informationskravet blev diskuteret, dvs. forhold som enten kunne udløse/fremskynde informationskravet eller evt. udskyde/overflødiggøre dette.

Et overblik over resultaterne af denne detaljerede gennemgang er præsenteret i en række matricer i Appendix 3. Denne oversigt viser også, hvilke informationskrav, som er ekstra informationskrav for nanomaterialer og som ikke allerede kræves i REACH.

Derefter gennemgik de mulige informationskrav en systematisk analyse af, hvordan de bliver adresseret på tværs af referencerne. F.eks. om et informationskrav burde inkluderes i den

foreslåede pakke for regulatoriske informationskrav for nanomaterialer, om der forelå tilgængelige testmetoder, om der var overbevisende videnskabelige argumenter i referencerne, samt i hvilket omfang der var konsensus mellem referencerne. På basis af denne analyse blev hvert muligt informationskrav tildelt en evalueringsscore mht. i) om informationskravet på kort sigt synes relevant som regulatorisk informationskrav, ii) relevansen som et muligt fremtidigt informationskrav (evt. efter yderligere forskning og udvikling) eller, iii) om informationskravet kan betragtes som mindre relevant for nanomaterialer. Denne score er anført i højre kolonne af matricerne i Appendix 3 og den tilhørende argumentation er summeret i kapitel 4.

Kapitel 4 summerer derudover en række vigtige overordnede aspekter som går igen under gennemgangen af referencerne. Det er aspekter og forhold, som ikke relaterer sig til et specifikt informationskrav, men er af mere generel og tværgående karakter.

På basis af disse aktiviteter blev der, som det centrale resultat af projektet, udviklet et forslag til informationskrav for nanomaterialer. Forslaget består af en række generelle forhold, som der skal tages højde for, hvis forslaget implementeres i lovgivning, samt et mængdebaseret (tonnage-baseret) trinvist forløb med stigende informationskrav. De foreslåede informationskrav er præsenteret i kapitel 5 og summeret nedenfor.

Forslag til informationskrav for nanomaterialer

Som udgangspunkt er det vigtigt at vurdere om og i givet fald afklare hvorledes regulatoriske informationskrav skal indarbejdes i lovgivningsmæssig og juridisk sammenhæng, bl.a.: i) på hvilken måde og af hvem skal informationen genereres og formidles videre; ii) skal der f.eks. som i REACH være registreringskrav, og hvis ja, iii) skal der så være et tilsvarende stof-informations-udvekslingsforum (et såkaldt "SIEF")?

Hvis der kræves registrering må det endvidere klarlægges, hvorvidt der kræves separate registreringer for de forskellige nanoformer, eller om alle nanoformer for et givent nanomateriale kan indeholdes i en samlet registrering. Før kravene kan implementeres, vil det derfor være nødvendigt at opnå konsensus og udarbejde retningslinjer og vejledning på disse områder. Ikke mindst vurderes det som afgørende, at *alle* nanoformer af et nanomateriale er udførligt beskrevet og karakteriseret. Mange kilder anfører således, at forskellige produktionsmetoder kan have stor indflydelse på og påvirke karakteriseringen og egenskaberne af nanoformen/nanomaterialet.

I forbindelse med opstilling af testkrav for nanomaterialer er der en række grundlæggende *tekniske og videnskabelige* forhold af mere generel og tværgående karakter, som bør klargøres, enten i selve lovgivningen og/eller i vejledninger.

- Al tilgængelig information for nanomaterialet skal fremskaffes og rapporteres, dvs. også information der går ud over informationskravene for den pågældende tonnagegrænse. Dette er ikke mindst med henblik på at opnå information om de særlige karakteristika, der er af betydning for nanomaterialets egenskaber.
- Generelle regler for tilpasning at testkravene bør gælde på tilsvarende vis som i REACH Annex XI, men med en række tilføjelser (se detaljer i kapitel 5):
  - den relevante testning skal tage hensyn til eksponeringsmæssige forhold for og forskellige egenskaber af de forskellige nanoformer. Forskellig anvendelse af de varierende nanoformer kan betyde, at forskellige eksponeringsscenarier er relevante og read-accross af data fra en nanoform til en anden skal være videnskabeligt baseret. Det må derfor understreges at tilgangen bør være afhængig af de forskellige nanoformer.
  - afhængigt af den videnskabelige relevans kan der anvendes “skalering” mht. til den toksikologiske potens, dvs. at farligheden i visse tilfælde kan vurderes i forhold til antal af partikler eller partiklernes samlede overfalde areal.
  - yderligere karakterisering af nanomaterialet i de forskellige faser af livscyclus kan blive nødvendig, hvis der er mulig eksponering i disse faser.

  - det bør overvejes om testning af nanomaterialet er nødvendig, hvis det klassificeres ligesom bulk/makroformen, i de tilfælde hvor de eksisterende data på bulk/makroformen viser så alvorlige sundhedsskadelige eller miljømæssige egenskaber, at det medfører den strengeste klassificering af stoffet. Testning kan dog stadig være relevant af andre grunde, f.eks. hvis der i risikovurderings-sammenhæng er behov for at fastsætte et nul-effekt niveau (DNEL/PNEC).
- Ved alle former for testning af nanomaterialer er det vigtigt at påpege den særlige håndtering af testdosis af nanomaterialer og anvendelse af det mest relevante dosismål. Dette anses pt. for at være en af de store udfordringer inden for testning af nanomaterialer.
- Ved afrapportering af test- og måle data mht. farlighed og eksponering er det essentielt at angive alle relevante dosismål ("metric(s)").

Det foreslåede **trinvise program for konkrete informationskrav** består af fire tonnageniveauer (mængdeniveauer) (Trin 1-4, se tabellerne i kapitel 5). Disse niveauer kunne være identiske med tonnageniveauerne anvendt i REACH eller de kan evt. nedsættes, som det foreslås af en række af de anvendte kilder, f.eks. med en faktor 10, som følge af nanomaterialers generelt højere toksikologiske potens (når potens vurderes på vægtbasis). Hvis der ønskes informationskrav ved meget lave tonnageniveauer (f.eks. ned til 10 kg/år – hvilket i denne rapport angives som "trin 0"), foreslås det, at informationskravene begrænses til parametre, der alene identificerer og karakteriserer nanomaterialet.

Sammenlignet med de informationskrav der er for almindelige kemikalier (f.eks. i REACH) forslås følgende "nye" informationskrav for nanomaterialer:

- Et specifikt udtrykt krav om information vedr. den krystallinske struktur*
- Størrelsesfordelingen af primærpartiklerne**
- Agglomerering/aggregering af partiklerne**
- Specifikt overfladeareal**
- Morfologi/form/længde-breddeforhold for nano-partiklerne/-fibrene**
- Information mht. overflademodificering
- Katalytiske egenskaber, foto-katalytiske egenskaber, potentiale for radikaldannelse (bør defineres yderligere)
- Overfladeladning/zeta-potentiale
- Støvindeks
- Egenskaber for skæbnen af nanomaterialer i vand (i tillæg til vandopløselighed, se detaljer i kapitel 4)
- Fotokemisk nedbrydning

* Er kun implicit omfattet af krav i REACH

**Der er ikke generel enighed om, hvorvidt disse informationskrav allerede er omfattet af REACH informationskravene vedrørende "granulometri", hvorfor kravene foreslås specifikt anført.

Det fremgår, at de fleste supplerende krav vedrørende nanomaterialer er relateret til identifikation / karakterisering af nanomaterialet, samt konkrete fysisk-kemiske parametre. Der foreslås ikke helt nye og anderledes informationskrav vedrørende miljø og toksikologiske egenskaber, men justeringer af adskillige af de eksisterende informationskrav. Dette omfatter tilpasning/ modificering af informationskravene og reglerne for, hvornår informationskravet kan fraviges eller bør fremskyndes, herunder (se yderligere detaljer i kapitel 4 og 5):

- Yderligere information/vejledning vedrørende toksikokinetik/ ADME egenskaber
- For akut toksicitet og toksicitet ved gentagen eksponering bør inhalationstest være førstevalg ved valg af eksponeringsvej
- Ved inhalationstest bør undersøgelsessprogrammet for dyrene udvides
- Ved *in vitro* mutagentest bør der fokuseres på anvendelsen af pattedyrsceller
- For skæbne i miljøet kræves data for adsorption-desorption, data fra simulerings-nedbrydningstest, og for bioakkumulering ved relativt lavere informationstrin end i REACH

- For økotoksikologiske informationskrav generelt kræves data fra akutforsøg og fra langtidsforsøg ved relativt lavere informationstrin end i REACH. Derudover foreslås det at fokusere mere på sediment-toksicitet.

For yderligere information og detaljer vedrørende de foreslåede tilpasningsregler i datakravforslaget henvises til kapitlerne 4 og 5.

Executive summary

Objective and scope

The overall objective of the present project is to develop a proposal for nanomaterial information requirements (substance identity, characterisation, physicochemical properties, toxicity, fate & behaviour and ecotoxicity) that at a later stage may be incorporated into legislation for information requirements and strategies for nanomaterials. The proposal is developed based on a review of existing scientific projects/reports prepared by various expert groups, associations and authorities.

The REACH approach/methodology for information requirements (REACH Annex VI-XI) is used as the backbone for the analysis of the various proposed information requirements. It was outside the scope of the project to develop detailed guidance text on specific tests.

Although the REACH methodology is used, the project should not be taken as an isolated proposal for updating REACH. It is rather a suggestion for a scheme which could also be implemented as stand-alone legislation for nanomaterials, via sector-specific or national legislation. It is outside the scope of the project to assess or propose which specific legislative instrument to be used for possible implementation.

Expert advisory group

An expert advisory group was established by the Danish EPA for consultation during the project (see also preface). This group met three times for in-depth discussions and also provided written comments four times during the project.

Methodology and results of review

In the first phase of the project, 26 relevant existing projects/reports addressing information requirements for nanomaterials were identified by the authors with input from the Danish EPA and the expert advisory group supporting the project. These references are listed in Appendix 1.

Each information source/reference was initially reviewed and summarised (Appendix 2) and 'key references' considered most relevant for the current project were identified. These references were then reviewed in more detail and it was assessed to which extent various possible/potential information requirements were addressed by each of the references. The extent to which the references discussed test methodologies and issues related to whether a given information requirement could possibly by triggered or waived under given circumstances (commonly termed "adaptations") was also assessed. An overview of the results of this review is presented in matrices in Appendix 3. This overview also indicates which extra information requirements/parameters - in addition to those already required in REACH - were identified for nanomaterials in the references.

As a next step, each possible/potential information requirement was analysed based on whether/how it was addressed across all references. Parameters for possible inclusion in a regulatory information requirement scheme for nanomaterials were identified based on the current availability of test methods, the scientific motivation and the degree of consensus among the references. Furthermore, the experience and the suggestions from the advisory group were included. Based on this, an evaluation score was determined in relation to whether an information requirement should be currently considered i) relevant for inclusion in a regulatory information requirement scheme, ii) a possible future information requirement (possible inclusion after further

R&D), or iii) considered irrelevant. This score is given in the right column in the matrices in Appendix 3 and the motivation is summarised in Chapter 4.

Chapter 4 further summarises a number of other important issues identified during the review; issues which are not endpoint specific, but of a more general and cross-cutting nature.

Based on these review activities, a proposal for a regulatory information requirement scheme for nanomaterials was developed as the main output of the project. This proposal consists of a number of important general issues to consider when introducing information requirements for nanomaterials in legislation, as well as a proposal for a tonnage-driven stepwise information requirement scheme. The proposed scheme can be found in Chapter 5 and is summarised below.

Proposed regulatory information requirement scheme for nanomaterials
As a prerequisite it would be important to consider how the requirements in a regulatory testing scheme should be accompanied by *legal* instructions in relation to the following: i) how and by whom this information should be generated and exchanged; ii) whether there should be a registration requirement as in REACH, and if so, iii) whether a Substance Information Exchange Fora – SIEFs is appropriate.

If a registration is required, this may particularly address whether separate registrations for different nanoforms are needed or whether all nanoforms of a given common chemistry may be registered as one nanomaterial, where the differences between the forms are addressed within the same registration dossier. Further consensus building and development of guidance on these issues would be required in connection with the implementation. In relation to this, the most important conclusion is that all nanoform(s) of a nanomaterial are explicitly described and characterised. As pointed out by several reviews and reports, different manufacturing processes might substantially influence the characteristics of a nanoform/nanomaterial.

Further, a number of *technical and scientific* issues of a more general and cross-cutting nature should be addressed in relation to a regulatory testing requirements scheme for nanomaterials (possibly in the legislation itself, but certainly in guidance):

- All available information on the nanomaterial should be obtained and reported, i.e. not only the standard information required at a given tonnage level. This should in particular indicate the need for providing information on characterisers known to influence the properties of the nanomaterial.
- General rules for adaptation of the standard testing requirements in line with REACH Annex XI, but with additions/emphasis relating to (details in Chapter 5):
  - Use of exposure-driven testing, taking into account that different nanoforms having different properties may be used differently and result in different exposure scenarios and testing needs. Therefore it should be stressed that use of these approaches should be done on a "form-to-form" basis.
  - Use of "scaling" for toxic potency considerations, e.g. scaling according to particle number or particle surface area, when scientifically relevant.
  - Characterisation of the nanomaterial in various phases of its lifecycle can be triggered by use/exposure considerations.
  - Possible waiving of testing of the nanoform in certain cases. In relation to use of existing data, it could be considered that if macro/bulk form(s) of the nanomaterials are very toxic and thereby trigger the most severe classification, testing of the nanoform might be waived in relation to classification and labelling considerations. Testing might still be needed for establishing no-effect levels (DNELs/PNECs) and for risk/safety assessment purposes.
- The importance of sample preparation and dosimetry in relation to all types of testing of nanomaterials should be stressed. This issue is currently considered one of the main challenges related to nanomaterials.

- Choice of metric(s) for reporting hazard (and exposure) data.

The **specific proposal for a stepwise information requirement scheme** consists of four tonnage levels (Level 1-4, see tables in Chapter 5), which could correspond to the REACH tonnage trigger levels or be lowered as suggested by a number of reviewed references (e.g. with a factor 10, due to the generally higher toxic potency of nanomaterials - in relation to weight as a metric - as compared to bulk/macro materials). This issue is, however, left open in the proposed scheme, as choice of a tonnage trigger level is a policy issue. On the other hand, if information is required at a very low tonnage level (e.g. down to 10 kg/year - in this report considered "Level 0"), an information requirements base set consisting solely of parameters for identification and characterisation of nanomaterials is suggested.

Compared to information normally required for chemicals, the following 'new' information requirements are suggested:

- Explicit requirement for information on Crystal structure*
- Primary particle size distribution**
- Agglomeration/aggregation**
- Specific surface area**
- Morphology/shape/aspect ratio**
- Information on surface modifications
- Catalytic properties, photo-catalytic properties, radical formation potential (to be further defined)
- Surface charge/zeta potential
- Dustiness
- Properties for the fate of nanomaterials in water (in addition to water solubility, see details in Chapter 4)
- Photo degradation.

* Considered implicitly required by REACH

** There appears to be lack of consensus about whether these information requirements are already covered by the REACH information requirement on 'granulometry' and it is therefore suggested to explicitly require these.

It can be seen that most of the 'nano-additional' information requirements suggested relate to the description/characterisation of nanomaterials and a few to other physicochemical properties, whereas no entirely new information requirements are suggested for environmental and human health properties.

On the other hand, for a number of existing information requirements, it is suggested to adapt the endpoints and/or to modify the adaptation rules, including (see further details in Chapters 4 and 5):

- Further information/guidance on toxicokinetics/ADME properties
- For acute and repeated toxicity: To consider the inhalation route as the first route of choice
- For inhalation toxicity: To consider extended examinations (Chapter 5)
- For *in vitro* mutagenicity: To focus on mammalian (non-bacterial) cells
- Environmental fate: To request data on adsorption-desorption, simulation testing for degradation, and on bioaccumulation at a relatively lower trigger level as compared to REACH
- For ecotoxicity testing: In general to request acute and long term testing at relatively lower trigger levels as compared to REACH and to focus more on testing of benthic/sediment species.

For information and further details on suggested adaptation rules for the information requirements included in the proposed testing scheme, see Chapters 4 and 5.

1. Introduction

1.1 Background

The European Commission concluded at an early stage that nanomaterials are covered by EU legislation in general[1] and that the provisions of the general EU chemicals legislation (REACH) also apply to nanomaterials[2]. However, nanomaterials are not usually explicitly mentioned or defined in the EU legislation, with a few exceptions (e.g. for cosmetics, biocides and some legislation related to food).

The REACH Implementation Projects on Nanomaterials (RIP-oNs)[3] developed proposals for how the current REACH guidance could be updated to address nanomaterial properties, and the European Chemicals Agency (ECHA) has translated most of these proposals into the guidance on Information Requirements and Chemical Safety Assessment[4].

As a follow-up to those activities, the NANO SUPPORT project was launched in which the European Commission Joint Research Centre (JRC) in cooperation with the European Chemicals Agency (ECHA) analysed and assessed how nanomaterials have been registered under REACH by the first REACH registration deadline (November 2010). Based on this analysis and assessment and the RIP-oNs, a number of options for how the REACH regulation could be adapted to specifically address the properties of nanomaterials have been proposed[5].

Various other organisations, associations, EU Member States and NGOs have suggested proposals of varying levels of detail on how the REACH regulation could be updated to address the properties of nanomaterials. This aspect will be further elaborated on in Task 1 of this project.

In October 2011, the European Commission adopted a recommendation for a definition of 'nanomaterial' to be used as a basis, when nanomaterials are addressed in individual pieces of EU legislation[6].

One of the key challenges in relation to adapting (chemicals) legislation to address the properties of nanomaterials is that they cover a very diverse group of materials in relation to e.g. chemical composition, particle size (distributions), shapes and surface modifications/treatments. This diversity triggers various physicochemical and (eco)toxicological properties. Furthermore, there are still significant knowledge gaps in relation to identifying the properties of nanomaterials. This situation is partly due to existing test guidelines in which the methodology is not necessarily suitable for the purpose of testing nanomaterials, although the guidelines according to the OECD (2009) review are generally considered to address relevant end-points for nanomaterials as well.

1.2 Objective and scope

The overall objective of the present project is to develop a proposal for nanomaterial information requirements (substance identity, characterisation, physicochemical properties, toxicity, fate and behaviour and ecotoxicity) that, at a later stage, may be incorporated into guidance or legislation for information requirements and strategies for nanomaterials. The proposal should include

[1] European Commission. REGULATORY ASPECTS OF NANOMATERIALS. COM(2008) 366 final, Brussels, 17.6.2008
[2] European Commission/CARACAL. Follow-up to the 6th Meeting of the REACH Competent Authorities for the implementation of Regulation (EC) 1907/2006 (REACH). Doc. CA/59/2008 rev. 1, Brussels, 16 December 2008
[3] http://ec.europa.eu/environment/chemicals/nanotech/index.htm#ripon
[4] See: http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[5] http://ec.europa.eu/environment/chemicals/nanotech/index.htm#support
[6] European Commission. COMMISSION RECOMMENDATION of 18 October 2011 on the definition of nanomaterial. OJ L 275/38.

considerations for information thresholds and triggering/waiving. The proposal should be developed based on existing scientific projects/reports addressing the issue of nanomaterial testing requirements in REACH and other legislation.

The REACH approach/methodology for information requirements (REACH Annex VI-XI) is used as the backbone for the analysis of the various proposed information requirement schemes addressed in this project. Despite the use of the REACH approach, the outcome of the project is a general information requirement/ testing scheme for nanomaterials providing more overall considerations regarding testing. It is outside the scope of the project to deliver actual guidance text on specific tests.

Furthermore, although the focus is on the REACH approach/methodology, the project should not be taken as an isolated proposal for updating REACH. It is rather a suggestion for a scheme, which could possibly be implemented as stand-alone guidance or legislation for nanomaterials, in REACH and/or in relation to nanomaterials addressed via sector-specific or national legislation. It is outside the scope of the project to assess or propose what route(s) of legislation would be most relevant. An impact assessment or other considerations might suggest that the proposed information requirements are only partially introduced or introduced in a gradual manner.

1.3 Short Readers' Guide

Chapter 2 of this report outlines the methodology applied in the project. Chapter 3 presents the collected available core documents and reports that form the basis for the project and gives short summaries from the initial review of these documents, regarding relevant types of information for use in this project. Based on this review, Chapter 4 identifies and discusses the information requirements for nanomaterials of potential regulatory relevance, and Chapter 5 puts forth a proposal for a systematic regulatory information requirement scheme for nanomaterials. Conclusions are provided in Chapter 6.

1.4 Terminology

For clarity some of the key terms used in this report are defined:

Nanomaterial

In this report, the term 'nanomaterial' will generally be understood as described under the recommended EU definition and further limited to manufactured nanomaterials[7]. Therefore, the nanomaterials covered in this project would normally fall under the scope of chemicals legislation.

Nanoform

A nanomaterial understood as e.g. nanosilver or nanotitaniumdioxide exists in different nanoforms with different characteristics such as particle size, surface area, crystalline structure, shape and surface modifications.

Surface modification

Nanomaterials may be modified on the surface via coating, surface treatment, functionalisation etc. Surface modification is used as a general term to cover all these different types of modifications. It is acknowledged that there is a difference between loosely bound coating (Van der Waal forces) and molecules more tightly bound (covalent bonding) to the surface, and that this difference may trigger different regulation, e.g. if nanomaterials with loosely bound coating are considered a mixture (i.e. two or more substances) rather than one substance. This detail, although important, is outside the scope of this project.

[7] 'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate 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 nm-100 nm. European Commission. COMMISSION RECOMMENDATION of 18 October 2011 on the definition of nanomaterial. OJ L 275/38.

Information requirement, test method, endpoint and parameter

An information requirement is generally understood as the entry in a legal text requiring information on e.g. physicochemical, toxicological and ecotoxicological properties.

Different test methods or other types of information (e.g. already available data, grouping/read-across or (Q)SAR data) may be used to generate information in response to the information requirement.

An endpoint or parameter defines more precisely what the outcome investigated during the testing is, e.g. mortality or behavioural changes in (eco-)toxicity studies. Thus, toxicological testing often looks at several endpoints/parameters within a given test.

For physicochemical testing, an information requirement may typically be the endpoint/parameter, e.g. the boiling point. Nonetheless, different (test) methods may be used to generate information on a given physicochemical property.

2. Methodology

The project has been undertaken as three tasks:

- Task 1: Collection and review of core relevant documents/reports
- Task 2: Assessment and identification of relevant information requirements for regulation of nanomaterials
- Task 3: Proposal/concept for information/testing requirements.

Overall, Tasks 2 and 3 were conducted in an iterative process. This way, consistency was ensured to the extent possible among the chapters of the report.

2.1 Task 1, collection and review of core documents and reports

2.1.1 Identification of references included in the project

A list of 26 references relevant in the context of this project has been elaborated (see Appendix 1). An initial list was compiled based on references outlined in the tender specifications, further input from the Danish EPA and references identified by the contractor. This list was circulated to the advisory group for consultation and proposals for additional references.

The main criteria for inclusion in the project were proposals based on thorough evaluations preferably agreed upon at an expert level and/or via stakeholder consultations with wide participation. In addition, some non-confidential documents circulated among the authorities and made available by the Danish EPA have been included as background information.

2.1.2 Review methodology

Each of the references has been reviewed and short summaries were prepared based on this initial review, focusing on the issues relevant for this project (see Appendix 2) and *not* on all parts and issues described in the reference. Based on this initial review, 14 'key references' for the purpose of identifying relevant information requirements for nanomaterials have been identified. The remaining 12 references (indicated as 'further references') may still be considered as relevant in the context of the project as they contain important background knowledge.

Emphasis was placed on identifying references dealing with technical and scientific issues concerning (i) identification/characterization and physicochemical properties, (ii) toxicological properties, and (iii) environmental fate and behaviour, and ecotoxicological properties. The reviews focused on identifying relevant information requirements, end-points and parameters that could be potentially relevant for inclusion in a data requirement scheme for nanomaterials.

In order to structure the work, three matrices have been generated - one for parameters in relation to identification/characterisation and physicochemical properties, one for information requirements for toxicological properties and one for information requirements for environmental fate and behaviour, and ecotoxicological properties (Appendix 3).

As a starting point the information requirements for chemicals as given in REACH Annexes VI-X are included in the matrices. Further relevant information requirements/end-points/parameters mentioned in the reviewed references have been added. In order to screen all the references for all the information requirements and to indicate to which extent they cover a specific information requirement, a scoring system was developed (see the further description of this scoring/screening system in Chapter 3). From the filled out matrices using the scoring system it can be seen which of the references cover a given information requirement relevant for nanomaterials, and also to which

extent this was more thoroughly discussed. Furthermore, the scoring system indicates whether the reference covers further details in relation to testing considerations and/or adaptation (triggering/waiving) issues. This initial scoring is not necessarily to be interpreted as a suggestion by the reference to include the information requirement in a testing scheme, as the scopes of the references are quite different. It could in fact be the opposite (e.g. that further R&D is needed) and some references do not directly suggest testing schemes for nanomaterials. The initial scoring is therefore more directed at providing an overview of what is discussed and where.

It should also be noted that an empty field in the matrix does not necessarily mean that a given reference did not find the specific information requirement relevant for nanomaterials, as it could have been considered implicitly relevant.

The matrices and their initial scorings for each information requirement have been used in Task 2 as a basis for further evaluation as to whether there is a priority for including the particular information requirement in an information requirement scheme for nanomaterials.

2.2 Task 2, Assessment and identification of regulatory relevant information requirements for nanomaterials

Task 2 aimed at identifying which information requirements/endpoints/parameters would be relevant for an information requirement scheme for nanomaterials to be developed in Task 3. This has been done based on a horizontal view of the completed matrices, which were filled in vertically (reference by reference) in Task 1. Based on a more detailed assessment of the arguments in the references, each information requirement has been given an evaluation score to indicate the relevance for i) all nanomaterials, ii) for some types/classes of nanomaterials, or iii) potentially relevant for nanomaterials in the future (e.g. if further R&D or test development is deemed necessary) and/or not relevant (see further description of this scoring/evaluation system in Chapter 4). In arriving at this conclusion, it has been taken into account what level of priority the information requirement has been given considering all key references and whether there seems to be a consensus among the references. In addition, expert input from the advisory group has been taken into account.

For the various information requirements it has been part of the assessment to evaluate to which extent methods for detection/testing of the parameters or end-points are available and applicable for nanomaterials, although detailed discussion of individual methods is outside the scope of the present project. It has also been assessed whether the references suggest any general or *nanospecific* adaptations for a given information requirement.

As some issues are of a more general nature and do not need to be repeated for each of the end-points, relevant cross-cutting issues in relation to information requirements for nanomaterials will be discussed separately, including sample preparation/dosimetry, sameness/read-across, registration triggers, etc.

2.3 Task 3, Proposal/concept for information/testing requirements

A pragmatic and structured data requirement approach was developed based on Tasks 1 and 2. A tiered and step-wise data requirement approach comparable to Annex VI – XI in REACH was followed, although as mentioned in the introduction, it is outside the scope of this project to provide advice on which type of regulation or regulatory context the data requirement approach should be applied.

Options for information triggers for nanomaterials/nanoforms have been discussed closely with the Danish EPA and the advisory group. Some indications are given, but final decisions concerning specific trigger levels are outside the scope of this project, as it is acknowledged that choice of triggering levels is a rather political decision. Within each of the levels, more specific triggers and waivers as well as the possibilities for read-across to data from the bulk chemical have been considered at a description level comparable to REACH Annex VII-X column 2 and REACH Annex XI. This was largely based on proposals identified in the reviewed references in Task 1 and adaptation arguments are described in Chapter 4.

3. Collection and review of core relevant documents/reports

The references identified to be of relevance for this project are provided in Appendix 1. The short summaries of the references are given in Appendix 2. The identified k*ey references* were then further screened for relevant information requirements for:

- Substance identification/characterization and physicochemical properties
- Toxicological properties
- Environmental fate and behaviour, and ecotoxicological properties

A score was allocated to each reference reflecting how and to what degree an information requirement was addressed in the reference. The results of this screening are presented in three matrices provided in Appendix 3.

As a starting point for the selection of information requirements/end-points/parameters in each of the matrices, the information requirements for chemicals in REACH Annexes VI-X were included.

In addition to this, further potentially relevant information requirements/end-points/parameters mentioned in the references in relation to nanomaterials are included in italics in the matrices in Appendix 3.

The detailed outcome of Task 1 is therefore presented in Appendices 1-3. These results served as a basis for an overall evaluation of the information requirements performed in Task 2.

3.1 Details of the scoring/screening system

To indicate in the matrix boxes whether a reference covered a specific information requirement/endpoint/parameter and the degree to which it was covered, a scoring or screening system was developed. The following scores were used:

+ covered/mentioned as 'relevant' or 'possibly/potentially relevant' for nanomaterials

++ more elaborate discussion of relevance for nanomaterials

with addition of the following notations if applicable:

A with additional discussions in relation to adaptation (triggering/waiving) of the information requirement

T with discussions in relation to testing issues e.g. further need for test method development/validation/guidance.

The scoring system has been developed as a practical screening tool in this specific project to provide an overview of the importance of the information requirement/end-point/parameter and also to indicate the level of detail of the description in the references. Due to practical reasons the scoring criteria are rather qualitative and broad; therefore, the scoring is likely to have been done in a somewhat subjective manner. Very strict scoring criteria were found to be difficult to use as the

references did not have identical scopes and therefore covered the description of relevant information in different manners.

4. Assessment and identification of relevant regulatory information requirements for nanomaterials

Some issues concerning evaluation and testing of nanomaterials are of a general nature. Rather than repeating these as relevant for each information requirement/end-point/parameter, these general issues are first described (Section 4.1). Thereafter, the details of the scoring systems used for evaluating the identified, potentially relevant, information requirements are outlined (Section 4.2). The subsequent sections then discuss the individual information requirements.

4.1 General issues relevant for information requirements and testing of nanomaterials

4.1.1 Use of existing tests methods

From the OECD (2009) review of the OECD test guidelines for their applicability to nanomaterials it was generally concluded that the majority of the end-points and the test guidelines regarding physicochemical, environmental fate, ecotoxicological and toxicological properties were relevant to nanomaterials, although methodological challenges in relation to the performance of the tests still have to be clarified. Especially for Test Guidelines examining environmental fate and ecotoxicity, further developments are needed regarding sample preparation and the availability of the nanomaterials to the test system and on detection and analysis of nanomaterials in the test system. Important for the use of the test guidelines are the guidance notes on sample preparation and dosimetry for nanomaterials (OECD, 2010[8]). For some of the existing toxicological guidelines, especially for inhalational testing, further inclusion of examinations for various relevant parameters is proposed.

4.1.2 Sample preparation, dosimetry and dose metric(s)

All references cover this as an important and overarching issue relevant for physicochemical, toxicological and ecotoxicological testing. The most important document that to a great extent is referenced by the other documents is the OECD (2010) document on sample preparation and dosimetry. With respect to the appropriate dose metric it is recommended that each dose level should be expressed as a dose in relation to surface area or particle number besides the traditional mass-based dose metric, as particle number and specific surface area may play important roles in determining and describing the toxicity and/or ecotoxicity, including the dose-response relationship of the nanomaterial. This is also noted by e.g. RIP-oN2 (2011) and NANO SUPPORT (2012). It should be realized that if e.g. surface area is driving the toxicity for a given material,

[8] It should be noted that these guidance notes were updated after termination of the evaluations performed in this document

expressing the dose-response in that metric might enable read-across between different particle sizes.

OECD (2010) further describes key aspects that may impact the behaviour/stability of the nanomaterial in the test sample and when introduced into the test system. OECD (2010) gives practical advice on how to prepare, handle and characterize the nanomaterial, when preparing the test sample and during the conducting of the test. Issues regarding the stability of the test sample with respect to dispersion and agglomeration of the nanomaterial are highlighted, e.g. it may be difficult to maintain comparable size distributions at the various dose levels, as agglomeration and dispersion of the nanomaterial are dependent on the concentration. Furthermore, different methods for delivering the test sample to the test systems are described, as well as challenges in relation to maintaining and documenting homogeneous exposure. Various interactions may be considered and thus potential interactions with the test media, possibilities for adsorption, agglomeration/ aggregation and degradation and transformation are key concerns in all testing, especially for *in vitro* and ecotoxicological testing. For the interpretation of the test data and documented exposure, it is important to follow, characterise and measure the nanomaterial during all phases of the test. For example, for inhalation testing a recommendation is given on how to monitor and characterize the nanomaterial exposure in the test atmosphere during the exposure period. It should be noted that OECD has recently updated their guidance recommendations in relation to sample preparation and dosimetry. In addition, certain projects such as the EU 7th Framework Programme (FP7) NANOREG project aim towards refinement and establishment of new procedures for nanomaterial characterisation for REACH registrations.

The importance of sample preparation and dosimetry are also stressed by e.g. RIP-oN2 (2011), which developed some proposed guidance text since adopted as guidance by ECHA. As well, NANO SUPPORT (2012) elaborates on the importance of sample preparation and dosimetry and stresses the need to know how a nanomaterial is administered to a test system in order to interpret the test results in relation to a specific nanoform/nanomaterial.

4.1.3 Characterisation throughout the life cycle

Characterisation of nanomaterials is generally considered a key issue in relation to assessing the properties of a given nanoform/nanomaterial. This is clearly expressed e.g. in the increasing demands from peer-reviewed scientific journals in relation to accepting manuscripts with experimental results.

Several references (e.g. Environmental Defense - DuPont, 2007; VCI, 2008; EFSA, 2011; NANO SUPPORT, 2012) point out that the characterisation (and thereby properties) of a nanomaterial may change throughout the lifecycle of a nanomaterial. Characterisation may differ between the nanomaterials as produced, as delivered, as used, as tested, as they are present in various environmental matrices, in the human body etc. Environmental Defense - DuPont (2007) suggests that a material may have to be characterised at multiple points, whereas e.g. VCI (2008) more generally points out that all 'uses' must be addressed.

Input/view from the Advisory Group. Specifically in relation to characterisation throughout the lifecycle there is consensus that characterisation of the pristine/as manufactured/as imported nanomaterials should formally be required. Possible need for further characterisation could be triggered based on exposure considerations throughout the uses in the nanomaterial lifecycle.

4.1.4 Sameness, read-across, grouping, QSAR

For 'conventional chemicals' it is often a question whether data from one chemical substance can be used to fulfil information requirements for another chemical substance.

For nanomaterials, properties may differ not only because of differences in chemistry, but also due to differences in size (distribution), surface area, shape, surface modification, agglomeration state, etc. These differences are often specifically intended in order to obtain the preferred nano-specific properties of a given material. A key challenge here is to evaluate to which extent specific parameters may differ (e.g. from batch to batch) without significantly affecting the properties of the

nanomaterial and, therefore, still be considered as the same substance/material. As pointed out above (Section 4.1.3), a given nanomaterial may change characterisation (and thereby properties) throughout its lifecycle.

A key question related to information requirements for nanomaterials is therefore to discern whether information requirements have to be fulfilled via testing, or whether possible alternative approaches such as read-across, grouping and QSAR models could be used. This question currently presents one of the most delicate dilemmas in relation to regulatory information requirements for nanomaterials. On the one hand there is a general consensus regarding the current lack of scientific basis for grouping/read-across or use of QSAR (and similar empirical) models, as these are not yet established/validated for nanomaterials (e.g. RIVM, 2009; RIP-oN2, 2011). On the other hand, it is also widely accepted that it is not possible to test all forms and lifecycle characterisation states of nanomaterials.

It could be suggested to test the 'worst case' form of a nanomaterial; however, one does not necessarily know which is the worst case form and secondly, this could ultimately lead to unnecessarily strict risk management for some forms. Assuming that the nanoform of a chemical is as at least as toxic as the bulk form could justify refraining from testing the nanoform if the bulk form is already classified in the worst-case category of a toxicological end-point. Testing might however be needed if a no-effect level is required for conducting a risk/safety assessment of the nanomaterial.

Overall, there is a need for further R&D and consensus building on this very important topic as also suggested by e.g. NANO SUPPORT (2012). This further development should consider whether and when read-across within certain groups/types of nanomaterials could be performed, e.g. when the toxicity of a released leading ion(s) would overrule particle properties and thus could be used for read-across.

One of the key conclusions from NANO SUPPORT (2012) is that a prerequisite for addressing different forms, including different nanoforms in a regulatory dossier, is that the forms addressed by the dossier are explicitly described upfront as part of the substance identification (which may possibly lead to different dossiers for different nanoforms) or as part of a characterisation within a given dossier. In addition to providing clarity about nanoforms within the scope of the dossier, it is also the basis for discussing which test data could or should be used in relation to those forms.

4.1.5 Adaptation (waiving/triggering)

Currently, as discussed in the previous section, there does not seem to be consensus for wide use of read-across and grouping.

Guidance proposed in RIP-oN2 (2011) and implemented by ECHA in recent guidance updates stresses that read-across, e.g. from bulk to nano and/or between nanomaterials, should only be done if scientifically justified. This may lead to either triggering or waiving depending whether the read-across leads to additional concern or whether the read-across justifies waiving a test. NANO SUPPORT (2012) suggests that REACH Annex XI (with general rules for adaptation), currently referring to possible application from one substance to another substance, should be revised to mention 'form to form' extrapolation when relevant.

Adaptation for individual information requirements is discussed in the below endpoint specific sections.

4.1.6 Registration triggers and timeline for registration

The lower REACH registration level of 1 tonne/year has been challenged by several references including proposals for a base set for all nanomaterials (RIVM, 2009; SRU, 2011) or for lowering the threshold to 10 kg/year (CIEL, 2012; SKEP, 2011). Recent policy papers outside the public domain, but made available to the authors of this report, also question the lower level, some without specifying what the alternative should be (European Parliament, 2012; NL, 2012) and one paper suggests 100 kg/year (German CA, 2012).

The staggered REACH registration deadlines for pre-registered phase-in substances are also challenged by some references, ranging from 'shortening' (NL, 2012) to proposals for 'no staggered deadlines' (RIVM, 2009) or to consider nanomaterials as non-phase-in substances (SKEP, 2011; CIEL, 2012), which would in practice also mean no staggered deadline.

4.2 Details of the scoring system used to evaluate the information requirements possibly relevant for nanomaterials

Each of the possible information requirements/end-points/parameters in the three matrices has been evaluated in the last column of the matrices in Appendix 3 according to the following second scoring system:

I agreement / high priority for information requirement

II potential future information requirement need

III low priority for information requirement

with the addition of the following notations if relevant:

α relevant for all nanomaterials

β relevant for some nanomaterials

Scoring “I” is applied when the information requirements is assessed to be relevant and possible for inclusion in a data requirement scheme at present, and scoring “II” should be considered at a later stage, following further R&D, test method development and/or consensus building.

The various information requirements/end-points/parameters are described and discussed below. The paragraphs should be seen as an attempt to summarise what has been found in the references as well as the arguments for the proposed evaluation. The descriptions are based on the information provided by the references.

The availability of methods for determination/testing of the end-points and their applicability for nanomaterials will be mentioned in order to get an impression of the relevance and practicability of the end-point/parameter in an information requirement scheme. Within the scope of this project, the focus will be on a general description with regard to the extent current methods and test guidelines are considered to be applicable for nanomaterials. Further details on availability and applicability of concrete test methods can e.g. be found in OECD (2009), RIP-oN2 (2011), SCCS (2012) and EFSA (2011). As can be seen below and in the key references, a suite of methods would be needed for some information requirements given the inherent differences between nanoforms/nanomaterials. This in particular relates to the information requirements discussed in Section 4.3.

Finally, issues relating to possible adaptation rules (triggering/waiving) are summarised.

4.3 Substance identification, characterisation, physicochemical properties

This section examines and reviews an extensive range of parameters covering:

- Substance identification and characterisation
- Physical state of the substance
- Dissolution and partitioning
- Reactivity
- Powder properties
- Surface chemistry
- Other related properties.

4.3.1 Name and molecular structure

Evaluation score (Appendix 3): Ia.

Relevance as regulatory information requirement for nanomaterials

The current REACH Substance identification requirements relating to name(s) and molecular structure are considered relevant for nanomaterials by the references addressing these (Environmental Defense - DuPont, 2007; RIP-oN1, 2011; NANO SUPPORT, 2012). It is assumed that references not discussing these take it for granted that this information is available.

Test method and guidance availability

Not relevant, unless it is considered relevant to add 'nano' to the name. Under REACH, adding 'nano' to the name would trigger the need for registering nanoforms separately from the macro/bulk form(s).

Issues related to triggering level and adaptation

This is considered basic information from the lowest tonnage level.

No adaptations are considered relevant for this information requirement.

4.3.2 Chemical composition, purity, impurities/main impurities, additives

Evaluation score (Appendix 3): Ia.

Relevance as regulatory information requirement for nanomaterials

Most references stress the importance of knowing the composition/purity of the nanomaterial. This information should be seen in connection with the information on surface modifications discussed in section 4.3.18.

Input/view from the Advisory Group. It can be noted that specific nanomaterials may be synthesized by the use of chemical or particulate catalysts, they may be shape-controlled, and also growth- and/or property-enhanced by the use of specific impurities. As for substances in general, care should be taken as to whether results of (eco-)toxicological testing is a result of the nanomaterial or possible impurities.

Test method and guidance availability

Existing methodologies and guidance for generating information on these parameters are also considered relevant for nanomaterials.

Issues related to triggering level and adaptation

This is considered basic information from the lowest tonnage level.

No adaptations are considered relevant for this information requirement.

4.3.3 Spectral data/HPLC and similar

Evaluation score (Appendix 3): Ia.

Relevance as regulatory information requirement for nanomaterials

Spectral data/HPLC are provided in support of the (im)purity profile of a substances. Such data can also be used to define substances which cannot be precisely described via other means, e.g. reaction mass products and other substances of Unknown, or Variable Composition, or of Biological Origin (so-called UVCB substances). Based on RIP-oN1 (2011) and NANO SUPPORT (2012), information on these parameters are just as relevant for nanomaterials as for conventional chemicals. Such data may be particularly relevant in relation to nanomaterials with surface modifications.

Test method and guidance availability

Existing methodologies and guidance for generating information on these parameters are considered relevant also for nanomaterials.

Issues related to triggering level and adaptation

This is considered basic information from the lowest tonnage level.

No adaptations are considered relevant for this information requirement.

4.3.4 Crystal structure

Evaluation score (Appendix 3): Iβ.

Relevance as regulatory information requirement for nanomaterials

Information on crystal structure is discussed by all references as highly relevant for metal based nanomaterials, which may exist in different crystalline forms. It is also suggested that the crystal structure may be closely related to the function/reactivity of a nanomaterial.

As part of the RIP-oN1 (2011) project, it was clarified by ECHA that existing guidance on substance identification under REACH already requires information on crystal structure for metal based chemical substance in general (i.e. also for non-nanomaterials). RIP-oN1 (2011) therefore implicitly considered crystal structure covered by the current REACH requirements and did therefore not find it necessary to suggest this parameter as a possible additional identifier for nanomaterials.

Input/view from the Advisory Group. It should be considered to broaden this information requirement to e.g. "atomic structure" to be able to cover also e.g. chirality of carbon nanotubes, different structures of fullerenes and "armchair/zig-zag" configurations.

Test method and guidance availability

Existing methodologies and guidance for generating information on crystal structure are also considered relevant for nanomaterials.

New guidance would be needed if the information requirement is broadened to include "atomic structure".

Issues related to triggering level and adaptation

This is considered basic information from the lowest tonnage level.

Adaptation should reflect that that this is a relevant property for nanomaterials, which may exist in different crystalline (atomic) states.

4.3.5 State of the substance

Evaluation score (Appendix 3): Iα.

Relevance as regulatory information requirement for nanomaterials

The typical qualitative description of the state of a substance (e.g. liquid, powder, gas) is considered equally relevant for all types of nanomaterials as for all other substances, although only explicitly addressed by some references.

It should be noted that the IUCLID 5.2 software used for collating and submitting information for REACH registrations under this endpoint gives the registrant the voluntary option of indicating "nanomaterial" as a form of the substances. Surprisingly, this voluntary option had only been used by one registrant by the first registration deadline (December 2010) (NANO SUPPORT, 2012).

Test method and guidance availability

Existing methodologies and guidance for generating information on state of the substance are also considered relevant for nanomaterials.

Issues related to triggering level and adaptation

This is considered basic information from the lowest tonnage level.

No adaptations are considered relevant for this information requirement.

4.3.6 Melting/freezing point

Evaluation score (Appendix 3): Ia.

Relevance as regulatory information requirement for nanomaterials

Many references do not address melting/freezing point and it is not included in e.g. the base set information suggested by Environmental Defense - DuPont (2007) and VCI (2008). References addressing this information requirement consider it as relevant for nanomaterials as for chemicals in general.

Although it may not be needed for an evaluation of the health and safety impacts of nanomaterials, it is used for waiving certain other physicochemical properties if the melting point is >300 °C, which is the case for many nanomaterials (e.g. in REACH).

Input/view from the Advisory Group. Melting point is also an important parameter as it is often used in arguments surrounding sameness discussions.

A suggestion is therefore made that information on this parameter is provided for all nanomaterials.

Test method and guidance availability

Existing methodologies and guidance for generating information on melting/freezing point are also considered relevant for nanomaterials.

Issues related to triggering level and adaptation

This is considered basic information from the lowest tonnage level.

No adaptations are considered relevant for this information requirement.

As noted, substances with melting points >300 °C may be used for waiving information for other physicochemical information requirements in REACH.

NANO SUPPORT (2012) notes that melting point depression may occur for nanoforms as compared to bulk forms, so care should be taken with uncritical read-across from the bulk form.

4.3.7 Boiling point

Evaluation score (Appendix 3): III.

Relevance as regulatory information requirement for nanomaterials

This endpoint is only addressed by RIP-oN2 (2011) and NANO SUPPORT (2012); in these references, it is considered as relevant for nanomaterials as for other chemicals. Under REACH it can be waived if melting point is >300 °C and would therefore not be needed for the current generation of nanomaterials.

In conclusion and based on the view of the advisory group, it is therefore not currently considered relevant.

Test method and guidance availability

Not applicable.

Issues related to triggering level and adaptation

Not applicable.

4.3.8 (Relative) density and particle concentration

Evaluation score (Appendix 3): Density: Iα. Particle concentration: II.

Relevance as regulatory information requirement for nanomaterials

Density (g/cm^3) is generally considered as relevant for nanomaterials as for any other chemical by most of the references. Based on experience from REACH registrations of nanomaterials, NANO SUPPORT (2012) points out that it is not always clear whether REACH registrants had provided the specific density (i.e. the density of a solid 'block' of the material) or the pour (powder) density. EFSA (2011) points out that pour density is needed in addition to the specific density for granular materials. It is suggested to include specific density and pour density as information requirements for nanomaterials.

EFSA (2011) and SCCS (2012) also suggest that information on particle and mass concentrations (number particles/cm^3 and number particles/g, respectively) should be provided. Currently there does not seem to be consensus that such parameters are needed and they are therefore categorised as potential future information requirements. These latter parameters should also be seen in light of what other characterisation parameters would be provided, possibly enabling recalculations from one to the other.

Test method and guidance availability

Existing methodologies and guidance for generating information on specific and pour density are also considered relevant for nanomaterials. Validation of specific density measurements are planned in connection with the EU FP7 NANoREG project starting in 2013. Standard operating procedures are planned to be proposed for regulatory use.

Issues related to triggering level and adaptation

Information on density is considered basic information from the first general tonnage level.

No adaptations are considered relevant for this information requirement.

4.3.9 Vapour pressure

Evaluation score (Appendix 3): Iβ.

Relevance as regulatory information requirement for nanomaterials

RIP-oN2 (2011) and NANO SUPPORT (2012) note that vapour pressure is as relevant for nanomaterials as for other chemicals, although the latter notes that as for boiling point, vapour pressure would be waived for most nanomaterials expected to have a boiling point >300 °C under REACH. The final evaluation as Iβ has taken into account the view expressed by the advisory group that vapour pressure may be relevant for some surface modified nanomaterials.

Test method and guidance availability

Existing methodologies for generating information on vapour pressure are also considered relevant for nanomaterials. Guidance may need to be adapted to highlight which surface modified nanomaterials require vapour pressure to be provided.

Issues related to triggering level and adaptation

This is considered basic information from the first general tonnage level.

The same type of adaptation as used in REACH Annex VII column 2 is suggested with a nano-specific modification relating to surface modification.

4.3.10 Surface tension and similar

Evaluation score (Appendix 3): II.

Relevance as regulatory information requirement for nanomaterials

Surface tension is addressed by RIP-oN2 (2011) and NANO SUPPORT (2012) only and considered as relevant for nanomaterials as for substances in general. Under REACH, information on surface tension is required for soluble and/or surface active substances. The latter may be the case for nanomaterials with surface modifications and, as a result, may be relevant for many nanomaterials.

Input/view from the Advisory Group. It was noted by the advisory group that this information requirement needs further R&D in relation to its relevance/applicability for (surface modified) nanomaterials.

Based on this, the evaluation score II was decided upon.

Test method and guidance availability

Although surface tension would not currently be included in a testing requirement scheme, it should be noted that OECD (2009) indicates without further elaboration that the current OECD guidelines are applicable under some circumstances or to some classes of nanomaterials.

Issues related to triggering level and adaptation

If needed, this would be considered basic information from the first general tonnage level.

The same type of adaptation as used in REACH Annex VII column 2 would be suggested with a nano-specific modification relating to surface modification.

4.3.11 Water solubility and other parameters for nanomaterials in water (dispersability, ion leaching, water dissolution kinetics, dispersion stability)

Evaluation score (Appendix 3): Iα (solubility)/ Iβ (others).

Relevance as regulatory information requirement for nanomaterials

Water solubility is addressed by all references as a key property. It is noted by several references (e.g. RIP-oN2, 2011; NANO SUPPORT, 2012) that some confusion exists in relation to terminology - also in peer reviewed scientific articles - as it is not always clear whether water solubility or dispersability is addressed. It is our understanding that both parameters (water solubility and dispersability) would be key properties. Water dissolution kinetics is also mentioned by several references as a key parameter; this parameter is therefore seen as highly relevant for nanomaterials. Understanding these parameters is of key relevance during environmental fate and behaviour and (eco-)toxicity testing. Dispersion stability is mentioned as a key parameter in RIP-oN2 (2011) and VCI (2008); this is therefore also seen as a potential information requirement, which may however merely be a parameter to control during testing for environmental fate and behaviour, and ecotoxicity, i.e. in connection with sample preparation/storage (discussed in this context in RIP-oN2, 2012).

Finally, NANO SUPPORT (2012) introduces the term 'ion leaching' indicating that this may be a different phenomenon than solubility.

It seems relevant to call for scientific consensus building in relation to defining more precisely what should be the information requirement package related to water solubility/dispersability/ion leaching/dissolution kinetics etc. and when implementing this package, clearly defining the terminology.

Test method and guidance availability

This issue should be addressed in relation to the above-proposed consensus building. It could logically take the testing strategy suggested in RIP-oN2 (2011) as the starting point. The EU FP7

NANoREG project starting in 2013 will aim specifically at developing standard operating procedures for these end-points to be proposed for regulatory use.

Issues related to triggering level and adaptation

The information requirements discussed above would be considered basic information from the first general tonnage level.

It is suggested to discuss possible adaptation rules as part of the suggested consensus building.

4.3.12 Partition coefficient n-octanol/water and fat solubility

Evaluation score (Appendix 3): II.

Relevance as regulatory information requirement for nanomaterials

Partition coefficient n-octanol/water is addressed by all references. However, as e.g. discussed by RIP-oN2 (2011), the use of this parameter may not be as straightforward as for organic chemicals. See also sections 'adsorption/desorption' (4.5.3) and 'bioaccumulation' (4.5.5) in relation to environmental fate & behaviour and ecotoxicity. Under REACH, the endpoint is waived for inorganic substances, which has also so far been the general approach by REACH registrants of nanomaterials (NANO SUPPORT, 2012).

However, this approach may be challenged in the case that the nanomaterials are surface modified with organic groups. In the guidance recommendations for this test guideline, RIP-oN2 (2011) points out that current OECD methods for determining this property would likely need to be modified (based on OECD, 2009) and that it can be difficult to interpret the results due to the difficulty in distinguishing between solubility and dispersibility given the small size of the particles. RIVM (2009) suggests fat solubility in particular as an additional base set information requirement for nanomaterials. It is not further specified what testing should be done. The scientific committees discuss solubility in relevant solvents without further specifying what these are. Overall, we therefore consider fat solubility and/or solubility in other solvents as a potential information requirement needing more investigation and consensus building before possibly being included as a regulatory information requirement.

Input/view from the Advisory Group

The view that further R&D is needed was supported by the advisory group, which in addition pointed out that it may be more relevant to develop/agree upon a methodology which more generally could express the hydrophilicity/hydrophobicity of the nanomaterial.

Test method and guidance availability

Although n-octanol/water partitioning coefficient would not currently be included in a testing requirement scheme, the above comments in relation to current OECD test guidelines and interpretation of results should be noted. The EU FP7 NANoREG project starting in 2013 will investigate the applicability of these characteristics for nanomaterials and may ultimately reach a proposed method for regulatory use.

Issues related to triggering level and adaptation

If needed, this would be considered basic information from the first general tonnage levels.

If needed, adaptation in line with the current REACH column 2 would seem relevant with a nano-specific modification relating to surface modification.

4.3.13 Flash point

Evaluation score (Appendix 3): III.

Relevance as regulatory information requirement for nanomaterials

Flash point is addressed by several references and generally indicated to be as relevant for nanomaterials as for conventional chemicals. However, as pointed out by e.g. NANO SUPPORT

(2012) and as reflected in the REACH column 2 adaptations, flash point is a property of liquids and would therefore generally not be relevant for nanomaterials. It is considered outside the scope of this project to consider whether liquid suspension of nanomaterials should be subject to information requirements. This information requirement is therefore considered to be of low priority.

Test method and guidance availability

Not applicable.

Issues related to triggering level and adaptation

Not applicable.

4.3.14 Flammability, explosive properties, self ignition temperature, oxidising properties

Evaluation score (Appendix 3): Iβ.

Relevance as regulatory information requirement for nanomaterials

These properties are all highly relevant for powders and are therefore also logically relevant for nanomaterials. This is also reflected by the references having addressed these properties. These are therefore suggested to be relevant properties for nanomaterials with similar waivers as those in REACH column 2.

Test method and guidance availability

Existing methodologies and guidance for generating information on these information requirements are also considered relevant for nanomaterials.

Issues related to triggering level and adaptation

This is considered basic information from the first general tonnage level.

The same type of adaptations as used in REACH Annex VII column 2 is suggested without nano-specific modification.

4.3.15 Granulometry / particle size (distribution)

Evaluation score (Appendix 3): Iα.

Relevance as regulatory information requirement for nanomaterials

All references stress (primary) particle size/size distribution as a key parameter. It is also the core element in the definition of 'nanomaterial' recommended by the European Commission. A recent JRC reference report (JRC, 2012) analyses the possibilities for size measurements in relation to the recommended definition. It is concluded that no single method can be applied for all nanomaterials as all methods have limitations and that dedicated guidance development is needed to support implementation in the short term. It seems logical to link information requirements for size (distribution) for nanomaterials to the guidance foreseen to support implementation of the recommended EU definition. However, if this guidance would e.g. provide a tiered approach for determining whether a material is 'nano' or not, it might not be enough for a clear and unambiguous characterisation of the size of the nanoforms/nanomaterials addressed in a registration. This is elaborated e.g. in the NANO SUPPORT (2012) project.

Some references (RIP-oN1, 2011; NANO SUPPORT, 2012) discuss whether information on size should be part of the 'substance identity' (which would normally trigger different registrations for different nanoforms) or 'characterisation' (where several forms of (nano) materials could be registered within the same dossier). However, no conclusions were reached during the technical discussions and the issue of 'identifier or characteriser' was left to a policy decision.

Test method and guidance availability

Several test methods are available for estimating the particle size (distribution) of a nanomaterial/nanoform. However, as e.g. depicted by the JRC reference report (JRC, 2012), these methods do not provide the same size (distribution) and have their strengths and weaknesses in relation to different types of nanomaterials.

Overall, there is therefore a need for method validations and further developments as agreement on material-specific reference methods, guidance development, consensus building etc. Such work should take into account the results of the RIP-oN1 and RIP-oN2 projects, as well as the JRC reference report (JRC, 2012). In addition the EU FP7 NANoREG project starting in 2013 will aim specifically at developing standard operating procedures for different methods to be proposed for regulatory use.

Issues related to triggering level and adaptation

This is considered basic information from the lowest tonnage level.

Adaptation rules should relate to which types of methods should be used for which types of nanomaterials.

4.3.16 Specific surface area, shape, agglomeration/aggregation

Evaluation score (Appendix 3): Iα (Shape possibly Iβ).

Relevance as regulatory information requirement for nanomaterials

There is consensus across the references that information on specific surface area, shape and agglomeration (weakly bound clusters of particles)/aggregation (strongly bound clusters of particles) is key information for characterising nanomaterials and for assessing the fate and toxicological and ecotoxicological properties of nanomaterials.

In RIP-oN2 (2011) it is discussed whether surface area and shape actually would fit under 'granulometry' or whether they would be 'new' information requirements under REACH. In any case, nano-specific guidance on these parameters has been developed and now included in the ECHA guidance updates on nanomaterials.

It is an open question whether information on shape is only needed if a material substantially deviates from spherical size, e.g. with an aspect ratio (i.e. length-width ratio) above a certain value. On the other hand, in case of low aspect ratio materials, it might be argued that it seems logical that some sort of information is available to demonstrate this.

RIP-oN2 (2011) does stress the need for information on agglomeration/aggregation. The importance e.g. in relation to sample preparation is substantiated, but is not suggested as a new information requirement. Nevertheless, as noted above, all references agree that this is a key property; therefore, it is suggested that this information requirement be included in a testing scheme as a starting point, realising that guidance should specify which methods to use and the relevant media for testing.

Test method and guidance availability

As for size there are several methods for determining surface area, shape/aspect ratio/morphology and agglomeration/aggregation. Although focus is on size measurements, methods for determining surface area are discussed in the JRC reference report (JRC, 2012) as surface area according to the recommended EU definition can be used for determining whether a material is 'nano' or not.

As for size, there is a need for further method development, agreement on reference methods, guidance development, consensus building etc. taking into account among other issues the results of the RIP-oN1 and RIP-oN2 projects, as well as the JRC reference report.

Issues related to triggering level and adaptation

Specific surface area, shape, agglomeration/aggregation are considered as basic information from the lowest tonnage level.

Adaptation rules should relate to which types of methods should be used for which types of nanomaterials, and possibly whether shape would only be needed for certain materials, e.g. only if aspect ratio is above a certain value.

4.3.17 Porosity

Evaluation score (Appendix 3): II.

Relevance as regulatory information requirement for nanomaterials

Porosity is suggested as a base set information requirement by Environmental Defense - DuPont (2007) and VCI (2008) and is also mentioned by EFSA (2011). RIP-oN2 (2011) suggests that further R&D is needed on this property. We have indicated it as a potential information requirement as i) there does not seem to be consensus on this information requirement, and ii) it should be closely considered as to whether information on porosity would give additional beneficial information for assessing the properties of a nanomaterial considering the already suggested characterisation requirements.

Test method and guidance availability

Although porosity would not currently be included in a testing requirement scheme, agreement on test guideline and guidance development for this endpoint would be needed if included as a standard information requirement.

Issues related to triggering level and adaptation

If included as an information requirement, it would logically be considered basic information from the lowest tonnage level.

Adaptation rules for non-porous materials would seem relevant, but the question would be how to demonstrate this.

4.3.18 Surface modifications

Evaluation score (Appendix 3): Ia.

Relevance as regulatory information requirement for nanomaterials

As noted in the introduction, surface modification should be understood in the broad sense for the purpose of this project.

All references, except Environmental Defense - DuPont (2007) and RIP-oN2 (2011) identify surface modifications as a key characteriser for nanomaterials/nanoforms as it is realised that surface modifications may significantly change the properties of a nanomaterial. RIP-oN2 (2011) does not closely address surface modifications as an information requirement as it was addressed in the RIP-oN1 project running parallel with RIP-oN2.

As for size, in RIP-oN1 (2011) and NANO SUPPORT (2012), it is left as a policy decision whether this information requirement should be an identifier or a characteriser.

It should be noted that during the RIP-oN1 project, ECHA clarified that the REACH FAQ (Frequently asked Questions) no. 6.3.8 “Do I have to register chemically surface treated substances?" relates to macro- and not to nano-particles[9]. It is also noted that industry stakeholders disagreed with this decision.

[9] For details, find FAQ 6.3.8 via: http://echa.europa.eu/da/support/faqs/frequently-asked-questions/frequently-asked-questions-about-reach

Test method and guidance availability

Given the range of different types of surface modifications and the variation in chemistry of surface modifications, a wide range of test methods may be applied. Guidance development related to generating information on surface modifications is likely needed. An initial procedure for identification and quantification of organic surface coatings and associated organics has been developed as part of the EU FP7 NANODEVICE project and the EAHC NANOGENOTOX project. The Standard operating procedure will be further developed and validated for regulatory use in the NANoREG project starting in 2013.

Issues related to triggering level and adaptation

This is considered basic information for all tonnage levels.

It is suggested not to have adaptations, as it would also be relevant to describe the absence of surface modifications (at least qualitatively).

4.3.19 Surface charge/zeta potential/isoelectric point

Evaluation score (Appendix 3): Iα or Iβ (to be decided at a later stage).

Relevance as regulatory information requirement for nanomaterials

The possible importance of surface charge/zeta potential is illustrated by almost all references addressing this information requirement. OECD (2010) notes that the zeta potential and/or the isoelectric point should be determined so it can be used for the fate assessment of particles in dispersions. Based on a review of the literature, RIP-oN2 suggests further R&D rather than requiring surface charge as an additional information requirement. In line with this, NANO SUPPORT (2012) has also not suggested surface charge as an additional characteriser. It is however acknowledged that most references would consider surface charge as an additional information requirement and therefore suggest surface charge/zeta potential as a desired information requirement. This idea is supported by the advisory group, where one member suggests reporting zeta-potential as a function of pH in a limited number of relevant biological and environmentally relevant media to assess the conditions and environments that might induce agglomeration and accumulation.

Test method and guidance availability

Based on OECD (2009), current methods also appear to be applicable to nanomaterials.

Issues related to triggering level and adaptation

This is considered basic information from the lowest tonnage level.

For sterically stabilised particles the zeta potential may not be a suitable parameter to estimate the fate of the particles. In such dispersions, the stability of the coating should be included in the characterization. This should be reflected in the adaptation rules to be developed.

4.3.20 Other surface properties (*surface structure, surface acidity, surface reactivity, surface energy)*

Evaluation score (Appendix 3): II.

Relevance as regulatory information requirement for nanomaterials

A number of other possible surface characterisers (surface structure, surface acidity, surface reactivity, surface energy) have each been considered in one reference. Therefore, little consensus exists on these properties as characterisers. We have therefore indicated these as potential future characterisers. As for other potential characterisers, possible inclusion of any of these would need to be considered in relation to whether significant new information is provided (in addition to characterisers already included) in an information requirement scheme.

Furthermore, surface acidity should be considered in relation to requirements for dissociation constant (see Section 4.3.23).

Test method and guidance availability

Would need methods and guidance development.

Issues related to triggering level and adaptation

Would be considered basic information from the lowest tonnage level.

Possible adaptations rules would need to be developed.

4.3.21 Other relevant characterisers

Evaluation score (Appendix 3): Iβ.

NANO SUPPORT (2012) suggests to describe (e.g. in REACH Annex VI) that knowledge available to the registrant about characterisers that are not already required, should be provided. In addition, it should be noted that REACH in general requires that all available information (also if not listed in the standard testing requirements) should be provided as part of a REACH registration.

The resulting opinion is that such a statement, although it might be self-evident, should be included in any regulatory testing scheme for nanomaterials.

4.3.22 Stability in organic solvents

Evaluation score (Appendix 3): Iβ.

Relevance as regulatory information requirement for nanomaterials

This property is only directly addressed by three references. Environmental Defense - DuPont (2007) suggests it as a possible higher tier test requirement, whereas RIP-oN2 (2011) and NANO SUPPORT (2012) consider it as relevant for nanomaterials as for conventional chemicals. The property is currently waived for inorganics via REACH column 2. In line with this, it was found to be waived by most registrants in the NANO SUPPORT (2012) project, although the project points out that care should be taken if a nanomaterial is surface modified with organics. This is therefore considered as an information requirement relevant for some nanomaterials.

Test method and guidance availability

Based on RIP-oN2, current test methods and guidance also appear to be applicable for nanomaterials.

Issues related to triggering level and adaptation

REACH (>100 tonne/year) as well as Environmental Defense - DuPont (2007) consider this a higher tier testing requirement.

An adaptation should be similar to the current REACH column 2 adaptation, although possible influence of surface modification should be addressed for nanomaterials.

4.3.23 Dissociation constant

Evaluation score (Appendix 3): Iβ.

Relevance as regulatory information requirement for nanomaterials

As for stability in organic solvents, this property is addressed by Environmental Defense - DuPont (2007) suggesting it as a possible higher tier test requirement, whereas RIP-oN2 (2011) and NANO SUPPORT (2012) consider it equally relevant for nanomaterials and conventional chemicals.

NANO SUPPORT (2012) found that most registrants had waived this endpoint due to the lack of functional groups, but points out that care should be taken if a nanomaterial is surface modified. Based on RIP-oN2 (2011), this information requirement should be seen in connection with surface acidity and surface charge.

We have currently considered this as an information requirement relevant for some nanomaterials.

Test method and guidance availability

OECD (2009) indicates the current OECD test guideline might be applicable under some circumstances or to some classes of manufactured nanomaterials. This would include specification of test medium and conditions.

Issues related to triggering level and adaptation

REACH (>100 tonne/year) as well as Environmental Defense - DuPont (2007) consider this a higher tier testing requirement.

An adaptation should likely be similar to the current REACH column 2 adaptation, although possible influence of surface modification should be addressed for nanomaterials.

4.3.24 Viscosity

Evaluation score (Appendix 3): III.

Relevance as regulatory information requirement for nanomaterials

This property is addressed by a few references indicating that it is not relevant for solids and thereby for nanomaterials.

We would also consider this irrelevant for nanomaterials.

Test method and guidance availability

Not applicable.

Issues related to triggering level and adaptation

Not applicable.

4.3.25 Catalytic properties, photocatalytic properties, radical formation potential

Evaluation score (Appendix 3): Iβ.

Relevance as regulatory information requirement for nanomaterials

The catalytic properties are considered higher tier testing requirements by Environmental Defense - DuPont (2007) and VCI (2008); they are indicated as highly relevant by the scientific committees (e.g. the generation of reactive oxygen species), and are also addressed by RIP-oN2 (2011). RIP-oN2 does however not suggest them as additional information requirements. Consequently, these have been indicated as relevant for some types of nanomaterials, e.g. nanomaterials developed to have these properties.

Test method and guidance availability

The references reviewed are not very specific on this issue, so there seems to be a need for method development, consensus building and guidance development for measuring these properties for nanomaterials. The EU FP7 NANoREG project starting in 2013 will aim specifically at developing standard operating procedures for this end-point and will consider different methods to be proposed for regulatory use.

Issues related to triggering level and adaptation

These are considered basic information from the first general tonnage level.

Adaptation rules to be developed.

4.3.26 Redox potential

Evaluation score (Appendix 3): II.

Relevance as regulatory information requirement for nanomaterials

Information on Redox potential is indicated as essential by EFSA (2011) and SCCS (2012), whereas RIP-oN2 (2011) acknowledges the possible importance, but suggests further R&D.

There seems to be lack of consensus on this parameter; therefore, it is indicated it as a potential future information requirement.

Test method and guidance availability

No specific test methods were identified in the addressed references, but it is assumed that available methods would be relevant for nanomaterials.

Issues related to triggering level and adaptation

This would be considered basic information from the first general tonnage level.

Possible adaptations would need to be agreed as part of the further development.

4.3.27 Dustiness

Evaluation score (Appendix 3): 1β.

Relevance as regulatory information requirement for nanomaterials

The importance of information on dustiness for nanomaterials is addressed by several references (VCI, 2008; RIVM (2009); EFSA (2011); RIP-oN2, 2011; SCCS (2012); NANO SUPPORT, 2012). RIP-oN2 (2011) and NANO SUPPORT (2012), for example, point out the importance of dustiness in relation to obtaining information on the potential for airborne exposure. RIP-oN2 (2011) notes that some guidance was already available on dustiness under the granulometry endpoint. Based on available registrations, NANO SUPPORT (2012) suggested specifying dustiness as a separate information requirement.

Test method and guidance availability

As e.g. discussed in RIP-oN2 (2011), EFSA (2011) and SCCS (2012), there are several methods for determining dustiness. RIP-oN2 (2011) also proposes how the REACH guidance could be further updated in relation to measuring dustiness.

Issues related to triggering level and adaptation

This is be considered a basic information requirement from the first general tonnage level, although it is noted that VCI (2008) suggests dustiness to be a higher tier requirement. RIVM (2009) prioritises dustiness as a parameter for base set requirements for nanomaterials.

This property would appear to be relevant for all powder-based nanomaterials.

4.4 Human toxicity

4.4.1 Absorption, distribution, metabolism and excretion (ADME)

Evaluation score (Appendix 3): 1α.

Relevance as regulatory information requirement for nanomaterials

All references indicate that knowledge on ADME is considered as highly important information in relation to nanomaterials. Critical issues are absorption from the various routes of exposure and distribution and accumulation in the organism. Concern is in particular expressed in relation to distribution of nanoparticles into the brain and through the placenta into the foetus and the consequences hereof (e.g. SCENIHR, 2009; EFSA, 2011). RIP-oN2 (2011) refers to the ENRHES project that has gathered the available information on ADME of nanomaterials and also mentions the following aspects to be of key concern: the potential for persistence and bioaccumulation, differences in toxicokinetics and any subsequent toxicity posed by variations in particle size, physical structure, chemical composition, mechanisms and interaction of the nanoparticles with cells and their compartments, and partitioning within and between tissues in organisms.

As well, transformation from nano- to non-nanoform in the organism is part of ADME.

RIVM (2009), EFSA (2011), SKEP (2011) and SCCS (2012) indicate data on ADME as an essential element in their proposals for data requirements and testing strategies.

Test method and guidance availability

For ADME it is essential that measuring methods are available for detection of a nanomaterial and its elemental composition in organs, tissues and other biological samples. In relation to this, labelling methods (radioactive isotopes or fluorescent dyes) are indicated as possible methods (SCENIHR, 2009; EFSA, 2011).

Input from the advisory group. For proper application of labelling methods, it must be ensured that the label is stable and uniquely associated with the nanomaterial. This would require analyses coupling chemical quantification and confirmation of the nanomaterial in the organs and tissues by imaging techniques such as electron microscopy.

SCCS (2012) focusing on cosmetics especially mentions testing for dermal absorption as an important issue for nanomaterials.

OECD (2009) indicates that the OECD guideline on toxicokinetics is only a general guideline developed in relation to conventional chemicals. Studies on kinetics on nanomaterials will have to be designed on a case-by-case basis rather than using a specific guideline. Labelled nanoparticles would likely be needed. Specifically the use of the OECD guideline, for *in vitro* skin absorption (TG 428) in relation to nanomaterials, is addressed and the use is questioned as mechanical aspects such as flexing of the skin may be relevant for the absorption of nanomaterials.

Overall, there is currently no clear and practical guidance on testing in relation to ADME for nanomaterials. NANO SUPPORT (2012) notes that ADME is relevant for all chemicals and suggests that the currently relatively limited REACH information requirements be reconsidered.

Issues related to triggering level and adaptation

In REACH, information on toxicokinetics kicks in at the >10 tonne/year level, whereas e.g. RIVM (2009) would require such information as the base set and e.g. Environmental Defense - DuPont (2007) and VCI (2008) have not included such information in their base set proposals.

It is suggested that basic knowledge regarding e.g. dermal absorption should be provided at the first general triggering level for information requirements on human health end-points, whereas additional information should be provided at higher levels in connection with repeated dose toxicity testing.

Information on ADME may be important to decide on strategy for further testing, e.g. in relation to carcinogenicity testing and reproductive toxicity testing, or to decide whether read-across can be performed, e.g. for the same nanomaterial with different particle sizes. Thus data on ADME may trigger or reduce further testing. However, at present, guidance on appropriate methods for detection and characterisation of nanoparticles within the body needs to be further developed (NANO SUPPORT, 2012).

4.4.2 Acute toxicity

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

Acute toxicity is by most references considered as an important parameter for nanomaterials. Exceptions are EFSA (2011) and Environmental Defense - DuPont (2007) that do not prioritize this end-point but emphasize the need for repeated dose toxicity testing.

Test method and guidance availability

In relation to conventional acute toxicity guideline testing, RIP-oN2 (2011) indicates that mortality and gross necropsy are crude measures for toxicity and recommends extended pathology/ histology to be performed in relation to nanomaterials to obtain further information.

In connection with acute inhalation testing, bronchoalveolar lavage (BAL) should be performed and the BAL fluid should be examined with respect to various toxicological indicators. OECD (2009) considers that acute toxicity guideline testing in principle is applicable for nanomaterials; however, extended histological examinations are recommended. For acute inhalational testing the inclusion of BAL and pulmonary cell proliferation end-points should be considered.

In addition to these *in vivo* tests, non-guideline *in vitro* testing may give information on mode of action e.g. on cytotoxicity, oxidative stress, potential for inflammation and immunotoxicity (e.g. EFSA, 2011; RIP-oN2, 2011). However, no exact guidance is currently available on how to incorporate this type of *in vitro* testing in a testing regime for nanomaterials and thus the use and the need for such *in vitro* testing have to be considered on a case-by-case basis. RIP-oN2 (2011) describes some of the *in vitro* tests that might be considered for the various mechanistic end-points.

Issues related to triggering level and adaptation

Information on acute toxicity would be needed at the first general tonnage level for information requirements. Testing on additional exposure routes should be performed at the next trigger level.

The inhalation route may often be the preferred route of exposure to nanomaterials, due to the dustiness of the fine powder as raw material, and to the increasing concern for adverse effects in relation to inhalation exposure to small-sized particles leading to large surface exposure in the lung. NANO SUPPORT (2012) suggests this priority to be specified in REACH Annex VII and VIII column 2. With respect to waiving of acute toxicity testing, it has to be considered that classification rules for acute toxicity are largely related to the mortality in acute toxicity studies and therefore waiving may lead to lack of information for classification purposes.

4.4.3 Skin and eye irritation

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

Most references address these information requirements and consider them as relevant for nanomaterials. Exceptions are Environmental Defense - DuPont (2007) and EFSA (2011), the latter rather logical given the focus on food and feed, and thus oral intake. As well, SCENIHR (2007, 2009) did not address these endpoints in detail, but it is interpreted that they are considered implicitly relevant. Overall, there seems to be consensus that these endpoints are important and relevant for nanomaterials.

Test method and guidance availability

OECD (2009) considers the existing *in vitro* and *in vivo* test guidelines applicable for nanomaterials.

Issues related to triggering level and adaptation

As a starting point, it seems reasonable to apply a strategy as suggested in REACH, requiring *in vitro* testing before entering into *in vivo* testing. Thus *in vitro* testing is considered relevant at the first general trigger level, followed by *in vivo* testing at the next trigger level.

Further, it seems appropriate to include adaptations in line with the current REACH Annex VII and VIII column 2 adaptations without modifications for nanomaterials.

Before testing, available data on possible macro/bulk form(s) should be considered as well.

4.4.4 Skin sensitisation

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

All references with the exception of SCENIHR (2009) and EFSA (2011) (focusing on food/feed and oral intake) consider skin sensitisation an important and relevant information requirement for nanomaterials.

Test method and guidance availability

OECD (2009) considers the existing test guidelines applicable for nanomaterials.

Issues related to triggering level and adaptation

There seems to be consensus that in line with REACH, this is an information requirement at the lowest tonnage level, the exception being RIVM (2009) indicating this to be a higher tier testing, driven by data from the base set.

It is suggested that information requirements for skin sensitisation should be applied at the first general tonnage level.

It seems appropriate to include adaptations in line with the current REACH Annex VII column 2 adaptation without modifications for nanomaterials.

If positive data on the bulk macro/form(s) is/are available this may justify waiving.

4.4.5 Mutagenicity

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

All references consider information on *in vitro* and, with the exception of VCI (2008), possibly *in vivo* mutagenicity testing important and relevant for nanomaterials. There also seems to be general consensus that *in vivo* mutagenicity testing could/should be triggered in case of positive *in vitro* tests. Several references (e.g. SCENIHR, 2007; OECD, 2009; RIP-oN2, 2011) point to the fact that solid particles and therefore several nanomaterials may not penetrate the bacterial cell wall. Therefore, RIP-oN2 (2011) suggested a guidance update - which has been implemented by ECHA - indicating that results from bacterial *in vitro* mutagenicity testing should not be used in isolation and NANO SUPPORT (2012) suggests changing the column 2 adaptation rules for this endpoint to explicitly ask for testing in non-bacterial assays. These references further pointed out that mutagenicity/genotoxicity of nanomaterials may occur via several mechanisms which may lead to either direct or indirect mutagenic effects; therefore, a suite of *in vitro* assays may be appropriate.

Test method and guidance availability

Please see the above in relation to *in vitro* bacterial assays. There seems to be a need to develop/validate further *in vitro* assays to be able to address more broadly the possible modes of actions for nanomaterials. It should also be noted that several references indicated the possible different methods of administering the nanomaterial to the *in vitro* test systems as well as to possible interactions between the nanoparticles and the test media.

OECD (2009) considers OECD *in vivo* mutagenicity assays applicable to nanomaterials; this seems to be supported by the other references reviewed.

Input from advisory group. There is currently no validation of any *in vitro* assays confirming the robustness of *in vitro* assays in producing no false negatives.

Issues related to triggering level and adaptation

There seems to be consensus in requiring *in vitro* testing in mammalian cells at the first general tonnage level. This should be followed by *in vivo* data at the next trigger level.

Adaptations similar to REACH Annex VII column 2 with nano-specific modifications taking the above discussion into account seems appropriate.

If positive mutagenicity data on the bulk form is available this may justify for read-across.

4.4.6 Repeated dose toxicity

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

All the references consider repeated dose toxicity studies and long-term studies very important for hazard characterization of nanomaterials. An overall concern is the potential for accumulation of insoluble nanoparticles in the lung after inhalation or accumulation in other organs to which nanoparticles may be distributed (e.g. distribution into the brain). Thus, it is suggested that examinations in relation to repeated dose toxicity studies should be extended further e.g. for inflammatory, cardiovascular, neurotoxic and immunotoxic responses (OECD, 2009; SCENIHR, 2009; EFSA, 2011; RIP-oN2, 2011; NANO SUPPORT, 2012).

Test method and guidance availability

For repeated inhalation toxicity testing, an OECD expert group has discussed the possibilities for making further recommendations with respect to determination of lung burden of the nanomaterial, distribution to other tissues, consideration of cell proliferation in different areas of the lung, examination for oxidative stress, fibrosis and collagen accumulation in the lung, and further histology on the olfactory bulb and the brain (OECD, 2012).

RIP-oN2 (2011) discusses how toxicity due to the lung-overload phenomenon for poorly soluble particles deposited in the rat lung may interfere with a more specific toxicity of the nanomaterial. Thus, toxicity related only to the lung-overload phenomenon may be of less relevance to humans. Consequently, rat inhalation studies should aim at sub lung-overload dosing. However, consensus and more guidance is needed in relation to establishing such exposure levels. This is one of the major issues addressed in the EU FP7 NANoREG project starting in 2013, which aims specifically at identifying the role of overload in long-term exposure to insoluble low-toxic and toxic compounds.

As for acute exposure, *in vitro* assays may help in understanding the mode of action with respect to, for example, the potential for inflammation, cytotoxicity and oxidative stress, e.g. ROS generation. Such data may guide the design of a repeated dose toxicity study in order to obtain the most relevant information.

In addition, obtaining data on ADME in connection with the repeated dose toxicity studies should be considered.

However, a more precise and targeted strategy on how to incorporate the various possible extensions in a testing strategy for repeated dose toxicity is not given; therefore, the examinations must be performed on a case-by-case basis on the available data on the physicochemical properties of the nanomaterial and the available ADME and toxicity data.

Issues related to triggering level and adaptation

EFSA (2011) (focusing on food and feed and therefore oral exposure) proposes directly to include an oral 90-day repeated dose toxicity study in their data requirement scheme for nanomaterials and does not request an acute toxicity study. Data from this 90-day study and data from ADME and genotoxicity testing should then further guide the possible need for a long-term study.

Environmental Defense – DuPont (2007) recommends a 28 day repeated dose toxicity study for nanomaterials in their base set information requirement, and as in EFSA (2011), does not require acute toxicity testing.

NANO SUPPORT (2012) indicates that waiving of repeated dose toxicity testing by the inhalation route should be justified by data indicating explicitly that this route is not considered as a relevant route of exposure.

Overall, it is thought that 28-day repeated dose toxicity testing should normally be required at the second trigger level (the level above the trigger level requiring the first acute toxicity study). This

should then be followed by 90-day testing at the following trigger level. Chronic toxicity testing may be required at the highest trigger level.

As for acute toxicity testing, the inhalation route may be considered the most relevant route of exposure for nanomaterials in powder form.

Data on high acute toxicity of the nanomaterial may trigger a further 28-day testing at the lowest tonnage level.

Overall, adaptation rules like those in REACH column 2 should be considered, but may not automatically be taken over in a testing scheme for nanomaterials.

Also, knowledge on critical effects from repeated dose toxicity from the macro/bulk form(s) may further guide and focus the testing of the nanomaterial e.g. for choosing the most relevant exposure route or to further focus on the toxicity in specific organs.

4.4.7 Reproductive toxicity

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

All references generally refer to this end-point as relevant for nanomaterials; however, it is generally considered as a requirement at a higher tier. Therefore, the need for data should normally be triggered by other data that gives concern for the end-point (Environmental Defense - DuPont, 2007; VCI, 2008; EFSA, 2011; RIVM, 2009).

Test method and guidance availability

OECD (2009) concludes that the test guidelines for reproductive toxicity are applicable in principle for nanomaterials. However, it is emphasized that the guidelines are developed in relation to oral exposure and that modification to inhalational exposure would be needed.

RIP-oN2 (2011) and SCCS (2012) discuss the use of three *in vitro* assays for embryotoxicity (the embryonic stem cell test for embryotoxicity; the micromass embryotoxicity assay and the whole rat embryo embryotoxicity assay) and conclude that they may be applicable for nanomaterials, but further research is needed before they can be included as regulatory requirements. Possible available information from such tests should be used in a weight of evidence approach.

Issues related to triggering level and adaptation

In general, the references that address testing for reproductive toxicity advise a targeted use of these tests. EFSA (2011) indicates that a trigger would be data from ADME studies or repeated dose toxicity studies, as well as knowledge and read-across from the substance if it exists in a non-nanoform should be considered.

RIVM (2009) considers testing for reproductive toxicity as higher tier testing and, as such, outside the base set requirements for nanomaterials. Therefore, only justified concern would trigger testing for reproductive toxicity at a tonnage level below what is normally required in REACH (i.e. < 10 t).

The reproductive toxicity screening study should be required at the second general trigger level i.e. at the same level as the toxicity study for 28 day exposure, as it would then be possible to conduct a combined study (also an option in REACH Annex VIII). Requirements for a prenatal developmental study and a 2-genereation study/ extended 1 generation study should be at trigger levels 3 and 4, respectively.

In general, a tiered approach with increasing demands for reproductive toxicity data as applied in REACH (Annex VIII->IX->X) would also seem appropriate for nanomaterials. The possibility of release of potentially reprotoxic ions from the nanomaterial may trigger for testing on the one hand, whereas on the other hand, read-across from bulk and waiving may be considered if the macro/bulk form(s) already has(have) been classified as Reprotoxic in category 1A or 1B.

4.4.8 Chronic toxicity/ carcinogenicity

Evaluation score (Appendix 3): 1α.

Relevance as regulatory information requirement for nanomaterials

Overall, very little has been discussed in relation to chronic toxicity/ carcinogenicity studies and the testing of nanomaterials in the references reviewed. However, it is indicated that this type of testing would be relevant in special cases if certain triggers indicate further concern for long-term exposure (e.g. VCI, 2008; EFSA, 2011).

Test method and guidance availability

When assessing the appropriateness of these test guidelines for nanomaterials, OECD (2009) indicates that the test guideline on chronic toxicity is less detailed with regard to investigating neurotoxicity than the 9o days study. Further, it is mentioned that the conduct of these studies is very expensive and therefore it the studies should only be used in exceptional cases.

In relation to the conduct of the studies, the considerations as described in the section regarding repeated dose toxicity studies should be taken into account as well.

Issues related to triggering level and adaptation

In general, it seems appropriate to require chronic/carcinogenicity studies only at the highest tonnage trigger level and/or in case of specific concern for nanomaterials as for conventional chemicals.

EFSA (2011) indicates that the justification that could trigger testing for chronic toxicity may stem from data on ADME, data from genotoxicity testing, or data from a 90-day study with evidence of toxic effects/ accumulation in organs and tissues. Read-across from macro/bulk form(s) and waiving may be considered if already classified for carcinogenicity in category 1A or 1B.

4.4.9 Phototoxicity

Evaluation score (Appendix 3): II.

Relevance as regulatory information requirement for nanomaterials

Test method and guidance availability

Only the SCCS (2012) specifically addresses testing for photoxicity and states that the OECD *in vitro* test on phototoxicty has not yet been validated for nanomaterials. OECD (2009) points out that phototoxicity testing is mainly used for cosmetics, specifically testing UV filters in sunscreens for phototoxicity.

Issues related to triggering level and adaptation

Phototoxicity may be considered as a relevant end-point for nanomaterials used in cosmetics and be triggered in specific other cases with high potential for dermal exposure; however, it does not seem appropriate to include this end-point in a standard testing scheme.

4.5 Environmental fate and behaviour, and ecotoxicity

4.5.1 Hydrolysis as a function of pH

Evaluation score (Appendix 3): 1β.

Relevance as regulatory information requirement for nanomaterials

This information requirement is covered only by some of the references. However, as it is of importance in relation to degradation, fate and behaviour of the nanomaterial in the environment, this information requirement should be prioritized, but only for those nanomaterials that contain a chemical group that may be subject to hydrolysis, e.g. esters, amide groups etc. Furthermore, this information requirement should be seen in the context of the discussion in relation to water solubility, as increased water solubility would also favour hydrolysis (Section 4.3.11).

Test method and guidance availability

Abiotic hydrolysis testing according to OECD test guidelines is considered relevant for nanomaterials only if they contain groups that could be subject to hydrolysis (OECD 2009).

NANO SUPPORT (2012) indicates that hydrolysis, although relevant for nanomaterials, will depend on water solubility and therefore, due to low water solubility of most nanomaterials, hydrolysis may be negligible during the time course of the normal test period.

Input/view from the advisory group. Examples of chemicals (e.g. certain pesticides) exist that have low water solubility, but that have rather short half-lives in the environment due to hydrolysis.

Issues related to triggering level and adaptation
REACH currently requires this information at the > 10 tonnes/year level.

Reconsidering this parameter in relation to water solubility would suggest that the endpoint should possibly be considered basic information. It is therefore suggested to include it at the first general triggering level in line with most other physico-chemical properties.

Adaptation rules should reflect that hydrolysis is only relevant for nanomaterials that contain a chemical group that may be subject to hydrolysis.

4.5.2 Photodegradation

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

Due to the persistence of many types of nanomaterials, it is indicated that photodegradation processes may play a role as a slow process for degradation of nanomaterials in the environment (SCENIHR, 2009; OECD, 2010).

Test method and guidance availability

Testing for photodegradation may be considered applicable and relevant for nanomaterials due to the possible long half-life of nanomaterials (OECD 2010).

Issues related to triggering level and adaptation

It is suggested to include photodegradation at the second general trigger level, where further specific end-points in relation to environmental fate are required.

No specific adaptations for this endpoint are foreseen.

4.5.3 Adsorption/ desorption (screening)

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

Data on adsorption/desorption is of key importance in relation to environmental fate and the prediction of binding to solid surfaces in the environmental media e.g. soil, sediment and sludge. This is recognised by the majority of the references and the testing for adsorption/desorption is therefore evaluated as a prioritized end-point.

Test method and guidance availability

It has been stated that the octanol-water partition coefficient (K_{ow}) for nanomaterials is not a suitable parameter for estimating adsorption of nanomaterials to organic matter (SCENIHR, 2009; NANO SUPPORT, 2012). Instead the distribution coefficient (K_d) should be determined experimentally.

In general, the OECD guidelines for this end-point are considered applicable for nanomaterials (OECD, 2009, NANO SUPPORT, 2012); however, it is uncertain how colloid suspensions (i.e. if the nanomaterial is not completely dissolved) may impact the test results.

Further, data on adsorption/ desorption may be relevant for other media.

Issues related to triggering level and adaptation

In REACH, adsorption/desorption screening data is currently an information requirement at the > 10 tonne/year level.

As knowledge concerning distribution in the environment is of utmost importance in relation to relevant toxicity testing and as Kow cannot be applied, it is suggested that adsorption/desorption screening data should be provided for soil at the first general triggering level.

Further screening and targeted testing on adsorption/desorption (or leaching studies) should be provided for other relevant media at the higher trigger levels.

The REACH Annex IX criteria for waiving studies on adsorption/desorption may not be relevant for most nanomaterials as the justification is based on a low K_{ow} value and on rapid decomposition of the substance. As the K_{ow} value is not suitable for prediction of the K_d value for nanomaterials and as most nanomaterials are rather persistent, waiving based on these arguments seems unjustified.

4.5.4 Biodegradation

This section covers ready biodegradation and further biodegradation tests.

With respect to various types of *abiotic* degradation reference is made to 'water solubility', 'dissolution kinetics', 'hydrolysis as a function of pH' and 'photodegradability'.

Evaluation score (Appendix 3): 1β.

Relevance as regulatory information requirement for nanomaterials

This end-point is stated to be an important parameter by most of the references. Degradation of nanomaterials may be associated to biotic degradation for carbon-containing nanomaterials or to non-biotic degradation of the nanomaterial e.g. dissolution or physicochemical transformation of an inorganic nanomaterial (OECD 2009; NANO SUPPORT, 2012; SKEP, 2011).

Test method and guidance availability

The OECD guidelines on biodegradation are developed for organic chemicals. However, some carbon-based nanomaterials may have low potential for biodegradation for structural reasons. It should be noted that functionalisation may be of organic nature and consist of biodegradable materials (RIP-oN2, 2011).

OECD (2009, 2010) concluded that only some of the test guidelines on biotic degradation are applicable to nanomaterials, and only for those of the nanomaterials that contain carbon that can be utilized for microbial growth. Inorganic nanomaterials should not be tested in any of the biotic degradation tests. A detailed evaluation was given of 25 tests on biodegradability; for many of these methods, limitations for use on nanomaterials were noted (e.g. high concentrations to be used or need for specific labelling). Among six OECD tests for ready biodegradability, two are not applicable for nanomaterials as they require carbon to be dissolved, and three tests require test materials in high concentration which may give rise to aggregation/agglomeration (OECD, 2009; SKEP, 2011).

Simulation tests for biological degradation in various environmental compartments are to a great extent challenged by the lack of applicable methods for detection and characterisation of nanomaterials in the various media (OECD 2009).

Furthermore, it is stated that if results from ready biodegradation testing indicate a degradation level below 10% then it would not be considered meaningful to carry out further tests with e.g. surface water, as only very low degradation would be expected (OECD 2009). As well, RIP-oN 2 (2011) recommends not to go further with testing using more elaborate aerobic biodegradation tests if very low biodegradation has been proven in aerobic degradation screening tests, and instead concludes the nanomaterial to be non-biodegradable.

Input/view from Advisory group. This is not necessarily the case as it may be meaningful to test organic nanomaterials with low biodegradation in an inherent biodegradation study or at low concentrations in simulation tests.

Biodegradation of substances used to cap or surface functionalize a nanoform would also need to be investigated due to their crucial role in environmental fate (NANO SUPPORT, 2012).

Going beyond the current understanding of biodegradation, NANO SUPPORT (2012) speculates that 'biodegradation' for nanomaterials perhaps should be seen as 'morphological changes' rather than 'chemical transformations'. In this understanding, it should be reassessed as to whether inorganic nanomaterials should automatically be excluded from Persistence, Bioaccumulation and Toxicity (PBT) assessments, which currently exclude inorganic substances.

Issues related to triggering level and adaptation

This end-point should be included in a testing scheme starting with screening tests for ready biodegradability at the first general triggering level followed by possible triggering of simulation testing at higher levels.

It has to be noted that biodegradation may not apply to the majority of the nanomaterials (i.e. all the inorganic nanomaterials or carbon-containing nanomaterials behaving as inorganics). For these substances, degradation in the environment depends on abiotic degradation processes.

Relevant testing for biotic and abiotic degradation has to be targeted in accordance with the chemical composition of the nanomaterial in order to choose relevant test methods. Furthermore, specific conditions apply to several of the biodegradation tests evaluated by OECD (2009) (e.g. high concentration or the need for labelling) which may influence their applicability for nanomaterials.

4.5.5 Bioaccumulation

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

Bioaccumulation is considered a relevant and important parameter for nanomaterials by all the references as most nanomaterials are considered to be persistent in the environment.

Test method and guidance availability

It is generally acknowledged that log K_{ow} cannot be used for predicting bioaccumulation for insoluble nanomaterials (OECD, 2009; SCENIHR, 2009; SKEP, 2011; RIP-oN2, 2011; NANO SUPPORT, 2012).

OECD (2009) and SKEP (2011) indicate that the existing OECD methods are considered appropriate to generate bioaccumulation data for nanomaterials - the OECD test guideline with fish and the OECD test guideline with sediment worms.

Input/view from the Advisory Group. However, it has to be recognised that there may be serious problems in the methodologies for determining the Bioconcentration factor (BCF) and Bioavailability factor (BAF) when dealing with particles instead of dissolved chemicals.

Dietary exposure should be considered as the most relevant exposure in accumulation testing with fish.

Issues related to triggering level and adaptations

RIVM (2009) considers that a bioaccumulation study may be triggered by the proposed base set data, i.e. a bioaccumulation test may be required at a lower tonnage level compared to the general REACH requirement tonnage level for this end-point (> 100 tonne/year).

NANO SUPPORT (2012) states that bioaccumulation should specifically be addressed for the nanoform of a chemical, as the nanoparticles may behave differently compared to the soluble form

and macro/bulk form(s). Therefore, waiving of the test cannot automatically be done by read-across to the non-nanoform.

It seems relevant to include bioaccumulation at a lower trigger level for information requirements, i.e. relatively earlier than in REACH where data is requested in Annex IX. It must also be considered that log K_{ow} cannot be used for prediction of bioaccumulation.

Appropriate waiving/triggering described in adaptation rules like the REACH testing annex column 2 does not seem relevant for the testing of nanomaterials.

4.5.6 Short-term toxicity tests (sludge, *Daphnia*, aquatic plants, fish, terrestrial invertebrates, microorganisms or plants)

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

Short term ecotoxicity is covered by most of the references and in general this end-point is considered as important and relevant for nanomaterials, as for chemicals in general. However, development of specific test systems/guidelines, with respect to further markers/parameters for toxicity, is considered relevant.

Test method and guidance availability

OECD (2009) considers that end-points measured in these test are relevant and applicable for nanomaterials. Because nanomaterials are physical entities, exposure and uptake are likely to involve processes not typical for soluble chemicals, and this may lead to further development of end-points more predictive for ecotoxicity. Use of other relevant dose metrics than the mass based dose metric is emphasized e.g. particles size, surface area, particle number or surface charge. However, RIP-oN2 (2011) does not currently indicate any clear scientific justification for moving away from the mass metric.

RIP-oN2 (2011) also recommends further R&D for relevant markers of ecotoxicity than the normal standard end-points (e.g. fish ventilation rate, - gill pathology, - mucus secretion, - brain pathology, and oxidative markers of stress, *Daphnia* heart rate, *Daphnia* hopping frequency, Trojan horse effects of nanomaterials etc.).

Issues related to triggering level and adaptation

SKEP (2011) describes the need for obtaining more knowledge on toxicity to other animal and plant species than from the aquatic environment, as this may lead to more targeted and relevant testing requirements in future. Therefore, NANO SUPPORT (2012) and SKEP (2011) express the need for more focus on soil and sediment organisms, as sewage sludge and sediments may be considered as sinks for nanomaterials due to binding of the nanomaterials to the solid matrices in these compartments.

SKEP (2011) recommends - at a standard requirement level - that short-term testing should be performed with terrestrial and benthic species in addition to short-term testing on fresh water algae as long as it not possible to predict the environmental distribution of nanomaterials with more certainty.

Overall, it seems appropriate to include short-term ecotoxicity testing at the first general tonnage triggering level, including testing in terrestrial/ benthic species.

However, a targeted approach is recommended, taking into account in which compartment emission takes place and considering environmental distribution.

Various mechanisms of uptake of nanoparticles may occur in organisms in the environment and the bioavailability may not necessarily be associated with the dissolved fraction. Therefore, waiving because of low water solubility may not necessarily be justified. NANO SUPPORT (2012) expresses doubts for the waiving criteria given in REACH annex VII point 9.1.2, where algae testing could be

waived based on low water solubility of the substance. As such, a justification is not considered valid for nanomaterials.

Current REACH column 2 adaptation rules may be difficult to apply as the bioavailability of nanomaterials may not necessarily be associated with water solubility.

4.5.7 Long-term toxicity tests (*Daphnia*, fish, terrestrial invertebrates, plants, sediment organisms)

Evaluation score (Appendix 3): 1a.

Relevance as regulatory information requirement for nanomaterials

Long term ecotoxicity is covered by most of the references and this end-point is considered relevant for nanomaterials, in particular because persistence or accumulation of non-degradable nanoparticles may result in prolonged exposure, supporting the need for chronic testing.

Test method and guidance availability

OECD (2009) considered that end-points measured in these tests are relevant and applicable for nanomaterials. Because nanomaterials are physical entities, exposure and uptake are likely to involve processes not typical for soluble chemicals. This may lead to further development of end-points more predictive for ecotoxicity. Use of relevant dose metrics other than the mass based dose metric is emphasized, e.g. particle size, surface area, particle number or surface charge. However, RIP-oN2 (2011) does not currently indicate any clear scientific justification for moving away from the mass metric.

Bioavailability and various uptake mechanisms of nanoparticles should be considered when choosing relevant species for chronic testing (SCHENIR, 2007; SKEP, 2011).

RIP-oN2 (2011) also recommends further R&D for relevant markers of ecotoxicity other than the normal standard end-points (e.g. fish ventilation rate, - gill pathology, - mucus secretion, - brain pathology, and oxidative markers of stress, *Daphnia* heart rate, *Daphnia* hopping frequency, Trojan horse effects of nanomaterials etc.) and stressed that based on the low water solubility of many nanomaterials, long-term testing should not be waived based on lack of toxicity in short-term testing.

SKEP (2011) emphasizes the need for long-term studies especially for evaluation of effects on reproduction and also indicates the importance of the detection of genotoxic and cytotoxic effects in the studies.

Issues related to triggering level and adaptation

SKEP (2011) recommends that the standard requirements for nanomaterials at the lowest tonnage level, in addition to short-term tests, should include information on chronic ecotoxicity and indicates that the OECD earthworm test is applicable in principle to nanomaterials.

RIVM (2009), and Environmental Defense - DuPont (2007) cover chronic toxicity on *Daphnia* in their base set information requirement proposal; however, further chronic testing may be triggered based on concern from the base set testing. VCI (2007) covers long-term ecotoxicity testing at a level for information requirement above the base set level.

Overall, it should be considered to include chronic ecotoxicity testing at a lower level than what is currently required under REACH (starting >100 tonne/year) and to consider whether terrestrial and benthic species should be given a more prominent role. Thus, it is suggested that testing on long-term toxicity for nanomaterials should start at the second general trigger level (with the possibility for being triggered at the lowest level) and involve further species at higher trigger levels. However, a targeted approach is recommended, considering the compartment in which the emission takes place and environmental distribution.

Current REACH column 2 adaptation rules are not necessarily relevant for nanomaterials.

The lack of ecotoxicity in short-term testing is not considered an argument for waiving a long-term study. On the contrary, REACH annex VII 9.1.1 and VIII 9.1.3 indicate that low solubility of a substance may be an additional argument for the need for long-term testing with *Daphnia* and fish, respectively (NANO SUPPORT, 2012).

5. Proposal for an information requirements scheme for nanomaterials

The chapter outlines the developed information requirement scheme for nanomaterials. It has been adapted based on discussions in two advisory group meetings and associated written comment rounds. It thus presents the integrated results of the project building on the work described in Chapters 3 and 4.

First, a number of general issues/"boundary conditions" for a regulatory information requirements scheme for nanomaterials are outlined (Section 5.1). These reflections are largely based on the "General issues relevant for information requirements and testing of nanomaterials" described in Section 4.1. The reader is referred to these discussions for further details. It has been the aim to capture some of the main issues to consider for nanomaterials, although it is far from complete, as this would entail a proposal for a full legal text including further associated guidance, which is outside the scope of this project.

Thereafter a proposal for a regulatory stepwise standard information requirements scheme is outlined in Section 5.2.

5.1 General issues/"boundary conditions" for the proposed information requirement scheme

The following issues are considered core issues for a regulatory information requirement scheme for nanomaterials that should be addressed in a regulatory text or in guidance form.

5.1.1 All available information

It should be pointed out that all available information on the nanomaterial should be reported, i.e. not only the standard information required at a given tonnage level. This requirement should in particular point to the need for providing information on characterisers which, according to the knowledge of the registrant, influence the properties of the nanomaterial.

5.1.2 General rules for adaptation of the standard testing requirements

In order to optimise testing, including reducing costs and use of test animals, a number of general adaptation rules appear to be reasonable. It is suggested to apply an approach as set out in REACH Annex XI addressing these types of situations:

1. Testing does not appear scientifically necessary (covering: use of existing data, weight of evidence, QSAR, *in vitro* methods and grouping/read-across). The current text in annex XI notes that these alternative methodologies should only be used when reliable, validated and/or scientifically justified.
2. Testing is technically not possible (e.g. the substance is explosive, highly reactive or unstable)
3. Substance-tailored exposure-driven testing

It is suggested to further specify the following in relation to a testing scheme for nanomaterials:

- Exposure-driven testing should be considered on a "form-to-form" basis to take account of the possibility for different properties in different forms of the same nanomaterial chemistry.
- Use of "scaling" (e.g. between nanoforms with different surface areas of what is otherwise the same nanomaterial) could be mentioned as a possible method in relation to read-across when scientifically justified. In any case, the use possible of scaling should be addressed in supporting guidance.
- Exposure-driven testing should specify that characterisation of the nanomaterial in various phases of its lifecycle can be triggered by use/exposure considerations. This issue should be further elaborated upon in guidance.
- In relation to use of existing data, it could be addressed that if macro/bulk form(s) of the nanomaterial is/are very toxic and thereby trigger the most severe classification, testing of the nanoform might be waived in relation to classification and labelling considerations. Testing might still be needed for risk/safety assessment purposes.

In any case, the practical application of the general adaptation rules would need consensus building and guidance development including all stakeholders.

5.1.3 Sample preparation and dosimetry

The importance of sample preparation and dosimetry in relation to all types of testing of nanomaterials should be stressed. Reference (probably in guidance) should be made to the latest available OECD guidelines.

5.1.4 Metrics

It should be specified in which metrics hazard (and exposure) data should be reported. Following e.g. RIP-oN2 and RIP-oN3 recommendations these would include at least two: the most scientifically relevant and the mass metric. A good characterisation during testing, as also pointed out by OECD, would allow expressing hazard test data in all three metrics normally discussed in relation to nanomaterials (mass-, surface area- and number-based). If all three metrics are available, it is suggested that all three are reported (the relevance of these dose metrics has especially been evaluated in connection to inhalational toxicity testing).

5.1.5 Some considerations regarding introduction of a regulatory information scheme

It is outside the scope of this project to clarify how to provide the information to the legally responsible authorities (whether there should be a registration, for example) and by what means (whether there should be, as in REACH, Substance Information Exchange Fora - SIEFs). However, if registrations are required, it should be addressed whether separate registrations for different nanoforms are needed or whether all nanoforms of a given common chemistry could be registered as one nanomaterial, where the differences between the forms are addressed within the same registration. In any case, consensus building and guidance development would be needed on these issues. Also, in case a regulatory information requirement scheme is implemented in relation to REACH, it must further be considered whether nanoform(s) could be registered together with available macro/bulk forms. Overall it appears to be important to stress that all nanoform(s) addressed are explicitly described. As pointed out by e.g. NANO SUPPORT (2012), different manufacturing processes might substantially influence the characteristics of a nanomaterial.

Furthermore, there could be a need for clarification of when or whether nanomaterials with "loose" coating should be covered as one substance/nanomaterial or whether this would be considered to be a mixture.

5.2 Proposal for a stepwise standard information requirement scheme for nanomaterials

A proposal for a stepwise standard information requirement scheme for nanomaterials has been developed based on the findings in the previous parts of the project and based on intensive consultation and discussion with the advisory group. The proposed scheme is presented in the tables on the following pages. The information requirements taken forward to the proposed scheme are those which obtained an evaluation score of either Iα or Iβ in Chapter 4. Many (the majority) of the information requirements are not only relevant for nanomaterials, but also known to be relevant for chemicals in general and covered by the standard REACH requirement scheme.

The "nano additional" information requirements or modifications that go further than required in REACH are highlighted in italics and with a shaded background in the tables.

The step-wise approach implies that the information requirements at the higher levels add on to the information obtained at the lower levels. Thus the proposal is based on the "REACH methodology" (i.e. with stepwise increased standard information requirements and associated adaptation rules), although it is outside the scope of this project to specify via which legal instrument the requirements could be implemented: as part of REACH, as a separate nanomaterial legislation or in relation to other legislation or guidance.

Although it has not been the core aim of this project to develop and discuss specific tonnage triggers, as these to a large extent are a rather political choice, some indications are given as it has proved difficult to suggest tiered testing requirements without any considerations of the triggering levels.

As discussed in Section 4.1.6, several references addressing REACH point out that nanomaterials are usually more potent than their bulk counterpart, and therefore suggest lowering the REACH tonnage triggers. These references still suggest using the 'tonnage' metric as the trigger and it is also the authors' impression that it would be too premature and too difficult to enforce alternative trigger metrics (as e.g. a surface area measure).

Inspired by the current REACH tonnage triggers and the triggers proposed by various references (Section 4.1.6), the choice has been to develop an information requirements scheme with four standard levels with tiered and increasing information requirements, and, in addition, to suggest a possible "Level 0" for information requirements at a (very) low/basic tonnage level (i.e. a zero level that solely defines the substance as a nanomaterial that is put on the market):

- Level 0 - (very) basic. This could e.g. correspond to > 10 kg/year
- **Level 1: E.g. > 100kg/year or > 1 tonne/year**
- **Level 2: E.g. > 1 tonne/year or > 10 tonne/year**
- **Level 3: E.g. > 10 tonne/year or > 100 tonne/year**
- **Level 4: E.g. > 100 tonne/year or > 1000 tonne/year.**

In relation to adaptation rules, the discussions under each endpoint in Chapter 4 are referred to, the exception being that the symbol "x*" in Tables 1-3 (see below) denotes when a given information requirement is not normally a mandatory requirement, but could be triggered.

In the right "Comments" column in the tables, an attempt is also made to indicate in keywords *why* it is believed that a given information requirement is needed for nanomaterials, as well as *why* it is required at a relatively low tonnage level. The reader is referred back to the endpoint descriptions in Chapter 4 for further details.

Table 1: Substance identification, characterisation and physicochemical properties

The requirements at "level 0" should be moved to "level 1" if "level 0" is not introduced.
Parameters and/or comments made shaded and in italics denote that this is "nano additional" information not covered (or only partly covered) by the reach information requirements.

Information Requirement	**Level 0 and higher (very) basic level**	**Level 1 and higher**	**Level 2 and higher**	**Level 3 and higher**	**Level 4**	**Comments, including why information requirements necessary**
Name	x	x				Obviously needed
Molecular and structural formula	x	x				Obviously needed
Chemical composition, purity, impurities/main impurities, additives	x	x				May significantly affect properties
Crystal structure	x	x				*May significantly affect properties*
Spectral data	x	x				In support of chemical composition/(im)purity profile
Primary particle size/ particle size distribution	x	x				*May significantly affect properties. An information requirement to some extent covered in standard REACH information requirement.*
Agglomeration/ aggregation	x	x				*May significantly affect properties. An information requirement not explicitly included in standard REACH information requirement.*
Specific surface area	x	x				*May significantly affect properties. An information requirement not explicitly included in standard REACH information requirement.*
Morphology/ shape/ aspect ratio	x	x				*May significantly affect properties. An information requirement not*

Information Requirement	Level 0 and higher (very) basic level	Level 1 and higher	Level 2 and higher	Level 3 and higher	Level 4	Comments, including why information requirements necessary
						explicitly included in standard REACH information requirements.
Surface modifications	x	x				*May significantly affect properties. An information requirement not included in standard REACH information requirements.*
State of substance	x	x				Important in relation to "understanding" the substance and in relation to exposure considerations.
Catalytic properties, photo-cat.; radical formation	x	x				*May significantly affect properties.* *Would be known if intentionally manufactured to possess these properties. An information requirement not included in standard REACH information requirements.*
Surface charge, zeta potential, isoelectric point		x				*May significantly affect properties. Very relevant in relation to local effects. An information requirement not included in standard REACH information requirements.*
Dustiness		x				*Important in relation to potential for airborne exposure. An information requirement not included in standard REACH information requirements.*
Melting/freezing point		x				Important for waiving information on some other physicochemical properties (if high melting/freezing point). Potentially relevant for sameness considerations.

Information Requirement	**Level 0 and higher (very) basic level**	**Level 1 and higher**	**Level 2 and higher**	**Level 3 and higher**	**Level 4**	**Comments, including why information requirements necessary**
Density (specific and pour)		x				Important e.g. for understanding occupational and environmental behaviour of the nanomaterial
Vapour pressure		x				May especially be relevant for nanomaterials with organic surface layers. See also REACH Annex VII column 2.
Water solubility, dispersability, ion leaching water dissolution kinetics, dispersion stability		x				*Extremely important in relation to understanding fate and behaviour. Only water solubility included in standard REACH information requirements.*
Hydrolysis as function of pH		x				Only relevant if nanomaterial contains chemical group(s) subjected to hydrolysis.
Dissociation constant			x			Important for understanding fate and behaviour
Stability in organic solvents			x			Important for understanding fate and behaviour
Photodegradation			x			*Important for understanding fate and behaviour. An information requirement not included in standard REACH information requirements.*
Flammability		x				Important for understanding physicochemical hazards
Explosive properties		x				Important for understanding physicochemical hazards
Self ignition temperature		x				Important for understanding physicochemical hazards

Information Requirement	Level 0 and higher (very) basic level	Level 1 and higher	Level 2 and higher	Level 3 and higher	Level 4	Comments, including why information requirements necessary
Oxidizing properties		x				Important for understanding physicochemical hazards

The information requirements on “Hydrolysis as a function of pH”; ” Dissociation constant” and “Stability in organic solvent” are compared to REACH suggested to be addressed at a relatively lower tonnage level for nanomaterials.

Table 2: Toxicological properties

Parameters and/or comments made shaded and in italics denote that this is “nano additional” information not covered (or only partly covered) by the REACH Information Requirements.
"X*" denotes when a given information requirement is not normally mandatorily required, but could be triggered.

Information Requirement	Level 0 and higher (very) basic level	Level 1 and higher	Level 2 and higher	Level 3 and higher	Level 4	Comments, including why information requirements necessary
Dermal absorption		x				*Considered as basic for further testing and choice of exposure route. Also important information for use in risk/safety assessment, as default dermal absorption factors from chemical in general cannot be used.*
ADME (other than skin abs.)		x*	x			*Extremely relevant for designing other tests, prepare testing strategies and in relation to justifying/applying grouping/read-across.*
Skin irritation *- in vitro*		x				Basic toxicological end-point that may guide (trigger/waive) further testing

Information Requirement	**Level 0 and higher (very) basic level**	**Level 1 and higher**	**Level 2 and higher**	**Level 3 and higher**	**Level 4**	**Comments, including why information requirements necessary**
Skin irritation *- in vivo*			x			Basic toxicological end-point that may guide (trigger/waive) further testing
Eye irritation *- in vitro*		x				Basic toxicological end-point
Eye irritation *- in vivo*			x			Basic toxicological end-point
Skin sensitisation		x				Basic toxicological end-point
Acute toxicity - inhalation (or oral if most relevant)		x				*Inhalation: Extended examinations for histopathology of the respiratory tract, BAL analysis, pulmonary cell proliferation.*
Acute toxicity - second exposure route			x			*Most relevant exposure route besides inhalation should be chosen based on physical chemical properties; relevant exposure scenarios; and ADME data (e.g. dermal absorption?)*
Repeated 28 days inhalation (or oral if most relevant)		x*	x			** Possibly triggered by high potency/acute toxicity* *Inhalation: Extended examinations for, histopathology of the respiratory tract, BAL analysis, pulmonary cell proliferation. oxidative stress, fibrosis, collagen accumulation in the lungs, and for cardiovascular, neurotoxic and immunotoxic response, lung burden/ADME (distribution)*
Repeated 90-days			x*	x		** Possibly triggered by high potency/28 days toxicity* *Inhalation: Same extended examinations as relevant for 28 day inhalation testing*

Information Requirement	**Level 0 and higher (very) basic level**	**Level 1 and higher**	**Level 2 and higher**	**Level 3 and higher**	**Level 4**	**Comments, including why information requirements necessary**
Repeated chronic				x*	x	** Possibly triggered by high potency or toxicity in 90-days study* *Inhalation: Same extended examinations as relevant for 28 D inhalation testing.*
Mutagenicity *- in vitro*		x				*In vitro* in *mammalian cells*
Mutagenicity *- in vivo*		x*	x			Triggered by positive *in vitro*
Carcinogenicity					x*	* Note adaptation rules described in section 4.4.8
Reproductive toxicity screening			x			Inhalation: *Same extended examinations as for 28 day inhalation study* If inhalation route is chosen in the screening study, the repeated 28-day study may be waived. The screening study may be waived if existing data (e.g. on bulk form) would trigger prenatal developmental testing or extended one (or two-) generation testing.
Prenatal developmental toxicity			x*	X (at least one species)	x (second species obligatory)	* May be triggered as indicated in REACH Annex VIII-IX-X *or based on existing data on bulk form*. *In addition ADME data and data on bulk form may trigger/waive testing.*
Extended one-generation / two generation reproductive toxicity			x*	x*	x (at least one species)	* May be triggered as indicated in REACH Annex VIII-IX-X *or based on existing data on bulk form. In addition ADME data and data on bulk form*

Information Requirement	Level 0 and higher (very) basic level	Level 1 and higher	Level 2 and higher	Level 3 and higher	Level 4	Comments, including why information requirements necessary
						may trigger/ waive testing.

The information requirements on ADME is specifically addressed at a relatively earlier trigger level than in REACH. Otherwise the sequence for requiring toxicological data for nanomaterials is in general identical to the sequence in REACH. The inhalational route is by default the preferred exposure route for acute and repeated dose toxicity testing. Repeated dose toxicity tests may be triggered at lower level compared to REACH.

Table 3: Environmental fate and behaviour, and ecotoxicity

Parameters and/or comments made shaded and in italics denote that this is "nano additional" information not covered (or only partly covered) by the reach information requirements.
"x*" denotes when a given information requirement is not normally mandatorily required, but could be triggered.

Information Requirement	Level 0 and higher (very) basic level	Level 1 and higher	Level 2 and higher	Level 3 and higher	Level 4	Comments, including why information requirements necessary
Adsorption/Desorption - screening and further information e.g. leaching tests (soil, sediment, sludge)		x (soil)	x (other relevant media)	x*		Testing of relevant media in relation to emission and exposure. * Possible triggering of further information
Bioaccumulation		x (most relevant species)	x*			*This tonnage level given the lack of Kow applicability.* *In fish dietary exposure should be preferred.* ** Further testing in other species may be triggered.*

Information Requirement	Level 0 and higher (very) basic level	Level 1 and higher	Level 2 and higher	Level 3 and higher	Level 4	Comments, including why information requirements necessary
Ready biodegradation		x				Degradation should be looked at in a more holistic context as physico-chemical degradation processes, rather than biological degradation, may be the predominant pathway for degradation of nanomaterials.
Simulation testing - ultimate degradation in surface water - soil simulation - sediment simulation - degradation products			x (most relevant media)	x (other relevant media)		Degradation should be looked at in a more holistic context as physical chemical degradation processes rather than biological degradation may be the predominant way for degradation of nanomaterials.
Activated sludge inhibition		x*	x			* Depending on potential exposure to sewage sludge
Acute toxicity - growth inhibition algae		x				Relevant given the expected exposure to waste water treatment plant species.
Acute or long-term *Daphnia*		x	(x)			If long term *Daphnia* test is performed the acute test may be omitted. Long term *Daphnia* test may postponed to level 2 if another long term study is conducted on level 1 (see below)
Acute toxicity, terrestrial or benthic species		x	x*			** Second acute test may be triggered based on considerations regarding emission /environmental distribution*
Long-term, terrestrial or benthic species		x*	x (at least one species)	x (second species)		** Long term toxicity test in sediment may be triggered due to the expected agglomeration/aggregation in most natural waters*

Information Requirement	Level 0 and higher (very) basic level	Level 1 and higher	Level 2 and higher	Level 3 and higher	Level 4	Comments, including why information requirements necessary
Acute toxicity -fish		x				The low tonnage level chosen based on arguments in SKEP (2011) and German CA (2012).
Long-term toxicity - fish			x*	x		* May be triggered
Long-term or reproductive toxicity to birds					x*	* May be triggered

Information requirement on “Ready biodegradation” and “Acute growth inhibition test on algae” are requested at the lowest tonnage level as in REACH. Other testing end-points are requested (or may be triggered) at relatively lower levels compared to REACH.

6. Conclusion

A number of expert groups, associations and authorities have discussed or suggested relevant information requirements for testing and assessing the hazards and risks of nanomaterials. Based on a review of these references, a proposal for a regulatory or advisory information requirement scheme for nanomaterials has been developed. In developing the proposal, it has been taken into account for which information requirements there seems to be consensus among the references reviewed, scientific motivation provided in the references (including whether testing is currently possible), as well as input and suggestions made by the expert advisory group having supported the project.

The proposed information requirement scheme is based on the "REACH methodology", i.e. a stepwise approach requiring more information at higher tonnage levels. It is important to stress, however, that the proposed scheme should not necessarily be seen as a proposal for updating REACH, as it could also be put forward as a stand-alone scheme for nanomaterials and used in relation to adapting other existing legislation, or it could be used for guiding. It has been outside the scope of this project to speculate further on possible regulatory implementation of the proposed scheme.

The specific proposal for a stepwise information requirement scheme consists of four tonnage levels (Level 1-4, see tables in Chapter 5), which could correspond to the REACH tonnage trigger levels or be lowered as suggested by a number of reviewed references (e.g. with a factor 10, due to the generally higher toxic potency of nanomaterials - in relation to weight as a metric - as compared to bulk/macro materials). This issue is, however, left open in the proposed scheme, as choice of a tonnage trigger level is a policy issue. On the other hand, if information is required at a very low tonnage levels (e.g. down to 10 kg/year - in this report considered "Level 0"), an information requirements base set consisting solely of parameters for identification and characterisation of nanomaterials is suggested.

Compared to information normally required for chemicals, the following 'new' information requirements are suggested:

- Explicit requirement for information on Crystal structure*
- Primary particle size distribution**
- Agglomeration/aggregation**
- Specific surface area**
- Morphology/shape/aspect ratio**
- Information on surface modifications
- Catalytic properties, photo-catalytic properties, radical formation potential (to be further defined)
- Surface charge/zeta potential
- Dustiness
- Properties for the fate of nanomaterials in water (in addition to water solubility, see details in Chapter 4)
- Photo degradation.

* Considered implicitly required by REACH

** There appears to be lack of consensus about whether these information requirements are already covered by the REACH information requirement on 'granulometry' and it is therefore suggested to explicitly require these.

It can be seen that most of the 'nano-additional' information requirements suggested relate to the description/characterisation of nanomaterials and a few to other physicochemical properties, whereas no entirely new information requirements are suggested for environmental and human health properties.

On the other hand, for a number of existing information requirements, it is suggested to adapt the endpoints and/or to modify the adaptation rules, including (see further details in Chapters 4 and 5):

- Further information/guidance on toxicokinetics/ADME properties
- For acute and repeated toxicity: To consider the inhalation route the first route of choice
- For inhalation toxicity: To consider extended examinations (Chapter 5)
- For *in vitro* mutagenicity: To focus on mammalian (non-bacterial) cells
- Environmental fate: To request data on adsorption-desorption, simulation testing for degradation, and on bioaccumulation at a relatively lower trigger level as compared to REACH
- For ecotoxicity testing: In general to request acute and long term testing at relatively lower trigger levels as compared to REACH and to focus more on testing of benthic/sediment species.

For information and further details on suggested adaptation rules for the information requirements included in the proposed testing scheme, see Chapters 4 and 5.

In addition to the proposed tonnage driven information requirements for nanomaterials, the proposal presented in Chapter 5 also highlights a number of issues of a more general and cross-cutting nature, which should be addressed in relation to a regulatory testing requirements scheme for nanomaterials, possibly in the legislation itself, but certainly in guidance:

- All available information on the nanomaterial should be obtained and reported, i.e. not only the standard information required at a given tonnage level. This should in particular indicate the need for providing information on characterisers known to influence the properties of the nanomaterial.
- General rules for adaptation of the standard testing requirements in line with REACH Annex XI, but with additions/emphasis relating to (details in Chapter 5):
  - Use of exposure-driven testing, taking into account that different nanoforms having different properties may be used differently and result in different exposure scenarios and testing needs. Therefore it should be stressed that use of these approaches should be done on a "form-to-form" basis.
  - Use of "scaling" for toxic potency considerations, e.g. scaling according to particle number or particle surface area, when scientifically relevant.
  - Characterisation of the nanomaterial in various phases of its lifecycle can be triggered by use/exposure considerations.
  - Possible waiving of testing of the nanoform in certain cases. In relation to use of existing data, it could be considered that if macro/bulk form(s) of the nanomaterials are very toxic and thereby trigger the most severe classification, testing of the nanoform might be waived in relation to classification and labelling considerations. Testing might still be needed for establishing no-effect levels (DNELs/PNECs) and for risk/safety assessment purposes.
- The importance of sample preparation and dosimetry in relation to all types of testing of nanomaterials should be stressed. This issue is currently considered one of the main challenges related to nanomaterials.
- Choice of metric(s) for reporting hazard (and exposure) data
- If registration is required: Whether these should preferably be done by consortia, as e.g. in REACH
- If registration is required: Whether these should be done for each nanoform (many registrations) or whether all nanoforms of a nanomaterial should be registered together, but with clear descriptions of the different forms within the dossier (fewer registrations).

Overall, introducing a testing requirement scheme for nanomaterials would require a number of political decisions, e.g. in relation to legal instruments to be used, tonnage triggers and scope of individual registrations (for a given nanomaterial chemistry or for each nanoform of that chemistry).

In addition, actual implementation would require further consensus building and guidance development in certain technical and scientific fields, which at relevant intervals should be aligned with scientific developments, not the least of which is the ongoing test guideline development in OECD and other fora.

Appendix 1: List of references addressed in the project

Key references (in chronological order)

Environmental Defense – DuPont (2007). Nano Partnership. Nano Risk Framework. STEP 2A: Develop Life Cycle properties profile and STEP 2B: Develop Lifecycle Hazard Profile p 37-53.

SCENIHR (2007). Opinion on the Appropriateness of the Risk Assessment Methodology in Accordance with the Technical Guidance Documents for New and Existing Substances for Assessing the Risks of Nanomaterials. Scientific Committee on Emerging and Newly Identified Health Risks.

VCI (2008). Responsible Production and use of Nanomaterials. German Chemical Industry Association - with focus on Guidance for a Tiered Gathering of Hazard Information for the risk Assessment of Nanomaterials (p 12-14).

SCENIHR (2009). Risk Assessment of Products of Nanotechnologies. Scientific Committee on Emerging and Newly Identified Health Risks.

OECD (2009). Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials. ENV/JM/MONO(2009)21.

RIVM (2009). Nanomaterials under REACH, Nanosilver a case study. RIVM, National Institute for Public Health and Environment report 601780003/2009.

OECD (2010). Preliminary Guidance Notes on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials. ENV/JM/MONO(2010)25.

EFSA (2011). Guidance on the risk assessment of the application of nanoscience and nanotechnologies in food and feed chain, Scientific Opinion. European Food Safety Authority. EFSA Journal 2011;9(5);2140.

RIP-oN1 (2011). REACH Implementation Project, Substance Identification of Nanomaterials (RIP-oN1). Advisory Report. European Commission (2011).

RIP-oN2 (2011). Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH (RIP-oN2). RNC/RIP-oN2/FPR/1/FINAL.

SKEP (2011). Nanomaterials in REACH – evaluation of applicability of existing procedures for chemical safety assessment to nanomaterials. Malkiewicz K, Pttitt M, Dawson KA, Toikka A, Hannsson SO, Hukkinen J, Lynch I, and Lead J. SKEP ERA-NET (2011).

NANO SUPPORT (2012). Scientific technical support on assessment of nanomaterials in REACH registration dossiers and adequacy of available information. European Commission (2012).

OECD (2012). Inhalation Toxicity Testing: Expert Meeting on Potential Revisions to OECD Test Guidelines and Guidance Documents. ENV/JM/MONO(2012)14.

SCCS (2012). Guidance on the Safety Assessment of Nanomaterials in Cosmetics. Scientific Committee on Consumer Safety. SCCS/1484/12.

Further references:

ENRHES (2009). Engineered Nanoparticles: Review of Health and Environmental Safety.

OECD (2010). Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme: First Revision, ENV/JM/MONO(2009)20/REV.

OECD (2010). List of Manufactured Nanomaterials and List of Endpoints for Phase One of the Sponsorship Programme for the Testing of Manufactured Nanomaterials: Revision.

Danish EPA (2011). Survey on basic knowledge about exposure and potential environmental and health risks for selected nanomaterials. Environmental Project No 1370, Danish Environmental Protection Agency.

SRU (2011). Vorsorgestrategien für nanomaterialen. Sondergutacheten. Sachverständigenrat für Umweltfragen. (Whole report in German languish).

SRU (2011). Precautionary Strategies for Managing Nanomaterials, Summary for policy makers. German Advisory Council on the Environment (English summary report).

CIEL (2012). Just out of REACH. How REACH Is Failing to Regulate Nanomaterials and How it Can Be Fixed. The Center for International Environmental Law, Switzerland.

ECHA Guidance nanoupdates (2012). Appendices to Chapter R7a-R7c of the Information Requirements & Chemical Safety Assessment (IR&CSA) guidance.

German CA (2012). Nanomaterials and REACH – Background Paper on the German Federal Authorities' Position. Background paper + Appendix I, II, III, VI, V, VI, VII. - received from DEPA.

JRC (2012). JRC reference report 2012. Linsinger T, Roebben G, Gilliland D, Calzolai L, Rossi F, Gibson N & Klein C. Requirements on measurements for the implementation of the European Commission definition of the term 'nanomaterial'. Report EUR 25404 EN.

European Parliament (2012). Letter of 6 July 2012 from the European Parliament to the European Commission - received from DEPA.

NL (2012). Letter of 6 July from the Dutch Ministry of Infrastructure and the Environment to the European Commission on behalf of 10 EU member states (Austria, Belgium, Czech Republic, Denmark, France, Italy, Luxembourg, Spain, Sweden and The Netherlands) and Croatia - received from DEPA.

Appendix 2: Short summaries from the initial review of references and further division into 'key' and 'further' references

Key references (in chronological order):

Environmental Defense – DuPont (2007). Nano Partnership. Nano Risk Framework. STEP 2A: Develop Life Cycle properties profile and STEP 2B: Develop Lifecycle Hazard Profile p 37-53.

Content

This framework was developed in close cooperation between the Environmental Defense Fund and DuPont and subject to intensive stakeholder consultation (government, industry and public interest groups). It aims at establishing a process that can be widely used by companies and other organizations for ensuring the responsible development of nanoscale materials. STEP 2A discusses establishment of a 'properties base set'; basically parameters relevant for identification, characterisation and physicochemical description of nanomaterials. In line with the EFSA (2011) and SCCS (2012) guidance documents summarized elsewhere in this appendix, the nano risk framework stresses that these basic properties (and possibly also the toxicity properties) *may change during the life cycle* as a consequence of processing (heating, milling, surface treatment/doping, change of production process e.g. from pilot to full scale, etc.), incorporation into liquid preparations or solid matrices, as well as a result of ultimate fate in the human body or the environment. It is stated that "For these reasons, it may thus be necessary to characterise the material at multiple points - unless there is good reason to expect that the material will remain unchanged". STEP 2B aims at characterising the materials potential health and environmental effects over the entire life cycle. Base set data for human health, ecotoxicity, fate & behaviour and physicochemical hazards (flammability, explosion properties, etc) are suggested. On top of this, further data should be generated as needed in an iterative manner considering the substance properties (STEP 2A) and the foreseen uses and exposures (i.e. exposure based adaption).

Triggers and waivers

In general, reference is made to existing guidelines (e.g. NTP and OECD) without evaluating their applicability for nanomaterials. Considerations for adaptation (need or not) in relation to individual endpoints appear to be generic considerations applicable for chemicals in general and not specifically related to nanomaterials. The idea of a base set for all nanomaterials and 'additional data as needed' is introduced.

Further use in this project

The project is considered a key reference in relation to all relevant information requirements for nanomaterials in a chemicals legislation/management context.

SCENIHR (2007). Opinion on the Appropriateness of the Risk Assessment Methodology in Accordance with the Technical Guidance Documents for New and Existing Substances for Assessing the Risks of Nanomaterials. Scientific Committee on Emerging and Newly Identified Health Risks.

Content

This document assesses to which extent the existing risk assessment methodology described in the Technical Guidance Documents for New and Existing Substances are valid for the assessment of nanomaterials. The relevance of the traditional toxicological end-points is highlighted and discussed for nanomaterials together with new areas of concern for nanomaterials. Of specific toxicological concern is mentioned the distribution of nanomaterials to the brain, toxicity driven by inflammatory processes and the potential for cardiovascular effects. For ecotoxicity, the use of log Kow for estimating organic carbon partition in environmental media and BCF is questioned and the criteria for PBT identification should be further evaluated for their applicability to nanomaterials.

The relevance of alternative dose metrics in relation to particle number and surface area is discussed for both toxicity and ecotoxicity. In general the risk assessment approach both in relation to toxicity and ecotoxicity is considered applicable for nanomaterials; however, experience is needed for further verification and adaptations. Especially further clarification with respect to methodology for estimating Predicted Environmental Concentrations (PECs) for nanomaterials and for identifying the relevant taxa/species for testing of nanomaterials is needed.

Triggers and waivers

The report gives a very rough and overall decision scheme for risk assessment mainly driven by general exposure considerations. However, more specific triggers/waivers for testing are not identified.

Further use in this project

The scientific evaluations, the concerns, and the proposals expressed in this document can be seen as early building blocks and as a basis for later opinions and recommendations from the EU scientific committees.

VCI (2008). Responsible Production and use of Nanomaterials. German Chemical Industry Association - with focus on Guidance for a Tiered Gathering of Hazard Information for the risk Assessment of Nanomaterials (p 12-14).

Content

The German Chemical Industry (VCI) has developed this publication to support implementation of the Global Responsible Care Core Principles for nanomaterials with particular focus on REACH. The document generally considers that nanoforms are not different substances than their bulk/macro form and therefore takes the starting point that nanoforms are registered along with other forms of the substance. It is recognised that the nanoform may have a different classification as compared to the bulk form. Pages 12-14 constitute a guidance on the tiered gathering of hazard information for the risk assessment of nanomaterials constituting a 'base set' and 'extended information' on a case-by-case basis. It is stated that the hazard information generated should duly reflect the spectrum of all identified uses, including uses of the substance in the nanomaterial state. It is also noted in the document that all identified uses, including uses representing less than one tonne/year, should be addressed.

Triggers and waivers

The REACH registration triggers are not challenged in this document. The idea of 'basic information' for the nanoform and 'extended information' on a case-by-case basis is introduced. Reference is made to the general adaptation principles in REACH Annex XI. No specific nanoform adaptations are discussed. It is indicated in the document that 'validated test methods may not exist' for some endpoints. No further discussion of the appropriateness of current test guidelines is provided in this reference.

Further use in this project

The project is considered a key reference in relation to all relevant information requirements for nanomaterials in a chemicals legislation/management context.

SCENIHR (2009). Risk Assessment of Products of Nanotechnologies. Scientific Committee on Emerging and Newly Identified Health Risks.

Content

This document from the Scientific Committee on Emerging and Newly Identified Health Risks points out relevant issues with regard to risk assessment of nanomaterials covering issues such as important parameters for characterization of the nanomaterial, estimation and measurement of exposure, and hazard identification/testing including absorption, distribution, metabolism and excretion (ADME) considerations. The document does not go into detail on how testing and data

requirements should be performed, but discusses several concerns for nanomaterials based on the current literature. With respect to human health, especially ADME, considerations and translocation of nanomaterials into the brain and across the placenta into the fetus are mentioned. Furthermore, data and inconsistencies of results from genotoxicity testing of nanomaterials are discussed and the need for further knowledge concerning the possible cardiovascular, neurotoxic and reprotoxic effects is emphasized. With respect to environmental fate, distribution and ecotoxicity, it is questioned how the traditional determination of water solubility, vapour pressure and determination of log Kow can be used for nanomaterials to predict environmental distribution. With respect to tests for degradation, aquatic, terrestrial and sediment toxicity issues regarding sample preparation and the availability of the nanoparticles to the test system are discussed. The lack of knowledge, experience and the performance of the tests are underlined and areas for further research and development are indicated, as currently only very little specific guidance can be given.

Triggers and waiver

A general and rough matrix driven by exposure considerations is given for identifying needs for further assessment.

Further use in this project

The recommendation in this opinion and the discussion of relevant data and testing of nanomaterials is given on a general level. Thus, the discussion and identification of relevant parameters for nanomaterials can be used as support for choosing relevant parameters for this project. Specific guidance for the testing or for a regulatory test strategy is not given, as the recommendations are more directed towards the needs for more scientific clarification and research.

OECD (2009). Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials. ENV/JM/MONO(2009)21.

Content

In the OECD (2009) document, a working group under the OECD Working Party on Manufactured Nanomaterials has made a preliminary review of the OECD test guidelines for their applicability to nanomaterials. Overall it was found that the majority of the end-points and the test guidelines regarding physicochemical, environmental fate, ecotoxicological and toxicological properties were relevant and applicable to nanomaterials. Especially for test guidelines examining environmental fate and ecotoxicity, further developments are needed regarding sample preparation and the availability of the nanomaterials to the test system and on detection and analysis of ENMs. Important for the use of the test guidelines are the further guidance document on sample preparation and dosimetry. For some of the toxicological guidelines, further examinations of relevant parameters were proposed.

Triggers and waivers

Considers to which extent a guideline is applicable for all nanomaterials with respect to relevant physicochemical parameters critical for the performance of the test (e.g. water solubility or whether the nanomaterial is an organic or inorganic chemical).

Further use in this project

The applicability of the OECD test guidelines (TGs) is mostly evaluated on an overall theoretical basis in relation to whether the end-point examined in the TGs would be relevant for NMs. As experience with the use of the test guidelines for nanomaterials is limited, it is still not possible to give further specific advice for the testing in relation to the majority of the test guidelines. Nevertheless, it is important that any proposal in this project regarding testing requirements can be supported by the evaluations/ recommendations from this OECD report.

RIVM (2009). Nanomaterials under REACH, Nanosilver case study. RIVM, National Institute for Public Health and Environment report 601780003/2009.

Content

This document was conducted by order of the Netherlands Ministry of Housing, Spatial Planning and the Environment (VROM) and examined, based on a case study on nanosilver, whether the data-requirements under REACH and the risk assessment procedures were to be considered sufficient in insuring safe use of nanomaterials. By doing a hypothetical registration of nano-silver, specific problems and needs were addressed for end-point parameters for physicochemical, toxicological and ecotoxicological properties, as well as issues in relation to risk assessment and DNEL/PNEC derivation. Based on this exercise, a proposal was made for a data requirement for nanomaterials under REACH. It was proposed to i) reconsider the tonnage trigger levels and the lower registration level of 1 ton/year for nanomaterials, ii) apply a basis set of data requirements for nanomaterial and iii) to require a Chemical Safety Assessment and Report (CSA/CSR) in connection with the registration for all tonnage levels. Additional testing beyond base set data should follow the existing data requirements scheme according to REACH Annexes VI-XI; however, with no staggered timeline for registration of nanomaterials. The use of QSAR and use of *in vitro* models is not considered to be at a stage for implementation for data requirements and use in risk assessment. The exception to this is *in vitro* testing for genotoxicity, cytotoxicity, oxidative stress and inflammation, as use of such data seems relevant.

Proposed toxicological information requirements:

> *At base set level:* toxicokinetic (ADME) testing; repeated dose toxicity (inhalation); *in vitro* gene mutation test; *in vitro* cytotoxicity test.
>
> *At higher tier level: in vivo m*utagenicity test; reproductive toxicity tests; sensitisation test

Proposed ecotoxicological information requirements:

> *At base set level:* algal growth test; chronic *Daphnia* test; transformation in environment, partitioning coefficients (Kp values).

At higher tier level: fish bioaccumulation test; chronic fish test

Triggers and waivers

The tonnage-based data requirement triggers are proposed to be re-evaluated for nanomaterials. Data on bulk form is not considered as a waiver for the base set data on a given nanomaterial, as these data are important for comparing the properties between the nano- and the bulk form. If sameness can be concluded from the base set, data waiving may be relevant for further end-point testing. Data on kinetics is emphasized and may be used, for example, as a waiver as occasionally documentation of no systemic uptake may turn the focus towards tests determining local effects instead of systemic toxicity.

Further use in this project

This document is considered useful for this project as the aim was to generate data requirements based on the existing knowledge and experience. The proposed data requirements further cover data on exposure although they are expressed on a more general basis and then refer to exposure data requirements in REACH Annex 1.

OECD (2010). Preliminary Guidance Notes on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials. ENV/JM/MONO(2010)25.

Content

This document is closely linked to the OECD (2009) ´Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials´, as the document contains cross-cutting issues with respect to handling and dosing of nanomaterials in test systems i.e. how to prepare and

administer dosing material in nanoform for *in vitro/ in vivo* test systems for toxicity, ecotoxicity, and fate and behaviour in the environment.

Therefore, the document contains guidance on storage of test material and provides information on factors that may affect stability with respect to agglomeration /aggregation. Further guidance is given on characterisation of the nanomaterial itself and for the nanomaterial in stock dispersions (primary particle size and particle size distribution, mass concentration in the stock dispersion, degree of agglomeration, pH, ionic strength, surface area, surface chemistry, surface charge, dispersion behaviour in water, octanol/water partition coefficient, and crystal structure). For ecotoxicity studies, guidance for dispersion of nanomaterial for aquatic media and preparation of test material for non-aqueous media is given.

Advice in relation to test method applicability and dosimetry is given in relation to tests regarding environmental behaviour (degradation, transformation and accumulation studies) that generally is considered relevant and applicable for nanomaterials.

For human health testing, specific aspects regarding the dosage and sample preparation of the nanomaterial test sample for oral, inhalational and dermal exposure studies are mentioned. Especially for inhalational studies, further guidance on the methods for characterisation and monitoring of the test atmosphere with respect to mass and number concentration, primary particle size and particle size distribution is given. For *in vitro* studies, various possibilities for interactions between the nanomaterial and the various constituents (e.g. proteins) in the *in vitro* test medium are mentioned.

With respect to dose metrics for the testing, it is advised to consider surface area and number concentration.

Triggers and waivers

Outside the scope of this reference.

Further use in this project

The considerations and recommendations in this document are of key relevance for the further work in this project, as the aspects described in this document are relevant for all further testing with nanomaterials. It should be noted that the OECD WPMN has recently published an update of this document.

EFSA (2011). Guidance on the risk assessment of the application of nanoscience and nanotechnologies in food and feed chain, Scientific Opinion. European Food Safety Authority. EFSA Journal 2011;9(5);2140.

Content

The European Food Safety Authority (EFSA) has developed a practical approach for assessing potential risks arising from applications of nanoscience and nanotechnologies in the food and feed chain. Guidance is provided on: i) the physicochemical characterisation requirements of engineered nanomaterials used e.g. as food additives, enzymes, flavourings, food contact materials, novel foods, feed additives and pesticides, and ii) testing approaches to identify and characterise hazards arising from the nano-properties which, in general, should include information from *in vitro* genotoxicity, ADME conditions and repeated-dose 90-day oral toxicity studies in rodents. The guidance allows for less information to be provided when no exposure to the nanomaterial can be verified.

Triggers and waivers

The document discusses exposure-based triggers/waivers for testing; however, these specifically address exposure in relation to use of nanomaterials in food. Triggers for further testing for reproductive toxicity (e.g. ADME data on the penetration of the placenta) and chronic toxicity/ carcinogenicity are indicated (e.g. data on accumulation or data on organ toxicity).

Further use in this project

The document that builds upon the previous opinions from the EU scientific committees identifies important parameters for identification and characterisation of nanomaterials and specifies available methods for determination of these parameters (see Annex 4). Furthermore, a specific testing strategy including ADME studies, *in vitro* and *in vivo* genotoxicity tests, and oral 90-day tests is presented. Thus, this EFSA document is important for further considerations when establishing a proposal for a testing requirement scheme for nanomaterials.

RIP-oN1 (2011). REACH Implementation Project, Substance Identification of Nanomaterials (RIP-oN1). Advisory Report. European Commission (2011).

Contents

The Commission Services initiated a number of REACH Implementation Projects on Nanomaterials (RIP-oNs) to evaluate the applicability of the existing REACH guidance to nanomaterials, and if needed, to develop specific advice on how the guidance could be updated to better reflect nanomaterials.

The objective of the project 'Substance identification of nanomaterials' (RIP-oN1) was to evaluate the applicability of existing guidance and, if needed, to develop specific advice on how to establish the substance identity of nanomaterials. The project was coordinated by the European Commission's Joint Research Centre, and carried out in cooperation with an expert group comprising members from Member State Competent Authorities, industry, NGO and ECHA. The experts were nominated by the Competent Authorities for REACH and Classification and Labelling (CARACAL) and the observers of this committee. Progress and (draft) results were reported to the Competent Authorities subgroup on Nanomaterials (CASG Nano), which deals with implementation issues concerning REACH and nanomaterials. CASG Nano was invited to provide written comments to various deliverables throughout the project. While there was general agreement in relation to which basic parameters would be relevant for describing nanomaterials, there was strong disagreement among stakeholders in relation to whether these parameters should be identifiers; i.e. included in the Substance Identification and thereby trigger separate registrations for nanoforms, or whether the parameters should be 'characterisers' used to describe different forms (including nanoforms) of a substances within one registration. Possible identifiers/characterisers discussed were particle size (distribution), shape/aspect ratio and surface treatment/functionalisation. There was agreement that crystalinity may be of key importance for nanomaterials; however, it was clarified by ECHA that this is already required as part of Substance Identification in REACH, and therefore there was no need to further address this property within the scope of this project. The study involved four case studies (nano-silver, Carbon nanotubes, nano-calciumcarbonate, nano-titaniumdioxide).

Triggers and waivers

Substance identification/characterisation would be relevant for all tonnage levels; i.e. from 1 tonne/year in REACH. It was outside the scope of the RIP-oN1 project to discuss the applicability of the 1 tonne trigger level.

Further use in this project

The project is considered a key reference in relation to identification/characterisation of nanomaterials.

RIP-oN2 (2011). Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH (RIP-oN2). RNC/RIP-oN2/FPR/1/FINAL.

Content

The objectives of the RIP-oN2 project were to develop specific advice on i) how REACH information requirements on intrinsic properties of nanomaterials can be fulfilled, including the appropriateness of the relevant test methods (and dosimetry) for nanomaterials and outline, when relevant, possible specific testing strategies, and ii) the information that is needed for safety

evaluation and risk management of nanomaterials and, in particular, if information is needed beyond or in addition to the current information requirements listed in REACH Annexes VI-X. The project was initiated by a review activity addressing international (incl. OECD and ISO/CEN) activities, results of EU Framework Programme 6 and 7 (FP6 and 7) projects and a review of the scientific literature. The latter was largely based on the ENRHES project (see under further references) and supplemented by a data search to cover up until March 2010. The project was overseen by the European Commission's Joint Research Centre and contracted out to a consortium led by the Institute of Occupational Medicine (and involving the European Chemical Industry Council - CEFIC). Preliminary and draft final project results were subject to intensive EU Member State, NGO and industry stakeholder consultation, including meetings and written comments.

Adaptation/waiving and registration triggers

The project did not address whether several forms of a substance should be registered independently or in the same registration dossiers. In line with this, it did not discuss the current REACH registration triggers. The project did go into some discussion in relation to testing adaptation, not the least in relation to the lack of a current knowledge base for read-across between nanoforms and between macro/bulk forms and nanoforms.

Further use in this project

Given the thorough examination of the scientific literature and the intensive stakeholder consultation, the project is considered a key reference in relation to all relevant information requirements for nanomaterials in a chemicals legislation context.

SKEP (2011). Nanomaterials in REACH – evaluation of applicability of existing procedures for chemical safety assessment to nanomaterials. Malkiewicz K, Pttitt M, Dawson KA, Toikka A, Hannsson SO, Hukkinen J, Lynch I, and Lead J. SKEP ERA-NET (2011).

Content

This project funded by SKEP (Scientific Knowledge for Environmental Protection) was conducted by University Institutes from Sweden, UK, Ireland and Finland. In the project, an assessment is made of the current applicability of REACH to cover nanomaterials. Recommendations are given in relation to a future regulatory policy and to technical-scientific issues in relation to characterisation and testing of nanomaterials. The recommendations have been presented at national and international meetings where feedback from stakeholders (academia, government and industry) was received. The report recommends that toxicokinetic/ADME studies are obligatory for all production volumes and that registration should start at a lower tonnage level than at present in REACH. A conversion factor of 100 to the mass based triggers is proposed for nanomaterial, i.e. the data requirements should start at 10 kg/ year. However, other alternative triggers such as total surface area or total particle number could also be considered as relevant. All types of nanoforms should be considered as different chemicals from bulk, and thus be considered as non-phase-in substances. Differences in surface modification, size, shape surface charge and crystalline structure may result in separate registrations for each nanoform. Parameters for characterisation are proposed. With respect to toxicological testing, no specific testing scheme is proposed; however, more emphasis should be directed to the surface-driven properties of the nanomaterials and to focusing testing on potential effects related to these properties compared to the traditional REACH tiered testing of bulk chemicals. In relation to environmental fate and ecotoxicity, the relevance of the dose metric expressed as surface area or in number concentration is discussed and the importance and concern for proper sample preparation and delivery of dose to test system is expressed. Nanospecific aspects in relation to testing for degradation, acute and chronic ecotoxicity testing and testing for bioaccumulation are discussed. The applicability of the guidelines for bioaccumulation should be assessed on various types of nanomaterials. As a starting point it is recommended that standard requirement in addition to an acute test with *Daphnia* should cover acute testing with a terrestrial and a benthic species, and that this should be supplemented with

further information on chronic toxicity. It is recommended that, based on simulation of the environmental distribution, an alternative ecotoxicity data requirement scheme should be developed where testing is targeted towards the most relevant species.

Triggers and waivers

The project proposes that nanomaterials always be treated as separate chemicals compared to bulk, and that the current triggers for REACH data requirements should be lowered e.g. using on a conversion/reduction factor of 100 associated with the existing tonnage based triggers. When more knowledge becomes available, the surface-driven properties should be used as triggers for more focused testing of nanomaterials. Increased knowledge and better simulation of environmental distribution may further target the strategy for ecotoxicity testing.

Further use in this project

With regard to testing and future strategies, the report covers particularly the environmental aspects in great detail and proposes an interim strategy for testing.

NANO SUPPORT (2012). Scientific technical support on assessment of nanomaterials in REACH registration dossiers and adequacy of available information. European Commission (2012).

Content

The objective of the NANO SUPPORT project was to suggest options for adapting the REACH Regulation to better reflect the properties of nanomaterials. This should be done based on an analysis of how nanomaterials had been registered by the first registration deadline (December 2010) and existing scientific knowledge about the properties of nanomaterials. The latter was mainly done by taking into account the findings from recent reviews done in the RIP-oN projects (see above). The options should mainly address how the REACH annexes could be amended, and options for adapting the enacting terms of REACH could be suggested if deemed relevant within the scope of the project. The options should be subject to an 'impact assessment' of the socio-economic impacts which would follow if the options would be implemented. This final phase of the project is on-going and considered outside the scope of the current project. The project was carried out in cooperation between the European Commission Joint Research Centre and ECHA. Preliminary and draft final results were subject to written stakeholder consultation and discussion in the REACH competent authority subgroup on nanomaterials (CASG nano), including NGO and industry stakeholder representatives.

The first phase on the project was to identify which nanomaterials had been registered by December 2010. This task was undertaken by ECHA which had to develop specific search tools, as there is no specific/explicit requirement for the registrant to request information about whether a substance is a nanomaterial or whether a given registration dossier addresses nanoform(s) of the substance. Based on largely automated searches and a screening of information on size (distributions) under the 'granulometry' endpoint, 45 dossiers (covering 34 substances) possibly addressing nanomaterials were identified. That task report is not in the public domain, partly because the dossier/substance names are considered confidential. The NANO SUPPORT report available to this project constitutes the tasks of the project dealing with analysis and assessment of the identified dossiers (although substance names are anonymised, see above) and development of options for possible adaptation of REACH. Initially, the 45 dossiers identified by ECHA were reduced to 25 dossiers (covering 19 substances) as it could not definitely be concluded that the 20 deselected dossiers addressed nanomaterials based on the information contained in those dossiers. In general, the project was challenged by the registration dossiers not explicitly addressing the covered nanoform(s). One of the main conclusions of the project is that a more detailed characterisation of the addressed nanoform(s) would be the starting point. Other information requirements, e.g. on environmental fate and behaviours and on (eco-)toxicological properties would only be relevant if the addressed nanoforms are clearly described and characterised upfront in the registration dossier.

The project does not take a stand as to whether this should be done as part of the substance identification (triggering separate registrations) or as part of a more detailed characterisation within the dossier.

Triggers and waivers

It was outside the scope of the project to consider REACH registration volume/tonnage triggers. In relation to the addressed endpoints, the project considers some of the column 2 adaptations in Annex XII-X, but largely addresses adaption in relation to possible amendment of REACH Annex VI and XI.

Further use in this project

The project is considered a key reference in relation to all relevant information requirements for nanomaterials in a chemicals legislation context, based on practical experience with registration of nanomaterials, scientific review of the literature (via RIP-oN results) and subject to stakeholder consultation.

OECD (2012). Inhalation Toxicity Testing: Expert Meeting on Potential Revisions to OECD Test Guidelines and Guidance Documents. ENV/JM/MONO(2012)14.

Content

The recommendations from this OECD expert meeting further build on the recommendations from the OECD guidance note on sample preparation and dosimetry. Suggested revisions for the OECD Test guidelines 403/412/413/436 inhalation test specifically address obtaining and maintaining control of exposure with respect to particle size and degree of aggregation/agglomeration and applying the most relevant test conditions in relation to human exposure. In addition to mass concentration, further dose metrics expressed as number and surface area should be determined. It was emphasized that inhalation exposure should be preferred compared to intra-tracheal instillation and aspiration exposure.

With respect to additional toxicological end-points, no agreed and specific recommendations were given, but relevant end-points were discussed (histopathology of the olfactory bulb and brain, measurement of cell differentials in bronchoalveolar lavage fluid (BALF) for inflammatory effects, cytotoxicity parameters such as lactate dehydrogensas (LDH) and lung permeability (total protein), histopathology of the parietal pleura and the subpleural proliferation of lung tissue, lung fibrosis and collagen accumulation, and measured lung burden).

Triggers and waivers

Outside the scope of this reference.

Further use in this project

It would be relevant to build on the recommendations from this report in the further work with this project in relation to inhalation testing.

SCCS (2012). Guidance on the Safety Assessment of Nanomaterials in Cosmetics. Scientific Committee on Consumer Safety. SCCS/1484/12.

Content

The document describes key issues relevant for risk assessment of nanomaterials in cosmetics. Important physicochemical parameters for characterization of the nanomaterial are identified and measurement methods are given. The testing methods used for hazard identification of conventional cosmetic ingredients are, to a broad extent, considered to be applicable for nanomaterials and specific evaluations of the testing of nanomaterials for the toxicological end-points are made. Furthermore, the SCCS concludes that validated and stand-alone *in vitro, ex vivo* and *in silico* models for the purpose of risk assessment of nanomaterials are not yet in place. The

SCCS emphasizes the need for further toxicokinetic (ADME) testing as this is crucial for evaluating the internal exposure and identification of target organs.

Triggers and waivers

The document proposes a risk assessment scheme where the need for nanospecific data is dependent on whether the nanomaterial is systemically available from the cosmetic product or whether only local effects may occur. More specific triggers and waivers are not given.

Further use in this project

The document refers back to the previous evaluations and opinions of the EU scientific committees and to the work in relation to the RIP-oN projects. The document identifies important parameters for identification and characterisation of nanomaterials and specifies available methods for determination of these parameters. Furthermore, the validity of *in vitro* testing of nanomaterials is discussed and the overall testing scheme for cosmetic ingredients is discussed and the relevance and applicability is evaluated in relation to nanomaterials. This SCCS document is the most recent and updated work from one of the scientific committees and is relevant for this project as a testing scheme for nanomaterials is discussed.

Further references:

ENRHES (2009). Engineered Nanoparticles: Review of Health and Environmental Safety.

Content

Engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES) was a 7th framework programme (FP7) project with the overall aim of performing a comprehensive and critical scientific review of the health and environmental safety of four classes of nanomaterials: fullerenes, carbon nanotubes (CNT), metals (focus on silver) and metal oxides (focus on TiO_2). The review considers sources, pathways of exposure, the health and environmental outcomes of concern, thus illustrating the state-of-the-art and identifying knowledge gaps in the field, in order to gather and assess evidence which has emerged to date and inform regulators of the potential risks of engineered nanoparticles in these specific classes. The final objective of the project was to perform a coherent evaluation of the feasibility of conducting a regulatory risk assessment for each material type and perform basic risk assessments to the extent possible based on the information presented within the review.

Further use in this project

The outcome of the ENRHES project was one of the key starting points for the RIP-oN2 project. The findings from the ENRHES study are therefore reflected in the RIP-oN2 project discussed as a key reference.

Triggers and waivers

These issues are discussed in relation to current lack of knowledge in terms of to read-across between nanomaterials and between bulk and nanoforms.

OECD (2010). Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme: First Revision, ENV/JM/MONO(2009)20/REV.

Content

The OECD Working Party on Manufactured Nanomaterials (WPMN), which was established in 2006, has launched a series of projects for addressing the safety challenges of nanomaterials. One of the most important projects is the sponsorship programme on the testing of manufactured nanomaterials. In this document, an agreed list of nanomaterials for which test sponsors could be identified is given. When identifying the specific parameters covered by the testing, it was not the intention to provide a full-scale testing scheme for the nanomaterials as initially it was more important to gain experience with testing of a selected set of end-points and, from the results, decide on further relevant testing.

Triggers and waivers

Outside the scope of this document.

Further use in this project

No further specific information on testing for the various end-points are given. However, the end-points and testing guidelines have to a great extent been identified as applicable and relevant for nanomaterials in the OECD working group that made an evaluation of the applicability of the existing OECD test guidelines (OECD 2009). Unfortunately, the current project cannot be governed from experiences and learning from the sponsorship testing, as results from the programme have not yet been finally evaluated and reported. However, it should be noted that the parameters covered by the sponsorship programme are also covered in the matrix tables used in this project.

OECD (2010). List of Manufactured Nanomaterials and List of Endpoints for Phase One of the Sponsorship Programme for the Testing of Manufactured Nanomaterials: Revision.

Content

This document mainly lists the end-points to be addressed in the sponsorship programme.

Further use in this project

The document does not add any information in addition to other OECD references included in the project and will therefore not be considered further.

Danish EPA (2011). Survey on basic knowledge about exposure and potential environmental and health risks for selected nanomaterials. Environmental Project No 1370, Danish Environmental Protection Agency.

Content

This project was initiated by the Danish EPA to provide an overview of the existing knowledge about seven of the most common nanomaterials (Fullerenes, nano-TiO2, zero valent nano-iron, nano-ceriumoxide, nano-silver, nanoclay and nano-SiO2), their environmental and health properties, the use of those nanomaterials and the possibility of exposure of humans and the environment. It was not within the scope of the project to systematically compare standard information requirement schemes against available information, but it was generally concluded that more information, in particular on characterisation (including surface functionalisation), environmental fate & behaviour and long-term testing of nanomaterials are needed. The report highlights the open issue of when, and if so how, data for the macro/bulk material could possibly be used for the nanoform.

Triggers and waivers

Outside the scope of this document.

Further use in this project

No direct use of this document is foreseen in the project.

SRU (2011). Vorsorgestrategien für nanomaterialen. Sondergutacheten. Sachverständigenrat für Umweltfragen. (Whole report in German languish).

and

SRU (2011). Precautionary Strategies for Managing Nanomaterials, Summary for policy makers. German Advisory Council on the Environment (English summary report).

Content

The German Advisory Council on the Environment (SRU) in these publications (German report and English summary report) makes recommendation on how to apply the precautionary principle in regulation and general risk management of nanomaterials. For several areas, recommendations are made. In relation to registration under REACH, it is concluded that extensive changes are necessary. Nanomaterials should be treated as if they were substances in their own right and registered as non-phase-in substances with dossiers of their own. A core data set (also for levels below 1 tonne) should have to be submitted to ensure a preliminary risk estimation and a Chemical Safety Report should be provided. Tonnage triggers must be reduced for nanomaterials and the standard information requirements need to be supplemented. The following data are to be included in the core data set: size distribution, solubility, bio-persistence, ADME, and data on acute and chronic toxicity. REACH Authorisation should be based more closely on the precautionary principle. It should also be possible to restrict or prohibit nanomaterials merely on the basis of an abstract concern. The German background report further contains a compilation of the knowledge regarding properties, uses, uptake in organisms, toxicology, ecotoxicology, exposure and risk

assessment on a series of nanomaterials: titanium dioxide, zinc oxide, aluminium and aluminium oxide, iron and ironoxide, silicium dioxide gold, silver, carbon black.

Triggers/waivers

A base data set is proposed at tonnage levels below 1 tonnes.

Further use in this project

The recommendations in this document is to a great extent comparable to the recommendations made by RIVM 2009 in relation to requirements for registration of nanomaterials under REACH, although data requirements are not specified to the same extent as in the RIVM report. In general, the thinking and arguments in the reports can be used as support for decisions in the context of this project.

CIEL (2012). Just out of REACH. How REACH Is Failing to Regulate Nanomaterials and How it Can Be Fixed. The Center for International Environmental Law, Switzerland.

Content

This NGO policy paper evaluates to what extent nanospecific issues and the safety of nanomaterials are addressed or could be covered within the existing REACH regulation. The document outlines several weaknesses of REACH in connection with regulation of nanomaterials, e.g. the lack of definition of a nanomaterial in REACH, the staggered registration deadline of a nanomaterial if a nanomaterial is not considered as a separate substance from the bulk substance with the same chemical identity, and the insufficient data requirements if the same tonnage based data requirement triggers apply for nanomaterials as for conventional chemicals. Based on these concerns, it is proposed that a nanomaterial definition should be included in REACH: that nanomaterials should be considered as non-phase-in substances, that the tonnage based triggers for data requirements should be lowered for nanomaterials, that a chemical safety assessment should be required for all registrations of nanomaterials, and that testing requirements should be updated with specific nano-provisions. An alternative for modifying REACH would be to implement the proposals in a stand-alone "nano-patch" to REACH with registration and data requirements starting from a trigger volume of 10 kg nanomaterial / year.

Triggers and waivers

The tonnage triggers for data requirements are proposed to be reduced. A starting point for data registration and data requirement of 10kg/ year is proposed for nanomaterials. It is proposed to consider nanomaterials as non-phase in substances.

Further use of the document in this project:

This is a policy document and not a technical document, as no specific description of the data requirements is given. However, it stipulates to use the processes and methods in REACH and adapt these to nanomaterials (disregarding whether the regulation of nanomaterials should be covered within or outside REACH), which is in line with the thinking in this project.

ECHA Guidance nanoupdates (2012). Appendices to Chapter R7a-R7c of the Information Requirements & Chemical Safety Assessment (IR&CSA) guidance.

Content

Based on the RIP-oN2 results, the European Chemicals Agency (ECHA) has updated the IR&CSA guidance in relation to Information Requirements. This was done as appendices to the existing information requirement chapters (R7a-R7c). The recommendations were updated via a rapid procedure as the RIP-oN2 project results had already been through extensive stakeholder consensus building, including several written comment rounds and meetings.

Further use of the document in this project

The content of these guidance update are fully covered by RIP-oN2 and therefore not discussed separately in this project.

German CA (2012). Nanomaterials and REACH – Background Paper on the German Federal Authorities' Position. Background paper + Appendix I, II, III, VI, V, VI, VII. -- received from DEPA.

Content

This German Competent Authorities document reflects the position of the German Federal Authorities on the regulation of nanomaterials under REACH. It discusses the EU definition of nanomaterials, the need for regulation under REACH and the use of size, shape and design either as possible identifiers for a substance (meaning separate registrations) or as characterisers for various forms of a substances (meaning common registrations with other forms of the same chemical composition). The position paper proposes registration requirements for nanomaterials at a tonnage level of 100 kg/year and further makes a proposal for a new annex to REACH (annex XVIII) with further nanospecific standard data requirements at a tonnage level for 1 ton/year or more for physicochemical properties, toxicological and ecotoxicological properties.

Triggers and waivers

Some suggestions for triggers and waivers are given, e.g. waiving and read-across are considered possible if the bulk form is classified in the most severe category for a classification end-point, whereas waiving cannot be performed on non-classification of the bulk form. Further testing may be triggered for fibrous nanomaterials in relation to biopersistency and critical dimensions of the fibers. A tonnage level threshold of 100 kg/years is suggested for nanomaterials.

Further use of the document in this project

Although not in the public domain and therefore not considered a key reference, this document is useful for this project as the argumentation and thinking behind a data requirement scheme can be used.

JRC (2012). JRC reference report 2012. Linsinger T, Roebben G, Gilliland D, Calzolai L, Rossi F, Gibson N & Klein C. Requirements on measurements for the implementation of the European Commission definition of the term 'nanomaterial'. Report EUR 25404 EN.

Content

This report elaborated by the European Commission Joint Research Centre advises on measurement methodologies in relation to the recommendation from the European Commission on a common definition of the term 'nanomaterial'. The report gives an overview of the capabilities of currently available measurement methods for particle size, including techniques such as electron microscopy, dynamic light scattering and centrifugal liquid sedimentation, among others. It also identifies measurement issues that remain to be solved. The conclusions highlight the practical challenges of measuring materials with widely varying properties. The report underlines that no single measurement method can be used for all materials to determine if each of them falls within the regulatory definition. Different methods will be required depending on the material under investigation. Therefore, a proper combination of measurement methods is required. The reliability of each of the measurement methods used in such combined, tiered approaches will need to be thoroughly checked in dedicated method validation studies.

Triggers and waivers

The idea of a tiered approach for identifying a material as nanomaterial or not is introduced.

Further use of the document in this project

The reference is important in relation to information requirements for size (distribution).

European Parliament (2012). Letter of 6 July 2012 from the European Parliament to the European Commission - received from DEPA.

Content

In 2009, the European Parliament (EP) called on the European Commission to undertake a full review of all relevant legislation within two years to ensure safety for all applications of nanomaterials. In the current letter from the European Parliament (signed by Carl Schlyter, vice president of the EP committee on the environment, public health and food safety) sent to the Commissioner for Environment Janez Potocnik (as representative for the Commission), the EP notes that the legislative review from the Commission is not yet available and that the briefing obtained from Janez Potocnik in a June 2012 meeting indicated that the Commission will not take sufficient action. In addition to requiring the Commission to consider all relevant legislation, the EP specifically for REACH calls on the Commission to ensure that nanomaterials are adequately addressed, including:

- reconsideration of the volume triggers for registration and chemical safety reports, which are considered 'not adequate' for nanomaterials

- reconsideration of the general information requirements, which are currently 'not sufficient' for nanomaterials

- address that there is no notification requirements for nanomaterials in articles.

Triggers and waivers

See above bullets.

Further use in this project

The letter highlights the EP position in relation to addressing nanomaterials in more detail in chemicals legislation, including a reconsideration of volume triggers and information requirements.

NL (2012). Letter of 6 July from the Dutch Ministry of Infrastructure and the Environment to the European Commission on behalf of 10 EU member states (Austria, Belgium, Czech Republic, Denmark, France, Italy, Luxembourg, Spain, Sweden and The Netherlands) and Croatia - received from DEPA.

Content

This letter acknowledged the valuable work that the European Commission has done in relation to establishing a definition for nanomaterials, but calls for further and quicker action. Reference is made to the 20 December 2011 resolution from the Council inviting the Commission to evaluate the need to develop specific measures for nanomaterials and to an Environmental Council meeting in June 2011 discussing the issue based on a Dutch note. In relation to REACH, the current letter calls on the European Commission without further delay to:

- Improve application to nanomaterials, including amending as appropriate REACH annexes and guidance, including aligning with the Commission Recommendation for a definition of nanomaterial (note: REACH annexes and guidance can be amended without the 'heavy' co-decision procedure)

- Through amendments of REACH or supplementary legislation (note: amending the enacting terms of REACH would require the 'heavy' co-decision procedure) consider to address:

- the current lack of definition of 'nanomaterial' in REACH
- applicability for nanomaterials of the current tonnage levels,
- a shortening of the staggered dead-lines for nanomaterials, and

- introducing specific information requirements for nanomaterials, including characterization.

Triggers and waivers

See above bullets.

Further use in this project

The letter highlights the position of several EU Member States in relation to addressing nanomaterials in more detail in chemicals legislation, including a reconsideration of volume triggers and information requirements.

Appendix 3: Matrices in support of review of identified references (Task 1) and evaluation of identified information requirements in relation to applicability for nanomaterials (Task 2)

Introductory remarks to the matrices:

As a starting point, the information requirements for chemicals as given in REACH Annexes VI-X are included in the matrices. Further relevant information requirements / end-points / parameters mentioned in the reviewed references have been added. *These added information requirements are marked in italics.*

In order to screen all the references for all the information requirements and to indicate to what extent they cover a specific information requirement, a scoring/screening system was developed. From the filled out matrices using the scoring system, it can be seen which of the references that covers a given information requirement relevant for nanomaterials and to what extent this was more thoroughly discussed. Furthermore, the scoring system indicates if the reference covered further details in relation to testing considerations and/or adaptation (triggering/waiving) issues. The following scores are used (Task 1):

\+ covered/mentioned as 'relevant' or 'possibly/potentially relevant' for nanomaterials

++ more elaborate discussion of relevance for nanomaterials

with addition of the following notations if applicable:

A with additional discussions in relation to adaptation (triggering/waiving) of the information requirement

T with discussions in relation to testing issues e.g. further need for test method development/validation/guidance.

It should be stressed that this initial scoring should not be interpreted as a suggestion by the reference to include the information requirement in an information requirement scheme as the scopes of the references are often quite different. It could in fact be the opposite (e.g. that further R&D is needed) and some references are not directly suggesting testing schemes for nanomaterials. Thus, the initial scoring is more to give an overview of what is discussed where.

It should also be noted that an empty cell in the matrix does not necessarily mean that a given reference did not find that information requirements relevant for nanomaterials, as it might be that the reference found that the information requirement is implicitly relevant.

In Task 2, each of the possible information requirements/end-points/parameters in the three matrices have been *evaluated in the last column* according to the following scoring system:

I agreement / high priority for information requirement

II potential future information requirement need

III low priority for information requirement

with the addition of the following notations if relevant:

α relevant for all nanomaterials

β relevant for some nanomaterials.

Matrix 1: Substance Identification, characterisation and physicochemical properties

	REACH inf. requirements Tonnage levels	OECD (2009)[1] (OECD TGs applicability)	Env. Def. - DuPont (2007)[2,3]	VCI (2008)[4]	SCENIHR (2007)	SCENIHR (2009)	EFSA (2011)	SCCS (2012)	RIVM (2009)[5]	SKEP (2011)	RIP-oN1 (2011)	RIP-oN2 (2011)[6]	NANO SUPPORT (2012)[7,8]	Evaluation
ANNEX VI.2[9]														
Name, etc.	**> 1tonne VI.2.1**		+						+		+		+	Iα
Molecular and structural formulae	**> 1tonne VI.2.2**		+						+		+		+	Iα
Chemical composition	**> 1tonne VI.2.3**	3	+	+	+	+	++T	++T	+T	++T	+		+	Iα
Purity	**> 1tonne VI.2.3.1**	3		+	+	+		++T	+	++	+		+	Iα
Impurities/ main impurities	**> 1tonne VI.2.3.2/VI. 2.3.3**			+					+		+		+	Iα
Additives	**> 1tonne VI.2.3.4**			+					+		+		+	Iα
Spectral data/HPLC/ description of analytical methods enabling reproduction	**> 1tonne VI.2.3.5/VI. 2.3.6/VI.2.3 .7**								+		+		+	Iα

	REACH inf. requirements Tonnage levels	OECD (2009)[1] (OECD TGs applicability)	Env. Def. - DuPont (2007)[2,3]	VCI (2008)[4]	SCENIHR (2007)	SCENIHR (2009)	EFSA (2011)	SCCS (2012)	RIVM (2009)[5]	SKEP (2011)	RIP-oN1 (2011)	RIP-oN2 (2011)[6]	NANO SUPPORT (2012)[7,8]	Evaluation
Crystal structure	*Not explicitly required in REACH, but considered part of REACH according to current guidance*	3	+	+	+	+	++T	+T	+T	++T	++		++ (as RIP-oN1)	Iβ
"Explicit description of nanoform(s) covered in a dossier"	*Not standard IR in REACH*												++	Iα
State of the substance	**> 1 tonne**		+			+			+				+	Iα
Melting/ freezing point	**> 1 tonne**	1			+				+		NA	+T	+	Iα
Boiling point	**> 1 tonne**								+		NA	+T	+	III
(Relative) Density	**> 1 tonne**	1	+	+	+		++T		+		NA	+T	+	Iα
Particle concentration (no/cm3 or no/g)	*Not standard IR in REACH*						++T	++T						II

	REACH inf. requirements Tonnage levels	OECD (2009)[1] (OECD TGs applicability)	Env. Def. - DuPont (2007)[2,3]	VCI (2008)[4]	SCENIHR (2007)	SCENIHR (2009)	EFSA (2011)	SCCS (2012)	RIVM (2009)[5]	SKEP (2011)	RIP-oN1 (2011)	RIP-oN2 (2011)[6]	NANO SUPPORT (2012)[7,8]	Evaluation
Vapour pressure	**> 1 tonne**	2			+				+		NA	+T		Iβ
Surface tension of aqueous sol.	**> 1 tonne**	2									NA	+A, T	+	II
Water solubility	**> 1 tonne**	2	+	+	+	++	++T	++T	+T	++T	NA	++T	++	Iα
Water dissolution kinetics	*Not standard IR in REACH*					+		++	++T	++		See water solubility	++	Iβ
Dispersion stability in water	*Not standard IR in REACH*			+A								+T		Iβ
Partition coefficient n-octanol/ water	**> 1 tonne**	2		+	+		++T	++T	+T		NA	++T	+	II
Fat solubility/solubility in organic solvent	*Not standard IR in REACH*	1				+	++	++	++T					II
Flash point	**> 1 tonne**			+					+		NA	+A, T	+	III
Flammability	**> 1 tonne**		+	+					+		NA	+T	+	Iβ
Explosive properties	**> 1 tonne**		+	+					+		NA	+T	+	Iβ
Self-ignition	**> 1 tonne**			+					+		NA	+T	+	Iβ

	REACH inf. requirements Tonnage levels	OECD (2009)[1] (OECD TGs applicability)	Env. Def. - DuPont (2007)[2,3]	VCI (2008)[4]	SCENIHR (2007)	SCENIHR (2009)	EFSA (2011)	SCCS (2012)	RIVM (2009)[5]	SKEP (2011)	RIP-oN1 (2011)	RIP-oN2 (2011)[6]	NANO SUPPORT (2012)[7,8]	Evaluation
temperature														
Oxidising properties	**> 1 tonne**		+A						+		NA	+T	+	Iβ
Granulometry/ particle size distribution	**> 1 tonne**	2/ 3	+	+	+	++	++T	++T	++T	++T	++	++T	++(T)	Iα
Agglomeration / aggregation	*Not explicit standard IR in REACH*	3	+	+	+	++	++T	++T	++T	++T	+	++T	++	Iα
(Volume or mass) Specific Surface Area	*Not explicit standard IR in REACH*	3	+	+	+	++	++T	++T	++T	++T	++	++T	++	Iα
Morphology/ Shape/aspect ratio	*Not explicit standard IR in REACH*	3	+	+	+	+	++T	++T	++T	++T	++	++T		Iα/Iβ
Porosity	*Not standard IR in REACH*		+	+A								+T(Further R&D)		II
Surface modifications (surface chemistry/ surface functionalisation/ surface	*Not standard IR in REACH*	3		+	+	+	++T	++T	++T	++T	++	+T (Further R&D)	++	Iα

	REACH inf. requirements Tonnage levels	OECD (2009)[1] (OECD TGs applicability)	Env. Def. - DuPont (2007)[2,3]	VCI (2008)[4]	SCENIHR (2007)	SCENIHR (2009)	EFSA (2011)	SCCS (2012)	RIVM (2009)[5]	SKEP (2011)	RIP-oN1 (2011)	RIP-oN2 (2011)[6]	NANO SUPPORT (2012)[7,8]	Evaluation
treatment, coating….)														
Surface Charge/ Zeta potential	*Not standard IR in REACH*	3	+	+A	+	+	++T	++T	++T	++T		+T(Further R&D)		Iα/Iβ
Surface structure	*Not standard IR in REACH*			+										II
Surface acidity												+T(Further R&D)		II
Surface reactivity	*Not standard IR in REACH*		+											II
Surface energy	*Not standard IR in REACH*											+ T(further R&D)		II
Other relevant characterisers	*Not standard IR in REACH*												++	Iβ
Stability in organic solvents	**> 100 tonnes**		+A									+T	+	Iβ
Dissociation constant	**> 100 tonnes**		+A									+T	+	Iβ
Viscosity	**> 100 tonnes**											+A, T	+	III
Catalytic properties	*Not standard IR in REACH*			+		+	++T	++						Iβ

	REACH inf. requirements Tonnage levels	OECD (2009)[1] (OECD TGs applicability)	Env. Def. - DuPont (2007)[2],[3]	VCI (2008)[4]	SCENIHR (2007)	SCENIHR (2009)	EFSA (2011)	SCCS (2012)	RIVM (2009)[5]	SKEP (2011)	RIP-oN1 (2011)	RIP-oN2 (2011)[6]	NANO SUPPORT (2012)[7],[8]	Evaluation
Photocatalytic properties	*Not standard IR in REACH*		+A	+A		+	++T	++				+T		Iβ
Radical formation potential	*Not standard IR in REACH*			+A								++T		Iβ
Redox potential	*Not standard IR in REACH*						++T	++T				+T(Further R&D)		II
Dustiness	*Not standard IR in REACH*			+A			++T	++T	++T			++T	++	Iβ

[1] OECD (2009). 1: guideline(s) applicable for NMs. 2: guidelines(s) applicable under some circumstances or to some classes of NMs. 3: relevant for NMs with some techniques available or covered by other standards than OECD TGs.

[2] Env. Defense - DuPont (2007): "+" indicates base set data. "+A" indicates additional data to be developed as needed.

[3] Env. Defense - DuPont (2007): Further lists 'Reactivity', 'Incompatibility', 'Decomposition' and 'Polymerisation' as possible additional relevant information requirements, in particular if such reactions could lead to release of energy or create hazardous materials. These rather loosely defined endpoints are not further considered in this report, although large parts of such 'hazardous' reactions are considered covered under physicochemical properties already addressed in this matrix.

[4] VCI (2008): "+" indicates base set data. "+A" indicates recommended extended information on a scientific case-by-case evaluation taking into account identified uses.

[5] RIVM (2009): + already covered by annex VII data/ testing requirements, but not further discussed; +T relevant parameters for ENMs already covered by annex VII data/ testing requirements; ++T additional parameters to be included in a base set requirement scheme for ENMs.

[6] The importance of characterisation of test material and sample preparation is stressed throughout the report.

[7] General issues: Require that nanoforms are explicitly addressed in the endpoint sections. Require detailed description of the test material/sample and sample preparation. Require scientific justification for grouping/read-across and other non-testing approaches for different forms.

[8] It is noted in several places of the report that the characteristics of the nanomaterials may change throughout the life cycle and that this needs to be addressed in relation to the identified uses and the tests performed.

[9] Intro to Annex VI.2: "For each substance, the information given in this section shall be sufficient to enable each substance to be identified. If it is not technically possible or if it does not appear scientifically necessary to give information on one or more of the items below, the reasons shall be clearly stated"

Matrix 2: Toxicological properties

	REACH inf.. requirements - tonnage levels	OECD (2009)[1] (OECD TGs applicability)	Env. Def. - DuPont (2007)[2]	VCI (2008)[3]	SCENIHR (2007)	SCENIHR (2009)	EFSA (2011)	SCCS (2012)	RIVM (2009)[4]	SKEP (2011)[5]	RIP-oN2 (2011)[6]	NANO SUPPORT (2012)[7]	**Evaluation**
ADME *Dermal absorption*	*Further extended compared to IR in REACH*	1*/2	+(skin) /+A	+A	++	++	++T	++T ++T	++T	++	++T	++	Iα
Acute toxicity -oral - dermal or - inhalation	 > 1 tonne > 10 tonnes > 10 tonnes	 1* 1* 1*		+	++			 ++T ++T ++T	+T	+	+A,T	++A,T	Iα
Irritation/ corrosion					+								Iα
Skin irritation/ corrosion, *in vitro*	> 1 tonne	1	+	+				++T	+T	+	+T	+	Iα
Skin irritation/ corrosion, *in vivo*	> 10 tonnes	1	+	+				++T	+T	+	+T	+	Iα
Eye irritation, *in vitro*	> 1 tonne	1		+				++T	+T	+	+T	+	Iα
Eye irritation, *in vivo*	> 10 tonnes	1		+				++T	+T	+	+T	+	Iα
Sensitization													
Skin sensitization	> 1 tonne	1	+	+	+			++T	++TA	+	+T	+	Iα
Mutagenicity													
Mutagenicity *in vitro*	> 1 tonne	2	+	+/+A	++T	++T	++T	++T	++T	+	+T	++A,T	Iα

	REACH inf.. requirements - tonnage levels	OECD (2009)[1] (OECD TGs applicability)	Env. Def. - DuPont (2007)[2]	VCI (2008)[3]	SCENIHR (2007)	SCENIHR (2009)	EFSA (2011)	SCCS (2012)	RIVM (2009)[4]	SKEP (2011)[5]	RIP-oN2 (2011)[6]	NANO SUPPORT (2012)[7]	**Evaluation**
Mutagenicity *in vivo*	may be triggered at all levels	1	+/+A		++T	+	+A	++A	++TA	+	+T	+	Iα
In vitro toxicological mechanisms E.g. cytotox, oxidative stress, immunotox.	*Not standard IR in REACH*		+A				++	++			+T	++	II
Repeated dose toxicity					++T				++T	+			
Repeated dose toxicity 28D -oral -dermal -inhalation	> 10 tonnes	 1 1 1*	+	+A				 ++T ++T ++T		+	+A,T	++A,T	Iα
Repeated dose toxicity 90D -oral -dermal -inhalation	> 100 tonnes	 1 1 1*	(+A)	+A			++T	 ++T ++T ++T		+	+A,T	++A, T	Iα
Effects parameters for RDT e.g. cardiovascular, neurotoxic,	*Not standard IR in REACH*		+A		+	+	++		++T		++T	+	Iα/ II

	REACH inf.. requirements - tonnage levels	OECD (2009)[1] (OECD TGs applicability)	Env. Def. - DuPont (2007)[2]	VCI (2008)[3]	SCENIHR (2007)	SCENIHR (2009)	EFSA (2011)	SCCS (2012)	RIVM (2009)[4]	SKEP (2011)[5]	RIP-oN2 (2011)[6]	NANO SUPPORT (2012)[7]	**Evaluation**
immunotoxic, and inflammatory effects													
Reproductive toxicity					+	+	++A		++TA				
Screening for reproductive/ developmental toxicity	> 10 tonnes	1	+A	+A				++T		+	+T	++	Iα
Pre-natal developmental toxicity	> 100 tonnes or triggered at > 10 tonnes	1	+A	+A				++T		+	+T	++	Iα
Two-generation reproductive toxicity study/ extended one-generation study	> 1000 tonnes or triggered at lower levels	1	+A	+A				++T		+	+T	++	Iα
Chronic toxicity study/ carcinogenicity	>1000 tonnes triggered	1	+A	+A	++T		++A		+T	+	+T		Iα
Photoinduced toxicity	*Not standard IR in REACH*							++T					II

[1] OECD (2009): 1. Applicable for NMs ; 1* Applicable for NMs but extension recommended; 2 Applicable for NMs but with limitations
Overall the relevance and applicability will depend on nano-specific test sample preparation and choice of relevant dose metric/ dosimetry

[2] Env. Defense - DuPont (2007): "+" indicates base set data. "+A" indicates additional data to be developed as needed.

[3] VCI (2008):): "+" indicates base set data. "+A" indicates recommended extended information on a scientific case-by-case evaluation taking into account identified uses.

[4] RIVM (2009): ++T relevant tests identified for base set testing and, ++TA higher tier testing driven from data from base set. +T The general REACH requirements in annex VII-X apply after the base set testing, not further discussed.

[5] SKEP (2011): Apart from ADME no specific discussion/recommendations are addressing the single toxicity tests/- parameters. More nano-specifc testing is requested based on further knowledge on surface properties. However at present it is indicted that the REACH annex VII-X information requirement should apply but at lowered tonnage levels.

[6] RIP-oN2 (2011): The importance of characterisation of test material and sample preparation is stressed throughout the report.

[7] NANO SUPPORT (2012): General issues: Require that nanoforms are explicitly addressed in the endpoint sections. Require detailed description of the test material/sample and sample preparation. Require scientific justification for grouping/read-across and other non-testing approaches for different forms. Require consideration of most appropriate/relevant metric with preferable presentation in several metrics.

Matrix 3: Environmental fate & behaviour and ecotoxicity

	REACH test requirements-tonnage level	**OECD (2009)[1] (guideline applicability)**	**Env. Def. - DuPont (2007)[2]**	**VCI (2008)[3]**	**SCENIHR (2007) [4]**	**SCENIHR (2009)[5]**	**RIVM[6] (2009)**	**SKEP (2011)**	**RIP-oN2 (2011)[7]**	**NANO SUPPORT (2012)[8], [9]**	**Evaluation**
Hydrolysis as a function of pH	> 10 tonnes		+	+					+T	++T	Iβ
Adsorption/ desorption screening	> 10 tonnes	++T	+	+A		+T	++T	++	++T	++A	Iα
Further information on adsorption/desorption	> 100 tonnes						+T		++T	++A	Iα
Ready biodegradability	> 1 tonne	++T	+ (organic ENMs)	+		+T	+T	++T	+T	++A,T	Iβ
Further degradation to be considered	> 10 tonnes						+T		+T	++A,T	Iβ
Degradation simulation testing - surface water - soil - sediment ID of degradation products	> 100 tonnes	++T				+T	++T		+T	++ A,T	Iβ
Further	> 1000 tonnes						+T		+T	++ A,T	Iβ

	REACH test requirements-tonnage level	OECD (2009)[1] (guideline applicability)	Env. Def. - DuPont (2007)[2]	VCI (2008)[3]	SCENIHR (2007) [4]	SCENIHR (2009)[5]	RIVM[6] (2009)	SKEP (2011)	RIP-oN2 (2011)[7]	NANO SUPPORT (2012)[8], [9]	Evaluation
information on degradation											
Photodegradation	*Not standard IR in REACH*	++T	+			+		+		+	Iα
Bioaccumulation in aquatic species	> 100 tonnes	++T	+(screen)	+A	++	+T	++TA	++T	+T	++A	Iα
Further information on fate and behaviour	> 1000 tonnes								+T	++A	Iβ
Activated sludge respiration inhibition test	> 10 tonnes	++T	+A			+T	+T		+T	+	Iα
Short-term toxicity test invertebrates (*Daphnia)*	> 1 tonne	++T	+	+	++	+T	+T	++T	+T	+	Iα
Growth inhibition test aquatic plants (algae)	> 1 tonne	++T	+	+	++	+T	++T	++T	+T	++A	Iα
Short–term toxicity fish	> 10 tonnes	++T	+		++	+T	+T	++T	+T	+	Iα
Long-term toxicity test invertebrates (*Daphnia*)	> 100 tonnes	++T	+A		++	+T	++T	++	++T	++A	Iα

	REACH test requirements-tonnage level	**OECD (2009)[1] (guideline applicability)**	**Env. Def. - DuPont (2007)[2]**	**VCI (2008)[3]**	**SCENIHR (2007) [4]**	**SCENIHR (2009)[5]**	**RIVM[6] (2009)**	**SKEP (2011)**	**RIP-oN2 (2011)[7]**	**NANO SUPPORT (2012)[8], [9]**	**Evaluation**
Long-term toxicity test fish	> 100 tonnes	++T	+A	+A	++	+T	++TA	++	++T	++A	Iα
Short term toxicity of terrestrial organisms: - invertebrates - micro-organisms - plants	> 100 tonnes	++T	+(invertebrates and plants/ +A (microorganisms)		++	+T	+T	++T	+T	++A	Iα
Long term toxicity of terrestrial organisms: - invertebrates - plants	> 1000 tonnes	++T	+A	+A	++	+T	+T	++	+T	++A	Iα
Long-term toxicity to sediment organisms	> 1000 tonnes	++T	+A	+A	++	+T	+T	++	+T	++A	Iα
Long-term or reproductive toxicity to birds	> 1000 tonnes	++T	+A						+T	+	Iβ
ADME studies on aquatic	*Not standard IR in REACH*		+A								II

	REACH test requirements-tonnage level	OECD (2009)[1] (guideline applicability)	Env. Def. - DuPont (2007)[2]	VCI (2008)[3]	SCENIHR (2007) [4]	SCENIHR (2009)[5]	RIVM[6] (2009)	SKEP (2011)	RIP-oN2 (2011)[7]	NANO SUPPORT (2012)[8], [9]	Evaluation
organisms											
Population/ecosystem-level studies	*Not standard IR in REACH*		+A								II

[1] OECD (2009). All ecotoxicity end-points are considered relevant for ENMs, however the appropriateness of the test guidelines for ecotoxicity is discussed in relation to general issues covering all TGs with respect to: material characterisation, exposure preparation and delivery, stability and consistency, and metrics and measurements.

[2] Env. Defense - DuPont (2007): "+" indicates base set data. "+A" indicates additional data to be developed as needed

[3] VCI (2008): "+" indicates base set data. "+A" indicates recommended extended information on a scientific case-by-case evaluation taking into account identified uses.

[4] SCENIHR (2007): is addressing the importance of acute and chronic ecotoxicity testing in a more general manner and does not refer to the specific test organisms

[5] SCENIHR (2009): is mainly addressing the end-points in an overall and general manner addressing aspect in relation to testing rather than discussing the tests individually.

[6] RIVM (2009): ++T relevant tests identified for base set testing and, ++T A higher tier testing driven from data from base set. +T The general REACH requirements in annex VII-X apply after the base set testing, not further discussed.

[7] The importance of characterisation of test material and sample preparation is stressed throughout the report.

[8] General issues: Require that nanoforms are explicitly addressed in the endpoint sections. Require detailed description of the test material/sample and sample preparation. Require scientific justification for grouping/read-across and other non-testing approaches for different forms. Require consideration of most appropriate/relevant metric with preferable presentation in several metrics.

[9] In general: Low solubility may not be may not be an argument for test waiving as the insoluble nature of some nanoparticles does not mean they are not bioavailable!

Information Requirements for nanomaterials – IRNANO

En gennemgang af eksisterende rapporter er basis for et forslag til tekniske informationskrav, som kan være relevant i lovgivningssammenhæng for nanomaterialer. Forslaget påpeger en række generelle tekniske forhold, som skal afklares og endvidere konkrete informationskrav, som er nye i forhold til almindelige kemikalier.

Based on a review of existing reports a proposal for technical information requirements for regulation of nanomaterials is presented. The proposal points out a number of general technical issues to be resolved and further specific information requirements for that are new compared to conventional chemicals.

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