Downloaded from orbit.dtu.dk on: May 13, 2024

DTU Library

Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW)

Hansen, Steffen Foss

Publication date:
2018

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):
Hansen, S. F. (2018). Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW). Technical University of Denmark.

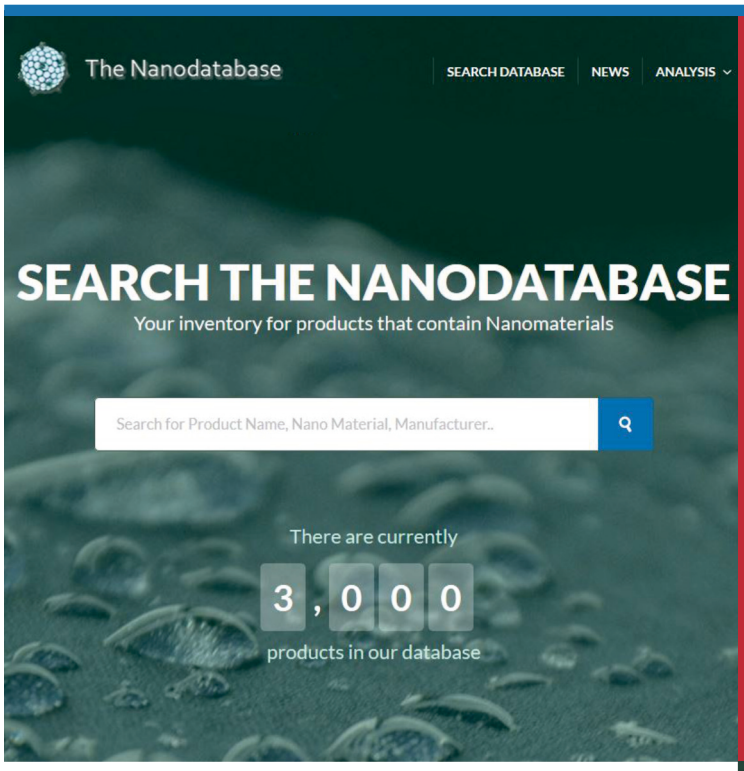
General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

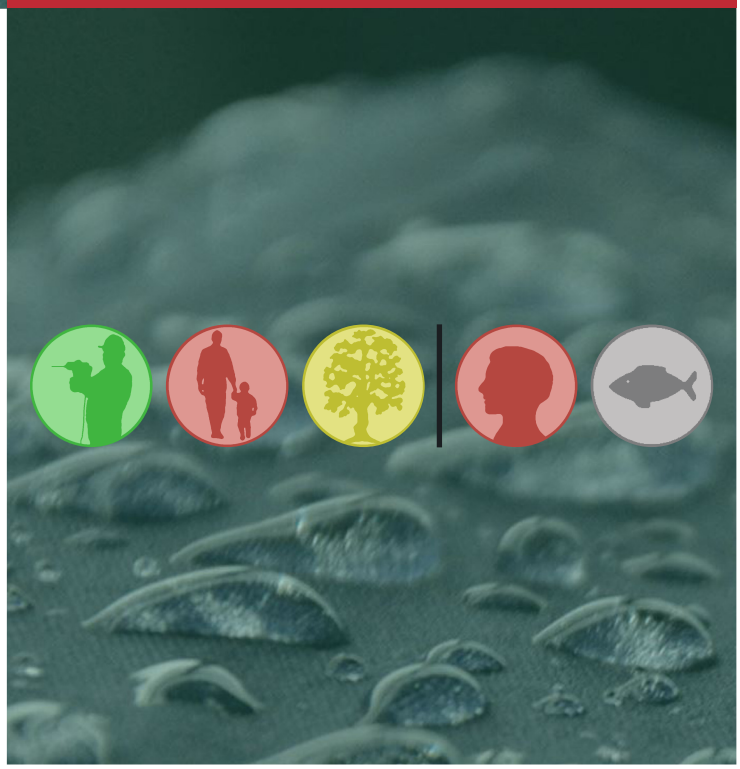
- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Technical University of Denmark

Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW)





Doctoral Thesis
Steffen Foss Hansen
August 2017

DTU Environment
Department of Environmental Engineering

Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW)

Steffen Foss Hansen

Doctoral Thesis
August 2017

Department of Environmental Engineering
Technical University of Denmark

Author: **Steffen Foss Hansen**

Title: **Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW)**

Year: 2018

Published by: Department of Environmental Engineering, Technical University of Denmark

Print: STEP

Address: DTU Environment
Department of Environmental Engineering
Technical University of Denmark
Bygningstorvet, building115
2800 Kongens Lyngby
Denmark

Phone: +45 4525 1600

E-mail: info@env.dtu.dk

Homepage: http://www.env.dtu.dk

ISBN: 978-87-93478-84-8

Denne afhandling er af Danmarks Tekniske Universitet antaget til forsvar for den tekniske doktorgrad. Antagelsen er sket efter bedømmelse af den foreliggende afhandling.

Kgs. Lyngby, den 6. februar 2018

Anders O. Bjarklev
Rektor

/Rasmus Larsen
Prorektor

This thesis has been accepted by the Technical University of Denmark for public defence in fulfilment of the requirements for the degree of Doctor Technices. The acceptance is based on an evaluation of the present dissertation.

Kgs. Lyngby, 6 February 2018

Anders O. Bjarklev
President

/Rasmus Larsen
Provost

Preface

The work presented in this doctoral thesis summarises the research that I have been involved in since 2009 with regard to the regulation and risk assessment of nanomaterials (NMs), specifically in regard to: 1) mapping current uses of nanomaterials in Europe, 2) understanding the limitations of existing legislation and, finally, 3) addressing the restraints of risk assessment and alternatives to risk assessment when it comes to nanomaterials.

The thesis itself focuses on extracting key research observations and findings from within each of these three areas and integrating them into a proposal for a new regulatory framework for the registration, evaluation and authorisation of nanomaterials. This proposed framework is termed Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW). The need for a new framework for the regulation of nanomaterials might not seem self-evident, and the view that it is urgently needed might be somewhat controversial.

Schopenhauer once said that "All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident." If the ideas presented in this doctoral thesis seem ridiculous or are violently opposed, then I hope that it is just because they – and REACT NOW – are about to be accepted as self-evident in the near future.

The elements of REACT NOW have been developed over time and are inspired by the Danish and European research projects in which I have been involved, the foremost being "EnvNano – Environmental Effects and Risk Evaluation of Engineered Nanoparticles," led by Principal Investigator Professor Anders Baun and funded by the European Research Council, "SUN – Sustainable Nanotechnologies," led by Principal Coordinator Professor Antonio Marcomini and funded by the EU FP7 Research Programme, and, finally, "Better Regulation of Chemicals," led by the Danish Ecological Council and funded by the Villum Foundation.

Further encouragement has come from the national and international public authority service and consultancy with which I have been engaged. This includes the Reach Implementation Project on Nanomaterials (RIP-oN 1) on Substance Identification of Nanomaterials, where I represented the European Environmental Bureau, and RIP-oN 2 and 3 on the development of specific advice on the implementation of REACH for nanomaterials, led by the Institute of Occupational Medicine. It furthermore includes reviews of environmental legislation for the regulatory control of nanomaterials, commissioned by the European Commission and led by Milieu Ltd. in 2011 and Ricardo Energy & Environment in 2016, reviews of the scientific state of the art when it comes to environmental effect and exposure, as requested by the Danish Environmental Protection Agency and led by COWI Denmark, and, finally, assisting in preparing a meeting report on human health, scientific evidence and the risk governance of nanomaterials for the World Health Organisation, Regional Office for Europe. Additional motivation and further indications of the need for REACT NOW has revealed itself to me through the effort that I have put in to fulfilling my role as a scientific and technical advisor for the European Environmental Bureau in the Nanomaterials Working Group, established by the European Chemicals Agency, as well as in the Partner Expert Groups (PEGs) on registration, QSARs and Grouping and End-point specific guidance.

The work presented in this doctoral thesis is based on 28 peer-reviewed papers published in the period 2009-2017 and is based on the research that I performed at the Department of Environmental Engineering, Technical University of Denmark and during my external stay at the European Environmental Agency as a guest researcher from November 2011-April 2012.

Althea Gibson once said that “No matter what accomplishments you make, somebody helped you.” And this is also true for the work presented in this thesis; there are a lot of people that I would like to thank. First of all, I wish to thank Professor Anders Baun and all the co-authors with whom I have had the pleasure of working with. Second, I would like to thank the members of the Nanorisk group and the Environmental Chemistry section at DTU Environment. And third, I would like to thank Torben Dolin for graphical assistance and Mette Topp Hansen for secretarial support. Finally, I would like to thank my parents and my brother for their relentless encouragement and Maria and our children for their unconditional support.

Copenhagen, August 2017

Steffen Foss Hansen

Executive summary

Nanotechnology and nanomaterials (NMs) have become an integrated part of our lives in the past decade, whether we realise it or not, and we have entered a phase where the early hype about the benefits of this mind-blowing technology is over.

Concerns have been raised throughout this period about the adverse impacts of NMs, and although these have previously been very loud, they are now slowly quieting down. This is not because we have resolved the challenges related to assessing and managing the risks of NMs but rather because we seem to have caught a sense of "nanorisk-immunity" where we gradually have become more and more indifferent to hearing about the potential risks of NMs.

Instead of implementing a regulatory framework tailored to NMs, the European Commission has initiated multiple reviews of state-of-the-scientific literature in regard to environmental, health and safety, and seems to be discussing the same risk assessment and regulatory challenges over and over. If history in regard to emerging risks and hazards can be used as a guide, we can now expect 15-20 years of univocal environmental, health and safety research that will not provide definitive answers but only dropwise glimpse into the true nature of the risks of NMs.

This thesis summarises the state of research and regulatory affairs within the field of nanomaterial regulation and risk assessment. Specifically, the focus is on areas of research with which I have been involved since 2009 in regard to: 1) mapping current uses of NMs in Europe, 2) understanding the limitations of existing legislation and, finally, 3) addressing the restraints of risk assessment and alternatives to risk assessment when it comes to NMs.

In order to obtain an overview of consumer products in Europe that are claimed to contain NMs or are claimed to be based on nanotechnology, we established an online inventory, The Nanodatabase (www.nanodb.dk), back in 2012 and started systematically to collect information about the proclaimed nanoproducts name, producers "nanoclaim", country of origin, used NMs, location of the NM in the product, most likely exposure route among other. The Nanodatabase originally contained a little more than 1,200 products and now has information about more than 3,000 products. Through our research, we found that most of the products fall into the category of "Health and Fitness" and "Home and Garden". The most used NMs are silver and titanium dioxide, but it is not possible to identify the NMs used for almost 60% of the products in the database.

The safety evaluation tool, NanoRiskCat, was developed and integrated into The Nanodatabase with the purpose of communicating what is known about the hazard and exposure potential of consumer products containing NMs. In its simplest form, the final NanoRiskCat evaluation of a specific nanomaterial in a given application can be communicated in the form of a short title describing the use of the NM and a colour code whereby the first three coloured bullets (●●●|●●) refer to the potential exposure of professional end-users, consumers and the environment – in that sequence – and the last two coloured bullets refer to the hazard potential for humans and the environment. The colours assigned to the exposure and hazard potential are green (●), yellow (●), red (●) and grey (●), corresponding to high, medium, low and unknown, respectively. A data analysis of the products in The Nanodatabase shows that for most product categories, the dominant route of

exposure is dermal, and that the NanoRiskCat exposure potential as well as human and environmental hazard potential of most products is either "high (●)" or "unknown (●)".

In order to address the potential risks of NMs and take the unique properties of NMs into account, a number of EU regulations and directives have been amended in recent years such as, for instance, the biocidal product regulation. However, the research presented in this thesis identifies three major weaknesses to the current regulation, namely how to define "nanomaterials", threshold values and information requirements not tailored to the nanoscale and how to overcome the obstacles of chemical risk assessment applied to NMs.

The outcome of this research has led me to conclude that the fact that NMs are covered by the scope of existing legislation is not enough to ensure the protection of human health and the environment. We therefore need a new regulatory framework tailored for NMs and their applications. A proposal of such a framework termed "Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW)" is proposed and presented herein.

The thesis consists of nine chapters. An introduction is provided in chapter 1. In chapter 2, what is known about the current uses of NMs is presented in detail, and it is established that there is a general lack of data and access to data on, for example, production volumes and uses of NMs which hampers qualitative and quantitative occupational, consumer and environmental exposure assessment of NMs – and this in turn impedes the completion of any kind of risk assessment. The latter has repetitively led to questions being raised by politicians, NGOs, academics and members of the public about whether current regulatory frameworks are up to the job, as many of them rely heavily on, for instance, the completion of meaningful risk assessments.

Chapter 3 is devoted to an analysis of the revisions that have been made to existing regulatory frameworks, such as REACH, BPR and food legislation, whereas Chapter 4 is allocated to an evaluation of proposed revisions made by a number of EU member states and REACH competent authorities such as German UBA, BfR and BAuA and the Swedish KEMI, as well as the NGOs CIEL, ClientEarth and BUND. It is concluded that the revisions that have been implemented for existing EU legislation and the proposed revisions by UBA, BfR and BAuA, KEMI and CIEL, ClientEarth and BUND collectively provide a lot of opportunities. However, a number of weaknesses have also been identified and these are elaborated on and discussed in Chapter 5, as they continue to dog the effective regulation of NMs and still need to be addressed.

In recognition of the challenges that traditional chemical risk assessments entail, and outstanding scientific research questions that still need to be resolved, no less than 50 alternative decision-support tools, or supplements to traditional risk assessments, have been explored and proposed in recent years. These are analysed in Chapter 6, in order to identify tools that could potentially be used to support a new regulatory framework tailored specifically for NMs and their applications throughout the life cycle. This evaluation is based on a series of recent scientific publications which provide substantial reviews of these alternative tools applied in regard to risk governance, worker protection, consumer exposure, environmental assessment, waste, etc. This led to the realisation that we need a tool that is

both regulatory-relevant and can be applied despite the lack of data and lack of access to information.

Safety evaluation plays a key role in REACT NOW and the safety evaluation tool NanoRiskCat developed by Hansen et al. (2014, 2017c) is presented in detail in chapter 7. A strength of NanoRiskCat is that it has been applied to more than 2,000 products claimed to include NMs or to be based on nanotechnology. The outcome of this is presented in this thesis. Finally, in Chapter 8, REACT NOW is introduced and key components of the framework are outlined.

As part of REACT NOW, I recommend that manufacturers and importers of NMs should be required to register their NM(s) prior to commercialisation and independent of production and import volumes.

For NM(s) already being sold, manufacturers and importers should be required to register and fulfil the REACT NOW requirements within a certain time period e.g. six months of the adoption of the framework. NMs are defined according to SCENIHR's definition and not the one recommended by the EC. Primary particle size distribution, shape (including aspect ratio), specific surface area and surface treatment are considered "identifiers" and not the "characterisers" as suggested by UBA, BfR and BAuA (2013). In practice, this means that any variation in size, shape, surface area and surface-treated NM that is commercialised in the EU has to be identified, named, registered and safety-evaluated separately, before it is placed into a separate registration dossier.

The European Chemicals Agency is identified as the European authority that should be responsible for the management and carrying out the technical and administrative aspects of REACT NOW, however the burden of proof of safety should be placed on industry to ensure that data are generated in good time. In order to ensure the protection of health and the environment, I recommend that the registrant should be required to explain a relevant product's functional use, provide justification for its use and carry out an effectiveness evaluation prior to the commercialisation of any nanomaterial.

Following the requirements of REACT NOW, all uses of NMs have to be evaluated according to NanoRiskCat. The health and environmental hazard information required as part of the information requirements focuses on enabling the application of NanoRiskCat. In regard to human health it includes High Aspect Ratio Nanoparticles (HARN), bulk CLP classification, acutely toxicity, genotoxicity and mutagenicity, carcinogenicity and respiratory toxicity. For the environment, it includes bulk CLP classification, aquatic toxicity, freshwater tests for degradation, bioaccumulation and a scientific review in regard to dispersive or long-range transport, ecosystem effects and novelty. It is important to note that NanoRiskCat uses a tiered approach and that the registrant only has to submit enough information to enable the categorisation of the health and environmental hazard potential of the specific NM into high (●), medium (●), low (●) or unknown (●).

Depending on the outcome of the NanoRiskCat evaluation, manufacturers and importers of NMs and producers of NM products might have to seek authorisation, which can only be given for specific uses of NMs and nanoproducts that are deemed necessary, efficient and have a functional use.

For NMs that have undergone a NanoRiskCat evaluation and have 1) a red professional end-user and/or a consumer exposure profile combined with a red human health hazard profile and/or 2) a red environmental exposure profile combined with a red environmental hazard profile, the registrant is required to complete an "Alternatives Assessment" and the agency responsible for REACT NOW is required to seek opinion on safe use from the European scientific committee of relevance. In such cases, authorisation should be granted, but only if the specific use under consideration is deemed safe and necessary.

Uses of NMs deemed not to be safe by the scientific committees e.g. dispersive uses of HARN, indoor consumer uses of spray products with NMs associated with respiratory toxicity, should not be granted authorisation and should not be given permission to be marketed in Europe. For all other combinations of exposure and hazard profiles, i.e. NanoRiskCat categories 2-4, the agency responsible for REACT NOW can ask for an opinion from the scientific committees of relevance on a case-by-case basis.

As a general rule, authorisation should only be given for specific professional end-user and consumer applications of NMs and nanoproducts, if they have a green human health hazard profile combined with a green professional end-user exposure profile and a consumer exposure profile, respectively. The same goes for uses that are expected to lead to environmental exposure that should only be granted authorisation if the NM in question has a green environmental hazard profile.

Should the agency or the scientific committees have questions about the safety of a given NM and its specific use, the agency can make a request for additional information, to be generated within 3 years, within which time conditional authorisation can be granted.

For combinations of yellow exposure and hazard profiles, conditional authorisation is possible for a time-limited period during which time the agency should request the generation of additional information by the registrant. In order to assist industry and especially Small and Medium-sized Enterprises in the process of implementing REACT NOW, technical and non-technical assistance is needed and should be provided by the European Commission Joint Research Centre and the European Chemicals Agency.

REACT NOW is the first attempt to present a comprehensive and transparent decision-making framework tailored to regulate the use of NMs, but as no framework is without either potential or limitations, the opportunities and weaknesses related to the implementation of REACT NOW are pinpointed. Strengths include that NanoRiskCat can be used despite lack of data and information, whereas the lack of clear-cut definitions of "necessity" and "effectiveness" could be considered a weakness along with the arguably crude exposure assessment in NanoRiskCat.

In the appendix, the 28 peer reviewed journal papers on which this thesis is based are included. It is worth pointing out that most of the topics briefly discussed and presented in Chapters 2-8 are detailed in the journal papers and that this thesis is written to present REACT NOW and to give the reader an overview of the original achievements of the work.

Danish summary

Uanset om vi er klar over det eller ej, er nanoteknologi og nanomaterialer i det seneste årti blevet en integreret del af vores liv. Vi er gået ind i en fase, hvor den tidlige hype om fordelene ved denne – mildt sagt forbløffende – teknologi er forbi.

Siden nanoteknologiens spæde begyndelse er der blevet rejst tvivl om de eventuelle negative miljø- og sundhedseffekter af nanomaterialer. Men som tiden er gået, er der blevet mere og mere stille omkring disse. Det er ikke, fordi vi har løst udfordringerne i forbindelse med risikovurdering og håndtering af nanomaterialer, men snarere fordi vi synes at være fanget af en følelse af "nanorisiko-immunitet", hvor vi efterhånden er blevet mere og mere immune overfor nyheder om de potentielle risici ved nanomaterialer.

I stedet for at implementere et nyt regelsæt skræddersyet til nanomaterialer, synes Europa-Kommissionen at foretrække at igangsætte diverse udredninger af den videnskabelige litteratur med hensyn til miljø og sundhed samt at diskutere de samme risikovurderings- og lovgivningsmæssige udfordringer igen og igen. Hvis erfaringerne fra tidligere tiders håndtering af nye risici og teknologier kan benyttes som en rettesnor, kan vi nu forvente 15-20 års miljø- og sundhedsforskning, der ikke vil give endegyldige svar på, hvorvidt nanomaterialer er farlige, og som kun dråbevist vil vise glimt af den sande natur af risikoen ved anvendelsen af nanomaterialer.

Denne afhandling sammenfatter vores nuværende viden indenfor risikovurdering og regulering af nanomaterialer. Konkret er fokus på de tre forskningsområder, som jeg har været involveret i siden 2009 med hensyn til: 1) at kortlægge af nuværende anvendelser af nanomaterialer i Europa, 2) at forstå begrænsningerne i den eksisterende lovgivning, og endelig 3) at adressere begrænsningerne som risikovurdering – og alternativer til risikovurdering – har, når det kommer til nanomaterialer.

For at få et overblik over forbrugerprodukter i Europa som enten hævdes at indeholde nanomaterialer, eller som hævdes at være baseret på nanoteknologi, etablerede vi i 2012 en online database, Nanodatabasen (www.nanodb.dk) og begyndte systematisk at indsamle information om påståede nanoprodukters navn, producentens "nanopåstand", oprindelsesland, anvendt nanomateriale, lokalitet af det anvendte nanomateriale i produktet og mest sandsynlige eksponeringsrute blandt anden. Nanodatabasen indeholdt oprindeligt lidt mere end 1.200 produkter og indeholder nu information om mere end 3.000 forskellige produkter. Igennem vores forskning har vi fundet ud af, at de fleste produkter falder indenfor kategorierne "Health and Fitness" and "Home and Garden". De mest anvendte nanomaterialer er sølv og titaniumdioxid, men det er vigtigt at påpege, at det ikke er muligt at identificere identiteten af det anvendte nanomateriale i næsten 60% af produkterne i databasen.

Evalueringsværktøjet, NanoRiskCat, blev udviklet og integreret i Nanodatabasen med det formål at kommunikere, hvad man ved om fare- og eksponeringspotentialet af produkter, som indeholder nanomaterialer. Det endelige resultat af NanoRiskCat evalueringen af et specifikt nanomateriale til en given anvendelse kan i sin simpleste form fremlægges i form af en kort titel, som beskriver anvendelse af nanomaterialet og en farvekode, hvor de første tre farvede bullets (●●●|●●) refererer til den potentielle eksponering for henholdsvis professionelle slutbrugere, forbrugere og miljøet – i den rækkefølge – og de sidste to bullets refererer til farepotentialet for mennesker og miljøet. Farverne, som kan allokeres til

eksponerings- og farepotentialet, er henholdsvis grøn (●), gul (●), rød (●) and grå (●), svarende til henholdsvis høj, medium, lav og ukendt. En dataanalyse af produkterne i Nanodatabasen viser, at dermal eksponering er den mest sandsynlige eksponeringsvej, og at NanoRiskCat eksponeringspotentialet såvel som menneske- og miljøfarepotentialet for de fleste produkter er enten "høj (●)" eller "ukendt (●)".

En række EU forordninger og direktiver så som, bl.a. biocidforordningen, er blevet ændret i de seneste år for at tage højde for de potentielle risici forbundet med nanomaterialer og for at tage højde for nanomaterialers unikke egenskaber. Dog viser den forskning, der præsenteres i denne afhandling, at der er tre store svagheder forbundet med den nuværende regulering, såsom: 1) hvordan man definerer "nanomaterialer", 2) tærskelværdier og oplysningskrav, som ikke er skræddersyet til nanomaterialer og 3) de massive videnskabelige udfordringer, der er ved at anvende traditionel kemisk risikovurdering som metode på nanomaterialer i praksis.

Resultatet af denne forskning har fået mig til at konkludere, at det, at nanomaterialer er omfattet af eksisterende lovgivning, rent juridisk ikke i sig selv er nok til at sikre beskyttelsen af miljøet og menneskers sundhed. Vi har derfor brug for en ny lovgivning, som er skræddersyet til nanomaterialer og deres anvendelser. I den sidste del af afhandlingen foreslås en sådan lovgivning kaldet Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW). Afhandlingen består af ni kapitler.

En kort introduktion gives i kapitel 1. I kapitel 2 præsenteres vores viden om de nuværende anvendelser af nanomaterialer. Det fastslås, at der er en generel mangel på data og adgang til data om, blandt andet vedrørende produktionsmængder og anvendelser af nanomaterialer. Den manglende viden hæmmer enhver form for kvalitativ og kvantitativ eksponeringsvurdering af nanomaterialer, hvilket igen hindrer enhver form for kemisk risikovurdering.

En række politikere, forskere, NGO'er og medlemmer af offentligheden har sat spørgsmålstegn ved, om den nuværende regulering er god nok. Blandt andet fordi mange af de mest relevante EU-forordninger og direktiver er stærkt afhængige af vores evne til at færdiggøre meningsfulde videnskabelige risikovurderinger.

Kapitel 3 er helliget en analyse af de ændringer, der er foretaget i den eksisterende lovgivning inden for kemikalie-, biocidholdige produkt- og fødevarelovgivningen. I kapitel 4 præsenteres en analyse og vurdering af de yderligere juridiske og tekniske revisioner, som er blevet foreslået af en række EU-landes REACH-kompetente myndigheder som de tyske UBA, BfR og BAuA og den svenske KEMI, samt NGO'erne CIEL, ClientEarth og BUND. Det konkluderes, at de ændringer, der er blevet gennemført i den eksisterende EU-lovgivning og de foreslåede yderligere ændringer, kollektivt indeholder en masse muligheder. Dog blev der ligeledes identificeret en række svagheder, og disse bliver uddybet og diskuteret i kapitel 5, da de fortsat obstruerer en effektiv regulering af nanomaterialer.

I erkendelse af de udfordringer, som anvendelsen af kemisk risikovurdering indebærer og de udestående videnskabelige usikkerheder, er mere end 50 alternative beslutningsmetoder eller supplement til kemisk risikovurdering blevet udarbejdet og foreslået i de senere år. Disse analyseres i kapitel 6 for at identificere metoder, der kan anvendes til at understøtte en

lovgivning, som er skræddersyet specielt til nanomaterialer og deres anvendelser. Denne evaluering er baseret på en række af de seneste videnskabelige publikationer, som systematisk gennemgår, hvorledes disse alternative metoder kan anvendes i forbindelse med risikohåndtering, beskyttelse af arbejdstagerne, forbrugernes eksponering, miljøvurdering, affald, osv. Dette fører til den erkendelse, at vi har brug for en evalueringsmetode, der er både lovgivningsmæssig relevant, og som kan anvendes på trods af manglende data og manglende adgang til information.

I kapitel 7 præsenteres evalueringsmetoden NanoRiskCat. En stor styrke i NanoRiskCat er, at metoden er blevet anvendt på mere end 2.000 produkter, som enten hævdes at indeholde nanomaterialer, eller som hævdes at være baseret på nanoteknologi.

Endelig introduceres REACT NOW i kapitel 8. Centrale elementer i den foreslåede lovgivning skitseres. Som en del af REACT NOW anbefales det, at producenter og importører af nanomaterialer bliver forpligtiget til at registrere deres nanomaterialer forud for kommercialisering og uafhængig af mængden, der produceres og/eller importeres.

For nanomaterialer, som allerede er på markedet, bør det kræves, at producenter og importører opfylder betingelserne i REACT NOW inden for en tidsperiode som for eksempel seks måneder. Nanomaterialer defineres i REACT NOW i henhold til Europa-Kommissionens videnskabelige komite, SCENIHR's forslag og ikke i henhold til den definition, som anbefales af Europa-Kommissionen. Primær partikelstørrelsesfordeling, form, specifikt overfladeareal og overfladebehandling betragtes som identifikatorer og ikke som karakteristika, som foreslået af UBA, BfR og BAuA (2013). I praksis betyder det, at enhver variation i primær partikelstørrelsesfordeling, form, specifikt overfladeareal og overfladebehandling skal identificeres, navngives, registreres og evalueres separat.

Det Europæiske Kemikalieagentur identificeres som værende den Europæiske myndighed, som bør være ansvarlig for forvaltningen og gennemførelsen af de tekniske og administrative aspekter af REACT NOW, mens bevisbyrden for at vise, at nanomaterialer er sikre, pålægges producenterne og importørerne af disse for at sikre, at relevant information og data genereres i tide.

For at sikre beskyttelsen af sundheden og miljøet anbefales det, at registranten er forpligtet til at forklare det pågældende produkts funktion, begrunde dets nødvendighed og gennemføre en effektivitetsevaluering forud for en kommercialisering. I forlængelse af disse krav skal alle nanomaterialer evalueres ved hjælp af NanoRiskCat.

De oplysninger vedrørende nanomaterialers fare for sundhed og miljø, som der stilles krav om, at producenterne og/eller importørerne indleverer, er fokuseret på at gøre det muligt at anvende NanoRiskCat. Det vil sige, at fokus er på, om nanomaterialet er et såkaldt "High Aspect Ratio Nanoparticles" (HARN), den nuværende klassificering og mærkning af ikke-nanoformen af materialet, dets akutte toksicitet, genotoksicitet og mutagenicitet, carcinogenicitet samt dets respiratoriske toksicitet.

Vedrørende miljøet drejer det sig hovedsaglig om den nuværende klassificering og mærkning af ikke-nanoformen af materialet, dets akvatiske toksicitet, ferskvands test for nedbrydning og bioakkumulering. Dertil kommer en videnskabelig gennemgang med hensyn til udbredelse og langtrækkende transport, økosystemets effekter og nyhedsværdi.

Det er vigtigt at bemærke, at NanoRiskCat bruger en trinvis fremgangsmåde. Registranten behøver kun at indsende nok information til, at der kan foretages en kategorisering af farepotentialet for miljø- og sundhed af det specifikke nanomateriale i dets specifikke anvendelse. Der anvendes 4 farvekategorier, nemlig 1) rød for, at farepotentialet er højt; 2) gul for, at farepotentialet er medium; 3) grøn for, at farepotentialet er lavt og endelig 4) grå for, at farepotentialet er ukendt.

Afhængigt af resultatet af NanoRiskCat evalueringen kan det være, at producenter og importører af nanomaterialer samt producenter af nanoprodukter skal søge om tilladelse til produktion og anvendelse. Generelt bør der – som hovedregel – kun gives tilladelse til specifikke anvendelser af nanomaterialer og nanoprodukter, når anvendelsen skønnes nødvendig, effektiv og funktionel. Som en konsekvens af NanoRiskCat evalueringen kan registranten efterfølgende blive forpligtiget til at gennemføre en vurdering af tilgængelige alternativer. Dette gør sig gældende for anvendelser af nanomaterialer, som resulterer i en NanoRiskCat evaluering med 1) et rødt eksponeringspotentiale for professionelle slutbrugere og/eller et rødt eksponeringspotentiale for forbrugere kombineret med et rødt potentiale for menneskers sundhed og/eller 2) en rød miljøeksponering kombineret med en rød miljøfare. I disse tilfælde skal der indhentes en udtalelse fra de relevante videnskabelige komiteer i Europa-Kommissionen om, hvorvidt nanomaterialet og dets anvendelse er sikker.

Brug og tilladelse til produktion, import og anvendelse bør kun gives, hvis den specifikke anvendelse skønnes at være nødvendig og sikker. Anvendelse af nanomaterialer, som de videnskabelige komitéer ikke anser for at være sikre, bør der ikke gives tilladelse til at markedsføre i Europa. Dette gælder fx udbredt anvendelse af HARN og indendørs forbrugeranvendelse af sprayprodukter med nanomaterialer forbundet med respiratorisk toksicitet. For alle andre kombinationer af eksponerings- og fareprofiler, dvs. NanoRiskCat kategorierne 2-4, kan agenturet anmode om en udtalelse fra de relevante videnskabelige komiteer i Europa-Kommissionen fra sag til sag.

Som en generel regel bør der kun gives tilladelse til specifikke anvendelser af nanomaterialer og nanoprodukter, hvis de har et grønt fare potentiale for menneskers sundhed kombineret med et grønt professionelt slutbruger- og forbrugereksponeringspotentiale. Det samme gælder for anvendelser, der forventes at føre til miljømæssig eksponering. Her bør der kun gives tilladelse, hvis det pågældende nanomateriale har et grønt miljøfare potentiale. Skulle de videnskabelige komitéer have spørgsmål til sikkerheden af et nanomateriale og dets specifikke anvendelse, kan agenturet anmode producenter/importøren om yderligere oplysninger. Disse skal genereres inden for 3 år, som er den periode, der kan udstedes en betinget godkendelse for. For kombinationer af gule eksponerings- og farepotentialer er betingede godkendelser mulige for en tidsbegrænset periode. I dette tidsrum skal agenturet anmode registranten om at generere yderligere specifikke oplysninger.

For at hjælpe industrien og navnlig små og mellemstore virksomheder med at implementere REACT NOW er der behov for teknisk- og ikke-teknisk bistand. Den skal leveres af den Europæiske Kommissions Joint Research Centre og det Europæiske Kemikalie Agentur.

REACT NOW er det første forsøg på at præsentere en omfattende lovgivning, der er skræddersyet til nanomaterialer og disses anvendelser.

Al lovgivning har styrker og svagheder. Det gælder også REACT NOW. Disse handler blandt andet om, at NanoRiskCat kan bruges på trods af mangel på data og information; om, hvordan man definerer "nødvendighed" og "effektivitet"; og om, at vurderingen af eksponeringspotentialet i NanoRiskCat velsagtens er noget simpel.

Denne afhandling er baseret på 28 peer review artikler, som er inkluderet i appendiks til afhandlingen. Det er værd at pege på, at de fleste af de emner, der kort bliver diskuteret og præsenteret i kapitel 2-8, er beskrevet i de 28 artikler. Denne afhandling er skrevet for at præsentere REACT NOW og for at give læseren et overblik over de videnskabelige resultater, som er opnået.

Table of Contents

PREFACE 1

EXECUTIVE SUMMARY 3

DANISH SUMMARY 7

LIST OF PUBLISHED PEER REVIEWED JOURNAL PAPERS 14

1. INTRODUCTION 16

2. PRODUCTION, CURRENT USES AND EXPOSURE PATHWAYS OF NANOMATERIALS 18
- 2.1 EXISTING INVENTORIES AND THE NANODATABASE 18
- 2.2 THE NANODATABASE AND USE OF NANOMATERIALS IN CONSUMER PRODUCTS IN THE EU 22
  - *2.2.1 Development of nanoproduct commercialisation 22*
  - *2.2.2 Distribution of nanoproducts in product categories and subcategories 23*
  - *2.2.3 Nanomaterials reported to be used 24*
  - *2.2.4 Biocidal Products and treated articles 25*
- 2.3 POTENTIAL ROUTE OF CONSUMER EXPOSURE 27
- 2.4 THE RELEASE OF NANOMATERIALS FROM CONSUMER PRODUCTS 30
- 2.5 THE ENVIRONMENTAL RELEASE OF NMS 31
- 2.6 SOLID WASTE FLOWS FROM NANO-ENABLED CONSUMER PRODUCTS 34

3. EXISTING LEGISLATION – OPPORTUNITIES AND WEAKNESSES 38
- 3.1 REGISTRATION, EVALUATION AND AUTHORISATION OF CHEMICALS (REACH) 46
- 3.2 BIOCIDAL PRODUCTS REGULATION (BPR) 48
- 3.3 FOOD LEGISLATION AND NANOMATERIALS 52

4. PROPOSED NEW REGULATORY FRAMEWORKS AND THEIR OPPORTUNITIES AND WEAKNESSES 56
- 4.1 GERMAN DOSSIER-IN-DOSSIER PROPOSAL FROM 2012 60
  - *4.1.1 Revisions needed, size as a characteriser, relevant forms and surface-treated NMs 60*
  - *4.1.2 Tonnage threshold 61*
  - *4.1.3 Information requirements and waiving 62*
  - *4.1.4 Substance evaluation, authorisation and restriction 63*
- 4.2 CIEL, CLIENTEARTH AND BUND'S "NANO PATCH" FROM 2012 63
  - *4.2.1 Policy issues that require attention 63*
  - *4.2.2 Legal elements of the "nano patch" 64*
  - *4.2.3 Evaluation 65*
  - *4.2.4 Report, notify, classification and labelling 65*
- 4.3 SWEDISH DRAFT PROPOSAL ON REGULATION OF NANOMATERIALS FROM 2013 65
  - *4.3.1 Registration of Nanomaterials 66*
  - *4.3.2 Information requirements 66*

5. ISSUES PLAGUING EU REGULATIONS OF NANOMATERIALS 67
- 5.1 DEFINITIONS OF NANOMATERIALS IN THE EU 67
- 5.2 SHOULD NANOMATERIALS BE CONSIDERED AS DIFFERENT FROM THEIR BULK COUNTERPARTS? 70
- 5.3 RISK ASSESSMENT LIMITATIONS IN REGARD TO NANOMATERIALS 73
  - *5.3.1 Attempts to complete risk assessment of nanomaterials 74*
  - *5.3.2 Hazard identification and effect assessments of nanomaterials 76*
  - *5.3.3 Exposure assessments of nanomaterials 76*
  - *5.3.4 Risk characterization of nanomaterials 77*
  - *5.3.5 Guidance and test methods relevant to safety assessment of nanomaterials 77*

6. ALTERNATIVES TO RISK ASSESSMENT 80
- 6.1 EXISTING REVIEWS OF ALTERNATIVE DECISION-SUPPORT TOOLS 80

6.2 Opportunities and Weaknesses of Existing Tools and Frameworks 91
7. NANORISKCAT AND SAFETY EVALUATION OF NMS 94
7.1 Evaluation of Exposure Potential in NanoRiskCat 94
7.2 Evaluation of Hazard Potential in NanoRiskCat 96
7.3 Application of NanoRiskCat in The Nanodatabase 100
8. REACT NOW 102
8.1 Scope and definition of NMs in REACT NOW 103
8.2 Registration of nanomaterials in REACT NOW 104
8.2.1 Substance identification and naming of NMs 104
8.2.2 Pre-market obligation to register in REACT NOW 105
8.2.3 Information requirements in REACT NOW 105
8.2.4 Is there a reasonable functional use and a technological need? 109
8.2.5 Is the use for which authorisation is sought usable and effective? 110
8.3 Evaluation and safety evaluation in REACT NOW 111
8.4 Authorisation and Categorisation 111
8.5 Alternatives Assessment 114
8.6 Restriction of NMs and the use of NMs in products in REACT NOW 117
8.7 Adequate labelling using the outcome of the NanoRiskCat evaluation 117
8.8 Administrative responsibility and technical assistance to be provided in REACT NOW 117
8.9 Opportunities and weaknesses of REACT NOW 118
9. CONCLUSION AND RECOMMENDATIONS 121
10. LIST OF REFERENCES 124
11. APPENDIX: PUBLISHED PEER REVIEWED JOURNAL PAPERS 144

List of published peer reviewed journal papers

1. Baun, A., Hartmann, N.B., Grieger, K.D., Hansen, S.F. 2009. Setting the Limits for Engineered Nanoparticles in European Surface Waters. Journal of Environmental Monitoring 11: 1774 – 1781.
2. Hansen, S.F. 2010. A global view of regulations affecting nanomaterials. WIRES: Nanomedicine and Nanobiotechnology 2(5): 441-449.
3. Ganzleben, C., Hansen, S.F. 2012. Nanomaterials as priority substances under the Water Framework Directive. European Journal of Law and Technology 2: 38-45.
4. Grieger, K.D., Hansen, S.F., Linkov, I., Baun, A. 2012. Environmental Risks of Nanomaterials: Review and evaluation of Frameworks. Nanotoxicology 6(2): 196-212.
5. Hansen, S.F., Baun, A. 2012. When Enough is Enough. Nature Nanotechnology 7: 409-411.
6. Hansen, S.F., Baun, A. 2012. European regulation affecting nanomaterials – review of limitations and future recommendations. Dose Response 10(3): 364-383.
7. Hansen, S.F. 2013. The European Union's chemical legislation needs revision. Nature Nanotechnology 8: 305–306.
8. Hansen, S.F., Nolde Nielsen, K., Knudsen, N., Grieger, K.D., Baun, A., 2013. Operationalization and application of “early warning signs” to screen nanomaterials for harmful properties. Environmental Science: Processes & Impacts 15: 190-203.
9. Boldrin, A., Hansen, S.F., Baun, A., Hartmann, N., Astrup, T.F. 2014. Environmental exposure assessment framework for nanoparticles in solid waste. Journal of Nanoparticle Research 16:2394 DOI 10.1007/s11051-014-2394-2.
10. Hansen, S.F., Gee, D. 2014. Adequate and anticipatory research on the potential hazards of emerging technologies: a case of myopia and inertia? Journal of Epidemiology and Community Health doi:10.1136/jech-2014-204019.
11. Hansen, S.F., Jensen, K.A., Baun, A. 2014. NanoRiskCat: A conceptual tool for categorization and communication of exposure potentials and hazards of nanomaterials in consumer products. Journal of Nanoparticle Research 16(1): 2195 DOI 10.1007/s11051-013-2195-z.
12. Hansen, S.F., Jensen, K.A., Baun, A. 2017. Erratum to: NanoRiskCat: a conceptual tool for categorization and communication of exposure potentials. Journal of Nanoparticle Research. 19:236. DOI 10.1007/s11051-017-3909-4.
13. Wickson, F., Hartmann, N. I. B., Hjorth, R., Hansen, S. F., Wynne, B., Baun, A. 2014. Balancing scientific tensions. Nature Nanotechnology 9: 870-870.
14. Hansen, S.F., Baun, A. 2015. DPSIR and Stakeholder Analysis of the Use of Nanosilver. NanoEthics 9(3): 297-319.
15. Syberg, K., Hansen, S.F. 2016. Environmental risk assessment of chemicals and nanomaterials - The best foundation for regulatory decision-making? Science of the Total Environment 541: 784–794.

16. Brinch, A., Hansen, S.F., Hartmann, N.B., Baun, A. 2016. EU regulation of nanobiocides: challenges in implementing the Biocidal Product Regulation (BPR), Nanomaterials 6(2), 33. doi:10.3390/nano6020033.
17. Hansen, S.F. 2016. The emergence of nanorisk-immunity. Frontiers of Nanoscience and Nanotechnology 2(3): 131-134.
18. Hansen, S.F., Heggelund, L.R., Besora, P.R., Mackevica, A., Boldrin, A., Baun, A. 2016. Nanoproducts – What is actually available to European consumers? Environmental Science: Nano 3(1): 169-180.
19. Heggelund, L.R., Hansen, S.F., Astrup, T., Boldrin, A. 2016. Semi-quantitative waste flow analysis of nano-enabled products in Denmark and the United Kingdom – Abundance, distribution and treatment. Waste Management 56: 584-92.
20. Liguori, B., Hansen, S.F., Baun, A., Jensen, K.A. 2016. Control banding tools for occupational exposure assessment of nanomaterials - Ready for use in a regulatory context. NanoImpact 2: 1–17.
21. Mackevica, A., Besora, P.R., Brinch, A., Hansen, S.F. 2016. Current uses of nanomaterials in biocidal products and treated articles in the EU. Environmental Science: Nano 3: 1195-1205.
22. Mackevica, A., Hansen, S.F. 2016. Release of nanomaterials from solid nanocomposites and consumer exposure assessment – A forward-looking review. Nanotoxicology 10(6): 641-653.
23. Mackevica, A., Olsson, M.E., Hansen, S.F. 2016. Silver nanoparticle release from commercially available plastic food containers into food simulants. Journal of Nanoparticle Research 18: 5 DOI 10.1007/s11051-015-3313-x
24. Mackevica, A., Olsson, M.E., Hansen, S.F. 2016. The release of silver nanoparticles from commercial toothbrushes. Journal of Hazardous Materials, 322(Part A): 270–275.
25. Hansen, S.F., Hjorth, R., Skjolding, L.M., Bowman, D.M., Maynard, A., Baun, A. 2017. A critical analysis of the environmental dossiers from the OECD sponsorship programme for the testing of manufactured nanomaterials. Environmental Science: Nano 4: 282 – 291.
26. Hansen, S.F. Sørensen, S., Skjolding, L.M., Hartmann, N., Baun, A. 2017. Revising REACH technical guidance on information requirements and chemical safety assessment for engineered nanomaterials for aquatic ecotoxicity endpoints – Recommendations from the EnvNano project. Environmental Science Europe 29:14 DOI 10.1186/s12302-017-0111-3.
27. Hjorth, R., Hansen, S.F., Jacobs, M., Tickner, J., Ellenbecker, M., Baun, A. 2017. The applicability of chemical alternatives assessment for engineered nanomaterials. Integrated Environmental Assessment and Management 13(1):177-87.
28. Hansen, S.F. 2017. React now regarding nanomaterial regulation. Nature Nanotechnology 12: 714-716.

1. Introduction

Nanomaterials (NMs) are increasingly used in production methods and in consumer products (European Commission 2012a, b, Hansen et al. 2016), however, major knowledge gaps still remain regarding the health and environmental risks posed by NMs (Wiesner et al. 2009, WHO 2013, Lynch 2015). Concerns have furthermore been raised about the potential lack of regulation, the lack of knowledge regarding the safety of nanomaterials and the lack of funding of research into environmental, health and safety (EHS) issues compared to investment into the research and technological development of nanotechnology (CIEL, ClientEarth and BUND 2012, WHO 2013, Schwirn et al. 2014, Hansen and Gee 2014).

We have recently seen a number of incidences of and reports on the adverse health effects of nanomaterials in laboratories and production sites around the world. Although nanomaterials may or may not have been involved directly in the adverse effects observed, the mere fact that these incidents are occurring is a cause of concern in the first place (Hansen 2016).

The strategy implemented by the European Commission, in order to address these concerns and research needs, has involved funding environmental, health and safety research and adopting a so-called "incremental" approach to implementing a minimum number of revisions to existing regulation relevant to the application of nanomaterials, e.g. food, cosmetics and chemicals (European Commission 2004a, CEC 2008a). The implementation of the incremental approach seems to have developed into a series of stopgap measures and has previously been questioned by Franco et al. (2007), Hansen and Baun (2012a) and Vogelezang-Stoute (2014), as it does not address the heart of the challenges we face related to risk assessment, risk management and the regulation of nanomaterials.

As noted by representatives from the European Commission at a 2014 OECD Expert Meeting on Categorisation of Manufactured Nanomaterials, the lack of specific risk management tools for assessing NM, means that case-by-case assessment is needed. Case-by-case assessment on the other hand is becoming increasingly difficult due to the sheer number of existing nanomaterials and new ones constantly being created. NMs are furthermore also difficult to regulate due to a lack of information, their complexity, and a regulatory framework tailored for chemicals rather than manufactured materials (Laursen 2014 cited in OECD 2016a).

In order to address these fundamental problems, the aim of this doctoral thesis is to develop the main components of a new suggested regulatory framework termed "Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses" ("REACT NOW"). Although some NGOs and European member state authorities have also developed suggestions along these lines, none has so far put forward or developed a framework tailored to manufactured nanomaterials that covers their full life cycle i.e. production, use, waste and environmental release.

This doctoral thesis consists of four main parts. The first part focuses on what is known about the current production, use and release of nanomaterials throughout the life cycle of nanomaterials (Chapter 2). The second part explores the benefits and limitations of existing regulation in the light of the revisions that have been implemented recently in various areas of regulation, e.g. REACH, biocides, food, water, waste (Chapter 3) and provides a discussion on the proposed suggestions made by NGOs and European member states (Chapter 4).

The third part identifies and discusses issues that have generally plagued the regulation of nanomaterials in the EU in general and risk assessment specifically (Chapter 5), including suggested alternatives to risk assessment when it comes to NMs (Chapter 6) and specifically, the safety evaluation tool, NanoRiskCat developed by Hansen et al. (2014, 2017c) (chapter 7).

The fourth and final part of the thesis focuses on introducing REACT NOW in regard to its core elements, namely registration, evaluation, authorisation, categorisation and safety evaluation. As no framework is without both potential and limitations, opportunities and weaknesses related to the implementation of REACT NOW will also be discussed in Chapter 8. Finally, conclusions and recommendations will be presented in chapter 9.

2. Production, current uses and exposure pathways of nanomaterials

When it comes to the production and the application of nanomaterials and nanotechnology, respectively, it is unclear what types of nanomaterials and products are currently being produced and are available on the European market, and how the nature of nanomaterials and products have developed over time. Furthermore, very little information is available with respect to what and to how much consumers and the environment are exposed, or at what point they might be exposed during the life cycle of nanomaterials and their applications, i.e. production, use, environmental release and waste (see Figure 1).

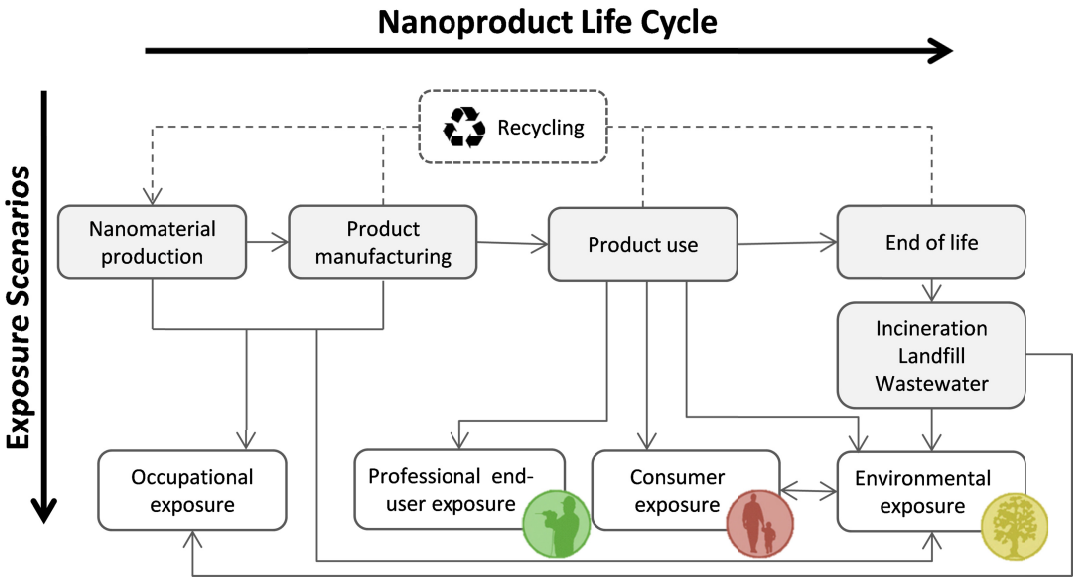


Figure 1: Simplified stages of the nano-enabled product life cycle and the fate of the released NMs (Mackevica 2016).

2.1 Existing inventories and The Nanodatabase

A number of inventories containing information about nanomaterials and nanoproducts do exist, such as the Consumer Product Inventory (CPI) of the Project of Emerging Nanotechnologies (PEN), the Nanoproduktdatenbank, maintained by the Bund für Umwelt und Naturschutz Deutschland (BUND), and the inventory established by the European Association for the Co-ordination of Consumer Representation in Standardisation (ANEC)/The European Consumer Organisation (BEUC), containing products available on the EU market claiming to contain nanosilver particles. The PEN inventory, which was the first of its kind, arguably tends to focus on the North American market and has only been updated about once a year since it originally launched in 2006 (PEN 2015, Vance et al. 2015). The BUND databank focuses mainly on products available on the German market and is only available in the German language, whereas the ANEC/BEUC focuses specifically on products with nanosilver and has not been updated since 2013 (BUND 2015, ANEC/BEUC 2015).

Cosmetics regulations in the EU require that the European Commission publishes a catalogue of nanomaterials used in cosmetic products by January 2014, but the European Commission has failed to do so, supposedly due to "anomalies" in notifications by the industry (Zainzinger 2015, Hansen et al. 2016). When the catalogue was finally published in June of 2017, it only contained the name of 43 materials (e.g. alumina, cellulose, colloidal

copper) and information about the category of cosmetics (e.g. face mask, nail varnish, sun protection products), exposure route (e.g. dermal) and whether the cosmetics is a rinse-off or leave on product (European Commission 2017). Brand name, nanomaterial function, particle size distribution, nanomaterial surface chemistry is among the information not included in the catalogue (Oziel 2017). Recently, the European Commission decided against the establishment of an EU-wide nanomaterial register, as it was not perceived as an appropriate way to provide information to consumers on nanomaterials, and because full coverage of all nanomaterials and mixtures would be difficult to achieve (Paun 2015). Conversely, the Belgian, Danish and French governments have proposed and established their own nanomaterial/product inventories, but any information collected so far has only been made available publically in an overview and summary format and has generally been considered not to "*...add much more to what it could be already known by an informed audience*" (BIRPO and RPA 2014).

Collectively, all of the above-mentioned inventories have a number of limitations. First of all, they are not continuously updated, meaning that months or even years may pass before the provided information is checked and revised. Secondly, the inventories contain a large number of "dead" products, i.e. products that are no longer on the market. Thirdly, some of them are not available to the public, thereby preventing consumers from easy access to information regarding the products they buy. None of the inventories provides analysis tools that would enable researchers and others to do their own independent analysis of the data and information. And finally, the inventories do not contain any health and safety information. A comparative analysis of the different databases and inventories is provided in Table 1.

Table 1: Overview of the scope, update frequency, sources, limitations and strengths of different databases and inventories (From Hansen et al. 2016).

Name	Est.	Scope	Update frequency	Sources	Limitations	Strengths	Reference
The Nanodatabase	2012	1) Products claimed to contain NMs or be based on NT 2) Products available to European consumers	Daily	1) Online search 2) Reporting by users	1) Based on claims 2) Specifically focused on EU	1) Updated daily 2) Possible for users to do their own analysis 3) Includes hazard potential evaluation (NanoRiskCat) 4) Publically available	Hansen et al. 2016, Aschberger et al. 2014
CPI	2006	1) Products claimed to contain NMs or be based on NT 2) Products available globally	Annually	1) Online search 2) Reporting by users	1) Based on claims 2) Only updated periodically 3) Tends to have focus on the American market	1) Evaluation of claims in regard to credibility 2) Publically available	CPI 2015, Wijnhoven et al. 2010, Vance et al. 2015
ANEC/BEUC	2010	1) Products claimed to contain nanosilver 2) Products available to European consumers	Unclear	1) Online search 2) Reporting by users	Not updated since 2013	1) Publically available	ANEC/BEUC 2015, Wijnhoven et al. 2010
CSF Nanotechnology in Food	2015	1) Food products claimed to contain NMs	Unclear	Other nanodatabases e.g. The Nanodatabase	1) Based on other databases	1) Publically available	CSF 2015
BUND Nanoproduktdatenbank	2010	1) Products claimed to contain NMs or be based on NT 2) Products available in Germany	Unclear	1) Online search 2) Reporting by users	1) Only available in German 2) Tends to have focus on the German market	1) Publically available	BUND 2010, 2015, Wijnhoven et al. 2010
French NM compulsory reporting scheme	2013	Substance manufactured at the nanoscale	Annually	Producers, importers or distributers of at least 100 g/year	1) Limited information made publically available e.g. chemical name and uses of NMs	1) Reporting mandatory by manufacturers	Paun 2013b, BIPRO and RPA 2014
Belgian NM registry	2016	Substance manufactured on the nanoscale	Annually	Producers of at least 100 g/year	1) Not publically available 2) Exemptions include e.g. cosmetic products, biocides, treated products	1) Reporting mandatory by manufacturers	Paun 2013a, BIPRO and RPA 2014, Chemical Watch 2014a

Danish nanoproduct registry	2014	Nanoproducts available in Denmark	Annually	Producers and importers to report products containing or releasing nanomaterials	1) Exemptions include food contact materials, cosmetics, mixtures, printed products, textiles containing NMs in colours or dyes; paints, wood preservatives, glues and fillers, that contain nanoscale pigments used solely as colorants, rubber products that contain nano carbon black or silicon dioxide and products containing a) unintentionally produced NMs, b) "fixed" NMs 2) Information about concentration of the nanomaterial in the product, particle size distribution and specific surface area is voluntary 3) Not publically available	1) Reporting mandatory by manufacturers	Paun and Chynoweth 2014, BIPRO and RPA 2014

In order to address these limitations, The Nanodatabase (www.nanodb.dk) was established in 2012 by DTU Environment, the Danish Consumer Council and the Danish Ecological Council. The Nanodatabase is an online inventory of products claimed by manufacturers or others in Europe (e.g. retailers, product reviews) to contain nanomaterials. Along with a description of the product, The Nanodatabase provides available exposure/hazard information. Moreover, to broaden its usefulness, The Nanodatabase is equipped with different analytical tools, thereby allowing the user to sort and extract data in different ways (Hansen et al. 2016).

2.2 The Nanodatabase and use of nanomaterials in consumer products in the EU

The following is based on information available in The Nanodatabase. In this part of the thesis, data that has been published by Hansen et al. (2016) and Mackevica et al. (2016a) are presented. Up-to-date information can be found at www.nanodb.dk.

2.2.1 Development of nanoproduct commercialisation

The number of products contained in The Nanodatabase has increased steadily over time: 1,212 products were originally in the database from the outset in 2012, and this number had risen to more than 2,200 by 2015 (see Figure 2). At the beginning of 2017, more than 3,000 products can be found in The Nanodatabase. This increase in the number of products is primarily the result of increased nanoproduct marketing, as nanomaterials are employed in new applications. A total of 59 products have been retracted from the market and 16 products have lost their "nanoclaim" since 2012.

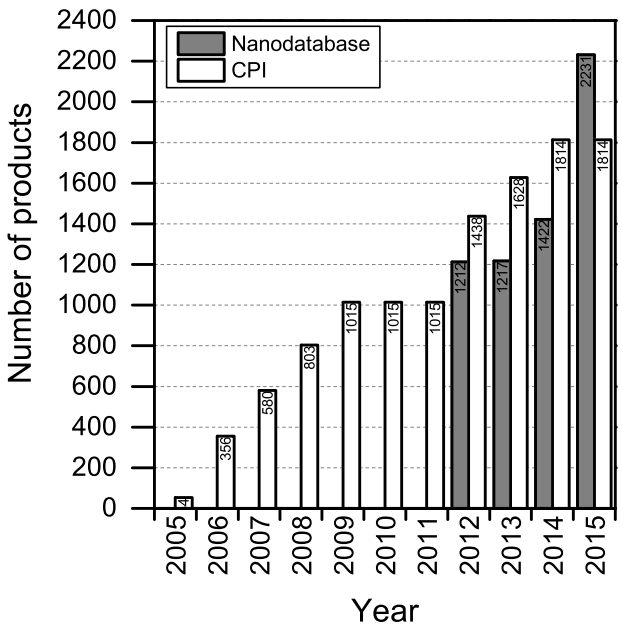


Figure 2: Number of products listed in The Nanodatabase in the period January 2012 to August 2015 and in the Consumer Product Inventory (CPI) in the period 2005-2015 (Hansen et al. 2016).

2.2.2 Distribution of nanoproducts in product categories and subcategories

Most of the products listed in The Nanodatabase belong to the product category "Health and Fitness" (55%), followed by "Home and Garden" (21%) and "Automotive" (12%) (see Figure 3).

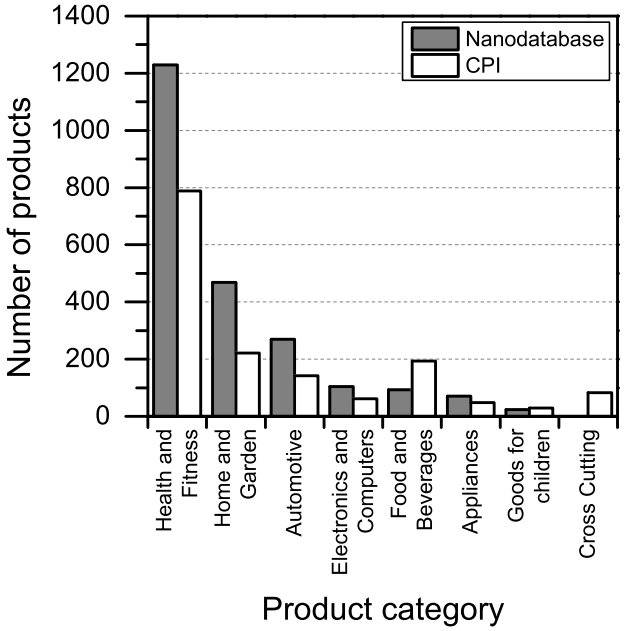


Figure 3: Distribution of products in categories in The Nanodatabase and the CPI

In The Nanodatabase, individual product categories include a number of subcategories, for instance personal care, clothing and cleaning (see Figure 4). In some cases, for example in the "Health and Fitness" category, products fall into several different subcategories, suggesting a broad range of applications of nanotechnologies in a specific field (see Figure 4a). In other cases, such as "Home and Garden", nanomaterial utilisation is restricted to fewer or single subcategories, thereby indicating potential for the further development and utilisation of nanotechnologies in this area (see Figure 4b).

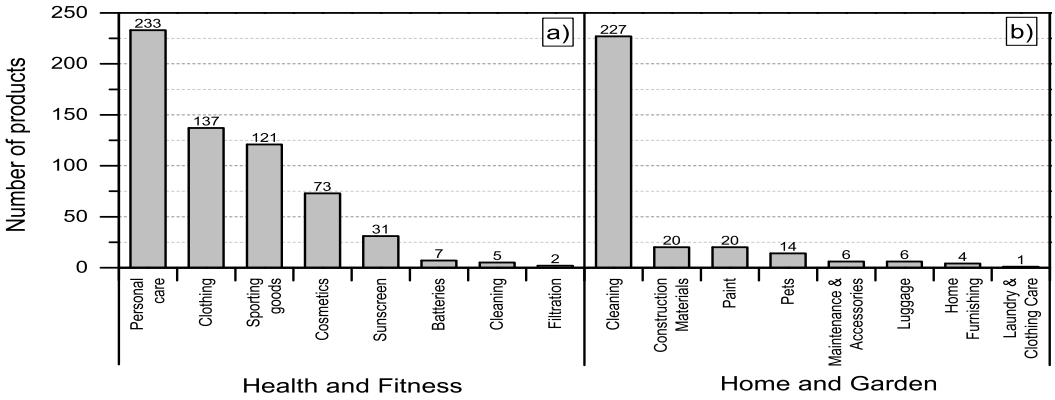


Figure 4: Distribution of a) "Health and Fitness" products in subcategories; b) "Home and Garden" products in subcategories.

2.2.3 Nanomaterials reported to be used

Figure 5 shows the identity of nanomaterials that are claimed to be used across the various product categories in The Nanodatabase.

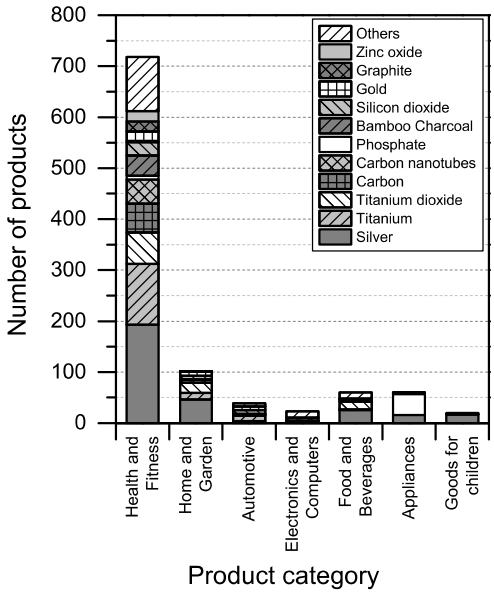


Figure 5: Identity of nanomaterials claimed to be used in different product categories. Products where the used nanomaterial is "unknown" are excluded. Please note that individual products may have more than one type of nanomaterial (From Hansen et al. 2016).

The analysis shows that silver is the most prominently used nanomaterial across all product categories (see Figure 5). Other nanomaterials are specifically relevant to specific product categories: carbon nanotubes and bamboo charcoal in "Health and Fitness"; titanium dioxide in "Health and Fitness" and "Home and Garden"; gold in "Appliances", "Health and Fitness" and "Home and Garden"; titanium in "Automotive", "Health and Fitness" and "Home and Garden" and phosphate in "Appliances". It should also be noted that for a large number of products it was not possible to identify and/or report the type of nanomaterial employed, due to the lack of information provided by the manufacturer. This was especially the case for the product categories "Automotive", "Electronics and Computers" and "Home and Garden", where 89%, 79% and 80% of the products, respectively, could not be associated with a specific nanomaterial type. The share of unknown nanomaterial was 15%, 17%, 35% and 47% for "Appliances", "Goods for Children", "Food and Beverages" and "Health and Fitness", respectively. The Nanodatabase (and CPI, the BUND Nanoproduktdatenbank and other public inventories) only contains products in which the manufacturer or others claim comprise nanomaterials, though nanomaterials are also used in consumer products where the manufacturer does not disclose this information publically. In 2012, the European Commission (2012b) published a so-called Staff Working Paper (SWP) to accompany the Second Regulatory Review on Nanomaterials. From this SWP, it is clear that a wide range of nanomaterials is used in products and processes that could potentially be relevant to consumers. For instance, silica is well known to be used widely in the food industry (e.g. for clarifying wine, beer and fruit juice), but according to the data collected in The Nanodatabase, its use is not declared in any of the more than 90 products listed in the "Food and Beverages"

category as of 2016 (Hansen et al. 2016). There are two products with nanosilica in this category, but both of them are reported by third parties to contain nanoparticles. Similarly, carbon black and carbon nanotubes are used widely in the automotive industry but do not appear under that category in the database.

The lack of reporting the identity of nanomaterials is a major limitation to any effort to obtain an overview of what kind are actually being used in products available to European consumers, as well as to any kind of subsequent exposure and hazard evaluation. Knowing the identity of the nanomaterial or chemical substance is the starting point for any exposure assessment, hazard evaluation or risk assessment. It is noteworthy that even for the category "Cosmetics", in which products containing nanomaterials must be labelled with the term "[nano]" as part of the list of ingredients according to the European Cosmetics Directive, the identity of the nanomaterial is not reported for almost 50% of the items found in The Nanodatabase (Hansen et al. 2016).

2.2.4 Biocidal Products and treated articles

A number of NMs are utilised as biocides, due to their antimicrobial or antifungal properties, but little is known about to what extent biocidal products containing NMs are available on the market. The current list of approved substances, under the Biocidal Product Regulation (BPR), and those substances being examined under the Review Programme, gives a good indication as to what kinds of nanomaterials might be used in biocidal products in the EU (Mackevica et al. 2016a). This list currently contains a number of materials which are commercially available in nanoform, namely basic copper carbonate, boric oxide, copper (II) oxide and copper hydroxide (Nanowerk 2016). It is unknown whether the nanoforms of these materials are sold as biocidal ingredients in Europe, although some are clearly being marketed as such, such as the "biocidal copper carbonate nanoparticles" sold by the German company nanoSaar (Hansen and Brinch 2014, Mackevica et al. 2016a). So far, only synthetic amorphous silicon dioxide (SAS) has been approved as an active substance in the BPR as a product type (PT) 18 (insecticide). Silicon dioxide (as a nanomaterial formed by aggregates and agglomerates) and silver adsorbed on silicon dioxide (HeiQ AGS-20) are currently under review for PT 18 and PT 9 categorisations, respectively (ECHA 2016a, b). Considering the list of existing active substances that are currently under review, it is clear that at least some of them might also be available in the nanoform, for instance silver, copper, dicopper oxide and silicon dioxide. See Table 2 for substances currently being examined under the review programme which might be available in the nanoform, and the product types in which they have been notified for use.

Table 2: Substances being examined under the Review Programme that might be available in the nanoform and the Product Types that they have been notified to be used in (From Mackevica et al. 2016a).

	PT1	PT2	PT4	PT5	PT7	PT9	PT11	PT18	PT21
Silver		X	X	X			X		
Silver phosphate glass		X			X	X			
Silver-Zinc-Zeolite		X	X	X	X	X			
Silver copper zeolite		X	X	X	X	X			
Silver adsorbed on silicon dioxide						X			
Silver zeolite		X	X	X	X	X			
Silicium dioxide								X	
Dicopper oxide									X
Copper									X

Many NMs are used in consumer products due to their biocidal activity; for example, the antibacterial properties of nanosilver and nano-copper are exploited in various products such as antifouling paints, cleaning products, socks, toothbrushes and many others (Mackevica et al. 2016a). Out of the 2,329 products in The Nanodatabase claimed to contain nanomaterials and estimated to be on the European market as of 2016, 342 contain nanosilver, 48 contain silicon dioxide and six contain copper (see Figure 6).

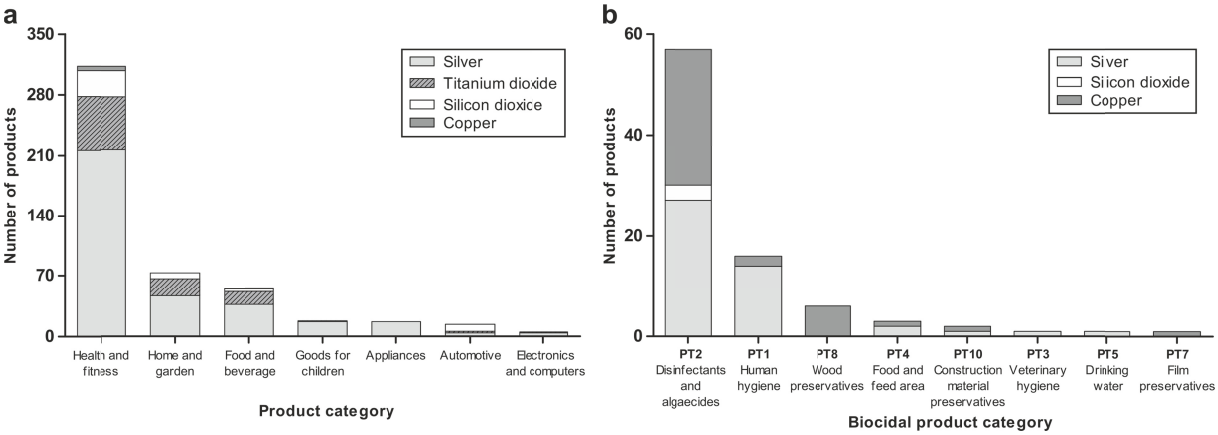


Figure 6: Biocidal substances found in nano-enable consumer products (6a) and the use of nano-enabled biocidal products in different biocidal product types (6b) (From Mackevica et al. 2016a).

Most of the products that use biocidal nanomaterials fall into the "health and fitness" (for example personal care products and clothing), "home and garden" (cleaning products) or "food and beverages" (food supplements, storage and cooking) categories. Around 100 products contain titanium dioxide, which can be considered as an active substance, though it must be noted that it is also widely used as a pigment. In about half of all the nanosilver-containing products in The Nanodatabase, the producers make antibacterial or antifungal claims.

According to an analysis carried out by Mackevica et al. (2016a), The Nanodatabase contains 88 biocidal products in total, and most of them are representing product types 1 and 2, i.e. human hygiene products and disinfectants and algaecides, respectively (Figure 6b). Silver is the nanomaterial that is most often used as the active substances in those biocidal

products (46 products), but almost half of them contain nanomaterials of unknown identity (39 products). Most of the biocidal products fall into the "home and garden" category, which is for the most part represented by different cleaning products, detergents and paints, corresponding to product type 2 – disinfectants and algaecides – according to the BPR (Figure 3).

In total, there are 202 nano-enabled treated articles reported in The Nanodatabase as of 2016, and most of them (157) have nanosilver as the active substance (see figure 7a). Other nanomaterials used in treated articles include bamboo charcoal, nano iron, gold and titanium. The largest proportion of nano-enabled treated articles (79%) fall into the "Health and Fitness" category, representing different textiles, personal care items and food contact materials (Figure 7b) (Mackevica et al. 2016a).

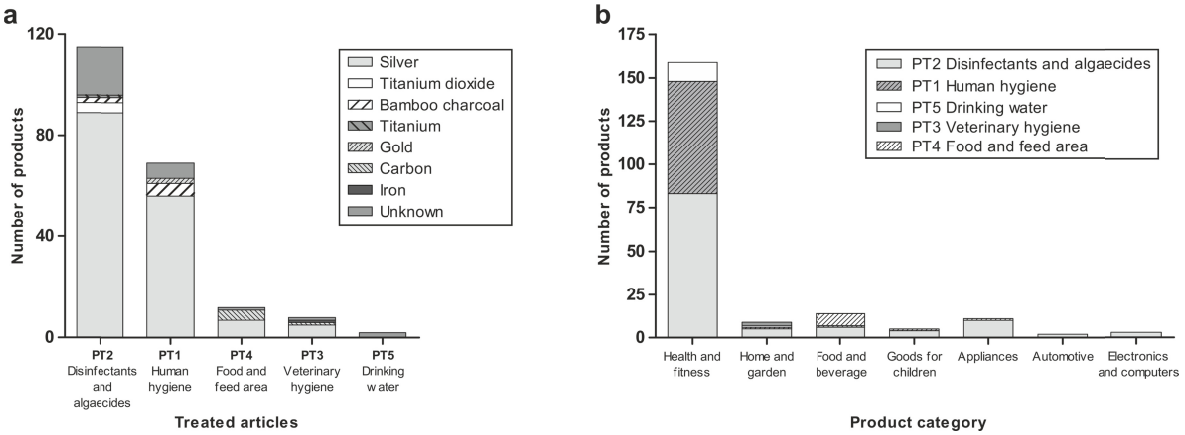


Figure 7: Nanomaterials used in different treated articles according to the biocidal product types (7a) and treated article product types distributed across different product categories in The Nanodatabase (7b) (From Mackevica et al. 2016a).

2.3 Potential route of consumer exposure

Another interesting aspect when it comes to understanding the health and safety aspects of nanoproducts is the potential route of exposure associated with use. We found that dermal exposure is the most prominent route of exposure for most product categories (Figure 8). Inhalation exposure may be significant for the "Automotive" and "Home and Garden" categories, whereas, as expected, oral exposure may be more significant when considering product categories such as "Food and Beverages" and "Health and Fitness". When looking at Figure 8, it is important to note that Figure 8 only displays the potential route of exposure across the individual product categories (if exposure takes place) but does not include any considerations regarding whether the exposure is high, medium or low.

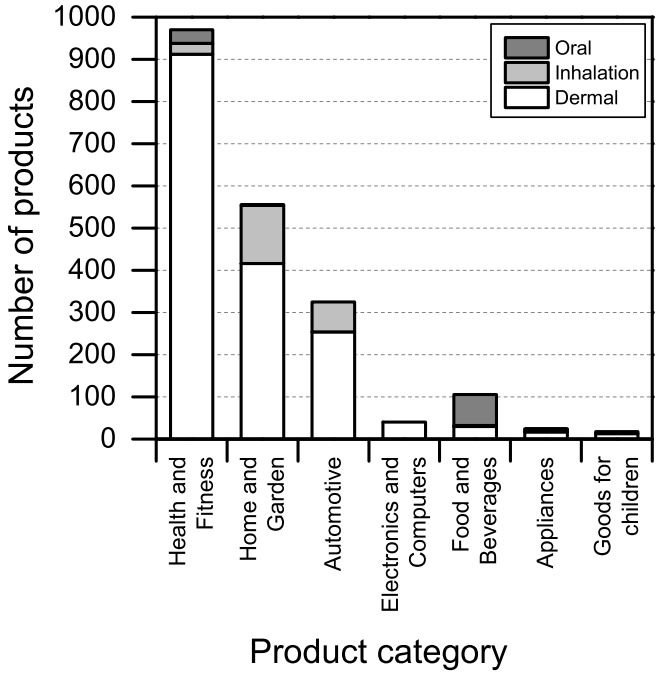


Figure 8: Potential route of exposure for individual product categories. Please note that individual products may have more than one route of exposure (From Hansen et al. 2016).

There are a lot of products in The Nanodatabase for which the identity of the nanomaterial is not reported. For nanoproducts in the database for which nanomaterials are reported, silver is the most prominent type when it comes to dermal exposure (see Figures 6 and 7), followed by titanium dioxide and bamboo charcoal. For inhalation, silver is also the most prevalent followed by titanium, titanium dioxide and gold. Finally, a total 34 products can lead to the oral exposure of nanosilver, whereas 17 and four products lead to oral exposure of nanotitanium dioxide and nanocalcium, respectively (see Figures 9 and 10).

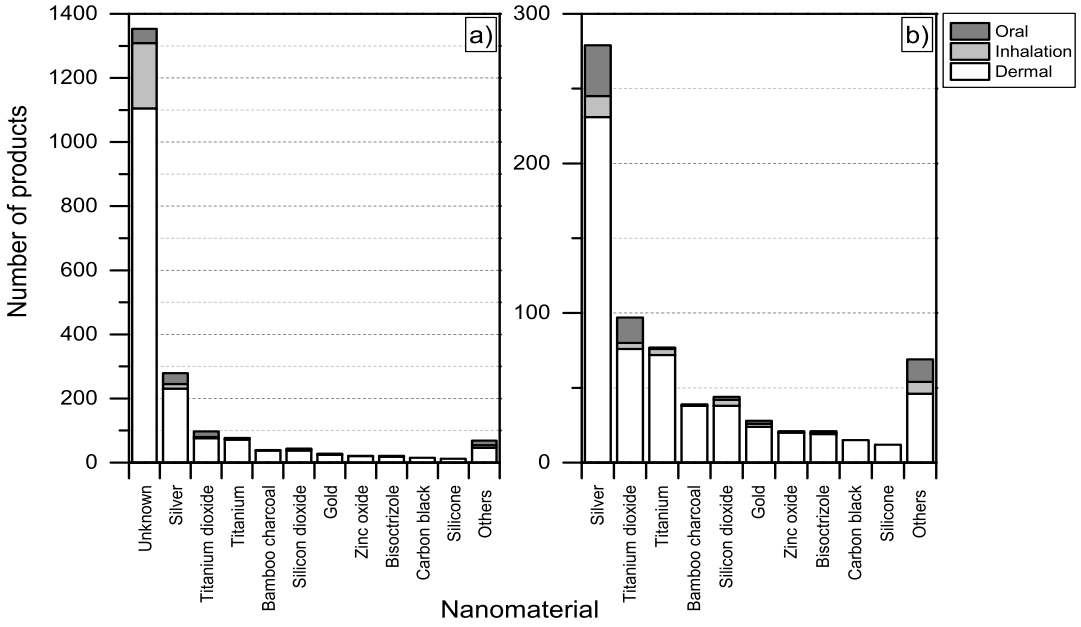


Figure 9: Potential routes of exposure with respect to individual nanomaterials a) including unknown and b) excluding products where the used nanomaterial is "unknown" (From Hansen et al. 2016).

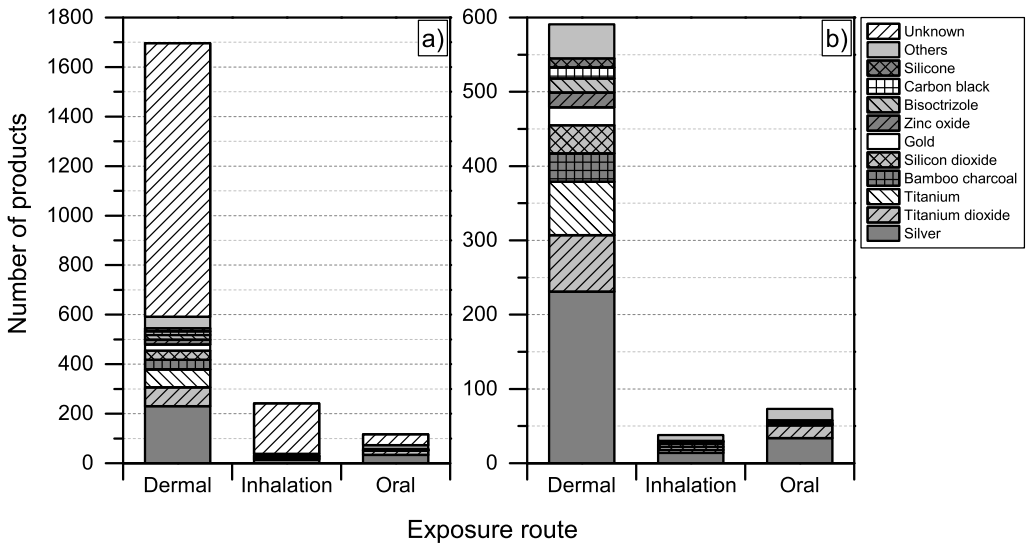


Figure 10: Identity of nanomaterials reported according to their potential route of exposure: a) including products for which the nanomaterial used is unknown and b) excluding products for which the used nanomaterial is unknown (From Hansen et al. 2016).

When considering the body parts that might be exposed during use of the nanoproducts in The Nanodatabase, it is clear that the palm only, the face and scalp (chin, cheeks, hair) and the upper torso (hips, back, trunk, chest, loins) are the areas of the body that might be most exposed (see figure 11) (The Nanodatabase 2017).

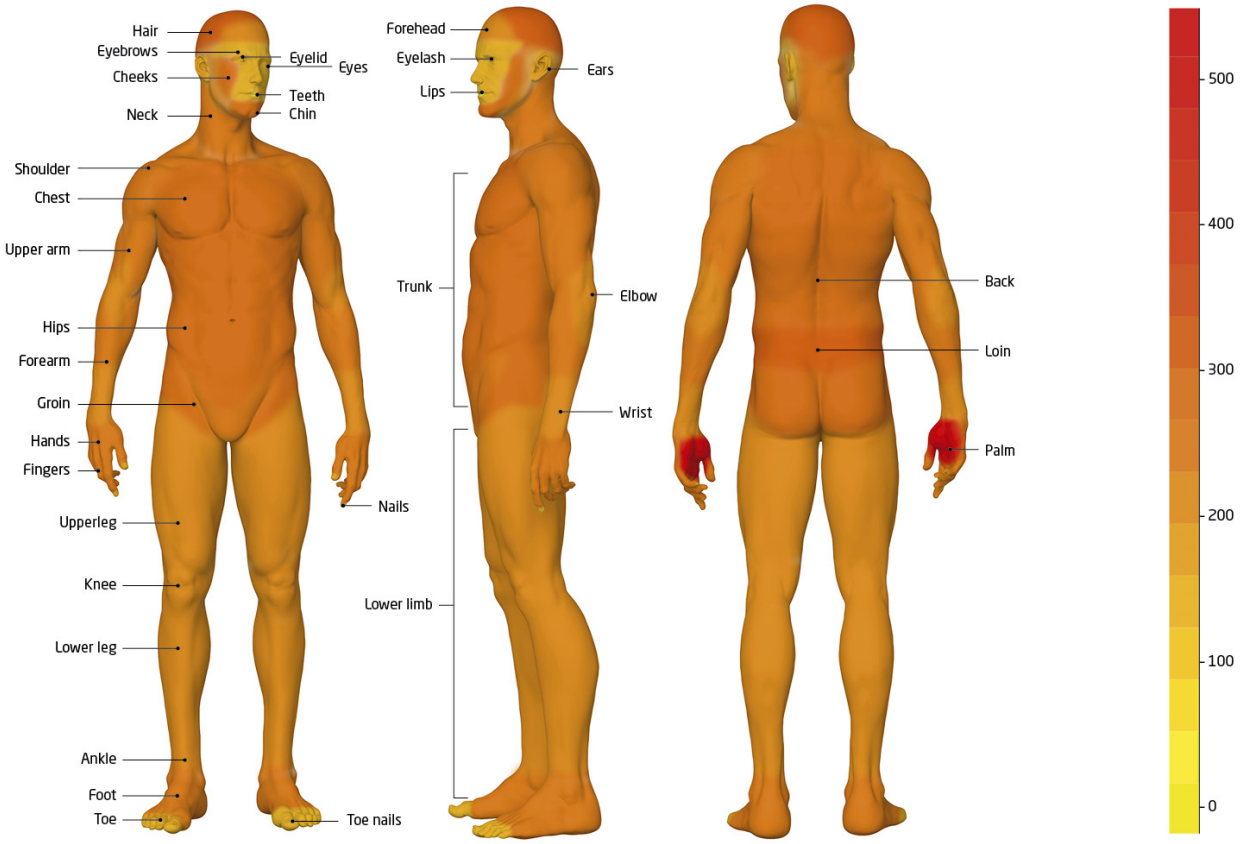


Figure 11: Number of products in The Nanodatabase distributed across human body parts

2.4 The release of nanomaterials from consumer products

In 2014, Froggett et al. (2014) published a review on the release of nanomaterials from solid nanocomposites, by identifying a total of 54 articles describing nanomaterial release (Froggett et al. 2014). In a more recent review, Mackevica and Hansen (2016) investigated the extent to which information and data found in the scientific literature could be used to perform a consumer exposure assessment according to REACH requirements. The numbers of scientific publications of relevance have increased substantially over the last years, and in total, 76 studies were identified (see Figure 12a). Most of the studies analysed the release of Ag and TiO2 from textiles and paints, as well as CNT and SiO2 from nanocomposites (see Figure 12b).

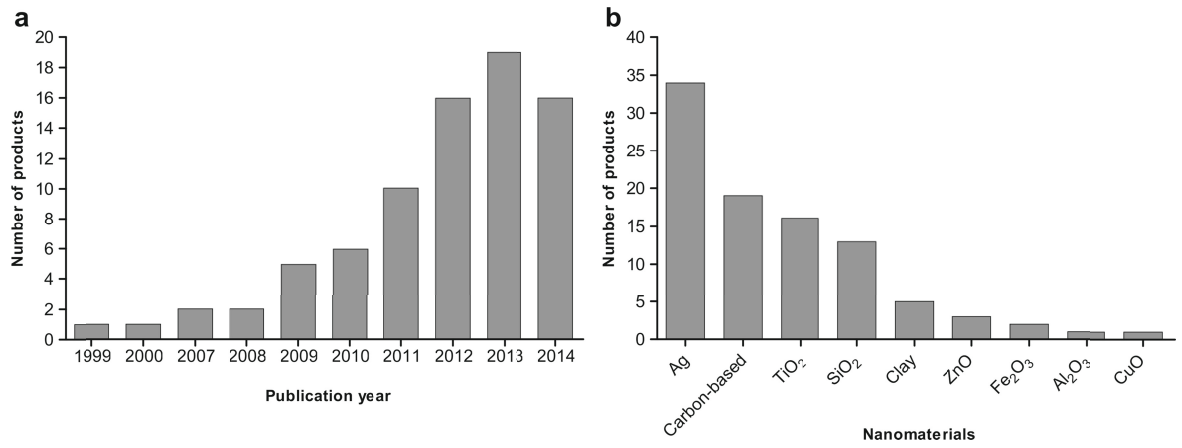


Figure 12: Published literature on release from NM-containing solid nanocomposites grouped by year of publication (12a) and published literature on release from NM-containing solid nanocomposites grouped by NM composition (12b) (From Mackevica and Hansen 2016).

An exception is a study by Mackevica et al. (2016b) on the release of total Ag and Ag NP from commercially available adult and children's toothbrushes. Using inductively coupled plasma-mass spectrometry (ICP-MS) analysis, single-particle ICP-MS and transmission electron microscopy (TEM), Mackevica et al. (2016b) found that the median size of the released Ag NPs ranged from 42 to 47 nm, and the maximum total Ag release was 10.2 ng per toothbrush.

The actual release of NM from tested products varies from study to study and is very dependent on the nature of the tested product, the experimental setup, imagined use scenarios, different production methods employed by different producers of seemingly the same product and even the batch of the tested product (Mackevica and Hansen 2016).

Very few studies have attempted to replicate findings from previous studies, and very few studies follow the standard test guidelines that might be available, which hampers our overall ability to interpret the value of the information and data generated. However, by investigating four brands of commercially available plastic food storage containers, using European Commission test standards (Commission Regulation (EU 10/2011) for plastic materials and articles intended to come into contact with food and SP-ICP-MS and TEM-EDS, Mackevica et al. (2016c) have attempted to replicate the findings of Hauri and Niece (2011) and von Goetz et al. (2013) in regard not only to Ag NP released from plastic containers and amounts leached from food containers, but also in regard to the size

distribution of particulate fractions. Mackevica et al. (2016c) found that the total mass and the median size of released particulate Ag were generally highest in 3% acetic acid for three out of four food container brands. The total content of silver in the containers varied from 13 to 42 l g/g. Similar to Hauri and Niece (2011), Mackevica et al. (2016c) found that the highest migration was observed in the 3% acetic acid food simulant for all four brands of containers, with total silver release up to 3.1 ng/cm2 after 10 days at 40°C (see Table 3).

Table 3: Dissolved and particulate Ag leached into food simulants, measured by spICP-MS (From Mackevica et al. 2016c).

Product	Release medium	Dissolved Ag (µg/L)	Particulate Ag (10^6 particles/L)	Particulate Ag (ng/L)	Median size (nm)
Fresher Longer™ Miracle Food Storage™ bags	MilliQ	-	37.6	13.9	30.3
	10% Ethanol	-	2.8	0.5	23.9
	3% Acetic acid	6.79	-	-	-
The Original Always Fresh Containers™	MilliQ	0.57	18.3	10.5	41.1
	10% Ethanol	0.66	9.5	7.1	35.5
	3% Acetic acid	10.71	2.0	27.5	89.6
Kinetic Go Green™ Premium	MilliQ	-	2.7	0.1	17.4
	10% Ethanol	0.13	7.4	2.5	26.9
	3% Acetic acid	3.18	4.2	27.8	67.2
Special Nanosilver Mother's milk pack	MilliQ	0.03	5.5	4.5	29.8
	10% Ethanol	-	5.8	1.4	25.5
	3% Acetic acid	7.51	1.9	18.3	63.8

Although the body of literature on the release of nanomaterials from consumer products is growing, little of the information provided in currently available studies is of relevance to REACH, because, for instance, less than half of the studies report their findings in a format that can be used for exposure assessment. Furthermore, most do not include any characterisation of the released particles (Mackevica and Hansen 2016). Although inhalation, dermal and oral exposure estimates can be derived using REACH guidelines on how to complete consumer exposure assessments, it is clear that the equations are not developed to take into consideration the unique properties of nanomaterials, and further research is needed in order to develop more relevant consumer exposure models of nanomaterials and nanoproducts, and to develop more generalised methods for representing nanomaterial release from different product groups in relevant environmental conditions (Larsen et al. 2015, Mackevica 2016, Mackevica and Hansen 2016).

2.5 The environmental release of NMs

Historically, the environmental concentration of chemical substances has been found to increase with their use in society, and we can therefore expect increasing future environmental concentrations of NMs in surface waters, air, groundwater and soils (Ganzleben and Hansen 2012a).

The environmental release of NMs may occur at different stages during the life cycle of a material e.g. production, use and end-of-life, and can occur via multiple pathways and from multiple sources especially given the diversity of NMs produced and commercialised as well as the diversity of nanoproducts. Potential point sources of NM emissions include spills

during production and transport, industrial emissions into the air, water and soil, emissions into the air from construction sites and incineration plants, effluents released into surface waters from urban wastewater treatment plants, landfill leachates into soil and groundwater and direct releases of NM into soils and groundwater for remediation purposes. Diffuse sources include NM release from products during use and re-use, NM leaching into groundwater and then into surface waters from landfills, the run-off from agricultural land of pesticides that contain NM and from sewage sludge and spilt lubricants that are washed off roads into stormwater discharges (Baun et al. 2009, Ganzleben and Hansen 2012 a, b).

Available data on point source emissions remain very limited, while a reliable estimate of diffuse source emissions from nanoproducts is currently hampered by the lack of information and lack of access to information about: volumes of NMs on the market; volume fractions incorporation into products; market penetration and use patterns and emissions of NM from products throughout the life cycle (Ganzleben and Hansen 2012 a, b). Once in the environment, the behaviour of NM will depend on its physicochemical properties (and nanoforms thereof), and on the environment into which they are released. The fact that NMs behave differently to dissolved chemicals limits the applicability of existing exposure models (Ganzleben and Hansen 2012b, Gottschalk et al. 2015). Insights into the environmental fate and pathways of NMs has increased in the last decade to the extent that aquatic reactions of NM, such as dissolution and aggregation, can be modelled in complex media, especially in the case of data-rich ENM materials such as Ag (e.g. Quik et al. 2011, Dale et al. 2013). The first attempts to group different NMs in regard to environmental fate and behavioural properties have been made, such as by Hartmann et al. (2014) (see Table 4).

Table 4: Relative importance of transformation processes for modelling the environmental fate of uncoated, non-functionalised forms of selected NMs (From Hartmann et al. 2014).

	Process	Importance of the environmental process in fate modelling					
		Low		*Medium*			*High*
(Photo) chemical	*Photochemical*	nZVI, CB	ZnO, CuO	Ag, CeO_2	TiO_2, CNT		
	Redox	TiO_2, CNT, CeO_2, CB	ZnO, CuO				Ag, nZVI
	Dissolution	TiO_2, CNT, nZVI, CB	CeO_2			CuO	Ag, ZnO
Physical	*Aggregation / Agglomeration*					Ag, ZnO	TiO_2, CNT, CuO, nZVI, CeO_2, CB,
	Sedimentation					Ag, ZnO	TiO_2, CNT, CuO, nZVI, CeO_2, CB
Interactions with surfaces/ substances	*NOM adsorption*					Ag, TiO_2, ZnO, CuO, nZVI,CeO_2	CNT, CB
	Sorption onto other surfaces/ retention in soil				Ag, ZnO, CuO	TiO_2, CeO_2	CNT, nZVI, CB
Biologically mediaed	*Biodegradation*	Ag, TiO_2, ZnO, CuO, nZVI, CeO_2, CB	CNT				
	Bio-modification		Ag, TiO_2, ZnO, CuO, nZVI, CeO_2, CB	CNT			

Attempts have also been made to model the environmental fate and pathways of NMs (see Ganzleben and Hansen (2012a) and Gottschalk et al. (2015) for a review), suggesting a number of data characteristics relevant to environmental exposure data for NM, including:

- Mass concentrations in the range of µg/L – pg/L and changes in concentrations over time;
- Particle size and shape and range of particle distribution, i.e. identifying and measuring the size fractions of different nanoforms;
- Available surface area;
- Distinguishing between NM and naturally occurring nanomaterials and
- Data on the degree of aggregation and dissolution, i.e. ongoing fate and behaviour (Ganzleben and Hansen 2012a).

However, there are quite a few gaps in our knowledge when it comes to the environmental fate and behaviour of nanomaterials and a number of processes have to be studied further, including chemical/photochemical transformation processes, dissolution/precipitation/ speciation processes, agglomeration/aggregation processes, biological transformation processes, sedimentation, adsorption and desorption processes and, above all, appropriate NM characterisation and measuring methods for NM in environmentally relevant media (Hartmann et al. 2014).

2.6 Solid waste flows from nano-enabled consumer products

The increasing use of NMs in society, and specifically in consumer products, means that NMs will eventually find their way into various forms of waste treatment processes (incineration, wastewater treatment plants, etc.) not originally designed to treat such materials (Heggelund et al. 2016, OECD 2016d). Very few experimental studies have investigated the fate and behaviour of pristine nanomaterials in simulated landfill conditions (e.g. Bolyard et al. 2013) and during incineration (Walser et al. 2012).

In order to gain a better understanding of the end-of-life waste treatment of nano-enabled consumer products, Heggelund et al. (2016) used The Nanodatabase to provide an overview of NMs flowing into and throughout waste systems in Europe, including in Denmark and the United Kingdom. First, the available nano-enabled products were categorised into waste material fractions. Then the types of NMs present in waste material fractions were estimated, followed by an estimation of the region-specific waste management of individual waste material fractions. Finally, the information obtained was combined to determine the distribution of NMs routed to specific waste treatment options (Heggelund et al. 2016). The largest of a total of nine different waste fractions identified by Heggelund et al. (2016) was found to be "Plastic, packaging", "Textile" and "Electronics", with 847, 390 and 306 products, respectively, out of a total of 2,312 products in The Nanodatabase. The most abundant NM across all waste fractions was found to be silver, but otherwise the second-most abundant NM was found to vary between different waste fractions (see Figure 13). Plastic packaging waste comprised the largest variety of NMs, namely 20 different NMs, which might be caused by the fact that this waste material fraction is generated from many different sources (product categories) such as the automotive, food & beverage and home & garden sectors.

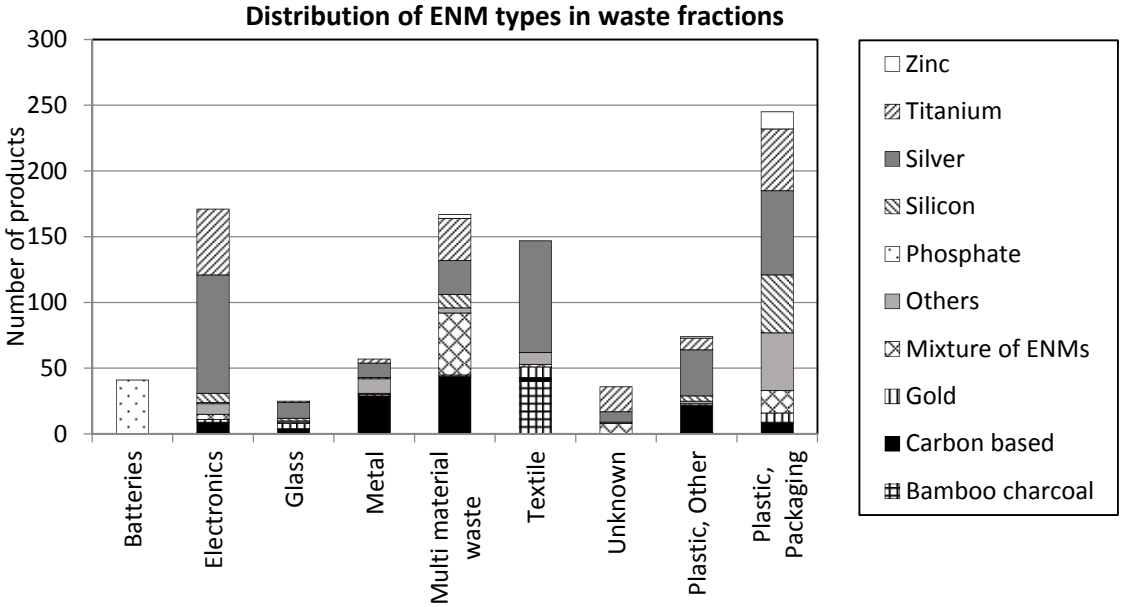


Figure 13: Distribution of ENM in the different waste material fractions according to data from nanodb.dk. The Y-axis represents the number of products containing a certain ENM (nanodb.dk). Please note that the products have been grouped according to which primary nanotechnology substance they contain, e.g. "Titanium" includes both titanium and titanium dioxide, and "carbon based" includes CNTs, carbon black, fullerenes and graphite (From Heggelund et al. 2016).

By combining information on the distribution of NM types in waste fractions with information on how the individual waste fractions are treated within the European Union (EU), Denmark (DK) and the United Kingdom (UK), Heggelund et al. (2016) estimated the relative distribution of nanoproducts to waste treatment technologies and found that more than 50% of nanoproducts are likely to end up in recycling processes for all three regions within the nine waste fractions identified (see Figure 14). Europe and the UK offer quite comparable incineration and landfilling treatment options, routing 19% and 13% to incineration and 26% and 29% to landfilling, respectively. Denmark, on the other hand, to a large extent, combines incineration with energy recovery, which results in 38% of nanoproducts ending up in waste incineration plants and only 8% in landfills.

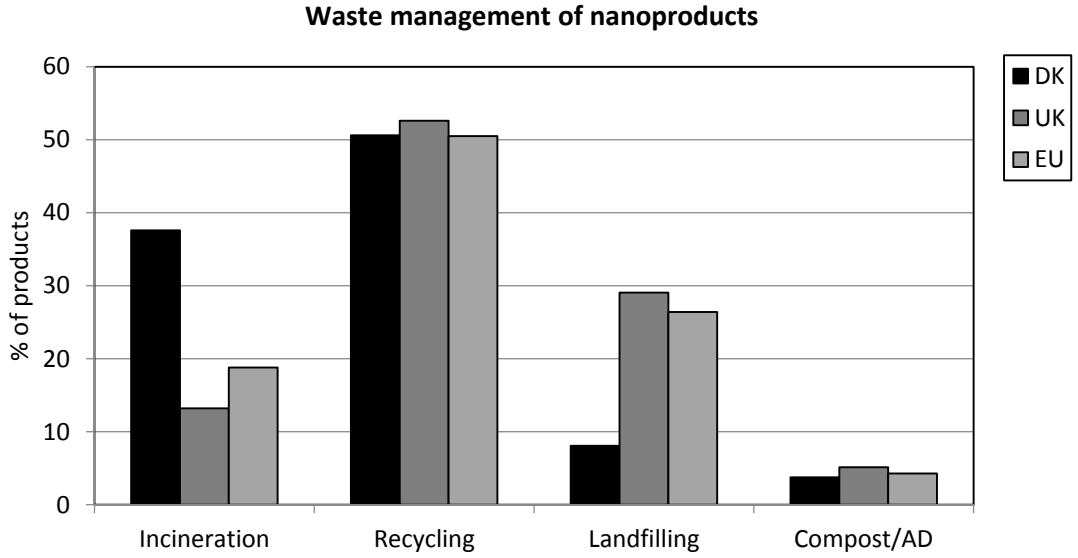


Figure 14: Relative distribution (%) of end-of-life nanoproducts into waste treatment options in the three analysed scenarios: Europe (EU), Denmark (DK) and the United Kingdom (UK) (From Heggelund et al. 2016).

By combining the distribution of NM types in waste fractions (Figure 13) and the relative distribution of EOL nanoproducts into waste treatment options in the EU, Denmark and the UK (Figure 14), Heggelund et al. (2016) finally derived the distribution of nanomaterials for the four different waste management options: incineration, recycling, landfilling and composting/anaerobic digestion (see Figure 15).

From Figure 15, one can see that 31% of EOL nano-enabled consumer products in Europe entering a waste incineration plant will contain nanosilver and that anaerobic digestion/compost is expected to be relevant for a few nanoproducts only. The distribution of NMs in the different waste management systems was found to be similar for Europe, e.g. the numbers of items containing silver and titanium NM were more or less the same, regardless of the management scenario. Some interesting regional differences were furthermore observed; the proportions of titanium- and carbon-based NMs were found to be higher in the UK landfill scenario, because greater amounts of plastic waste (both packaging and other plastic) are disposed of in landfills in the UK compared to Denmark, whereas bamboo charcoal and nanogold are expected to be present in Danish landfills, due to the larger amounts of textile waste.

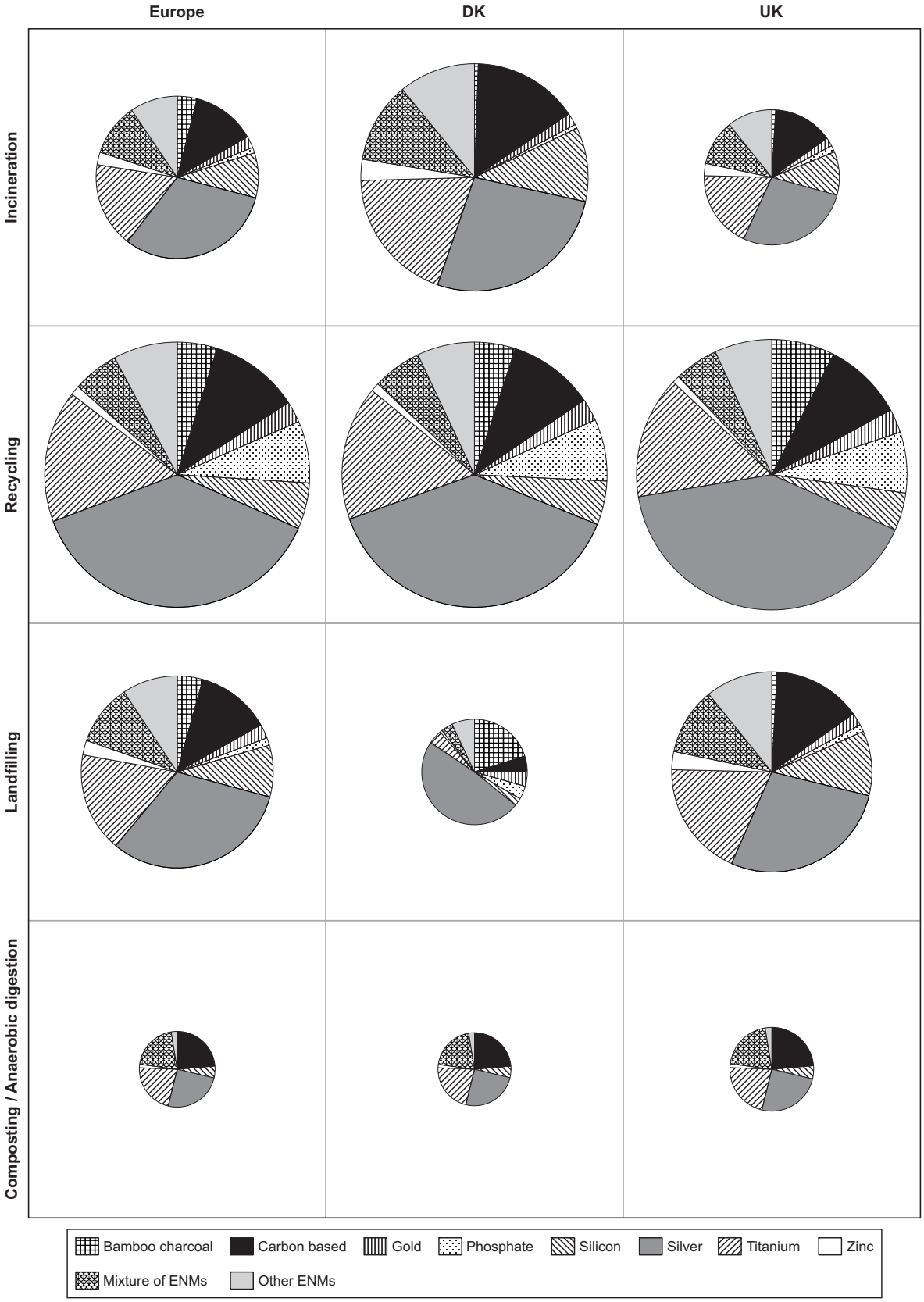


Figure 15: Distribution of nanomaterials for the four different waste management options: incineration, recycling, landfilling and composting/anaerobic digestion. The figure illustrates the percentage of products entering a waste treatment option that will contain a certain ENM. Note: the area of the pie is proportional to the number of products entering individual treatments, thus reflecting the size of the bars in Figure 14 (From Heggelund et al. 2016).

In order to assess the environmental exposure of nanoparticles from solid waste, Boldrin et al. (2014) proposed a five-step framework (see Figure 16) and applied it to three different examples: nanosilver in polyester textiles, nano-scale titaniumdioxide in sunscreen lotion and carbon nanotubes in tennis racquets. Boldrin et al. (2014) found that considerable amounts of these nanoproducts entered waste management systems, based on data available in 2011 (globally 23.7×10^3 Mg of polyester textiles, 715–1,430 Mg of sunscreen lotion and 313–825 Mg tennis racquets). On a global scale, this would result in 0.8–5.6 Mg of nanosilver, 14–143 Mg of nanoTiO2 and 0.5–1.2 Mg of CNTs being released annually into the environment, based on potential waste management practices and exposure routes (Boldrin et al. 2014).

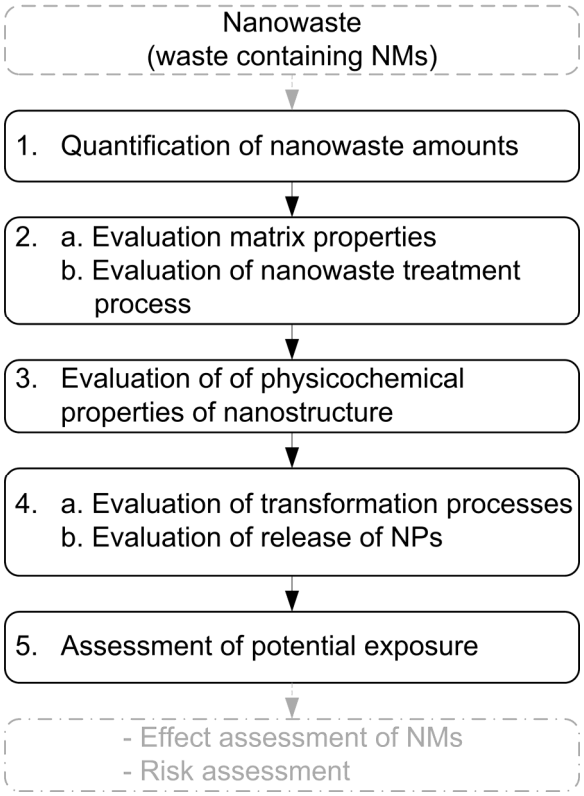


Figure 16: Proposed framework for an environmental exposure assessment of nanoparticles in solid waste. The framework includes steps 1–5. When combined with results from an effect assessment, the results of the exposure assessment may be used as an input into the environmental risk assessment of nanoparticle emissions from waste (lower dotted box, outside the scope of the present study).

Boldrin et al. (2014) observed that the main challenges in relation to further research into nanomaterials and waste were: 1) the transformation of nanomaterials within waste treatment technologies, 2) release mechanisms in conditions relevant for waste disposal, 3) exposure assessments performed at the local level and within a precise context, (4) the characterisation of nanowaste and the development of appropriate analytical methods and (5) a definition of appropriate regulatory limit values and nanowaste data reporting.

3. Existing legislation – opportunities and weaknesses

Numbers of EU regulations and directives have been amended in recent years, namely REACH, BPR, food, cosmetics and eco-labelling. A range of advisory reports have also been published to support this legislation, the most important of which are provided by Aitken et al. (2011), Hankin et al. (2011), Christensen et al. (2012), Rauscher et al. (2015), SCENIHR (2005, 2007, 2009), EFSA (2009, 2011) and ECHA (2012a-c, 2016). Figure 17 presents a timeline of the implementation of key EU regulations, directives as well as the publication of key advisory reports and technical guidance.

In the following an analysis of REACH, the BPR and the relevant food legislation will be presented. The analysis focuses on regulations that have been revised in order to meet the specific challenges that nanomaterials present. REACH, BPR and relevant food legislation will be analysed in depth in this chapter, but all amended regulations and directives have been subject to an analysis of their opportunities and weaknesses and are included in Table 5. Opportunities are considered to be aspects that improve the current situation, should they materialise and be implemented successfully; nonetheless, given that many of the opportunities place a burden on industry, EC or EU member states, this cannot always be taken for granted. Weaknesses are understood as elements that we already know are vague, difficult to fulfil or require the impossible, given the current state of knowledge. For details on legislation that has been amended, see Hansen and Baun (2012a), Gellert et al. (2015) and Broomfield et al. (2016). For a review of relevant regulations and directives that have yet to be amended, and their limitations when it comes to nanomaterials, see Ganzleben et al. (2011), Hansen and Baun (2012a), Gellert et al. (2015) and Broomfield et al. (2016).

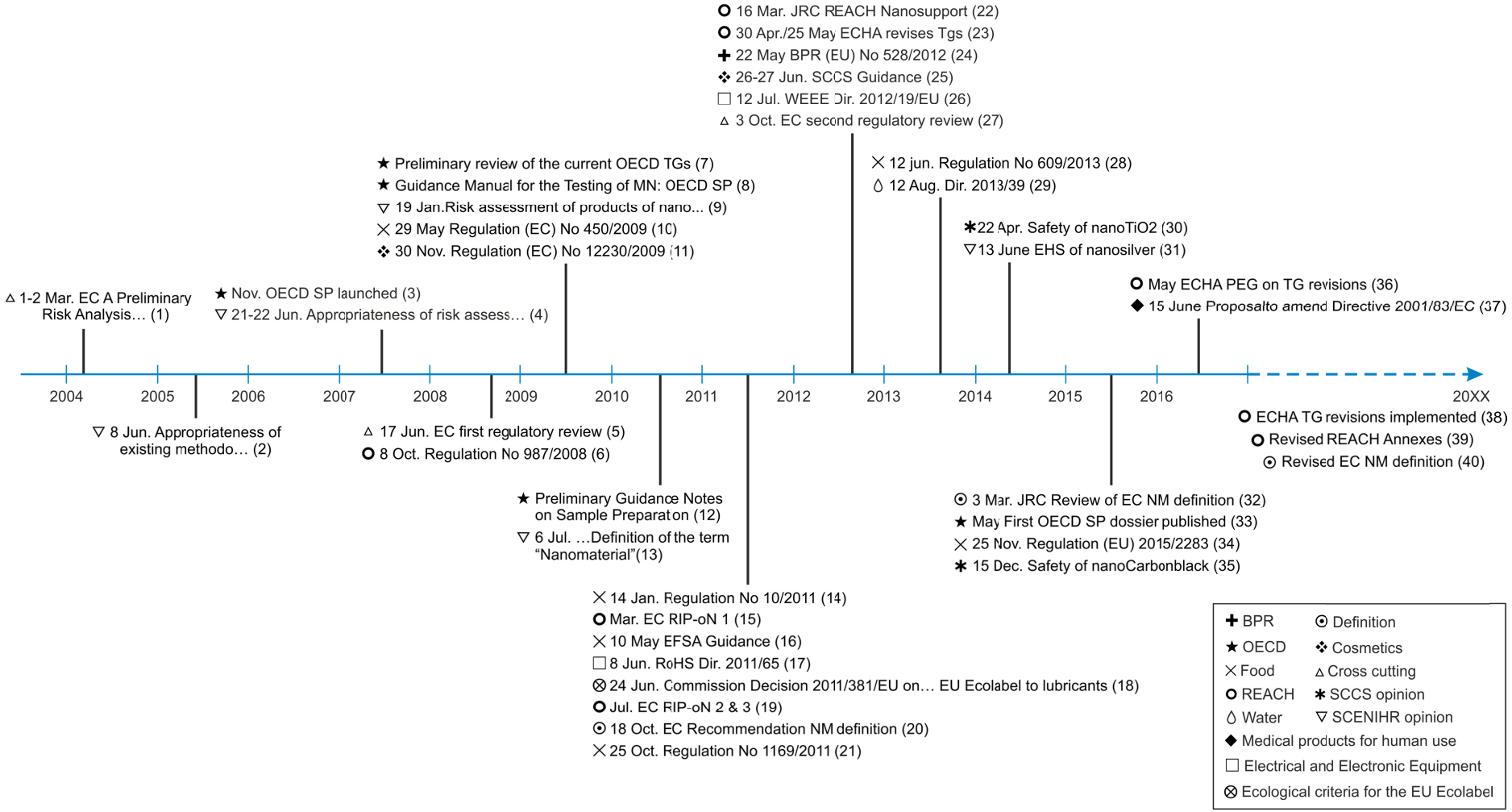


Figure 17: Timeline of the implementation of key EU regulations, directives as well as the publication of key advisory reports and technical guidance.
1) European Commission 2004a, 2) SCENHIR 2005, 3) OECD 2008, 4) SCENHIR 2007, 5) CEC 2008a, 6) CEC 2008c, 7) OECD 2009a, 8) OECD 2009b, 9) SCENIHR 2009, 10) CEC 2009, 11) EP and the Council 2009a, 12) OECD 2010, 13) SCENIHR 2010, 14) European Commission 2011a, 15) European Commission Joint Research Centre 2011, 16) EFSA 2011, 17) EP and the Council 2011a, 18) European Commission 2011b, 19) Hankin et al. 2011, Aitken et al. 2011, 20) European Commission 2011c, 21) EP and the Council 2011b, 22) Christensen et al. 2012, 23) ECHA 2012a-d, 24) EP and the Council 2012a, 25) SCCS 2012b, 26) EP and the Council 2012b, 27) European Commission 2012a, 28) European Commission 2013a, 29) EP and the Council 2013, 30) SCCS 2014b, 31) SCENIHR 2014, 32) Rauscher et al. 2015, 33) OECD 2016c, 34) EP and the Council 2015, 35) SCCS 2015a, 36) ECHA 2016c, 37) Council of the European Union 2016, 38) ECHA 2016c, 39) Roberts 2016, Bergeson and Hutton 2016, 40) Roberts 2016.

Table 5: Overview of regulations and directives that have been amended in the EU in regard to nanomaterials and their opportunities and weaknesses

Legislation	Opportunities	Weaknesses	References
Cosmetics *Scope* Substance/mixtures intended to be placed in contact with external parts of the human body, teeth, etc. with the purpose of cleaning or perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odour	*Pre- and post-market notifications* • For cosmetics, already on the market, manufacturers have to inform the European Commission about the presence, identity and form of nanomaterials and exposure conditions • Six months prior to the commercialisation of cosmetic products not yet placed on the market, manufacturers have to submit a notification to the EC including, among others, information about size, quantitative annual estimates of marketed NMs and the toxicological profile *Pre-market safety assessment* • Prior to placing a cosmetic product on the market, manufacturers have to ensure that a safety assessment has been performed • The SCCS is provided to give guidance on test methodologies which take into account specific characteristics of nanomaterials *Labelling* • The presence of nanomaterials in products has to be indicated clearly in the list of ingredients via the name of the nanomaterial followed by the word "nano" in brackets *Scientific opinion on safety* • On the EC's request the Scientific Committee on Consumer Safety (SCCS) is to give its opinion within six months on the safety of a nanomaterial for use in the relevant cosmetic product categories *Authorities reporting* • The EC has to make a publicly available catalogue of all nanomaterials used in marketed cosmetic products, indicating, for example, cosmetic product categories and exposure conditions	*Definition* • Unclear NM definition in regard to terms such as "insoluble", "bio-persistent" and "intentionally manufactured" *Pre- and post-market notifications* • Pre-market notification only required if the cosmetic product has not already been placed on the market before 11 January 2013 *Pre-market safety assessment* • Pre-market safety assessment is challenging especially when it comes to establishing the toxicological profile of substances and possible impacts on the toxicological profile due to particle size	Bowman et al. 2009, Hansen and Baun 2012b, Vogelezang-Stoute 2014, Gellert et al. 2015,

	• The EC has to prepare an annual status report outlining, for instance, the present and future use of nanomaterials in cosmetic products, the number of notifications and any progress made regarding nano-specific safety assessment methods		
WFD *Scope* Priority substances in the field of water policy	*Risk screening* Revised methodology for COMMPS scheme now able to identify NMs as priority substances	*Definition* • No specific reference is provided to NMs but rather to particle size *Risk screening* • Lack of monitoring data on nanomaterials in EU surface waters hampers the applicability of the revised methodology for the COMMPS scheme • No nanomaterials were included in any international agreements or EU legislation on hazardous substances *Risk assessment* • Virtually impossible to conduct risk assessments and determine whether any nanomaterials give rise to an equivalent concern as PTB substances (i.e. persistent, toxic and able to bio-accumulate) • The establishment of environmental quality standards (EQS) for priority substances is hampered by uncertainties related to the use of mass-based thresholds for establishing EQS • Questionable whether the principles for deriving EQSs for chemicals can be transferred directly to NPs *Enforcement* • Lack of appropriate end-of-pipe measures to control discharges of nanomaterial pollutants from point sources • Impossible to categorise NMs as specific pollutants of river basins because of the absence of appropriate monitoring techniques	Baun et al. 2009, Ganzleben et al. 2011, Ganzleben and Hansen 2012b, Gellert et al. 2015, Broomfield et al. 2016

Table 5 continued: Overview of regulations and directives that have been amended in the EU in regard to nanomaterials…

Legislation	Opportunities	Weaknesses	References
REACH *Scope* Manufacturing/import of chemicals including nanomaterials		*Definition* Unclear substance definition when it comes to NMs *Registration* • Size not listed as information necessary to enable each substance to be identified • The 1 ton/year threshold would hardly be reached for many nanoparticles • Registration is not required when the concentration of a substance in the final product is lower than 0.1% w/w *Information requirements* No specific registration or information requirements for nanomaterials *Risk assessment* • Four elements of risk assessment not tailored for NM • Unclear whether wholesale hazard information is appropriate for nanoforms OECD TGs not developed for dispersed NM but for soluble chemicals instead	CIEL, ClientEarth and BUND 2012, Hansen and Baun 2012b, Hansen 2013, UBA, BfR and BAuA 2013, Schwirn et al. 2014, Gellert et al. 2015, Syberg and Hansen 2016
Food legislation *Scope* Information for consumers, food additives and novel foods	*Risk assessment* • Scientific appropriateness and technical adaptations/ adjustments of the performed test have to be provided for NMs • Obligation of the applicant to take the latest EFSA guidance documents into account when submitting a technical dossier on food additives • Technical dossier on food additives should include all available data relevant for risk assessment • Data required for risk assessment of food additives: particle size distribution, physicochemical characteristics and NM toxicology	*Definition* • Unclear what constitutes "significant changes to the production process or starting materials" of a food additive and what it means that food additives are produced "through nanotechnology" • Definition of "novel foods" excludes NMs marketed before 15 May 1997 • Definition of NM different from other non-food regulations, thereby creating inconsistency across legislative areas and meaning that a NM could be a NM according to one regulation and not according to another	Hansen and Baun 2012b, Vogelezang-Stoute 2014, Gellert et al. 2015

- Verification has to be provided that the proposed use does not mislead the consumer and that there is a reasonable functional and technological need that cannot be achieved by other means
- The applicant has to provide a description of the analytical methods, thus allowing the identification and quantification of the additive or its residues in food

Scientific opinion on safety

- On the EC's request, the European Food Safety Authority (EFSA) is to give its opinion within six months on whether a novel food may pose a safety risk to human health, by considering possible effects on vulnerable groups of the population and verifying that the most up-to-date test methods are used to assess safety where a novel food consists of engineered nanomaterials
- EFSA shall, upon request, provide an opinion on food additives that should include, among others, an overall risk assessment highlighting uncertainties and limitations, where relevant

Authorisation

- The use of nanomaterials requires prior authorisation
- A reasonable technological need for food additives has to be present that cannot be achieved by other economically and technologically practicable means
- Use of food additive must not mislead consumers
- Use of a food additive must have advantages and benefits for consumers

Labelling

Specific labelling requirements which do not mislead the consumer

- Hard to operationalise terms in the definition, such as physico-chemical properties that are different due to SSA and/or different from bulk

Risk assessment

- Unclear how applicants are to provide "Scientific evidence demonstrating that the novel food does not pose a safety risk to human health" in light of the uncertainties identified and noted by EFSA (2009, 2011)

Authorisation

- Unclear how "reasonable technological need" is to be determined for food additives, considering other economically and technologically practicable means

Table 5 continued: Overview of regulations and directives that have been amended in the EU in regard to nanomaterials…

Legislation	Opportunities	Weaknesses	References
EU Ecolabel Regulation *Scope* Products and services which have a lower environmental impact than other products in the same group	*Life cycle considerations* Criteria must be determined on a scientific basis, by considering the whole life cycle of products *Information requirements* • It is necessary that applicants list all ingoing substances by mentioning ingoing quantity, the function of the substance and the form it takes in the final product formulation • Information provided by applicants must relate to the forms or physical states of the substance or mixtures as used in the final product *Evaluation* • Consideration of uncertain consequences associated with the widespread use of nanosilver in hygiene products *Restriction* Nanoforms of hazardous substances intentionally added to three product categories, i.e. all-purpose cleaners have to be excluded for any concentration	*Definition and information requirements* Inconsistencies across different EU ecolabel criteria decisions in regard to information requirements on nanoforms and NM definition and whether reference is made to forms and physical state of substances, or no reference is made at all *Restriction* Relies on CLP categorisation of hazardous substances which might not be adequate for NMs	Broomfield et al. (2016)
Biocides *Scope* Production and import of nanomaterials and treated products	*Risk assessment* • Specific risk assessment must be performed separately for the nanomaterial • Scientific appropriateness and technical adaptations/ adjustments of the performed test have to be provided when it comes to nanomaterials	*Registration* Hard to operationalise EC recommendations on NM definition *Risk assessment* • Four elements of risk assessment not tailored for NM • OECD TG not developed for dispersed NM but for soluble chemicals instead *Authorisation* Approval of an active bulk substance does not automatically cover a corresponding NM form *Labelling* Label required providing information of the names of all nanomaterials in the product and information on any specific, related risks	Gellert et al. 2015, Hansen 2015, Brinch et al. 2016, Mackevica et al. 2016a

Medicines and medical devices *Scope* Medicinal products for human and veterinary use, medical devices, active implantable medical devices and in vitro diagnostic medical devices	*Designed to reduce risks* In the proposal on medical devices, in order to amend, among others, the Directive 2001/83/EC concerning medicinal products for human use, devices shall be designed and manufactured in such a way as to reduce to a minimum, risks linked to the size and the properties of the particles used *Authorisation* Explicit prior authorisation of devices that incorporates or consists of a nanomaterial *Safety assessment* Pre-market safety assessment should ensure that the benefits outweigh any identified risks or adverse side-effects *Labelling* Requires label to indicate that the device incorporates or consists of a nanomaterial, unless the nanomaterial is encapsulated or bound so that it cannot be released into the patient or user's body	*Definition* • Most directives do not mention or define NMs • Unclear whether "novel nanomedicine" is to be defined as a medicinal product or as a medical device • Definition of NM in the proposal on medical devices, in order to amend, among others, the Directive 2001/83/EC concerning medicinal products for human use, is hard to operationalise, as it follows EC recommendations on NM definition *Information requirements* • No specific registration or information requirements for nanomaterials *Risk assessment* Risk assessment, safety and quality requirements may not be suitable to address various aspects relating to nanomedicine and novel applications of nanotechnology	Baun and Hansen 2008, Hansen and Baun 2012b

3.1 Registration, Evaluation and Authorisation of CHemicals (REACH)

In mid-2007, Regulation (EC) No 1907/2006 of the European Parliament and of the Council of the European Union, known as "Registration, Evaluation and Authorisation of Chemicals" (REACH), came into force (EP and the Council 2006). Although not originally intended to address nanomaterials, REACH has evolved into one of the key pieces of European legislation in this regard (CEC 2008a, European Commission 2012a, Azoulay 2012, Hansen and Baun 2012b, Hansen 2013). In short, REACH consists of four elements:

1. Registration, i.e. data collection on chemical use and toxicity;
2. Evaluation, i.e. examination by governments of the need for the additional testing and regulation of chemicals;
3. Authorisation of chemicals, i.e. requirements for firms to seek permission to use chemicals of high concern and
4. Restrictions or a complete ban on certain chemicals that cannot be used safely.

As something of a new approach, the responsibility for providing data and information in the registration and authorisation phases of REACH shifted onto manufacturers and importers. The registration process would happen gradually, and by 30 November 2010 manufacturers and importers had to register substances produced or imported in quantities of more than 1000 tons per year. The same applied to substances produced in quantities of more than 100 tons and which had been classified as very toxic to aquatic organisms, as well as substances produced in amounts more than 1 ton that had been classified as Category 1 or 2 carcinogens, mutagens or reproductive toxicants. By 1 June 2013, producers or importers of substances in quantities of more than 100 tons had to register, and by 1 June 2018, the registration of substances produced in quantities of more than 10 tons will have to be completed (EP and the Council 2006). Only seven nanomaterials were listed during the first two registration periods (Jones 2013).

Carbon and graphite were taken off the list of substances exempted from registration under REACH in 2008, in order to ensure that nanomaterials such as C60 and carbon nanotubes would fall under the scope of REACH, if produced in sufficient tonnage per year, per producer or importer (Hansen 2010).

Although a number of substances, e.g. nanosilver and various forms of carbon nanotubes, have been registered as nanomaterials under REACH, the regulation does not specifically mention the word "nanomaterials", and size is not listed as information necessary to make it clear that each substance should be identified (CIEL, ClientEarth and BUND 2012). Furthermore, there are no specific registration or information requirements for nanomaterials (EP and the Council 2006), which might help explain why so few nanomaterials have been registered under REACH to date (Azoulay 2012, Hansen 2013). After the first round of REACH registration in 2010, only three dossiers were registered, meaning that "nanomaterial" was selected as the substance's form in IUCLID5.2 (Jones 2013), whereas a total of seven substance registrations and 18 CLP notifications had been made voluntarily as of February 2012 (Christensen et al. 2012). In response to the very few registrations of NMs, the European Commission asked the European Commission Joint Research Centre (JRC) and the European Chemicals Agency (ECHA) to assess how nanomaterials had been addressed in REACH registrations and CLP notifications by assessing

the adequacy of available information in the REACH registration dossiers from the first round of REACH registrations. One of the key challenges associated with assessing the selected dossiers was found to be the ambiguity of the scope of the registration dossier and the lack of clarity about the registrants' intentions regarding which nanomaterials/nanoforms fall under the scope of the registration. This included ambiguity that cascaded through the dossiers, as it not only applies to the identity/characterisation of the registered substance, but also to the provided information on the exact form/particle size of the tested material for many physico-chemical and hazard end-points (Christensen et al. 2012, Hansen 2013). For instance, only a few dossiers distinguish between "bulk" and "nano", and differences in characteristics between nanoforms of the same substance were not addressed at all. Test data provided for physico-chemical, human health and environmental end-points were furthermore found, generally, not to describe the test material in great detail, and any description of sample preparation varied or was lacking (Christensen et al. 2012). As noted by Christensen et al. (2012), "The impact of this ambiguity on the assessment of dossiers containing nanomaterials/nanomaterials cannot be overstated."

Although there is no tonnage-related exemption under REACH regarding authorisation, restriction or classification and labelling requirements, a second limitation is that substances manufactured or imported in volumes of less than 1 ton/year do not need to be registered. Hence producers or importers are not required to provide toxicological data or assess any kind of environmental exposure. As noted by Chaundry et al. (2006), Franco et al. (2007) and Azoulay (2012), this threshold would hardly be reached for many nanoparticles. Chaundry et al. (2006) estimated that the majority of applications are likely to fall outside the scope of REACH on the basis of the low tonnage currently used in gram-to-kilogram quantities – something which was later confirmed when the German REACH competent authority failed to collect nanomaterial exposure data from German companies and attributed this to having asked for information on activities related to production, use and processing involving nanomaterials in quantities of more than 10 kg/year (BAuA 2008, CIEL, ClientEarth and BUND 2012). As a consequence, ECHA has asked the European Commission for clarification on whether the registration requirements for substances on the EU market in low amounts could be changed, as very toxic chemicals are often sold in small amounts (Chemical Watch 2014b, Hansen and Baun 2015).

Furthermore, the usually low concentration of nanomaterials in the final product could potentially exclude some from the REACH legislation, since no registration is required when concentrations of a substance in the final product are lower than 0.1% w/w. However, a general lack of access to information about product formulation and nanoparticle concentrations hampers the determination of substance concentrations by weight (Franco et al. 2007, Hansen and Baun 2012b). A great deal of effort has been put into revising the technical guidance provided by ECHA. In 2010, the EC established the first of three so-called "REACH Implementation Projects on Nanomaterials" (RIP-oNs). The outcome of RIP-oN1 was the identification of two possible options, namely to address nanomaterials either as "well-defined substances" or as "substances of defined chemical composition and additional identifiers" (European Commission Joint Research Centre 2011).

Based on RIP-oN2, on information requirements, and RIP-oN3, on chemical safety assessments, ECHA updated some of its guidance back in 2012, especially in regard to

sample preparation, exposure quantifications, measurement, dose metrics, etc. (Chemical Watch 2012, Hankin et al. 2011, Hansen and Baun 2015). Further updates to the guidance are currently being discussed and are out for consultation in so-called "partner-expert groups", based on draft guidance documents concerning nanomaterials developed by ECHA (ECHA 2016c).

Recommendations from RIP-oN2 address a range of issues, including physiochemical properties, toxicological and ecotoxicological end-points, which would require a modification to the REACH annexes (Hansen 2013). However, for such modifications, once adopted, to be implemented, nanomaterials must first be identified systematically (Azoulay 2012). Since 2013, there has been a lot of discussion about whether and how to update the REACH Annexes. The European Commission has put forward six different options ranging from maintaining the current situation under REACH and adopting no new policy actions (option 1) through focusing on enhancing the competitiveness and innovation of companies by reducing the economic burden of REACH compliance (option 5) and by introducing changes to certain REACH Annex provisions to clarify what companies are expected to do. These include revised or additional end-points for nanomaterials and additional emphasis on the generation of targeted information on risk regarding the influence of particle- and nanomaterial-specific properties (option 6) (European Commission 2013b). It generally seems that industry branch organisations prefer option 5, whereas NGOs prefer option 6 (Hansen and Baun 2015). What the modifications to the REACH Annexes will eventually look like, and when they will be implemented, is unclear at this moment in time, but they have been under scrutiny by the EC's Regulatory Scrutiny Board since February, 2016 and are planned for early 2017 (European Commission 2016, Roberts 2016, Bergeson and Hutton 2016).

3.2 Biocidal Products Regulation (BPR)

Chemicals with claimed antibacterial properties, such as nanosilver, are regulated as "biocidal active substances" or as "biocidal products" in the EU under the EU Biocidal Products Regulation (BPR) (EP and the Council 2012a). A key feature of the BPR is the specific provisions regarding nanomaterials (Hansen and Brinch 2014). In the BPR, nanomaterials are defined as "a natural 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" (EP and the Council 2012a). This definition is in most aspects in line with the European Commission's recommended definition, although "incidentally created NPs" have been omitted from the BPR definition of NMs as well as the possible replacement of the 50% threshold by a lower one (Hansen and Brinch 2014).

Besides being the first piece of legislation to adopt the definition of NMs recommended by the European Commission, the BPR is also the first to specify that approval of an active substance does not cover a corresponding NM form, except where this is mentioned explicitly. Furthermore, in order to gain authorisation for a biocidal product containing nanomaterials, a specific risk assessment must be performed separately for the nanomaterial in question, and it is not possible to apply for a simplified authorisation if the biocidal product contains nanomaterials (EP and the Council 2012a). These requirements were implemented to address concerns about the safety of nanomaterials, and as a result the

BPR provides the most ambitious piece of nano-specific legislation yet to be implemented by European legislators. Prior to being allowed to commercialise their active substance or biocidal product, a manufacturer has to submit a dossier to the European Chemicals Agency that fulfils specific information requirements outlined in the Annexes of the BPR (EP and the Council 2012a). These requirements include information on the physio-chemical properties of the chemical/nanomaterial in question, for what type of products the active substance is to be used, expected exposure patterns as well as toxicological and ecotoxicological information. This information has to be obtained by following the methods specified in the Test Methods Regulations (EP and the Council 2009b), which again are equivalent to OECD guidelines for the testing of chemicals. It is noteworthy that the BPR requires that an explanation has to be provided on the scientific appropriateness of the test when it comes to nanomaterials and, where applicable, on the technical adaptations/adjustments that have been made in order to respond to the specific characteristics of these materials. The BPR furthermore specifies that it is possible to use other scientifically suitable methods if a test method is considered inadequate or not included in the BPR. Justification for the appropriateness of these alternative methods, however, is required (EP and the Council 2012a), and fulfilling these BPR requirements can be quite challenging, as analysed and reported by Brinch et al. (2016) who explored how nano-specific testing requirements in the BPR might be fulfilled in the case of copper oxide nanoparticles. They found that while useful information and data are available in the open literature (see Figure 18), most of the studies do not take into consideration the OECD's nano-specific test guidelines (see Figure 19). About a third of all the studies report on four or less of the parameters suggested by the OECD, and the studies that report most, report on seven to nine of these factors. This makes it difficult for companies as well as regulators to fulfill the BPR information requirements for nanomaterials, for instance due to the lack of best practices regarding stock suspension preparation and characterisation, exposure suspensions preparation and conducting ecotoxicological tests (Brinch et al. 2016).

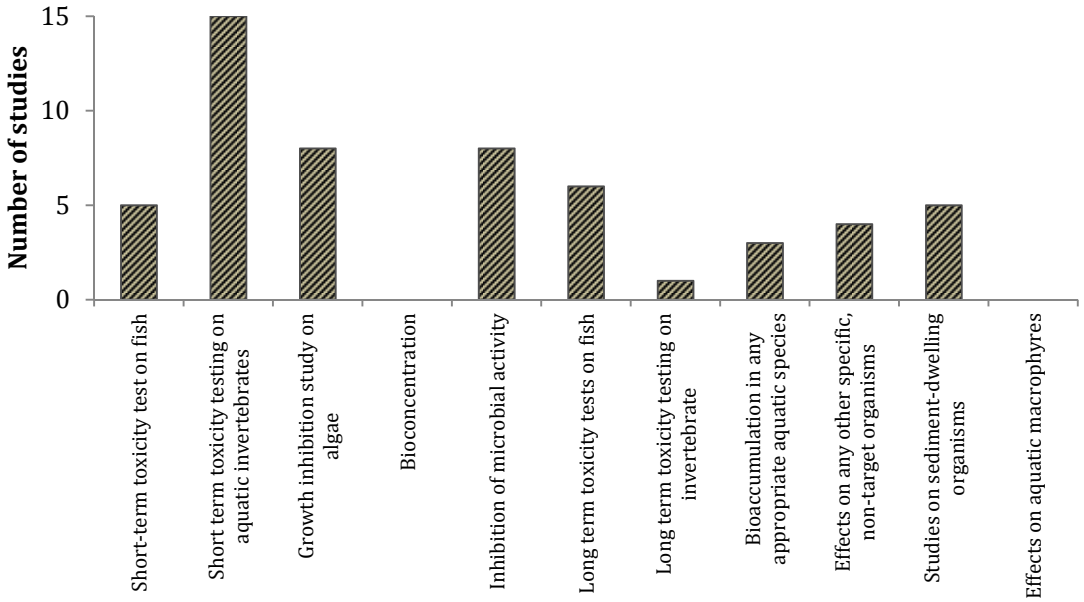


Figure 18: Number of studies potentially fulfilling the Biocidal Product Regulation (BPR) information requirements for ecotoxicity tests (From Brinch et al. 2016).

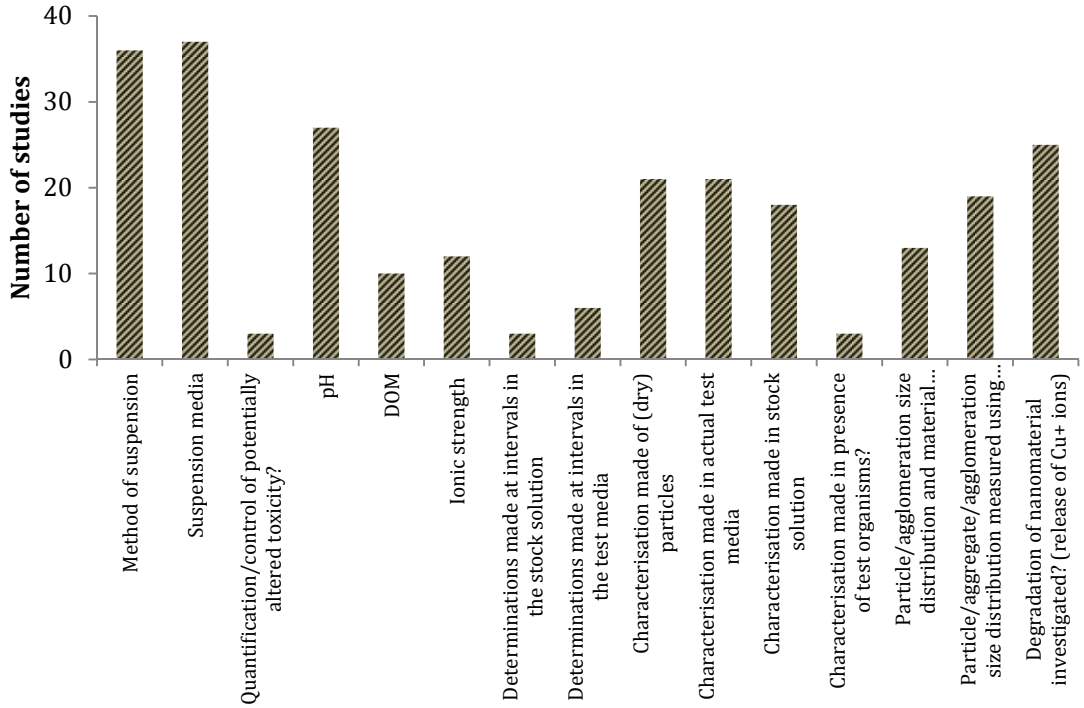


Figure 19: Number of ecotoxicity studies on copper oxide nanoparticles considering the reporting and characterization parameters recommended in the Organisation for Economic Co-operation and Development (OECD) guidance document (OECD 2012).

Synthetic amorphous silicon dioxide (SAS) is the only NM that has been approved as an active substance to date, and it is approved as such under product type (PT) 18 (insecticides). According to the assessment report, SAS is a NM according to the NM definition in the BPR, as it consists of primary particles sized < 25 nm, whereas the active substance will be an aggregate of primary particles sized 1-6 µm. Therefore, the hazard and risk of the individual silicon dioxide NPs were not evaluated in the dossier, as aggregates are considered to be the

smallest stable particles under normal handling and use conditions (France 2014).

Silicon dioxide nanoforms formed by aggregates, agglomerates and silver adsorbed on silicon dioxide (HeiQ AGS-20) are currently under review for PT 18 and PT 9 (fibre, leather, rubber and polymerised material preservatives), respectively (ECHA 2016a, b). HeiQ AGS-20 consists of stable 1-50 μm particle aggregates containing primary particles on the nanoscale, and in an opinion piece, the Biocidal Products Committee (BPC) (2014) has explained that AGS-20 is to be regarded as a biocidal active substance. In the opinion, the BPC (2014) refers to the approval of SAS and states that it could be outlined that AGS-20 is a stable aggregate with primary particles in the nanoscale, with additional specification of particle size and volume specific surface area (BPC 2014). The latter indicates that the SAS evaluation could create a precedence when it comes to approving nanomaterials (Mackevica et al. 2016a). The use of nanosilver as a biocidal active ingredient under the EU's biocidal product regulations review programme is currently being assessed by the Swedish Chemicals Agency (KEMI), which is known as "the competent authority." KEMI, at the time of writing, is on public record stating that their work is progressing slowly and that it is not possible for them to say whether there are sufficient data to carry out a risk assessment on silver nanoforms, as the data which have been submitted by industry follow the usual data requirements for bulk substances (Chemical Watch 2011, Mackevica et al. 2016a).

Other assessment reports mention specifically that they do not cover the nanoform of that active substance and that the nanoforms of these substances are not included in the reports. For instance, for basic copper carbonate, the assessment states that "the applicant is not currently placing nanoforms of basic copper carbonate on the market. Therefore, the submitted dossier and the finalised assessment report do not cover potential nanoforms of this copper compound, should such forms exist" (Standing Committee on Biocidal Products 2011).

Besides active substances and biocidal products, the BPR also contains provisions that apply to products which incorporate a biocidal product or have been treated with one. Products can only be treated with active substances which have been approved in the EU for that specific purpose. Moreover, treated products have to be labelled with a label providing information on the names of all nanomaterials contained in the product, followed by the word "nano" in brackets e.g. "[Ag]". The label furthermore has to include information on any specific related risks of the nanomaterial.

It is not clear which products commercially available in the EU have been treated with nanomaterials or incorporate a biocidal form. It is, however, well known that, for instance, nanosilver and nano-copper are used in consumer products because of their antibacterial properties (Brinch et al. 2016, Mackevica et al. 2016b, c). In a study of biocidal products and treated articles in The Nanodatabase, Mackevica et al. (2016a) found that for about 50% of all nanosilver-containing products, the producers make antibacterial or antifungal claims, which means that the products are likely to fall under the provisions of the BPR. However, Mackevica et al. (2016a) also reported that it was not possible to "determine whether nanomaterials were actually present in the products with claims about "nano" by looking at the labels of the products, and it was not possible to evaluate whether the products claiming to have biocidal properties are actually effective as antimicrobials."

3.3 Food legislation and nanomaterials

Until recently, none of the EU regulations applicable to agriculture, food or food packaging considered or mentioned nanoscale products or materials, but in 2011 the regulation on the provision of food information to consumers made it clear that "all ingredients present in the form of engineered nanomaterials shall be clearly indicated in the list of ingredients (EP and the Council 2011b). The names of such ingredients shall be followed by the word "nano" in brackets." This approach is similar to the one adopted in regard to cosmetics, but whereas nanomaterials were defined as "*an insoluble or bio-persistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm*" (EP and the Council 2009a) in the cosmetics regulations, "engineered nanomaterial" was defined in the regulations as "[...] *any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale. Properties that are characteristic of the nanoscale include: (i) those related to the large specific surface area of the materials considered; and/or (ii) specific physico-chemical properties that are different from those of the non-nanoform of the same material*" (EP and the Council 2011b). The regulation provides no further clarification as to what these properties might be, or how they are to be determined and by whom. This definition is markedly different from the one in the cosmetics regulation and the one proposed by the European Commission that has been adopted in, for instance, the BPR (EP and the Council 2012a).

In late 2015, the new European Regulation on Novel Foods was adopted and entered into force (EP and the Council 2015). In the regulation, the term "Novel Foods" is defined as "any food that was not used for human consumption to a significant degree within the Union before 15 May 1997" and which can be categorised as, among others, "food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997" or "food consisting of engineered nanomaterials defined in a manner similar to the regulation on the provision of food information to consumers" (EP and the Council 2011b).

During the legislative procedure, the definition of NMs was discussed, and the Committee on the Environment, Public Health and Food Safety of the European Parliament suggested amending the proposed definition by the EC and having a 10% nanoparticle threshold for a food ingredient to qualify as "nano", as recommended by EFSA's Scientific Committee Unit (EFSA 2012) (citing concerns about uncertainties over safety), instead of the Commission's proposed 50% (European Parliament 2014). The justification for adopting the EC NM definition and avoiding the definition in *Reg. 1169/2011* was that the latter dealt with labelling and was not appropriate for risk assessment, which was the subject of the Novel Food Regulation, and that if the "*50% threshold was applied even for risk assessment purposes, there would be the serious risk that some nano-ingredients will not be captured by the definition, and would therefore not be subject to risk assessment*" (Committee on the Environment, Public Health and Food Safety 2014). Ultimately, the European Parliament decided to adopt the same definition of NM as in the regulation on the provision of food

information to consumers (see EP and the Council 2011b), because, for consistency and coherence purposes, it is important to ensure a single definition of an engineered nanomaterial in the area of food law (EP and the Council 2015).

The Novel Food Regulation makes it clear that the use of nanomaterials requires prior authorisation. As part of the authorisation procedures for a novel food, the applicant has to provide, among others, a description and detailed composition of the novel food, scientific evidence demonstrating that it does not pose a safety risk to human health and a proposal for the conditions of intended use and for specific labelling requirements which do not mislead the consumer (EP and the Council 2015). As part of the scientific evidence on safety risk, the applicant has to provide an explanation for the scientific appropriateness of any test methods used and, where applicable, for the technical adaptations or adjustments that have to be made in order to respond to the specific characteristics of a nanomaterial (EP and the Council 2015). Upon request by the European Commission, the European Food Safety Authority (EFSA) shall give its opinion on whether or not a novel food may pose a safety risk to human health, by considering possible effects on vulnerable groups of the population and verifying that the most up-to-date test methods are used to assess safety where a novel food consists of engineered nanomaterials.

It is important to note that although the regulation that entered into force ended in 2015, many of its provisions will only become applicable from 1 January 2018, including the ones on nanomaterials.

Besides the regulation on the provision of food information to consumers, and the novel food regulation, the regulation on food additives mentions “nanotechnology” and requires that when there are significant changes to the production process or the starting materials of a food additive, a new entry in the Community list of food additives approved for use in foods, or a change in the specifications, has to be made before it can be placed on the market despite the fact that it might already be included in a Community list (EP and the Council 2008a). This means that food additives produced via nanotechnology resulting in a change in particle size shall be considered as different additives and may only be authorised if, among others, a) they do not pose a safety concern to the health of the consumer at the level of use proposed on the basis of the available scientific evidence, b) there is a reasonable technological need that cannot be achieved by other economically and technologically practicable means, c) its use does not mislead the consumer and d) it has advantages and benefits for the consumer in regard to, for example, preserving nutritional quality, meeting special dietary needs, enhancing the quality or stability of a food or aiding in the manufacture, processing, preparation, treatment, packing, transport or storage thereof (EP and the Council 2008a).

The procedures for approving food additives in regard to deadlines for various stages of the process, the role of the parties involved and the principles that apply are laid down by Regulation No 1331/2008 on establishing a common authorisation procedure for food additives, food enzymes and food flavourings (EP and the Council 2008b), whereas procedures surrounding the content, drafting and presentation of applications, information requirements and risk assessment, for instance, are laid down in Commission Regulation No 234/2011 (Commission 2011). Regulation No 234/2011 provides general provisions on data required for risk assessment as well as specific data required for risk assessment and the risk management of food additives.

General provisions include the obligation of the applicant to take into account the latest guidance documents adopted or endorsed by EFSA when drafting and submitting the technical dossier, and that this dossier should include all the available data relevant to the purpose of the risk assessment (i.e. fully published papers of all references cited, or full copies of the original unpublished studies). Literature search strategies should also be documented in the application regarding any assumptions made, keywords used, databases used, time period covered, limitation criteria and outcomes of the literature search. Toxicological studies used for risk assessment should be conducted in facilities which follow the OECD Principles of Good Laboratory Practice (GLP), and studies not conducted according to standard protocols, data interpretation and justification on their appropriateness for risk assessment should also be provided. The burden is on the applicant to provide an overall conclusion in regard to the safety of the proposed uses of the substance and evaluate the potential risks in the context of known or likely human exposure.

Specific provisions and data required for the risk assessment of food additives that are relevant when it comes to nanomaterials include information on a) particle size, particle size distribution and other physicochemical characteristics, b) stability, reaction and fate in foods to which the additive is added, c) proposed normal and maximum use levels, d) a dietary exposure assessment and e) information on toxicokinetics, subchronic toxicity, genotoxicity, chronic toxicity/carcinogenicity and reproductive and developmental toxicity. When it comes to data required for the risk management of food additives, the applicant has to provide in the technical dossier information verifying that the proposed use does not mislead the consumer and that there is a reasonable functional and technological need that cannot be achieved by other economically and technologically practicable means, including investigations into the efficacy of the food additive for the intended effect at the use level proposed, advantages and benefits for the consumer and analytical methods allowing the identification and quantification of the additive or its residues in food.

Once the Commission has received an application, it shall, where necessary, request EFSA to verify the suitability of the data for risk assessment within 30 days, and prepare, if appropriate, an opinion. This opinion should include, among others, an assessment of biological and toxicological data, a dietary exposure assessment and an overall risk assessment establishing – if possible and relevant – a health-based guidance value, highlighting uncertainties and limitations, where relevant (Commission 2011).

EFSA (2009) has already provided a scientific opinion on the potential risks arising from nanoscience and nanotechnologies on food and feed safety, noting a range of specific uncertainties when it comes to the risk assessment of nanotechnologies and their possible applications. These specific uncertainties relate to, for instance, the limited knowledge of (likely) exposure to possible applications and products, difficulties in characterising, detecting and measuring NMs in food/feed and limited information on optimal toxicokinetics and toxicological testing methods. Despite these uncertainties, EFSA (2009) considers the usual risk assessment paradigm (hazard identification, hazard characterisation, exposure assessment and risk characterisation) as applicable to NMs, and it sees current toxicity testing approaches as being a suitable starting point for the case-by-case risk assessment of NMs, concluding that nanotechnology aspects shall be considered when risk assessment guidance documents in the food and feed area are reviewed. Furthermore, they recommend that nanomaterial risk

assessment in the food and feed areas should consider the specific properties of nanomaterials in addition to those common to equivalent non-nanoforms (EFSA 2009).

Following a request made by the European Commission, EFSA (2011) prepared a practical guidance for assessing the application of nanomaterials in food and feed application, including guidance covering risk assessments for food and feed applications relating to food additives, enzymes, flavourings, food contact materials, novel foods, feed additives and pesticides. Most notably, EFSA provided guidance on the physico-chemical characterisation requirements for and testing approaches to identifying and characterising hazards arising from nano-properties. Since physico-chemical parameters may change in various environments, the former should be determined ideally as manufactured (pristine state), as delivered for use in food/feed products, as present in the food/feed matrix, as used in toxicity testing and as present in biological fluids and tissues. The latter should include information from in vitro genotoxicity, absorption, distribution, metabolism and excretion and repeated dose 90-day oral toxicity studies in rodents, if the ENM persists in the food/feed matrix and in gastrointestinal fluids. Importantly, the guidance allows for reduced information to be provided if data verify and indicate no migration from food contact or when complete degradation/dissolution is demonstrated with no absorption of engineered nanomaterials as such (EFSA 2011).

4. Proposed new regulatory frameworks and their opportunities and weaknesses

A number of NGOs, EU member states and REACH competent authorities have independently proposed a series of REACH revisions that go beyond simply revising the REACH Annexes as the EC has currently suggested (CIEL, ClientEarth and BUND 2013, KEMI 2013, UBA, BfR and BAuA 2013). In the following these proposals will be presented, while an overview of their opportunities and weaknesses can be found in Table 6.

Table 6: Overview of proposed new regulatory frameworks in regard to their scope, opportunities and weaknesses

Legislative proposal	Opportunities	Weaknesses	Reference
German Dossier-in-Dossier proposal *Scope* NMs	*Information requirements* Very detailed when it comes to what information requirements should be triggered when, e.g., requiring REACH (eco)toxicological information at a lower tonnage level	*Substance identification* Size is termed a characteriser, but for pragmatic reasons only and out of concern that considering size as an identifier and considering surface-treated NMs as a substance on its own will lead to the splitting into numerous new substances *Definition* • The definition of NM in the proposal is hard to operationalise, as it follows EC recommendations on NM definition • The term "Most relevant form" is vague and not defined *Registration* Unclear how the registrant is to justify which of the surface-treated nanoforms could be considered together in one registration. Criteria for this issue have yet to be developed *Information requirements* Not clear what it means that two forms of "a substance differ significantly" and when a difference is "relevant" and hence when information has to be provided for different forms of a substance in a dossier and when additional testing might be necessary *Evaluation* Unclear how all the required information and data will be used to evaluate different nanoforms and feed into the authorisation process *Authorisation* Unclear under which circumstances authorisation could be granted *Restriction* It is unclear what would trigger restrictions of the whole NM, bulk or selected NM forms or respirable granular and fibrous particles and what these restrictions could be *Risk assessment* • Four elements of risk assessment not tailored for NM Obtaining (eco)toxicological information at a lower REACH tonnage level does not overcome that OECD TGs have not been developed for dispersed NM and that received information might not be relevant for NMs	Schröder 2012, UBA, BfR and BAuA 2013, Schwirn et al. 2014

Table 6 continued: Overview of proposed new regulatory frameworks in regard to their scope, opportunities and weaknesses

Legislative proposal	Opportunities	Weaknesses	Reference
CIEL, ClientEarth and BUND's "nano patch" *Scope* NMs and any use of them	*Registration* • Clear registration dates are to be staggered over a period of three years following the entry into force of the regulation on the basis of production volumes of 10 kg, 100 kg and 1000 kg • A separate dossier required for NM forms if produced in quantities of more than 10 kg per year *Notification* Obligation to notify ECHA about products on the market that contain nanomaterials *Labelling* Require suffix "nano" to all products that have list of ingredients *Register of nanomaterials* A register of NMs will be established containing information on the quantities produced, distributed or imported if a minimum of 1 kg of a NM is produced, imported or distributed *CLP* Suggest that CLP Article 40 applies to NMs and whether the lack of classification in some hazard classes is due to lack of data, inconclusive data or data which are conclusive although insufficient for classification	*Definition* • The definition of NM in the proposal is hard to operationalise, as it follows EC recommendations on NM definition *Information requirements* • Information to be submitted as part of the Chemical Safety Assessment (CSA) is to be volume dependent and set out in Annex 2 of the regulation, but the details of Annex 2 are not specified further in the proposal and it is not clear how information requirements are volume-dependent *Evaluation* • It is stated that priority should be given to substances that have wide dispersive use, and substances registered above 1 tonne, but it is not clear how NMs are to be evaluated *Authorisation* Unclear under what circumstances authorisation could be granted *Restriction* Unclear in what circumstances restrictions should be implemented *Risk assessment* • Four elements of risk assessment not tailored to NMs • Not clear how the hazards and risks deriving from nanomaterials, including tailored test guidelines, can be documented as part of the CSA	CIEL, ClientEarth and BUND 2012

Sweden's Kemi nanomaterials regulation *Scope* NMs, NMs in mixtures and NMs in articles	*Registration* • NMs are regarded as substances in their own right • Registration is required if more than 10 kg is manufactured or imported per year, calculated on the basis of average production or import volumes for the three preceding calendar years *Information requirements* • Information requirements laid out in REACH Annexes VII + VIII + IX and X are to be applied to 10 kg, 100 kg, 1 tonne and 10 tonnes, respectively • Exposure information should be included in dossiers for nanomaterials produced between 10- 100 kg • Chemical safety report is to be included in the registration when in quantities of 100 kg or more per year, per registrant *Down-stream users* • The obligation to prepare a Chemical Safety Assessment applies to downstream users as well, if they use a nanomaterial or mixture containing nanomaterials in a total quantity of less than 10 kg per year *Notification* A notification has to be provided by producers or importers of articles containing nanomaterials if the NM is present in quantities of more than 10 kg per producer or importer per year	*Definition* NMs are defined according to Commission Recommendation of 18 October 2011 on the definition of nanomaterials (2011/696/EU) *Information requirements* • Not clear how "special consideration to the specificities of nanomaterials, e.g. sample preparation and dosimetry" can be taken • As Annex I to this regulation has yet to be inserted, it is not clear what information has to be included in the "study summaries" and "robust study summaries"	KEMI 2013

4.1 German Dossier-in-Dossier proposal from 2012

4.1.1 Revisions needed, size as a characteriser, relevant forms and surface-treated NMs

Several German federal institutions and agencies, including the Federal Environment Agency (UBA), Federal Institute of Risk Assessment (BfR) and the Federal Institute for Occupational Safety and Health (BAuA), have been engaged in a process with the aim of developing a proposal with regard to the regulation of nanomaterials within REACH. The process has been underway for at least two years, and its results have been presented at the Competent Authority for REACH and CLP (CARACAL) Subgroup (CASG) Nano 8 meeting (Schröder 2012) and published in UBA, BfR and BAuA (2013) and Schwirn et al. (2014).

While noting that the European Commission's proposal on a definition of nanomaterials has yet to be implemented in REACH, and that there are no legal obligations to provide nano-specific data, the proposal takes outset in three notions about nanomaterials and REACH. The first notion is that chemical legislation needs to be revised on the grounds of the precautionary principle, due to uncertainties related to evaluating the risks of nanomaterials (UBA, BfR and BAuA 2013, Schwirn et al. 2014). The second notion is that nanomaterials fall under the definition of a chemical substance as defined under REACH and are covered by REACH (Schröder 2012, Schwirn et al. 2014). The third notion is that the bulk and the nanoform types of a given material should be covered in one REACH registration dossier, as both have the same chemical composition and are chemically identical despite the fact that size changes lead to changes in the properties of a substance (Schröder 2012, Schwirn et al. 2014).

The latter implies that particle size is seen as a "characteriser" used to distinguish forms of the same REACH substance within the same REACH registration dossier and not as an "identifier" i.e. something that uniquely defines and identifies a nanomaterial. In practice, this means that all information on one substance is kept in one REACH dossier, within which different information requirements could/should apply to bulk and NM and additional testing might be necessary if the properties of two forms of a substance "differ significantly" (Schröder 2012, UBA, BfR and BAuA 2013, Schwirn et al. 2014), thereby leading to the "dossier-in-dossier" proposal. The German "dossier-in-dossier" proposal does not specify what or how it is to be determined whether two forms of a substance differ significantly, but it does note that morphological properties (e.g. size, crystalline structure, shape, rigidity), water solubility and surface characteristics (e.g. surface charge, hydrophobia, photocatalytic properties, functional groups, agglomeration, volume-specific surface area) are the most important parameters which distinguish nanoforms from bulk forms, and between different nanoforms (UBA, BfR and BAuA 2013), and that a difference between nanoforms should be considered as "relevant" if it is likely that it would lead to a change in the hazard profile (Schwirn et al. 2014). It is noted throughout the German proposal that criteria for determining "relevance" still have to be developed, but it could be, for instance, quantitatively the most significant form, functionally the most important form or the form of probably the greatest toxicological relevance (UBA, BfR and BAuA 2013).

It is pointed out that surface treatment may influence and govern the risk profile of NMs to a crucial degree, while surface-treated NMs are regarded as a special nanoform of the treated source material and are to be included in the registration of the source material (UBA, BfR and BAuA 2013). It is not viewed as being feasible to consider surface-treated NMs as

substances in their own right, as basically any conceivable combination of different substances A and B would be possible with surface treatment, thereby leading to the problem of the extreme splitting of similar materials into various substances on their own, and that tonnage bands which trigger a registration obligation would not be reached as a consequence (UBA, BfR and BAuA 2013).

That is why the German proposal is to apply the substance identity approach, with the 80 wt.% criterion meaning that if the surface-treated nanomaterial consists of at least 80 wt.% of the core material, it is to be regarded as a separate nanoform of the core material. On the other hand, it has to be defined as a new substance if the surface-treated nanomaterial consists of less than 80 wt.% of the core material. This means that the registrant has to demonstrate that the different nanoforms can be jointly considered, or have to be separately considered, for further test performances and fulfilment of the REACH requirements (UBA, BfR and BAuA 2013, Schwirn et al. 2014).

UBA, BfR and BAuA (2013) furthermore argue that it is challenging to "… develop clear criteria which would allow defining and checking under which conditions surface treatment results in a new substance and how the different surface treatments can be defined in relation to one another." It is, however, not clear why this is specifically the case for the option of regarding surface-treated NMs as substances in their own right and not, for instance, the option that the Germans propose, namely to apply the 80/20 rule. It is well-known that "at present, there is no standardized method for determining the degree of surface treatment," as noted by the UBA, BfR and BAuA (2013).

4.1.2 Tonnage threshold

Revisions are also found to be necessary with regard to current tonnage thresholds and information requirements, in order to make REACH concepts legally binding in relation to NMs (Schröder 2012). The German proposal requires the adoption of REACH articles as well its annexes. Tonnage thresholds are suggested to be lowered to 100 kg/a, without any argumentation being made for why this should happen. For NMs produced in quantities ≥ 100 kg/a (aggregated tonnage), reduced registration requirements for all different nanoforms should apply and be limited to: substance identity, characterisation of the material(s)/form(s), a description of its use(s) and all other available data (Schröder 2012, UBA, BfR and BAuA 2013, Schwirn et al. 2014).

For NMs produced in quantities ≥ 1 t/a (aggregated tonnage), full registration should furthermore include one or more chemical safety reports considering every form collectively or separately, depending on the choice of the registrant, and which fulfils the nano-specific information requirements for the specific tonnage band to be laid down in a new and yet to be established Annex XVIII (Schröder 2012, UBA, BfR and BAuA 2013, Schwirn et al. 2014).

If different nanoforms of one substance are manufactured, data requirements depend on the individual tonnages that are manufactured as well as the aggregated tonnage. If the aggregated tonnage is 200 t/a and nanoforms 1, 2, 3 and 4 are manufactured in quantities of 150 t/a, 10 t/a, 1 t/a and 39 t/a, the data requirements should correspond to ≥ 100 t/a, ≥ 10 t/a, ≥ 1 t/a and ≥ 39 t/a, respectively.

If the aggregated tonnage is 200 t/a and no nanoform is in the tonnage band of the aggregated tonnage, e.g. nanoforms 1, 2, 3 and 4 are manufactured in quantities of 60 t/a, 70 t/a, 1 t/a and 69 t/a, the data requirements corresponding to ≥ 100 t/a would have to be fulfilled for the "most relevant nanoform," e.g. nanoform 3, despite the fact that only 1 t/a is manufactured in. Data requirements for nanoforms 1, 2 and 4 will then correspond to the data requirements for ≥ 10 t/a (Schröder 2012, UBA, BfR and BAuA 2013).

Although quite important, the German proposal does not define the term "most relevant form" further, and other elements therein seem in some regard to contradict the presence and possibility of identifying such a form. For instance, the UBA, BfR and BAuA (2013) appendix states that "To date it is not possible either to make sound assumptions with respect to the selection of the probably most critical material on the effect side or to make predictions of the environmental fate and exposure," and that "To date no reliable information is available to which variations are acceptable for individual parameters. In many cases it will remain a case by case decision. It is desirable to develop appropriate screening tests, where applicable, to gain experience on comparability." In light of these statements, how can one therefore determine "the most relevant form," given that it is not possible to make sound assumptions and no reliable information is available?

4.1.3 Information requirements and waiving

The German proposal argues that nano-specific information requirements are needed and suggest that a new Annex XVIII should be "oriented on existing Annexes but with some amendments/additions," including the comprehensive characterisation of nanoforms as part of substance registration in regard to morphological parameters (e.g. size, shape and crystal structure), surface properties (e.g. charge, surface reactivity, functional group, dispersibility) and solubility in different media (Schröder 2012, Schwirn et al. 2014).

Amendments furthermore include moving some toxicological testing requirements to lower tonnages, e.g. genotoxicity already at 1 t/a and requiring 28-day, 90-day and chronic and carcinogenicity studies to be conducted by inhalation as administration route (Schröder 2012, UBA, BfR and BAuA 2013).

For ecotoxicology, the German proposal suggests that many of the REACH information requirements are moved to a lower tonnage level for nanomaterials, meaning that REACH Annexes VII and VIII would already apply from 1 t/a. Annex IX and the chronic sediment test from Annex X would apply from 10 t/a, and Annex X would apply from 100 t/a, except for the chronic plant test and the reproduction test for birds, which remain at 1000 t/a (Schröder 2012, UBA, BfR and BAuA 2013). Furthermore, it is suggested that chronic tests be required instead of acute examinations at lover tonnage levels and that information requirements must cover sediment and soil organisms (Schwirn et al. 2014). Finally, a fish-feeding study is to be given preference over the BCF test in the case of bioaccumulation, as the BCF often fails to provide a realistic picture of the accumulation behaviour of NMs (UBA, BfR and BAuA 2013).

According to the German proposal, information requirements have to be fulfilled separately for the individual forms, if substance nanoforms differ in a relevant way (UBA, BfR and BAuA 2013, Schwirn et al. 2014). What is "relevant" is again not specifically defined, as noted above.

Sub-chronic and chronic toxicity studies are considered to be essential, and waiving due to low water solubility is not considered appropriate, albeit waiving is possible on a case by case basis with reference to data from bulk form(s) and other nanoforms with the same chemical substance identity or with reference to read-across from a bulk/nanoform to a nanoform with different chemical substance properties. It may also be possible to waive tests in individual cases if the bulk material is classified in the highest category and this classification is also applied to the NMs, though criteria and guidance for waive tests still need to be developed (Schröder 2012, UBA, BfR and BAuA 2013).

While noting that surface characteristics probably play a greater role for NMs than the volume characteristics of the materials, the German proposal requires that the registrant demonstrates that the different surface-treated nanoforms can be jointly considered or have to be separately considered for further test performances and REACH requirements. The precise procedure for how to obtain a precise delimitation needs further clarification (UBA, BfR and BAuA 2013, Schwirn et al. 2014).

4.1.4 Substance evaluation, authorisation and restriction

The German proposal provides limited information on how the substance evaluation is to be performed and what the criteria might be for authorisation and restriction. Nonetheless, it does state that substance evaluation, authorisations and restrictions could be implemented for the whole NM, selected forms of the NM or only for the bulk form of the substance or respirable granular and fibrous particles.

4.2 CIEL, ClientEarth and BUND's "nano patch" from 2012

In 2012, CIEL, ClientEarth and BUND published an initial concept note called "Draft proposal for Regulation of the European Parliament and of the Council on the marketing and use of nanomaterials amending Regulation 1907/2006," outlining the basic idea of a horizontal piece of legislation covering nanomaterials. The proposal was the result of several years of work on the issue of nanomaterials, in which CIEL, ClientEarth and BUND (2012) suggest that the best way to address shortcomings in the regulation of nanomaterials is to have a separate horizontal instrument that is based on a set of general principles which apply to all nanomaterials on the market across all relevant fields (chemicals, products and environmental protection legislation).

As REACH is the cornerstone for assessing and regulating chemical substances in the EU, CIEL, ClientEarth and BUND furthermore suggest that REACH is amended through a "nano patch," so that it also becomes the cornerstone for filling regulatory gaps on nanomaterials and nanotechnologies as well as sectoral chemicals legislation, thereby making the latter "nano-fit" (CIEL, ClientEarth and BUND 2012).

4.2.1 Policy issues that require attention

The notion that there is a need for a separate horizontal instrument as well as REACH amendments is based on a number of policy issues identified by CIEL, ClientEarth and BUND as needing attention and which, overall, mean that workers' protection measures may prove to be neither adequate nor sufficient, due to the lack of information on nanomaterials (CIEL, ClientEarth and BUND 2012).

The first problem is that there is no commonly agreed definition of NM that applies to all regulatory frameworks relevant to nanomaterials and that the assessment of the nanoforms of a given substance is not required to be separate from the bulk form of the substance. According to CIEL, ClientEarth and BUND, the result of this issue is that manufacturers, users and importers of nanomaterials are free to refer to data from the bulk form of a substance when documenting hazards and risks. As a consequence, information will not be tailored to the specific properties that the nanomaterial might have in terms of toxicity and ecotoxicity, which again makes it hard to define and implement appropriate risk management measures.

The second problem is that the nanoforms of existing substances would be treated as phase-in substances under REACH. As a result, no toxicological and ecotoxicological information will be provided on the nanoforms, as only physiochemical data for phase-in substances has to be submitted, unless the parent substance is likely to be a CMR or a PBT, or if it falls into a hazard class of the CLP for substances with dispersive and diffuse uses. The same goes for exposure information as well as the availability of information further down the supply chain.

Third, the current volume thresholds do not account for NMs usually produced in much smaller quantities than their bulk counterparts.

Fourth, the lack of finalised and recognised testing guidelines which are fit enough to test properly for potential nanomaterial hazards constitutes a serious issue, and even in the case where the testing guidelines will not need to be adapted, the test will need to be carried out on the specific nanoform to yield adequate information (CIEL, ClientEarth and BUND 2012).

Finally, fifth, it is not possible to obtain a complete overview of which nanomaterials are on the EU market, due to the lack of registration and notification requirements when it comes to the use of NMs. This might delay regulatory action, e.g. a recall of affected products, if a NM is found to pose a health or an environmental risk, and the lack of market transparency also affects consumers, who are unable to make informed choices about purchasing nanoproducts (CIEL, ClientEarth and BUND 2012).

4.2.2 Legal elements of the "nano patch"

The proposal by CIEL, ClientEarth and BUND (2012) consists of one part comprising general provisions applicable to all nanomaterials in the EU and one part that focuses on amending existing regulatory instruments such as REACH and the Cosmetics Products Regulation.

The proposal aims at regulating nanomaterials and shall apply to any usage thereof. Nanomaterials are defined according to the European Commission's Recommendation 2011/696/EU, and a central tenet of the proposal by CIEL, ClientEarth and BUND (2012) is that the Commission's proposal is adopted in all legislation that might be relevant, and that the existing definitions of NMs are amended in the Cosmetics Products Regulation and the regulation on food information to consumers.

According to the proposal, all nanomaterials imported into or placed on the market in the EU have to be registered under REACH, along with a separate dossier for bulk materials if produced in more than 10 kg per year. Additionally, ECHA must be notified about products on the market that contain nanomaterials. The 10 kg weight was chosen as it was initially

proposed in the REACH negotiation and was the threshold for the notification of new substances in place under the previous directive on classification, packaging and labelling (CIEL, ClientEarth and BUND (2012). The registration dates are to be staggered over a period of three years following the entry into force of the regulation on the basis of production volumes of 10 kg, 100 kg and 1000 kg. Nanomaterials that have been assessed separately from their bulk form under other EU legislation, e.g. food contact materials and biocides, are exempted from registration.

A Chemical Safety Assessment, according to REACH, has to be completed for all registered nanomaterials, and the information submitted is to be volume-dependent and set out in Annex 2 of the regulation. The information requirements to be submitted aim to document the hazards and risks deriving from nanomaterials, including tailored test guidelines, while the technical and scientific tasks related to the notification and registration are to be carried out by ECHA; besides that, the specifics of Annex 2 are not quantified further in the proposal (CIEL, ClientEarth and BUND 2012).

4.2.3 Evaluation

When it comes to evaluation, CIEL, ClientEarth and BUND (2012) call for ECHA to perform compliance checks for all registered nano-substances, giving priority to substances that have wide dispersive use and those registered above 1 tonne. All registered nanomaterials are furthermore to be included in the CoRAP within two years of registration.

4.2.4 Report, notify, classification and labelling

According to the proposal made by CIEL, ClientEarth and BUND (2012), manufacturers and importers are required to notify ECHA of information required under Article 40 of the CLP Regulation, including, among others, the classification of the substance and an indication of whether the lack of classification in some hazard classes is due to lack of data, inconclusive data or data which are conclusive but insufficient for classification.

Furthermore, CIEL, ClientEarth and BUND (2012) propose that the requirement to add the suffix “nano” to the name of the ingredient should be expanded from food, cosmetics and biocidal products to all products that are required to have labels detailing ingredients, e.g. detergents, aerosols, sprays and paints (CIEL, ClientEarth and BUND 2012).

In order to achieve a better understanding of the uses of nanomaterials, and to allow their traceability throughout the supply chain, operators are finally obliged to report quantities of substances and their uses in the nanoform through which they are produced, distributed or imported into the EU, if a minimum of 1 kilogram of a nanomaterial is produced, imported or distributed. This information is to be put into a register of nanomaterials (CIEL, ClientEarth and BUND 2012).

4.3 Swedish draft proposal on regulation of nanomaterials from 2013

In 2013, the Swedish Chemical Agency (KEMI) presented its preliminary ideas on the future regulation of NMs, laying down rules for manufacturing and marketing of nanomaterials, NMs in mixtures and NM in articles. In the Swedish proposal, NMs are defined according to Commission Recommendation of 18 October 2011 on the definition of nanomaterial and regarded as substances in their own right.

4.3.1 Registration of Nanomaterials

Manufacturers or importers of a nanomaterial, either on its own or in one or more mixture(s) in quantities of 10 kg or more per year, are required to register. Quantities per year shall be calculated on the basis of the average production or import volumes for the three preceding calendar years. Pre-registration is also required for "phase-in nanomaterials," defined in the Swedish proposal as a nanomaterial that was placed on the market on the date for entry into force of this regulation. Similarly, producers or importers of articles containing nanomaterials have to notify ECHA if the nanomaterial is present in those articles in quantities totalling over 10 kg per producer or importer per year.

4.3.2 Information requirements

As part of the registration process, various information requirements have to be fulfilled. The information specified in REACH Annex VII is to apply for nanomaterials manufactured or imported in quantities of 10 kg or more per year, per manufacturer or importer, whereas REACH Annexes VII and VIII apply to 100 kg or more, REACH Annexes VII + VIII and IX to 1 tonne or more and finally REACH Annexes VII + VIII + IX and X to NMs manufactured or imported in quantities of 10 tonnes or more. It is important to note that tests on nanomaterials should be carried out with special consideration given to the specificities of nanomaterials, e.g. sample preparation and dosimetry, according to the proposal made by KEMI.

Exposure information is to be included in the technical dossier for nanomaterials produced in quantities of 10 to 100 kg, whereas a chemical safety report is to be included in the registration when in quantities of 100 kg or more per year, per registrant. The obligation to prepare a chemical safety assessment applies to downstream users as well, if they use a nanomaterial or mixture containing nanomaterials in a total quantity of less than 10 kg per year.

The REACH requirement to provide so-called "study summaries" and "robust study summaries" (see REACH Articles 10 (a) (vi) and (vii)) shall also apply to NMs in the proposal made by KEMI (2013), but it should furthermore include the information derived from the application of Annex I to this regulation. However, Annex I to this regulation has yet to be inserted.

5. Issues plaguing EU regulations of nanomaterials

As pointed out in Table 5 and 6, a number of issues are, and have been, plaguing the EU regulation of nanomaterials for some time now despite recent revisions to certain existing legislation. These include: 1) how to define nanomaterials, 2) whether nanomaterials should be considered as different from their bulk counterparts and 3) how to deal with the profound limitations of risk assessment when it comes to nanomaterials. Collectively, they raise the question about whether to continue adapting existing legislation or whether it might be better to develop a new regulatory framework tailored for nanomaterials.

5.1 Definitions of nanomaterials in the EU

Many different definitions of nanotechnology and nanomaterials exist in the literature. One of the most cited definitions is the one applied by the US National Nanotechnology Initiative, which defines nanotechnology as follows: "Nanotechnology is the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications. (…). At this level, the physical, chemical, and biological properties of materials differ in fundamental and valuable ways from the properties of individual atoms and molecules or bulk matter" (Nanoscale Science Engineering and Technology Subcommittee 2004).

At the moment, terms such as nanotechnology, nanomaterials and nanoparticles are understood in a variety of ways (Hansen 2010, Arts et al. 2014, Roebben et al. 2014, Boholm and Arvidsson 2016). It is clear from the many proposed definitions that NMs and/or NPs need to be in the nanometre range and have properties different from bulk materials; nonetheless, terms such as "roughly 1 to 100 nanometers", "dimension between approximately 1 and 100 nanometers" and "differ in fundamental and valuable ways from bulk matter" are in many cases too vague to provide a clear legal foundation (Hansen 2010).

A clear definition of nanomaterials is vital, as it will eventually help define the scope of any subsequent regulation, and determine which nanomaterials and applications are covered, which producers have to comply with the regulations and then and what they will have to comply with successfully (Hansen 2010, Roebben et al. 2014, Boholm and Arvidsson 2016).

Back in 2009, the European Parliament made a resolution calling for the "*introduction of a comprehensive science-based definition of nanomaterials in Community legislation as part of nano-specific amendments to relevant horizontal and sectoral legislation*" (European Parliament 2009), but it is evident from Table 5 that different definitions of nanomaterials have subsequently been implemented in the different pieces of EU legislation that have been amended.

In 2011, the EC adopted a definition of a nanomaterial as: "*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. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %"* (European Commission 2011c). Fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should furthermore be considered as nanomaterials by default (European Commission 2011c).

REACH and Ecolabelling legislation do not define nanomaterials, but in the case of REACH the EC definition is used in guidelines relating to legal provisions that address nanomaterials (Rausher et al. 2015). The BPR only adopts parts of the definition of nanomaterials recommended by the European Commission, omitting "incidentally" created NPs (Brinch et al. 2016, Mackevica et al. 2016a), whereas a nanomaterial is defined as "an insoluble or bio-persistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm" under the Cosmetic Regulation (EP and the Council 2009a), while food legislation again has a NM definition completely different from other non-food regulations. Only the regulation on medical devices follows EC recommendations on NM definitions, which thereby creates general inconsistency across legislative areas and means that a NM could be a NM according to one regulation and not according to another.

The EC definition furthermore has a number of limitations or implementation challenges that are important to keep in mind.

First of all, it equates nanomaterials with nanoparticles, not making the important distinction between the two. Nanomaterials include not only nanoparticles, but also materials with nanostructures on the surface as well as bulk materials with nanostructures (Hansen et al. 2007, Roebben et al. 2014, Rauscher et al. 2015).

Second, generally agreed methods and technical standards on how to measure particle size distribution are not yet available, and we especially lack methods that can be used to characterise agglomerates and aggregates and non-spherical particles. In the REACH registration dossiers analysed by Christensen et al. (2012), the methods used for measuring the particle size distributions of nanomaterials were found to be inappropriate, as they do not detect particles in the 1-100 nm range and do not distinguish between primary particles, aggregates and agglomerates. It is well known that particle size is linked strongly to the manufacturing process. Hence, in order to enable robust assessments, a combination of methods have to be applied supported by a description of sample preparation and information about the nanomaterial production process (Christensen et al. 2012, Linsinger et al. 2012, Rauscher et al. 2014, 2015).

Third, the current definition refers to natural, incidental and manufactured materials and thereby applies to all materials regardless of their origin, meaning that nanoparticles stemming from volcanoes and forest fires fall under the definition (Rauscher et al. 2015). According to Arts et al. (2014) and Roebben et al. (2014), the EC definition of NMs is the only one that does include natural and accidentally occurring nanoparticles, whereas all other definitions are restricted to intentionally produced, manufactured or engineered NMs. This is counterintuitive, especially considering that the purpose of nanotechnology is to design, control and manufacture technologies and materials at the nanoscale and has little to do with the random combustion processes that go on during forest fires and volcanic eruptions.

Arguably hard or impossible to define, the definition also does not consider or attempt to make a distinction between nanomaterials that have "unique properties" and materials that have no novel properties whatsoever (Lövestam et al. 2010, Roebben et al. 2014), which seems to be in stark contradiction to the whole concept and historical foundation of nanotechnology, where terms such as "unique properties" and "new phenomena" are often used in association with nanotechnology and nanomaterials (Nanoscale Science Engineering

and Technology Subcommittee 2004, European Commission 2004b).

Finally, although there might not be a scientific threshold applying to when a material is to be considered "nano" (Arts et al. 2014, Roebben et al. 2014), the 50% threshold seems set arbitrarily high. The EC definition was inspired by SCENIHR, who, after considering the "essential scientific elements of a working definition for the term "nanomaterial" for regulatory purposes" proposed that a "material is considered to be a nanomaterial, and nano-specific risk assessment has to be performed when >0.15% (or a specified percentage) of the number size distribution is <100 nm". The 0.15% was recommended by SCENIHR, as it represents the mean size plus/minus three times the standard deviation and would mean that any material would be a nanomaterial when >0.15% of the material, based on number concentration, has a size below 100 nm (SCENIHR 2010). Although SCENIHR does state that the values could be 0.15% "or any specified percentage", there seems to be good distance between the 0.15% and the 50% that the EC ended up recommending in their proposal for a definition.

From the actual operationalisation of the EC NM definition in the BPR, these limitations or implementation challenges have already shown themselves in regard to the assessment and approval of Synthetic Amourphous Silica (SAS). The Assessment Report prepared by France clearly states that the approval covers SAS as a nanomaterial in the form of stable 1-6μm aggregates with primary particles of < 25 nm. However, when it comes to assessing the hazard and risk, it was the aggregates – and not the nanoparticles – that were subject to the evaluation. The reason given in the Assessment Report is that the aggregate comprises of strongly bound or fused particles that are the smallest stable particles found in normal handling and use conditions. Exposure to nanoscale primary particles is therefore not expected during the specific intended biocidal use. Although it might be reasonable to include handling and use considerations when it comes to defining NMs and whether NM aggregates have to be subject to nano-specific testing requirements under the BPR, it does seem to somewhat contradict the intention of the EC definition of NM and the BPR. The EC definition of NMs, as also adopted in the BPR, is quite clear on the notion that aggregates and agglomerates of primary particles are to be considered as NMs, and the BPR is quite specific on the fact that a nano-specific risk assessment is required and arguments have to be made in regard to the nano-relevance of the test performed that provides the basis of the assessment. Hence, it seems contradictory to argue that no hazard or risk assessment has be done, due to the smallest stable particles being 1-6μm (Hansen and Brinch 2014).

Similarly, under REACH, some potential practical issues have arisen as some registrants specifically refer to their substance as a "nanomaterial" in physical and chemical properties reported in the registration, but subsequently they conclude that the substance is not a NM in the same section of the dossier and report that the size distribution of a sample's particles, counted under TEM, do not conform with the European Commission definition of nanomaterials, as only 39 ± 2.8% of all particles in the measured test material were found to be between 1 nm and 100 nm (Broomfield et al. 2016). It seems that we might have a problem with the NM definition when everyone – and even REACH registrants – speaks of a given material as a "nanomaterial" in their daily operations, but not when it comes to regulation, as it does not fall under the EC definition of a NM because only ≈ 40% - and not >50% of the particles were found to be 1-100 nm.

From the drafting and recasting of existing food regulation, it is evident that there have also been significant discussions by experts on how to define nanomaterials in the food area. In the food field, EFSA initially endorsed a definition similar to that of SCENIHR, considering NMs as "… *any material that is deliberately created such that it is composed of discrete functional parts, either internally or at the surface, many of which will have one or more dimensions of the order of 100 nm or less*" (EFSA 2009). The elements "*deliberately*" and "*of the order to 100 nm or less*" were initially considered as sufficiently valid parameters in identifying NMs, but the later EFSA's Scientific Committee Unit (EFSA 2012) recommended adopting the EC definition of a 10% nanoparticle threshold for a food ingredient to qualify as a "nanomaterial" instead of a 50% threshold, citing concerns about uncertainties as to safety. In the end, the European Parliament ended up using the same definition as in other areas of food law, in order to ensure uniformity across EU food legislation (EP and the Council 2011b), though it left terms such as "*intentionally produced material*", "*dimensions of the order of 100 nm or less*", "*discrete functional parts*" *and* "*specific physico-chemical properties that are different from those of the non-nanoform of the same material*" open to interpretation.

Work has been underway in order to evaluate the EC definition, and the JRC have developed a series of scientific-technical reports to assist the EC in taking into account any experience gained during the use of the EC definition (Rauscher et al. 2015). In its final report, the JRC (Rauscher et al. 2015) argued that terms such as "particle," "size" and "external dimension" should be defined more rigorously, in order to leave less room for interpretation. Among others, the JRC (Rauscher et al. 2015) additionally pointed out that although variable thresholds may allow regulators to address specific concerns in certain application areas, they may also confuse customers and lead to an inconsistent classification (as nanomaterial or not) of the same material based on the field of application (Rauscher et al. 2015, Roebben et al. 2014).

Updates to the definition were expected in mid-2016 (Roberts 2016), but there is no telling when the proposed updated definition will be implemented in existing legislation, and at least until then the many sometimes conflicting definitions of NM in the EU legislation will create additional confusion and complicate efforts to develop a sensible, effective policy (Hansen 2010).

5.2 Should nanomaterials be considered as different from their bulk counterparts?

The European Commission has long argued that nanomaterials in general fall under the scope of existing legislation (CEC 2008a, European Commission 2012a, b), which again has raised the question of "whether a nano-equivalent of a substance with different physicochemical and (eco) toxicological properties from the bulk substance would be considered as the same or as new substances under existing regulation of, for instance, chemicals" (Chaundry et al. 2006 Azoulay 2012).

Whether nanomaterials are considered to be equivalent to or different from the bulk material will have a major impact on the requirements put on manufacturers prior to placing products on the market. For instance, if a nanomaterial is considered to be the same as a registered bulk material, the appropriateness of the hazard information data should be open to discussion. On the other hand, if the nanomaterial is considered a different substance, hazard

information would, for example, have to be generated for the registration dossier under REACH, if it is produced in quantities of more than 1 ton/year (Chaudhry et al. 2006, Führ et al. 2006, Azoulay 2012, Hansen and Baun 2012b).

The BPR makes it very clear that the approval of an active substance does not cover a corresponding NM form, except where this is mentioned explicitly; for instance, the Novel Food Regulation makes it clear that the use of nanomaterials requires prior authorisation.

The European Commission has argued that nanomaterials are covered by the definition of chemical substances under REACH, which defines a substance as a "*chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition*" (EP and the Council 2006, art. 3). According to the EC, any registration dossier on an existing chemical substance, already placed on the market as a bulk substance, will have to be updated to include specific properties of the nanoform of that substance when the nanoform is introduced onto the market (CEC 2008a, Hansen 2010). Furthermore, REACH competent authorities "have clarified that the REACH provisions apply to nanomaterials and that registrants should attempt to apply the existing guidance in their registrations" (CEC 2008a, Christensen et al. 2012).

Despite the EC's and REACH competent authorities' attempts to provide clarification, information and especially hazard information on nanomaterials, there is still a profound lack of information in the REACH dossiers. This means that it is not always clear which form was tested and whether the claim made by the registrant that the nanoform has the same toxicological properties as the bulk form is valid (UBA, BfR and Baua 2013, Depallens cited in Buxton 2016). Industry is not legally obliged to provide this information, as it is not part of the standard information requirements in REACH Annexes VI-XI, as noted repetitively by UBA, BfR and BAuA (2013) and the European Commission in their second regulatory review of NMs. Hence, it is not surprising that there is profound ambiguity in the scope of many of the registration dossiers and registrants' intentions regarding which nanomaterials/nanoforms fall under the scope of the registration (Christensen et al. 2012). According to Christensen et al. (2012) any options for adapting REACH must begin by resolving such ambiguities and explicitly requiring registrants to describe the scope of the registration dossier, specifying whether different forms are covered and providing justification for when data are shared and when they are not shared between different forms. Registrants should furthermore explicitly be required to provide more detailed characterisations of nanomaterials/nanoforms. In order to clarify REACH requirements for nanomaterials in the standard information requirements found in REACH Annexes VI-XI, the JRC and ECHA (Christensen et al. 2012) have suggested that the following information requirements are explicitly included as a minimum: a) primary particle size distribution with an indication of the number fraction of primary particles smaller than 100 nm, b) other particle size distributions representing possible agglomerated/aggregated forms during usage and following the (environmental) release of substances, c) a description of surface functionalisation/treatments, d) shape based on the recommendations of the RIP-oN2 project (Hankin et al. 2011) and e) the volume-specific surface area and/or mass-specific surface area (Christensen et al. 2012).

Despite recommendations made by the JRC and ECHA back in 2012, there are still no legal obligations to provide nano-specific data on these end-points in the registration dossiers, as they are not part of the standard information requirements.

In its second regulatory review on NMs in 2012, the European Commission (2012a) argued that REACH "sets the best possible framework for the risk management of nanomaterials when they occur as substances or mixtures but more specific requirements for nanomaterials within the framework have proven necessary", noting that "there is no prescription to undertake specific tests for each different form, or to spell out the way in which the different forms have been addressed in the registrations, although the REACH dossier structure allows this and the technical advice from ECHA encourages it". In 2010, the hope was that that the publication of the EC recommendation on a NM definition, as well as the finalisation of the RIP-oN 1-3 plus REACH competent authorities clarifying that "the REACH provisions apply to nanomaterials", would encourage registrants to attempt to apply the existing guidance as part of their registrations (Christensen et al. 2012). This, however, has not been the case to date, as only four additional nanomaterials were registered under the second REACH registration deadline (Jones 2013). The EC and ECHA are now trying to define nanoforms further and to provide additional guidance on the registration of nanomaterials as well as testing for human health and environmental end-points and QSARs and Grouping before the third and final REACH registration deadline, but the REACH Annexes have still to be revised (Hansen and Baun 2015, Hansen et al. 2017a).

Nanoforms are defined as "a form of a substance that meets the requirements of the EC definition and has a specific shape and a specific surface chemistry as additional parameters" (ECHA 2016d), while ECHA has specified that when reporting on size as defined in the EC recommendation, particle shape and surface chemistry should be seen as minimum criteria for the registration of nanoforms. The latter criterion ECHA calls "essentially a wild card", as any combination of treatments may be applied. At the moment, a substance that has one present constituent greater than 80% w/w is defined as a mono-constituent, and the identity of the substance is based on the identity of the main constituent despite the fact that it may contain up to 20% w/w impurities. This is known as the 80/20 rule. A substance that has one or more constituents present at > 10 but < 80% (w/w) is defined as a multi-constituent substance. Constituents in the range of > 10 but < 80% (w/w) contribute to the substance name, whereas constituents present at < 10% are considered as impurities (European Commission Joint Research Centre 2011).

Knowing that much of what makes NMs unique is related to increased specific surface area and surface chemistry, and not their mass, concern has been raised that if the 80/20 rule was applied to surface-treated nanomaterials, the surface treatment would be considered to be an impurity and hence would not contribute to the identity and the name of the substance. This would specifically be a concern when the contribution of the surface treatment was less than 20% for a mono-constituent NM or less than 10% (w/w) for a multi-constituent NM. Surface treatment/surface chemistry was also discussed in detail in the RIP-oN1 project, but no consensus could be reached in terms of whether surface treatment/surface chemistry should be considered an "identifier" to distinguish a REACH substance from another REACH substance or as a "characteriser" used to distinguish forms of the same REACH substance within the same REACH registration dossier, or whether surface functionalisation/treatment

should trigger the need for a separate registration. However, there was agreement that it was relevant for the inherent property data and on the hazard/risk assessment (European Commission Joint Research Centre 2011, Christensen et al. 2012). In an analysis of the first round of REACH registrations relevant to nanomaterials, Christensen et al. (2012) observed that the extent of surface treatment was only indicated in one dossier out of 45 selected for further analysis, whereas about half included information indicating that the registered substances could be surface-treated.

When it comes to size, ECHA refrains from going into the scientific and technical challenges related to the definition and leaves it to the registrants themselves to determine which manufacturing outputs fulfil the "nanomaterial criteria and then determine how to fulfil their obligations for all sizes and ultimately report the relevant size ranges in their dossiers depending on the information collected/generated" (ECHA 2016d). On the other hand, registrants will not be able to demonstrate that they have adequately "addressed their obligation to collect/generate a base set of relevant Annex VII-XI data" without this information, or that "the hazard profile is meaningful for all forms registered by them" (ECHA 2016d).

On the one hand, this means that it is up to the registrant to determine whether their nanoform fulfils nanomaterial criteria, how to fulfil their obligations regarding all sizes and report relevant size ranges and whether to report on surface treatment/surface chemistry. On the other hand ECHA has stated that without this information, it cannot be ensured that the hazard profile is meaningful for all forms registered. Nevertheless, there are no legal obligations to provide information on nanoforms in regard to particle size, shape and surface chemistry in the registration dossiers, as this information is not part of standard REACH information requirements.

As noted by Christensen et al. (2012), it is basically still up to each registrant to decide, e.g. whether the registered material should be considered/described as a NM and whether it should be registered on its own or as a nanoform together with other forms of a substance. It is furthermore up to the registrant to decide on what nano-specific information to provide on the nanoform/nanomaterials, what nano-specific issues to address in the registration dossier, how to assess this information and what nano-specific conclusions to draw in the assessments in various parts of the dossier (Christensen et al. 2012). As a consequence, we have ended up in the situation that many feared, namely that a nanomaterial can basically be considered by the registrant to be the same as a registered bulk material, without any regulatory scrutiny. Consequently, the appropriateness of the submitted hazard information data is very much open to discussion (Chaudhry et al. 2006, Führ et al. 2006, Azoulay 2012, Hansen and Baun 2012b).

5.3 Risk assessment limitations in regard to nanomaterials

Current risk assessment procedures with corresponding regulations for nanomaterials have been based on procedures extrapolated from chemical risk assessment (mainly of chemical or physical agents) (Rocks et al. 2008), which traditionally consists of four steps, namely hazard identification, hazard characterisation, exposure assessment and risk quantification (see Figure 20).

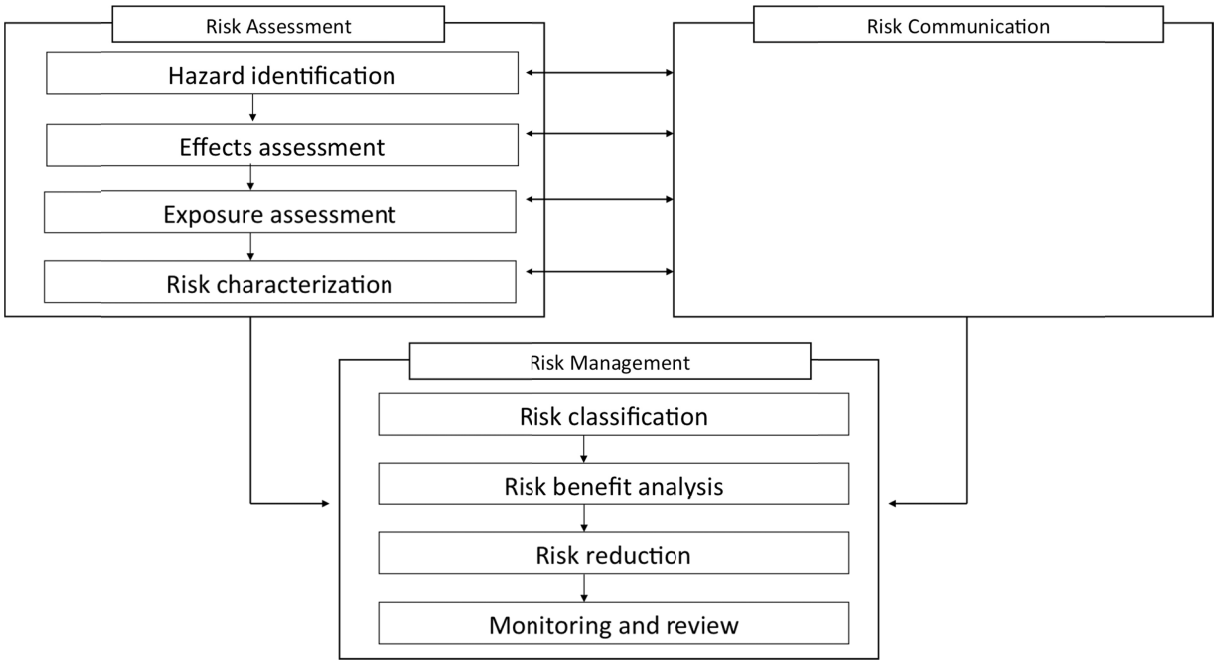


Figure 20: Risk analysis of chemicals, consisting of risk assessment, risk management and risk communication. Risk assessment is said to consist of hazard identification, effect assessment exposure assessment and risk characterisation, whereas risk management is said to consist of risk classification, risk benefit analysis, risk reduction and monitoring and review. Based on van Leeuwen (2007) and ECHA (2009).

5.3.1 Attempts to complete risk assessment of nanomaterials

Only a few attempts have been made at completing human health or environmental risk assessments of nanomaterials (Shinohara et al. 2009, Stone et al. 2010, Kjølholt et al. 2015). Under EU cosmetic legislation, the SCCS has provided opinions on the safety of a range of nanomaterials for use in relevant cosmetic product categories, e.g. ZnO, TiO2, carbon black and silica (SCCS 2012, 2014a, b, 2015a, b). Similarly, EFSA has made statements on the safety assessment of the substance silicon dioxide, for use in food contact materials, as well as re-evaluated the use of silver and titanium dioxide as a food additive (EFSA 2014, 2016a, b). SAS has been risk assessed as an insecticide under the BPR by its registrants, and the dossier has been evaluated by France in regard to both human health risk assessment as well as environmental risk assessment (France 2014).

As one might expect, given the different NMs and uses considered, the assessments differ in regard to their conclusions about overall safety. In their opinions on the human safety of ZnO, SCCS concluded that the use of up to 25% nanoZnO as a UV filter in sunscreens (non-spray) was safe, but that "the use of ZnO in cosmetic products which may result in inhalation is of concern", could not be considered safe and that "cosmetic products containing ZnO particles (nano or non-nano) with coatings that can promote dermal penetration will also be of concern" (SCCS 2012a, 2014a). For TiO2, SCCS reached a similar conclusion, in that up to 25% nanoTiO2 as a UV filter in sunscreens (non-spray) does not pose a risk, after application to healthy, intact or sunburnt skin, but noted that "the main consideration in the current assessment is the apparent lack of penetration of TiO2 nanoparticles through skin". As such they recommended not "to use nanoTiO2 in sprayable applications" and not to use TiO2 with substantially high photocatalytic activity in sunscreen formulations (SCCS 2014b, 2016a). For carbon black, the SCCS (2015a) concluded that the use of > 20 nm nano-

structured carbon black at a concentration up to 10%, as a colourant in cosmetic products, does not pose any risk of adverse effects in humans after application to healthy, intact skin. SCCP (2015a) stressed that this opinion did not apply to applications that might lead to inhalation exposure to carbon black nanoparticles (SCCS 2015a). Similarly, in the opinion of 2,2'-methylene-bis-(6(2H-benotriazol-2-yl)-4-(l,1,3,3-tetramethylbutyl)phenol) (MBBT), SCCP (2015c) argued that the use of nano-structured MBBT as a UV filter in dermally applied cosmetic products did not pose a risk of adverse effects in humans after application to healthy, intact skin at a concentration up to 10%. However, on the other hand, they noted that there are indications of severe inflammatory effects of microfine MBBT in the respiratory tract and that caution is warranted against the use of the material in applications that could lead to exposure to the consumer's lungs by inhalation (SCCS 2015c). For silica, hydrated silica and silica, surface modified with alkyl silylates (nano form), many inadequacies and gaps in the data were identified relating to physicochemical properties, toxicological data and exposure assessment. This led SCCS to conclude that "the evidence, both provided in the submission and that available in scientific literature, is inadequate and insufficient to allow drawing any firm conclusion either for or against the safety of any of the individual SAS material, or any of the SAS categories, that are intended for use in cosmetic products" (SCCS 2015b). Finally, SCCS (2016b) found that the safety of nano-hydroxyapatite materials, when used up to a concentration of 10% in oral cosmetic products, cannot be decided on the basis of data submitted by applicants or retrieved from a literature search.

In its statement on the safety assessment of the substance silicon dioxide, silanated for use in food contact materials, EFSA (2014) concluded that there was no detectable migration of silicon dioxide, silanated to any particle size, from low-density polyethylene film into appropriate food simulants and that the substance therefore did not raise safety concerns for consumers in the currently authorised conditions of use. For silver and its use as a food additive, EFSA, on the other hand, concluded that the available information was insufficient to assess the safety of silver and that major knowledge gaps included the chemical identification and characterisation thereof, for instance in regard to the quantity of nanoparticles and the release of ionic silver as well as similar information on the material used in available toxicity studies. This made it impossible for EFSA to establish the relevance of the available toxicological studies on the safety evaluation of silver as a food additive (EFSA 2016a). For TiO2, EFSA (2016b) found that most of the extensive database on TiO2 nanomaterials was not considered to be relevant in the evaluation of TiO2 as a food additive, as "data provided by interested parties and from the literature" indicate that TiO2 should not be considered as a nanomaterial, at least according to the NM definition proposed by the EC, as the nano-sized (< 100 nm) fraction was less than 3.2% by mass.

Under the BPR, only SAS has been subject to substance evaluation, though hazard and risk related to the individual particles of silicon dioxide with a nanometric size were not assessed in this dossier. The explanation given was that the exposure to nanoscale primary particles was not expected during the specific intended biocidal use (France 2014).

5.3.2 Hazard identification and effect assessments of nanomaterials

In general, hazard identification and effect assessments in chemical risk assessment are quite extensive tasks that require substantial amounts of data and resources. Hazard identification of chemical or physical agents is traditionally based on inherent physical, chemical, biological and toxicological properties. End-points usually considered include acute toxicity, repeated dose toxicity, irritation, sensitisation potential, mutagenicity, clastogenicity (i.e. the propensity to cause a point mutation as compared to disrupting a chromosome), carcinogenicity and reproductive toxicity (Rocks et al. 2008). The wide range of end-points, along with the diversity of nanomaterials and their properties, makes it an overwhelming challenge to conduct in vitro and in vivo evaluations of biological effects (CCA, 2008). Preliminary results suggest that in vitro testing may not always accurately predict hazards, and large in vivo studies are very sparse and difficult to reproduce. The parts of the ECHA guidance on the use of in vitro or alternative testing strategies has not been updated since 2007 (ECHA 2016f) and the role of alternative testing strategies in risk assessment of nanomaterials is still being discussed both when it comes to human health risk assessment (Stone et al. 2016) and environmental risk assessment (Hjorth et al. 2017a).

The possibility of other, possibly unknown end-points can furthermore not be excluded. Hazard characterisation involves the establishment of a dose (concentration)-response (effects) assessment. Several studies – especially in vitro – e.g. on C60, single- and multi-walled CNT, and various forms of metal nanoparticles have reported dose-response relationships, and based on these some predicted no-effect concentrations have even been estimated (Mueller and Nowack, 2008, Park et al. 2008, Kjølholt et al. 2015).

Interpreting the results reported in the literature, and extrapolating these to the wide array of nanomaterials, is difficult at present, since nanomaterials that have been tested differ substantially from other nanomaterials with regard to: 1) physical-chemical properties such as chemical composition, shape, etc. and 2) end-points tested in relation to duration of exposure and methods (e.g. assays) and standards used (Hansen et al. 2007). In addition, based on the knowledge taken from studies on nanoparticles detailed in Stone et al. (2010) and Mikkelsen et al. (2011), it has been suggested that the biological activity of nanoparticles might not always be dose-dependent but is instead dependent on physical and chemical properties not routinely considered in toxicity studies (Oberdörster et al. 2005).

5.3.3 Exposure assessments of nanomaterials

Consumer, occupational and environmental exposure assessments are normally completed based on collective consideration of the characteristics of substances, products, processes, task/work activities, conditions and risk management measures as well as exposure modelling and estimations and exposure measurement, provided they are reliable and representative (ECHA 2010). A number of estimation modelling tools are available, all of which have their own individual strengths and weaknesses. Information about substance properties, production processes and end products, such as molecular weight boiling point/vapour pressure, exposure duration and risk management measures, are often needed as input data.

As with hazard identification and characterisation, exposure data are lacking and no full exposure assessment has been published so far for any type of nanomaterial or group of nanomaterials. This is partly due to technical difficulties in measuring nanomaterial exposure

in the workplace and in regard to consumer exposure, and partly because the biological and environmental pathways of nanomaterials are still largely unexplored in detail (NIOSH 2006, CCA 2008, Owen and Handy 2007, Gottschalk et al. 2015). However, some efforts have been made to estimate, predict or model occupational, consumer and environmental exposures in terms of levels of exposure (e.g. Hansen et al. 2008a, Wijnhoven et al. 2009, Gottschalk et al. 2015, Mackevica and Hansen 2016), while the applicability of current exposure assessment methods and guidelines has also been discussed (SCENIHR 2009, OECD 2009a, Ganzleben and Hansen 2011). These efforts have been hampered by the lack of information (or access to it) e.g. about manufacturing conditions, levels of production, industrial applications and uses in both industrial and consumer products (Maynard et al. 2006, Hansen et al. 2008a, Ganzleben and Hansen 2012b).

5.3.4 Risk characterization of nanomaterials

The final risk characterisation or risk evaluation involves critically reflecting on the data behind each step of the risk assessment and determining what the overall assessment of the risk will be (CCA 2008, WHO 2013). It is clear that with the current state of knowledge each of the first three steps in a risk assessment holds general as well as specific limitations and challenges. Risk characterisation being at the end of the line, the sum or maybe even the power all of these limitations are conveyed in the calculation of risk quotients for nanoparticles.

5.3.5 Guidance and test methods relevant to safety assessment of nanomaterials

Precise, detailed guidance on NM safety assessments is still under discussion, and all current initiatives related to developing science-based NM risk assessments can be considered an "on-going regulatory activities", as noted by Arts et al. (2014): The European Chemicals Agency (ECHA) is in the process of revising nano-related appendices in the existing Technical Guidance to accompany the ongoing revisions to the REACH annexes VIII, IX and X on information requirements (Schwirn et al. 2014, ECHA 2016c, Hansen and Baun 2015). The literature on environmental fate and effects of nanomaterials has expanded vastly since the latest version of the nano-related appendices to REACH Technical Guidance in 2012 (Peijnenburg et al. 2015, Juganson et al. 2015) and numerous European research projects e.g. MARINA, NanoValid and NanoReg have made and published overview articles (e.g. Bondarenko et al. 2013, Hund-Rinke et al. 2015, Hund-Rinke et al. 2016). In most of these projects, however, an incremental approach to revision of the OECD guidelines has been applied, assuming that the test methods, developed for soluble chemicals, can be made applicable to nanomaterials through methodological adaptation. The properties of nanomaterials however clash with the fundamental prerequisite of many of these test methods, i.e. that the test substance is water soluble, implying that it distributes in the test system by molecular diffusion. Since this has repeatedly been proven not to be the case for nanomaterials, it follows that the test methods for soluble chemicals are not suitable for nanomaterials (Hansen et al. 2017a).

In the guidance documents that ECHA provides in order to assist manufacturers and importers of chemicals and biocides and biocidal products, and which SCCS (2012b) provide on cosmetics and EFSA (2010) on food and feed, several references are made to the OECD

TGs for information and guidance on how to complete specific tests. OECD TGs have been subject to intense investigation regarding their applicability when it comes to nanomaterials.

In 2009, the OECD carried out a review of its test guidelines and concluded that "in general the OECD guidelines are applicable for investigating the health effects of nanomaterials with the important proviso that additional consideration needs to be given to the physicochemical characteristics of the material tested". The OECD also found that basic toxicological practices are adequate for the ecotoxicological testing of nanomaterials, but that guidance on preparation, delivery, measurement and metrology was currently insufficient (OECD 2009a). This finding was subsequently confirmed in 2012, based on a preliminary analysis of the OECD sponsorship programme, which ran from 2007-2015 (OECD 2016b, Jones 2012) and again after the programme had ended in 2015, when the OECD stated "The tests showed that the standard test guidelines used for normal chemical substances are in the most part suitable for use on nanomaterials. Changes to the Test Guidelines, to better understand the intrinsic properties of nanomaterials, are now providing a clear framework for OECD countries to move forward in the examination of nanomaterials" (OECD 2016c).

However, an independent analysis of the documentation and analyses of the OECD's Sponsorship Testing Programme for Nanomaterials does not support the conclusion that the test guidelines used for regular chemical substances are in the most part suitable for use on nanomaterials, for instance when it comes to ecotoxicological testing. According to Hansen et al. (2017b), most of the studies on physical-chemical characterisation, environmental fate and behaviour and ecotoxicological information were not designed to investigate the validity of the test guidelines. Most contributors to the sponsorship programme applied existing guidelines for chemicals with little, or no, reporting on test performance when used on nanomaterials. The few studies in the dossiers that do discuss the validity of the tests and explain the modifications that they made to the tests provide substantial points of concern about the general applicability of the OECD test guidelines. Furthermore, the analysis by Hansen et al. (2017b) indicates that very few studies were carried out for each end-point, making it hard to generalise about any single technical guideline being generally applicable. Hansen et al. (2017b) concludes that the published dossiers present an incomplete portfolio of nanomaterial toxicity evaluations that are difficult to draw substantive conclusions from rather than providing a clear framework for OECD member countries to move forward in the examination of nanomaterials.

The BPR requires that an explanation has to be provided on the scientific appropriateness of the test when it comes to nanomaterials and, where applicable, on the technical adaptations/adjustments that have been made in order to respond to the specific characteristics of these materials. In light of the findings of Hansen et al. (2017a, b) and Brinch et al. (2016), this must be said to be quite challenging to achieve in reality. A similar requirement is present under the Novel Food Regulation (EP and the Council 2015), but many of the limitations of risk assessment are applicable not only to chemicals, biocides and biocidal products, but also to food, feed and cosmetics, as they rely on the same test methods (EFSA 2010, SCCNFP 2002), since REACH, the BPR (CEC 2008b) and many of the test methods according to regulation EC 440/2008 are equivalent to the OECD's TG (Brinch et al. 2016). As pointed out by EFSA (2011) and SCCS (2012b, 2013), uncertainty in regard to physico-chemical characterisation, as well as all elements of risk assessment, are profound

and pervasive, including that it is not routinely possible to identify, characterise and detect ENM in situ in cosmetics, food or the feed matrix, due to 1) a lack of suitable and validated test methods to cover all possible applications, aspects and properties of NMs and 2) uncertainties related to the applicability of current standard biological and toxicological testing methods to NMs (EFSA 2011, EFSA 2016a, SCCS 2012a, SCCS 2012b, 2013, SCCS 2014a, SCCS 2014b).

It is now clear that standards for chemical testing are not appropriate for nanoparticles according to Wickson et al. (2014). Development of tests standards and guidelines is a tedious process and seems to be a never-ending attempt to balance scientific tensions (Wickson et al. 2014). Wickson et al. (2014) have identified three so-called "double-binds" that collectively led them to warn regulators against requiring data based on standard testing. Double-binds are defined as persistent types of dilemmas whereby two choices are in tension and success in one inevitably creates problems in the other. The first double-bind identified relates to the notion that standardization is long overdue as nanoproducts are already commercially available, while any clear pattern in (eco)toxicological testing has yet to emerge on which standardization could be based. The second bind insinuates that there is a contradiction between pursuing and requiring tests that are performed under real use and environmental conditions on the one hand and on the other require that the data is generated using well-controlled and standardized experimental set-ups that are less realistic and that aim at ensuring mutual cross-national acceptance of data for classification. Finally, there is a bind in the tendency to create selective ignorance when deciding to pursue knowledge according to one particular approach over others (Wickson et al. 2014).

Overall, as pointed out by Savolainen et al. (2013) in an evaluation of Nanosafety 2015-2025, "current resources or test methods are not likely to enable safety assessment of the numerous novel nanomaterials", and "we still lack a fundamental understanding of how nanomaterials interact with living systems and, thus, we are not yet in a position to assess the relevant end-points for nanomaterial toxicity". Discussing an environmental risk assessment of NMs, Klaine et al. (2012) similarly stated that "A consensus view exists that the paucity of usable data on the environmental hazard of nanomaterials has created unacceptable uncertainty in risk analysis from the regulatory decision-making perspective".

6. Alternatives to Risk Assessment

In recognition of the above-mentioned challenges that traditional chemical risk assessments entail, and because of the outstanding scientific research questions that still need to be resolved, a number of alternative decision-support tools or supplements to traditional risk assessment have been explored and proposed in recent years. Examples of these include the "Control Banding Nanotool," developed to assess and control the risks behind nanomaterials when working in the laboratory (Paik et al. 2008, Zaik et al. 2009), and the more holistic "Swiss precautionary matrix," developed by Höck et al. (2008, 2011, 2013) and the LICARA nanoSCAN (van Harmelen et al. 2016). A number of concepts and tools also exist which were originally developed to cater for the safe handling of chemicals, such as "Comprehensive Environmental Assessment" (Davis 2007), "MultiCriteria Decision Analysis" (Linkov et al. 2007, Tervonen et al. 2009), Stoffenmanager (van Duuren-Stuurman et al. 2012) and GreenScreen (Sass et al. 2016), which have also recently been explored in regard to nanomaterials (see Figure 21). Figure 21 provides an overview of 50 alternative decision-support tools or supplements to traditional risk assessment that have been explored and proposed in recent years. The alternative decision-support tools span from focussing solely on occupational risks to being very broad in scope encompassing occupational risks, health risks, environmental risks, benefits and acceptability. Tools that focus on occupational risks tend to be control banding tools that can be applied on nanomaterials/particles, nanoproducts and powders, whereas tools that are very broad in scope tend to be risk governance tools that focus on nanoparticles. Tools and supplements to traditional risk assessment that have elements of risk governance were developed between 2006 and 2010, whereas a large number of tools were developed on occupational, health and environmental risks between 2005-2010 in a range of areas such as control banding, hazard and risk evaluation and life-cycle evaluation. After 2009, the development of Control banding tools dominates whereas only a few tools have been developed within other areas such as, for instance, risk evaluation and risk management since 2010.

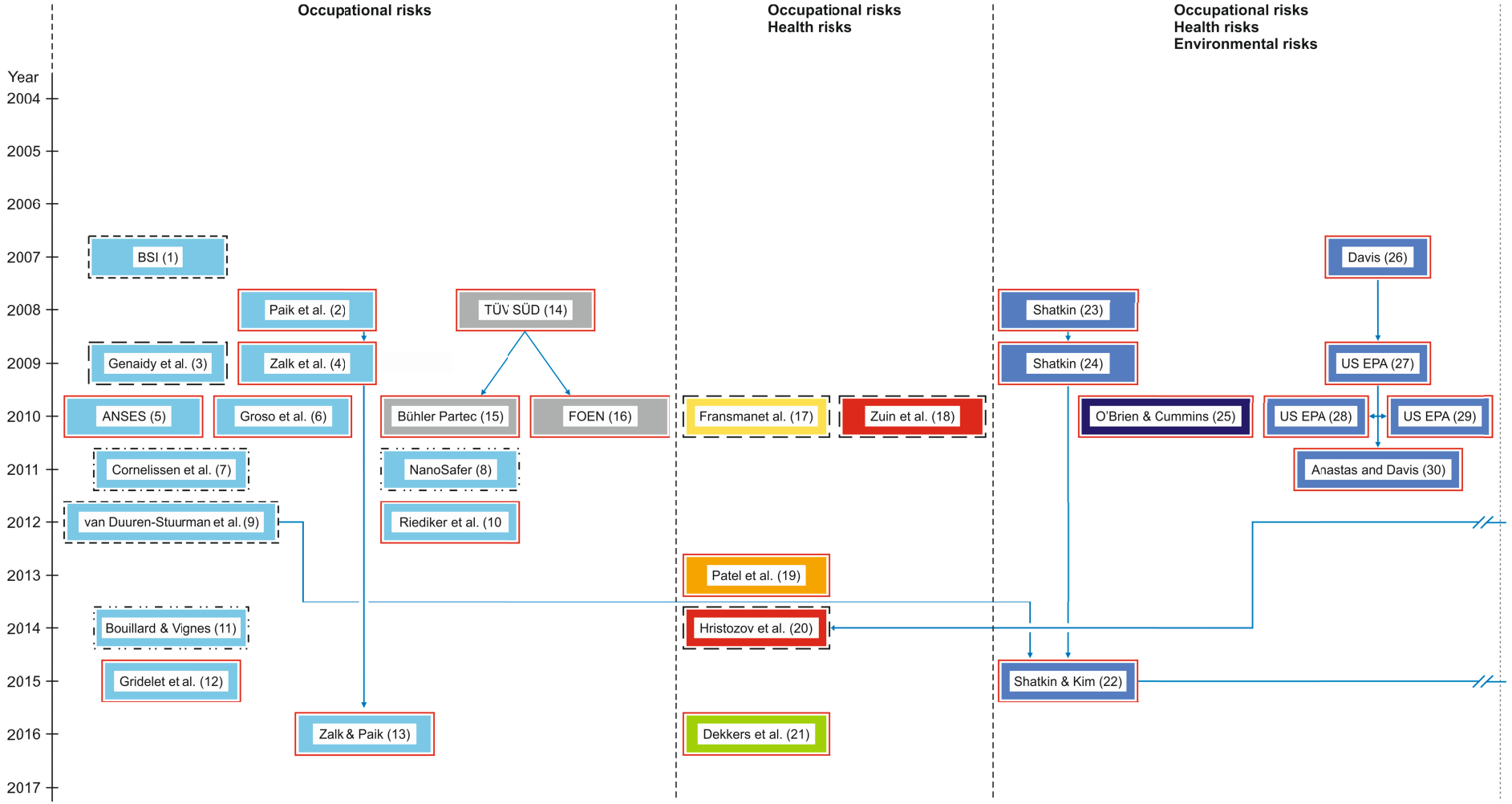
6.1 Existing reviews of Alternative Decision-Support Tools

There have been quite a few reviews of alternative decision-support tools when it comes to nanomaterials (Hansen et al. 2011, Grieger et al. 2012, Brouwer et al. 2012, Hristozov et al. 2012, 2016, Som et al. 2012, Fleury et al. 2013, Arvidsson et al. 2016, Liguori et al. 2016, Romero-Franco et al. 2017).

In 2011, Hansen et al. (2011) evaluated concepts, approaches and frameworks with the intention of estimating and controlling the risks inherent in nanomaterials. The tools were compared in regard to 1) focus/applicability (e.g. work environment, consumers, environment), 2) method (e.g. Qualitative/quantitative), 3) exposure and hazard input parameters (e.g. frequency of exposure, level and extent of exposure, 4) scale assessment of exposure and hazard level (linear 4-step scale, assignment of severity factor between 0-10), 5) risk evaluation (e.g. serious risks to occur soonest, a combination of the severity score and probability score into four possible risk levels), 6) risk handling ("hierarchical risk handling" based on COSHH principles) as well as 7) opportunities and weaknesses (see Table 7).

Control banding tools are often included in the reviews of alternative decision-support tools despite the fact that many of the reviews' authors state explicitly that the use of their

suggested approach should never replace a comprehensive risk assessment by experts (Brouwer 2012, Fleury et al. 2013). Brouwer (2012) compared six control banding approaches (see Table 8) and found that they were very similar in their overall approach when it comes to combining hazards and exposure into control or risk bands. However, Brouwer (2012) also noted that the six approaches differed in regard to structure, applicability domains and the assignment of the hazard and exposure bands, which may again affect the consistency of the resulting outcome amongst the various control banding tools. Based on his analysis, Brouwer (2012) concluded that it is impossible to evaluate the performance of the different approaches at present and called for enhanced transparency elucidating the differences that users have to take into consideration during the selection of a tool for a specific scenario of application.


Occupational risks
Occupational risks
Health risks
Occupational risks
Health risks
Environmental risks
Year
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
BSI (1)
Paik et al. (2)
TÜV SÜD (14)
Genaidy et al. (3)
Zalk et al. (4)
ANSES (5)
Groso et al. (6)
Bühler Partec (15)
FOEN (16)
Cornelissen et al. (7)
NanoSafer (8)
van Duuren-Stuurman et al. (9)
Riediker et al. (10
Bouillard & Vignes (11)
Gridelet et al. (12)
Zalk & Paik (13)
Fransmanet al. (17)
Zuin et al. (18)
Patel et al. (19)
Hristozov et al. (20)
Dekkers et al. (21)
Shatkin (23)
Shatkin (24)
O'Brien & Cummins (25)
Shatkin & Kim (22)
Davis (26)
US EPA (27)
US EPA (28)
US EPA (29)
Anastas and Davis (30)

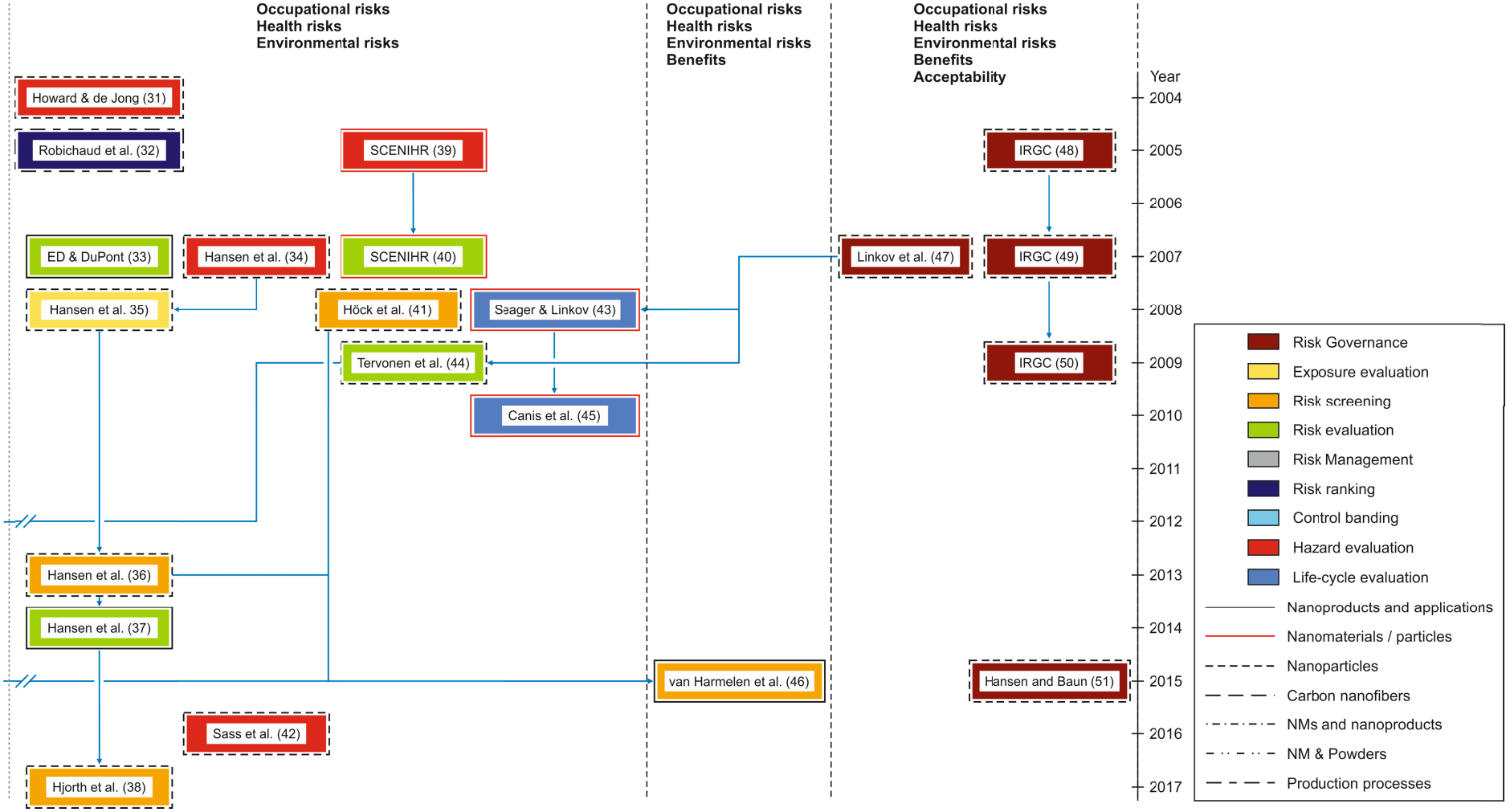


Figure 21: Alternative decision-support tools or supplements to traditional risk assessment have been explored and proposed in recent years.

1) BSI 2007, 2) Paik et al. 2008, 3) Genaidy et al. 2009, 4) Zalk et al. 2009, 5) Ostiguy et al. 2010, 6) Groso et al. 2010, 7) Cornelissen et al. 2011, 8) Kristensen et al. 2010, Jensen et al. in prep. 9) van Duuren-Stuurman et al. 2012, 10) Riediker et al. 2012, 11) Bouillard and Vignes 2014, 12) Gridelet et al. 2015, 13) Zalk and Paik 2016, 14) TüV SüD 2008, 15) Bühler Partec (2010), 16) FOEN (2010), 17)Fransman et al. 2010, 18) Zuin et al. 2010, 19) Patel et al. 2013, 20) Hristozov et al. 2014, 21) Dekkers et al. 2016, 22) Shatkin and Kim 2015, 23) Shatkin 2008, 24) Shatkin 2009, 25) O'Brien and Cummins 2010 26) Davis 2007, 27) US EPA 2009, 28) US EPA 2010a, 29) US EPA 2010b, 30) Anastas and Davis 2011, 31) Howard and de Jong 2004, 32) Robichaud et al. 2005, 33) ED and Dupont 2007, 34) Hansen et al. 2007, 35) Hansen et al. 2008a, 36) Hansen et al. 2013a, 37) Hansen et al. 2014, 2017c, 38) Hjorth et al. 2017b, 39) SCENIHR 2005, 40) SCENIHR 2007, 41) Höck et al. 2008, 42) Sass et al. 2016, 43) Seager and Linkov 2008, 44) Tervonen et al. 2009, 45) Canis et al. 2010, 46) van Harmelen et al. 2015, 47) Linkov et al. 2007, 48) IRGC 2005, 49) IRGC 2007, 50) IRGC 2009, 51) Hansen and Baun 2015.

Table 7: Summary of the main characteristic of the different frameworks (Adapted from Hansen et al. 2011).

Name	BSI Nanomaterials Handling Guide	CB Nanotool	Swiss Precautionary Matrix		Nanorisk framework	MCM risk-based classification system
Reference	BSI (2007)	Paik *et al.* (2008)	Höck *et al.* (2008, 2011, 2013)	Genaidy *et al.* (2009)	ED & Dupont (2007)	Tervonen *et al.* (2009)
Focus/	Work environment	Work environment	Workers, consumers, environment	Work environment	Workers, consumers, environment	Human and environment
Scope	Nanoparticles	Nanoparticles	Nanoparticles	Nanomanufacturing	Applications	Nanoparticles
Method	Qual. /quan.	Qual. /quan.	Qual. /quan.	Quan.	Qual. /quan.	Qual. /quan.
Strategy	Hazard evaluation + Exposure assessment + Handling risks	Hazard evaluation Exposure assessment + recommended risk handling	Hazard evaluation + Exposure assessment + Assessment of risk handling need	Hazard evaluation + Exposure assessment + Handling risks	Describe, evaluate, decide, update; life-cycle, hazard-, exposure-, risk profiles	Selection of criteria, identifying options, ranking and selecting optimal option(s)
Exposure assessment input parameters	1) Work procedure; 2) Who is exposed; 3) What is the exposure route; 4) When does exposure occur; 5) Frequency of exposure; 6) Level and extent of exposure; 7) Source of exposure potential; 8) Protection possibility	1) Determination of the number of employees in completing the activity; 2) Frequency of the activity; 3) Time extend of the activity; 4) Amount of nanomaterial used in each cycle of the activity; 5) Dustiness index or evaluation of mistiness	1) Type of exposure (air, liquid or in a matrix); 2) Amount of nanomaterial a worker is normally exposed to during a day; 3) How much nanomaterial can a worker be exposed to in a worst case?	Not specified	Among others: 1) Number and locations of manufacturing sites; 2) Current and expected production; 3) Industrial function; 4) Maximum concentration used; 5) required controls, etc.	Not applicable
Scale assessment of exposure level	Assessment, estimation and measurements	Linear 4-step scale based on points given for the five exposure parameters/ measurements	Airborne exposure scaled by the 2 last parameters; normal/ accidental conditions	Logarimic 5-step: Frequent, Probable, Occasional, Remote, Improbable	Not specified	Not applicable
Hazard evaluation input parameter	CMAR Fibrous Insoluble Soluble	Surface chemistry; Particle shape; Particle diameter; Solubility; CMAR (nano- and bulk materials); Dermal toxicity (nano- and bulk materials); Occupational Exposure Level	Redox activity and/or catalytic activity; Stability in physiological and environmental conditions	Not specified	Short-term tox; skin sensitization + pene-tration; genetic toxi-city tests; biological fate + behavior; chro-nic inhalation/Inge-stion /dermal tox stu-dies; developmental, reproductive, neuro, genotox and EDS- studies	Agglomeration and aggregation; Reacti-vity; critical func-tional groups; particle size, and contaminant dissociation, size; bioavailable and bioaccumulation po-tential and toxic potential

Scale evaluation of hazard evaluation	None	1) Assignment of severity btw 0-10 p., 2) derivation of the overall score btw 0-100 p., 3) assignment of the probability estimation (0-100)	Input parameters are scored btw 1-9	Catastrophic (Deaths); Critical (Severe injuries); Marginal (Minor injury); Negligible (No illness or injury)	Not specified	Mean size of particles in units of nanome-ters. Other criteria scored from 1 to 5 via expert judgment
Risk evaluation	1) most serious risks to health; 2) risks that are likely to occur soonest; and 3) risks that can be dealt with soonest	Combining severity score and probability score into four possible risk levels (RL)	Total score of the precautionary need V = N * (W * E + S) and classified as "A" (V= 0-20) and "B" (V> 20)	Five risk levels e.g. "Very high" or "red" based on probability–severity values.	Evaluation of nature, magnitude and probability of risk types	Classification into extreme, high, medium, low, and very low risk categories
Risk handling	Hierarchical COSHH risk handling	Control of bands and exposure control	Unspecified	Haddon's system	Focusing on minimizing exposure	Unspecified
Special circumstanc es	Nanomaterial specific maximum exposure standards	Unknown parameters are assigned 75 % of the maximum score	Nanoscale ≤ 500 nm; Unknown parameters assigned max high-risk score; Actual/ estimated daily/ worst case inhalation	For each of the intervention strategies four criteria were applied: applicability, benefit, cost and feasibility	Sharing of product info, hazard, exposure and risk profiles with stakeholders is recommended	Uses an outranking model termed Stochastic multicriteria acceptability analysis (SMAA-TRI)
Opportuni-ties	Pro-active in the sense that risk handling can be implemented immediately	High usability, Pedagogical color code, clear results that limit "paralysis by analysis"	Step-by-step guide is clear and easy to apply; considers workers, consumers, environment taking a life-cycle perspective	Scenarios are illustrated as activity appellations without any further description of the circumstances	Clear guide on how to organize, document, and communicate information	High level of transparency in selection of criteria which enables the users to define their own criteria
Weaknesses	Relies on having good information about the hazardous nature of materials, the effectiveness of control approaches and convenient and accessible ways to monitor exposure. This information might not always be available	Unclear how severity scores and probability were assigned e.g. to particle shape and dustiness and not clear why unknown parameters are assigned 75 % of the maximum score	Dubious use of default values for redox activity or catalytic activity; Unclear why unknown parameters are assigned 100% of the high-risk score; Questionable quantitative derivation of whether there is a precautionary need for action; Overall classification scores seems arbitrary	Unclear hazard input parameters and assignment of risk codes	High data requirements often not available; unclear how to evaluate nature, magnitude and probability of risk types, as independent validation by stakeholders is hard to obtain	Low level of transparency in the qualitative assignment of scores between 1 and 5 to various nanomaterials. Unclear how specific weight bonds were assigned

Table 8: Summary of the most important characteristics of the various CB tools (From Brouwer 2012).

	Hazard banding			Exposure banding							Matrix	
	Allocation system			Source domains/type of activities*							Number of bands/levels	
CB too Short name	Binary	Score	*N*	Synthesis	Powder handling	Application Ready-to-use products	Abrasion	Emission potential	Exposure potential	*N*	CB	RL
Precautionary Matrix	-	+	1	(+)	(+)	(+)	(+)	+	-	1	2	-
NanoTool	-	+	4	+	+	-	-	+	-	4	4	-
ANSES	+		5	(+)	+	+	+	+	-	4	5	-
Stoffenmanager Nano	+	-	5	+	+	+	(+)	-	+	4	-	3
NanoSafer	+	+	4	-	+	-	-	-	+	5		5
Guidance	+	-	3	+	+	+	+	+	-	3	3	-

*Based on Schneider et al. (2010).
1 Precautionary matrix does not distinguish separate hazard and exposure bands.
N Number of bands.
CB Control band.
RL Risk Level.
+ Used/addressed by tool.
- Not used/addressed by tool.
(+) only implicitly addressed by tool.

In a similar 2016 review of control banding tools, Liguori et al. (2016) reviewed the Control Banding Nanotool, IVAM Technical Guidance, Stoffenmanager Nano, ANSES CB Tool, NanoSafer and the Precautionary Matrix, in order to evaluate their use-domains, types, extent, use and availability of input parameters, their output format and finally their potential use and maturity in regard to meeting the minimum requirements for occupational exposure assessment under REACH (see Table 9). It was found that the tools varied with regard to application domains, inclusion criteria, requested input parameters, exposure assessments, derived risk levels and output formats. The tools were furthermore found to be based on different concepts and assumptions, which could be explained by the fact that they were developed for different purposes. Overall, a direct inter-comparison and combination of the different models into a larger holistic framework was found not to be immediately possible, and calls were made for the harmonisation of input parameters and output, to allow for the establishment of an exposure assessment framework with different levels of information requirements (Liguori et al. 2016).

Table 9: Key information and application domains of the Control Banding tools considered in this study (Adapted from Liguori et al. 2016).

Name	NM Definition	Target group/scope	# of input parameters	# of input parameters used			# of control bands			"Outcome" RM recommendation
				Nano-relevance	Haz. scaling	Exp. scaling	Haz.	Exp.	Risk	
CB Nanotool (6,7)	ASTM[a] (1)	NM researchers/ Risk ass. + man.	45	-	15	5	4	4	4	Risk Level (RL). Recommendations
IVAM Guidance (8)	Own (2) define-tion similar to EC[b] (3)	Workers/Occu-pational hygiene	27	-	2	1	3	3	3	Control level bands. Hierarchic occupational hygiene
Swiss Precautionary Matrix (9-11)	ISO/TS 27687[c] (4)	Employees, consumers + environ. / Source id. + risk reduction	28	7	6	6	n.a.	n.a.	2	Need for action/no action
Stoffen-manager Nano (12)	ISO/TS 27687[c], SCENIHR[d] (5)	Employers and em-ployees/ Risk prio-ritization of risks + implementation of control measures	47	-	2	26	5	4	3	Risk priority bands. Ranking priority of needed actions
ANSES CB Tool (13, 14)	ISO/TS 27687[c], EC[b]	Small to large enterprises/Exposure prevention	10	1	5	3	5	4	5	Control level (CL). Technical solutions for exposure prevention
NanoSafer (15, 16)	ISO/TS 27687[c], EC[b]	SMEs/Precautionary risk assessment	29	5	5	13	4	5	5	Risk Level (RL). Recommendation and actions to be taken into consideration

a) ASTM International, 2007; b) European Commission, 2011c; c) ISO, International Organization for Standardization, 2008; d) SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks, 2010; (1) *ASTM – definition:* As nanotechnology is a rapidly developing field, it will be necessary to continually reassess the terms and definitions contained in this standard, for purposes of revision when necessary. The intent of the terms and definitions in this standard is to describe "...materials containing features between approximately 1 and 100 nm and to differentiate those properties different from properties found in either molecules or the bulk (interior) of larger, micron-sized systems."*;* (2) *IVAM – definition:* A nanoparticle is a particle with three dimensions in the range of 1 – 100 nm. A fibrous particle does have two dimensions in the nano range of 1 – 100 nm; (3) *ISO/TS 27687 – definition:* Nano-object: Material confined in one, two, or three dimensions at the nanoscale. This includes nanoparticles (all three dimensions in the nanoscale), nanofibres (two dimensions in the nanoscale) and nanoplates (one dimension in the nanoscale). Nanofibres are further divided into nanotubes (hollow nanofibre), nanorods (solid nanofibre) and nanowire (electrically conducting or semiconducting nanofiber); (4) *EC – definition:* 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*;* (5) *SCENIHR – definition:* Nanomaterial: Any form of a material that is composed of discrete functional parts, many of which have one or more dimensions of the order of 100 nm or less. 6) Paik et al. 2008, 7) Zalk et al. 2009, 8) Cornelissen et al. 2011, 9) Höck et al. 2008, 10) Höck et al. 2011, 11) Höck et al. 201, 12) van Duuren-Stuurman et al. 2012, 13) Ostiguy et al. 2010, 14) Riediker et al., 2012, 15) Kristensen et al. 2010, 16) Jensen et al. in prep

Grieger et al. (2012) analysed a number of environmental tools and approaches and compared them to 10 criteria, including transparency, precaution and life cycle perspective, which have been proposed by a variety of sources as important parameters for the environmental and health risk analysis of nanomaterials (Grieger et al. 2012). Denominators for these tools were that they had been proposed as alternatives for environmental risk assessment. They found that most frameworks were flexible for multiple nanomaterials, suitable for multiple decision contexts, included life cycle perspectives and precautionary aspects, were transparent and able to include qualitative and quantitative data. Nevertheless, Grieger et al. (2012) also found that most frameworks were primarily applicable to occupational settings, with a few minor environmental considerations, and that most of them had not been thoroughly tested on a wide range of nanomaterials (Grieger et al. 2012) (see Table 10).

Table 10. Evaluation of selected frameworks proposed by large organizations/ regulatory bodies for environmental risk analysis of NMs (From Grieger et al. 2012)

	Criteria									
Framework	1. Variety of NM	2. Multiple decision contexts	3. Uncert. Analysis	4. Life cycle perspect.	5. Iterative or adaptive	6. Timely decision making	7. Transparent	8. Stakeholders	9. Precaution	10. Qual./ quan. data
IRGC Risk Governance Framework**	X	X	X	x	x	-*	x	X	x	X
CEA*,**	X	X	X	X	A	A	x	X	x	X
Nano Risk Framework**	X	X	X	X	X	-*	X	x	X	X
Nano LCRA***	X	X	X	X	x	-	x	-*	x	X
MCDA*	X	X	X	A	A	A	X	A	A	X
CENARIOS**·***	X	X	-	x	X	A	x	N/R	x	x
Precautionary Matrix **·***	X	-	-	X	A	A	x	N/R	x	X
XL Insurance Database Protocol*	X	X	-	x	A	A	x	N/R	A	X

Note: literature documenting theory and applications range from peer-reviewed journal articles (*) to organizational reports (**) and other non-peer reviewed material (***) (e.g., presentation slides, webpage, book chapter). X = criterion is obvious and embedded in the framework and demonstrated through application; x = criterion is included to some extent or to a lesser degree or not fully demonstrated in application; A = criterion is not directly included in the framework but can be easily adapted or included and which has been demonstrated through application; - = criterion is absent from the framework; N/R = criterion was not relevant to the framework; * = Considered or mentioned to be important but not included or integrated in framework specifically.

Table 11. Nano risk assessment (RA) and risk management (RM) frameworks and their characteristics. (Adapted from Hristozov et al. 2012)

Framework	Scope	RA/RM	Iterative structure	Policy model	Refers to conventional RA and RM paradigm?	REACH oriented?	Data requirements
ED & DuPont (2007)	HHRA[a]/ ERA[b]	RM	Yes	Trans-parent	Yes	No	Phys-chem properties; (eco-)toxicity; biological/ environmental fate and behaviour; hazard data; exposure
IRGC (2006)	HHRA/ ERA	RM	Yes	Trans-parent	Yes	No	Phys-chem properties; (eco-)toxicity biological/ environmental fate and behaviour; exposure
Liao et al. (2008)	HHRA	RA	No	N/A	Yes	No	Toxicity; biological fate and behaviour; exposure
Oberdorster et al. (2005)	HHRA	RM	No	Decisi-onist	Yes	No	Phys-chem properties; toxicity/ecotoxicity; exposure
SCENHIR (2007)	HHRA/ ERA	RA	No	N/A	Yes	No	Phys-chem properties; (eco-)toxicity; exposure
Tyshenko & Krewski (2008)	HHRA/ ERA	RM	Yes	Trans-parent	Yes	No	Phys-chem properties; toxicity/ecotoxicity effects; exposure data

[a]Human health risk assessment; [b]Ecological risk assessment.

Hristozov et al. (2012) reviewed available data and nano risk assessment approaches from a regulatory perspective in regard to their added value, in light of present limitations and uncertainties, and found that most of them were designed to serve preliminary risk screening and/or research prioritisation, but they did not support regulatory decision-making and were not REACH-oriented (see Table 11). In a more recent publication, Hristozov et al. (2016) reviewed forty-eight frameworks and tools to facilitate risk assessment of NMs and grouped into 7 different types: Control banding, risk screening, occupational and consumer exposure, environmental fate and exposure, hazard assessment, physicochemical characterization, and decision support tools. Evaluating the identified frameworks and tools up against sixteen criteria e.g.: Nano-specific requirements, lifecycle thinking, pre-assessment phase, exposure-driven approach, iterative and adaptive structure, transparency of objectives and communication with all involved stakeholders, document applications, allowing for/giving directions on grouping and read-across of NMs, tools, easy to use, quantitative information, uncertainty analysis, assessment tier, transparency in application. Hristozov et al. (2016) found that none of the frameworks and tools fulfilled all the criteria and called for the development of a new tool that integrates data and current models to support risk assessment and management of NMs.

Finally, Arvidsson et al. (2016) investigated existing screening risk assessment methods for nanomaterials and found a total of 20: ANSES, CB Nanotool 2.0, early warning signs, Genaidy's method, Groso's method, Guidance, Hierarchical Rank Aggregation, LICARA nanoSCAN, Nano-Evaluris, NanoHAZ, NANoREG, NanoRiskCat, NanoSafer, Occupational Hazard Band for Nano, Precautionary Matrix, Relative Risk Analysis, Risk Trigger Scores, Stoffenmanager Nano, TEARR and the WCD model. In their review, Arvidsson et al. (2016).

Many of these were included in the reviews by Hansen et al. (2011), Grieger et al. (2012), Brouwer et al. (2012), Hristozov et al. (2012, 2016) and Liguori et al. (2016) but many had not been reviewed earlier. Despite identifying 20 methods the number could easily have been much higher as Arvidsson et al. (2016) did not include several of the tools reviewed in other papers, such as in IRGC (2005, 2007, 2009), SCENIHR (2007) and Tervonen et al. (2009), or some of the more recent approaches proposed, such as Alternatives Assessment (Hjorth et al. 2017b) and GreenScreen Nano (Sass et al. 2016). Nevertheless, Arvidsson et al. (2016) found that most methods focused on occupational human health risks, while fewer focused on environmental risks.

Overall, many of the methods were found to share features in regard to e.g. scoring and ranking of risk on ordinal scales, but the scoring and ranking procedure varied in complexity and the exact scales differed. Some methods are relatively simple and require few hazard input parameters, while others are more complex, and require many input parameters, some of which are difficult to determine (Arvidsson et al. 2016).

6.2 Opportunities and Weaknesses of Existing Tools and Frameworks

Generally, it is clear that there is an urgent need for adaptive, transparent, easily comprehensible, communicational and yet robust scientific methods, approaches and frameworks to evaluate the potential of exposure, and hazard and risk related to the production and application of nanomaterials (Hansen et al. 2011, Grieger et al. 2012,

Hristozov et al. 2012, 2016, Fleury et al. 2013, Ligouri et al. 2016 and Mackevica and Hansen 2016, Romero-Franco et al. 2017).

When comparing the opportunities and weaknesses of existing tools and frameworks it is important to note that such a comparative analysis can never do full justice to all tools and frameworks. The methods, approaches and frameworks presented herein are all helpful in the primary evaluation of the potential hazards, exposures and risks related to the production and application of nanomaterials, although they might not all be equally helpful in meeting the goals of regulators and risk assessors in a given situation (Hansen et al. 2011, Hristozov et al. 2016, Ligouri et al. 2016, Romero-Franco et al. 2017).

Many of the tools, such as Genaidy et al. (2009), the Nanorisk framework (ED & DuPont 2007) and LICARA NanoSCAN (van Harmelen et al. 2016) are developed in order to help developers, SMEs and producers of nanomaterials complete crude risk estimations and risk-benefit estimations. In that sense, their scope is much broader than just limited to risk assessment (see figure 20). The hope is that this will make developers and producers focus on minimising exposure, or that it will facilitate the implementation of various more or less stringent control measures to protect workers in the primary production and handling of nanomaterials. In that sense, they may enable and support the implementation of effective risk handling procedures that can be applied despite a lack of full scientific knowledge (Hansen et al. 2011, Brouwer 2012, Ligouri et al. 2016). However, only some of the methods and frameworks, e.g. the Swiss Precautionary Matrix and the MCM risk-based classification system, involve professional end-users, consumers and the environment, which might be helpful in some situations and unnecessary in others.

Although varying considerably in focus and scope, most of the approaches and frameworks provide guidance on how to make a crude assessment of the hazards and exposure associated with a nanomaterial and its use(s). In regard to the hazard of nanomaterials, all but the framework proposed by Genaidy et al. (2009) set up a series of criteria or hazard end-points that have to be considered.

It is, however, not always clear why a given criterion was included or excluded from the analysis. Furthermore, some of the criteria are based on mass, which many of the authors of the proposed frameworks themselves state is not sufficient to deal with nanomaterials. Among others, the Swiss Precautionary Matrix, the MCM risk-based classification system and the CB Nanotool assign numbers or ranges to the extent of various reported effects, which makes the frameworks easy and transparent to use in the sense that these numbers are assigned to various effects by default, and the scoring process can be validated by others.

However, how the numbers or ranges have been assigned to the various effects is less transparent. In this sense, these tools are able to cope with less extensive input data information in regard to hazard identification and hazard characterisation.

Regarding nanomaterial exposure, most approaches and frameworks use an estimate of the likelihood of exposure or a more-or-less precise relative scale. These are useful for identifying activities with potential risks of exposure, as shown through the completely qualitative model proposed by Genaidy et al. (2009).

One weakness of these tools, however, is that they do not provide a strong basis for estimating an actual exposure level. It would be helpful to identify whether, for instance, a high likelihood of exposure would also give cause to “high exposure.” The CB Nanotool

provides the ability to assess the exposure level based on the amount of material handled, and the frequency of the activity. The system developed by BSI and the Swiss Precautionary Matrix use either a simple assessment or actual exposure measurements, the latter of which require the use of a series of fairly complex measurement methods to estimate the fraction of the nanomaterial airborne in the workplace. The development of a quantitative model would make it possible to complete exposure assessments before nanomaterials are used on a large scale. New methods are under development and hopefully they will help to solve some of these problems, but there is a long way before we have models comparable to those we now have for assessing atmospheric and environmental exposure to chemicals. In this regard, these tools combined are able to cope with less extensive input data information in regard to exposure assessment. Overall, they seem less prone in the final risk evaluation to the vulnerability of exposure assessment.

Combining the hazard and exposure assessments, all of the tools and frameworks derive an overall score which is again linked to a classification (e.g. A, B, Cor “high”, “medium”, “low”), and so the results of the process make it easy to summarise and communicate risks. They, however, carry the risk of masking the process, any evidence and the line of argumentation used to derive the overall score and subsequent classification. A number of frameworks translate the overall score into a set of recommendations for generally prescribed management measures. Such an approach, for example, is explored in the Swiss Precautionary Matrix and the CB Nanotool. In order for these recommendations to be generic they have to be very broadly defined, which perhaps implies making them too general and non-specific in relation to providing input into real decision support. Overall, these tools seem to be less prone in the final risk evaluation to the vulnerability of one or more of the preceding steps regarding hazard identification, hazard characterisation and exposure assessment. Except for NanoRiskCat, which was developed to be applicable despite a lack of information, most of the tools available today have fairly high input data requirements, and some of the scientific information needed in order to apply them is inconclusive at the moment or even non-existent. Lack of information and data is part of the reality today, even for nanomaterials that are applied in high quantities. NanoRiskCat seems to be the only safety evaluation tool that has been designed to support regulatory decision-making and which is REACH- and CLP-oriented (Hansen et al. 2011, 2014, Hristozov et al. 2012, Romero-Franco et al. 2017).

7. NanoRiskCat and Safety Evaluation of NMs

NanoRiskCat is a systematic tool that was originally developed to support companies and regulators in their first-tier assessment of and communication on what they know about the hazard and exposure potential of consumer products containing engineered nanomaterials (Hansen et al. 2014, 2017c). However, as noted by Hansen et al. (2014), NanoRiskCat can also be used to set default guidance for when regulatory measures are to be implemented, e.g. the need to consider the implementation of precautionary measures, depending on the outcome of the NanoRiskCat evaluation.

The scope of NanoRiskCat covers evaluating the nanomaterial as an ingredient as it occurs in a given product and considering its physical conditions and immediate availability. However, NanoRiskCat does not include an evaluation of the amount of nanomaterial in the product, exposure and effects from the other constituents or impurities in the product. In this sense, NanoRiskCat is a tool that can be used for safety evaluation, risk screening, ranking and categorisation, but it cannot be used for risk assessment per se.

Figure 22: Example of a NanoRiskCat evaluation on exposure and hazard potential for a given nanoproduct. The first three coloured dots always refer to exposure potential during intended use for professional end-users, consumers and the environment, respectively. The last two dots refer to the apparent hazard potential for humans and the environment, respectively. Each dot can be assigned one of four different colours, with red, yellow, green and grey indicating high, medium, low and unknown, respectively (From Hansen et al. 2014).

In its simplest form, the final evaluation outcome for a specific nanomaterial in a given application will be communicated in the form of a short title (e.g. TiO_2 in sunscreen or MeO in ship paint), describing the use of the nanomaterial, and a colour code, whereby the first three coloured bullets (●●●|●●) always refer to the potential exposure of professional end-users, consumers and the environment – in that sequence – and the last two coloured bullets always refer to the hazard potential for humans and the environment. The colours assigned to the exposure and hazard potential are green (●), yellow (●), red (●) and grey (●), corresponding to high, medium, low and unknown, respectively.

The short titles aim at describing the scope and boundaries of the NanoRiskCat evaluation, and hence the evaluated nanoproduct must be clearly specified along with the specific nanomaterial(s) used in the product, if known, and its intended use (Hansen et al. 2014, 2017c).

7.1 Evaluation of Exposure Potential in NanoRiskCat

Appraising the exposure potential in NanoRiskCat involves evaluating potential exposure to professional end-users, consumers and the environment for the specific nanomaterial in the evaluated nanoproduct. The use of existing REACH exposure assessment models is questionable for the time being, though, partly because the substantial amount of data on a nanomaterial's identity, uses and release during use, required to complete a consumer exposure assessment according to ECHA (2010) guidance, is not available (Mackevica and Hansen 2016). In NanoRiskCat, the exposure potential is therefore evaluated based on 1) the

location of the nanomaterial i.e. bulk, on the surface, liquid or airborne and 2) a judgment of the potential for nanomaterial exposure based on the description and explanation of each process, use category, etc. (Hansen et al. 2014, 2017c). The evaluation of the exposure potential in NanoRiskCat is inspired by Hansen et al. (2007, 2008) and orders consumer products into four different exposure categories: 1. Red = High exposure potential. 2. Yellow = Medium exposure potential. 3. Green = Low exposure potential. 4. Grey = Unknown due to lack of information.

In NanoRiskCat, a red colour code is given to products which contain "nanoparticles suspended in liquids" or result in "airborne nanoparticles" during use (see Figure 23). For "surface-bound nanoparticles," the exposure potential is assumed to be medium and such products are assigned a yellow colour code (Hansen et al. 2008a, 2014). Finally, if the products contain "nanoparticles suspended in a solid," it is thought that there is a low or negligible exposure potential associated with their intended use and they should, as a general rule, be assigned a green colour code (Hansen et al. 2014, 2017c).

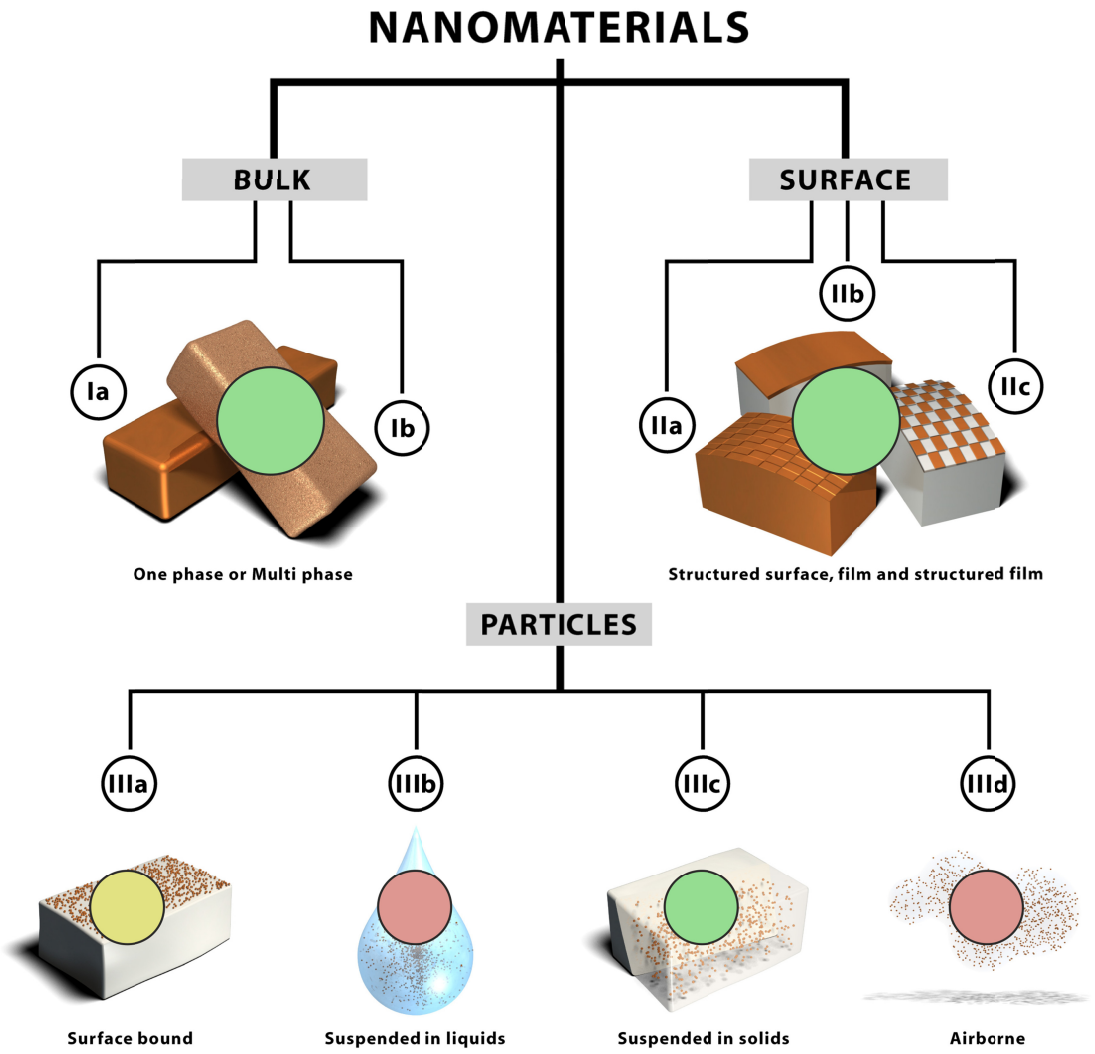


Figure 23: Default colours assigned to the exposure potential for professional end-users, consumers and the environment in NanoRiskCat based on the location of the nano-element, if no other information is available (adapted from Hansen et al. 2007, 2008).

7.2 Evaluation of Hazard Potential in NanoRiskCat

The hazard potential for humans is evaluated based on whether the nanomaterial in question is known as a compound to have low solubility in water (biodurable), fulfils the fibre paradigm, is regulated more stringently than nuisance materials and has CMR properties or other adverse effects (see Figure 24a and Hansen et al. 2014, 2017c). On the other hand, the evaluation of the environmental hazard potential is based on the first lesson learned by the European Environment Agency (2001), namely "Acknowledge and respond to ignorance, uncertainty and risk in technology appraisal", and specifically assess whether the nanomaterial in question is known to be novel, readily dispersed, persistent, bioaccumulative and/or has been reported to be hazardous to environmental species (see Figure 24b). For guidance on how to assess, for instance, the novelty, persistency and dispersibility of NM, see Hansen et al. (2013a, 2014).

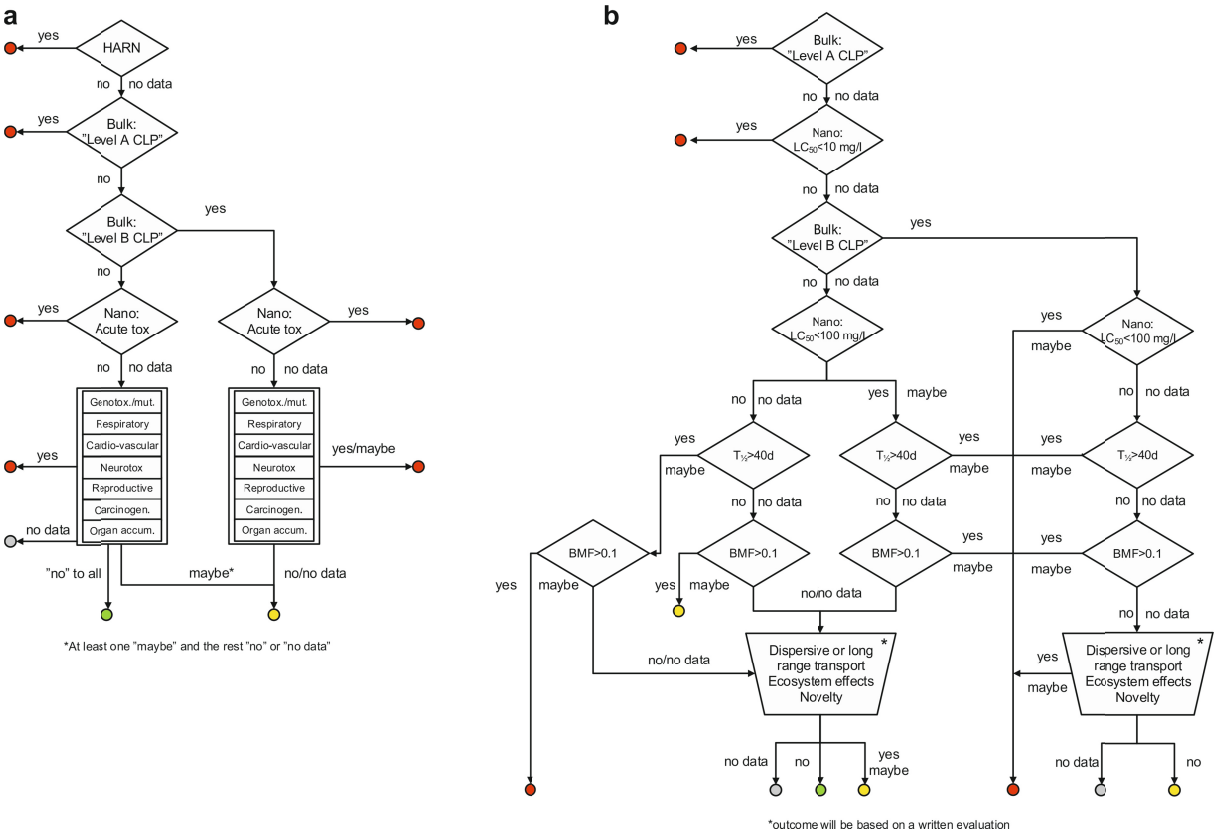


Figure 24: Roadmap for assigning a colour code to the human (Figure 24a) and environmental (Figure 24b) hazard potential in NanoRiskCat. Red, yellow and green indicate a high, medium and low indication of a deleterious effect, whereas grey indicates too limited data to make an assessment. *) at least one "maybe" and the rest "no" or "no data."

To help communicate the scientific reasoning behind assigning a human health hazard classification and why a given nanomaterial was assigned red, yellow or grey, a range of human health (HH) sentences and Environmental Effect (EE) sentences have been developed (see table 12 and 13). The options listed in table 12 and 13 are meant to justify primarily whether the conclusion has been reached based on classification of the bulk form of the materials and/or *in vivo* or *in vitro* data on the nanomaterial, and in regard to what endpoint. See Table 14 for an overview of the human health and environmental hazard potentials for the nanomaterials most frequently claimed to be used in products currently in The Nanodatabase.

Table 12. HH-sentences to explain the color code for human health hazard in NanoRiskCat (Adapted from Hansen et al. 2014).

Sentence no.	Color	Description
HH 1		Based evidence of HARN
HH 2		Based on bulk CLP classification 1-4 for acute toxicity
HH 3		Based on CLP classification 1 for skin corrosion/irritation, eye damage/irritation/respiratory and skin sentization
HH 4		Based on bulk CLP classification 1 or 2 germ cell mutagenicity/carcinogenicity, reproductive toxicity, specific target organ toxicity
HH 5		Based on bulk CLP classification 1 for aspiration toxicity
HH 6		Based on nano acute tox
HH 7		a. Based on *in vivo* evidence of an effect when testing the nanomaterial i.e. one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation
		b. Based on *in vivo* evidence of a combination of two or more of the following i.e. one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation
HH 8		a. Based on *in vitro* evidence of an effect when testing the nanomaterial i.e. one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation
		b. Based on *in vitro* evidence of a combination of two or more of the following i.e. one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation
HH 9		Based on bulk classified as a CLP category 2 regarding skin corrosion/irritation/ serious eye damage/irritation as well as *in vivo* evidence of hazards from testing of the nanomaterial
HH 10		Based on bulk classified as a CLP category 3 regarding specific target organ toxicity – single exposure as well as *in vivo* evidence of hazards from testing of the nanomaterial
HH 11		Based on bulk classified as a CLP category 2 regarding skin corrosion/irritation/ serious eye damage/irritation as well as *in vitro* evidence of hazards from testing of the nanomaterial
HH 12		Based on bulk classified as a CLP category 3 regarding specific target organ toxicity – single exposure as well as *in vitro* evidence of hazards from testing of the nanomaterial
HH 13		Based on *in vivo* evidence indicating at least one hazard from testing of the nanomaterial
HH 14		Based on *in vitro* evidence indicating at least one hazard from testing of the nanomaterial
HH 15		Based on bulk classified as a CLP category 2 regarding skin corrosion/irritation/ serious eye damage/irritation as well as evidence of no hazards from testing of the nanomaterial
HH 16		Based on bulk classified as a CLP category 3 regarding specific target organ toxicity – single exposure as well as evidence of no hazards from testing of the nanomaterial
HH 17		Based on bulk classified as a CLP category 2 regarding skin corrosion/irritation/ serious eye damage/irritation as well as not enough data on possible hazards from testing of the nanomaterial
HH 18		Based on bulk classified as a CLP category 3 regarding specific target organ toxicity – single exposure as well as not enough data on possible hazards from testing of the nanomaterial
HH 19		Based on not enough *in vitro* and/or *in vivo* data being available on hazards from testing of the nanomaterial
HH 20		Based on the identity of the nanomaterial not being disclosed or available, which hampers any human hazard evaluation
HH 21		Based on no information or data being available in the scientific literature

Table 13. EE-sentences to explain the color code for environmental effects in NanoRiskCat (Adapted from Hansen et al. 2014).

Sentence no.	Color	Description
EE 1		Based on bulk CLP classification of Acute 1 or Chronic 1 or Chronic 2
EE 2		Based on nanospecific LC50 or EC50 < 10 mg/l
EE 3		Based on possible or confirmative evidence of nanospecific LC50 or EC50 < 100 mg/l and T1/2 > 40 d
EE 4		Based on possible or confirmative evidence of nanospecific LC50 or EC50 < 100 mg/l and a biomagnification factor (BMF) > 0.1
EE 5		Based on evidence of T1/2 > 40 d and a BMF > 0.1
EE 6		a. Based on bulk CLP classification of Chronic 3 or Chronic 4 and nanospecific effects (LC50/EC50 < 100 mg/l or T½>40d or BMF > 0.1)
		b. Based on bulk CLP classification of Chronic 3 or Chronic 4 and T1/2 > 40 d and a BMF > 0.1
		c. Based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty
EE 8		Based on a BMF > 0.1
EE 9		Based on an evaluation of dispersive or long range transport, ecosystem effects and novelty
EE 10		Based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty
EE 11		Based on an evaluation of dispersive or long range transport, ecosystem effects and novelty
EE 12		Based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty
EE 13		Based on the identity of the nanomaterial not being disclosed or available, which hampers any environmental hazard evaluation
EE 14		Based on no information or data being available in the scientific literature

Table 14. Human health and environmental hazard potentials and HH- and EE-sentences for the nanomaterials most frequently claimed to be used in products in The Nanodatabase.

NM	Human health	Environment
Unknown	HH 20. Based on the identity of the nanomaterial not being disclosed or available, which hampers any human hazard evaluation	EE 13. Based on the identity of the nanomaterial not being disclosed or available, which hampers any environmental hazard evaluation
Ag	HH 7b and 8b. Based on in vivo and in vitro evidence of a combination of two or more of the following, i.e., one of the following genotox/ mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 2. Based on nanospecific LC50 or EC50 < 10 mg/l
Ti	HH 21. Based on no information or data being available in the scientific literature	EE 14. Based on no information or data being available in the scientific literature
TiO_2	HH 8b. Based on in vitro evidence of a combination of two or more of the following, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 2. Based on nanospecific LC50 or EC50 < 10 mg/l
C	HH 7a. Based on in vivo evidence of an effect when testing the nanomaterial, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 14. Based on no information or data being available in the scientific literature
CNTs	HH 1. Based on evidence of HARN	EE 3. Based on possible or confirmative evidence of nanospecific L50 or EC50 < 100 mg/l and $T_{1/2}$ > 40 days
P	HH 21. Based on no information or data being available in the scientific literature	EE 14. Based on no information or data being available in the scientific literature
Bamboo charcoal	HH 21. Based on no information or data being available in the scientific literature	EE 14. Based on no information or data being available in the scientific literature
SiO2	HH 7b. Based on in vivo evidence of a combination of two or more of the following, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 2. Based on nanospecific LC50 or EC50 < 10 mg/l
Au	HH 13. Based on in vivo evidence indicating at least one hazard from testing of the nanomaterial	EE 3. Based on possible or confirmative evidence of nanospecific L50 or EC50 < 100 mg/l and T1/2 > 40 d
Graphene	HH 7a. Based on in vivo evidence of an effect when testing the nanomaterial, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 14. Based on no information or data being available in the scientific literature
ZnO	HH 8b. Based on in vitro evidence of a combination of two or more of the following, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 1. Based on bulk CLP classification of Acute 1 or Chronic 1 or Chronic 2

As can be observed in table 14 there is a large variation in the HH- and EE- sentences associated with the human health and environmental hazard profiles and there is not one single determinant that makes all materials go "red". For instance, for nanoZnO, it is due to properties of the bulk form of the material, whereas for TiO2 and SiO2 it is due to the acute toxicity of the nanoforms of the material, and finally, for carbon nanotubes and gold, it is due to a combination of toxicity and persistency (Hansen et al. 2014, 2017c).

7.3 Application of NanoRiskCat in The Nanodatabase

One of the strengths of NanoRiskCat is that it has been applied to more than 2,300 consumer products in The Nanodatabase (Hansen et al. 2016).

Figure 25 shows the distribution of NanoRiskCat consumer and environmental exposure profiles across different product categories. The consumer and environmental exposure potential was found to be high (i.e. red) for many of the products that were intended for direct application on skin and could cause subsequent environmental release (see Figure 25; Hansen et al. 2016). Out of the 1,311 products for which the nanomaterial is not reported, 64% have a red NanoRiskCat profile when it comes to consumer and environmental exposure. For nanosilver, nanotitanium dioxide and nanosilica the numbers for a high exposure potential are 46%, 98% and 98%, respectively (Hansen et al. 2016).

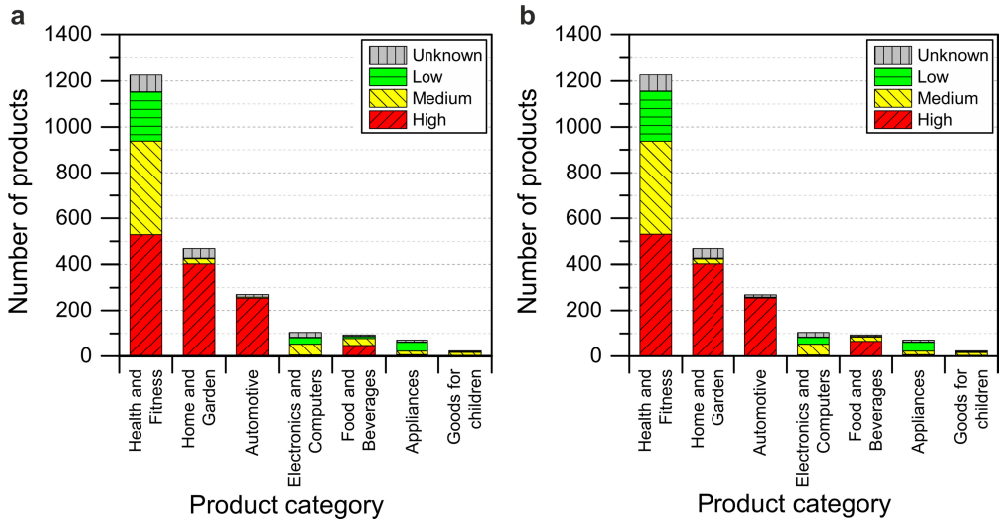


Figure 25: Distribution of NanoRiskCat consumer exposure profiles across different product categories. Red, yellow, green and grey colours indicate high, medium, low and unknown potential of consumer exposure (Figure 25a). Distribution of NanoRiskCat environmental exposure profiles across different product categories. Red, yellow, green and grey colours indicate high, medium, low and unknown potential of environmental exposure (Figure 25b) (reprinted from Hansen et al. 2016).

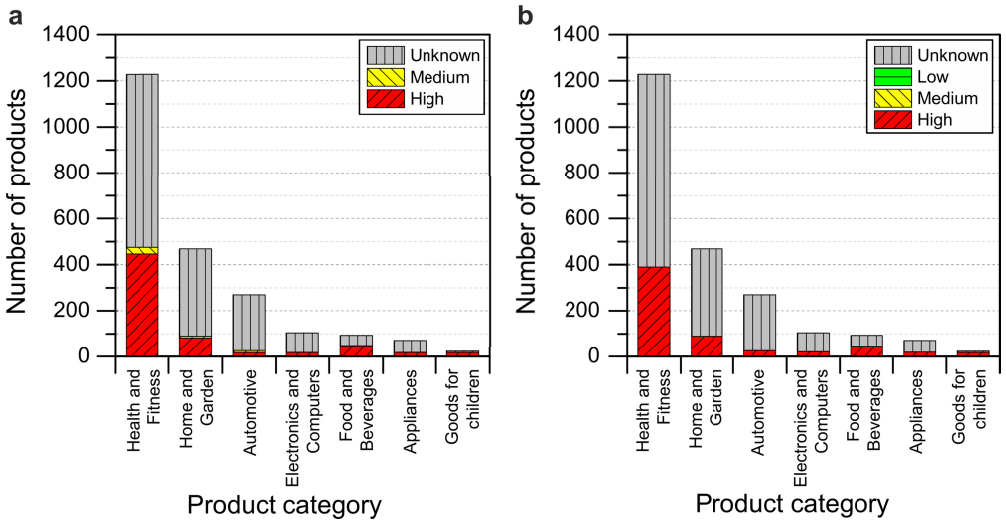


Figure 26: Distribution of NanoRiskCat human hazard profiles across different product categories. Red, yellow, green and grey colours indicate high, medium, low and unknown hazard potential (Figure 26a). Distribution of NanoRiskCat environmental hazard profiles across different product categories. Red, yellow, green and grey colours indicate high, medium, low and unknown hazard potential (Figure 26b) (reprinted from Hansen et al. 2016).

When it comes to the NanoRiskCat human hazard and environmental hazard evaluation, it turns out either red or grey for a majority of the products (see Figure 26). The "Grey" human hazard potentials are due to the unknown identity of the nanomaterial used. Without even knowing the chemical composition of the nanomaterial, it is impossible to make any kind of hazard evaluation (Hansen et al. 2016).

The subcategories that have most products with a red NanoRiskCat for human health profile are "Personal Care" (157 products), "Sporting Goods" (129 products), "Cosmetics" (82 products), "Clothing" (63 products) and "Cleaning" (52 products). For environmental hazards, the subcategories that have most products with a red NanoRiskCat profile are "Personal Care" (167 products), "Cosmetics" (82 products), "Clothing" (67 products) "Sporting Goods" (67 products) and "Cleaning" (59 products).

The fact that so many products end up having a red human hazard NanoRiskCat profile could indicate that the hazard evaluation is biased towards assigning "high potential" (i.e. the red colour) to the products. However, this is not the case, as various nanomaterials are assigned the red colour for different reasons, as explained by Hansen et al. (2014). For instance, for nano zinc oxide, the red colour is due to properties of the bulk form of the material, whereas titanium dioxide and silica result in a red human hazard evaluation because of the acute toxicity of these two specific nanomaterials. Finally, for carbon nanotubes and gold, the red hazard profile is due to a combination of toxicity and persistency (Hansen et al. 2016).

8. REACT NOW

The limitations of existing legislation in regard to definitions, risk assessment and test methods raise questions about the overall meaningfulness of the so-called "incremental approach" adopted by the European Commission, as it seems to have turned into an ever-increasing number of small adaptations to existing legislation, thereby placing an additional burden on already stretched agencies (Hansen 2010, 2013, Vogelezang-Stoute 2014). In view of the pace of development in the field of nanomaterials and their applications, it seems that a complete reworking of existing regulatory frameworks is needed, in order for the incremental approach to be successful. However, a complete reworking of existing regulations is very rare, as noted by Davies (2006), who, more than a decade ago, argued that only the establishment of a separate, specific regulation on nanomaterials could be tailored to the unique properties of nanotechnology. More recently, representatives of the European Commission have also noted that NMs are difficult to regulate, due to lack of information, their complexity and a regulatory framework custom-made for chemicals rather than for manufactured materials (Laursen, 2014 cited in OECD 2016a).

Based on the analysis in Chapters 2-7, I see the implementation of a new regulatory framework for NMs as the only way in which to ensure the safe use of NMs for humans and for the environment, but so far, no one has been able to put forward a flexible and holistic option that is able to provide timely decision support before the risks of nanomaterials have materialised themselves. That is why I propose the adoption of a framework called Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW), key elements of which are presented below, while the workflow process is presented in Figure 27 (Hansen 2017).

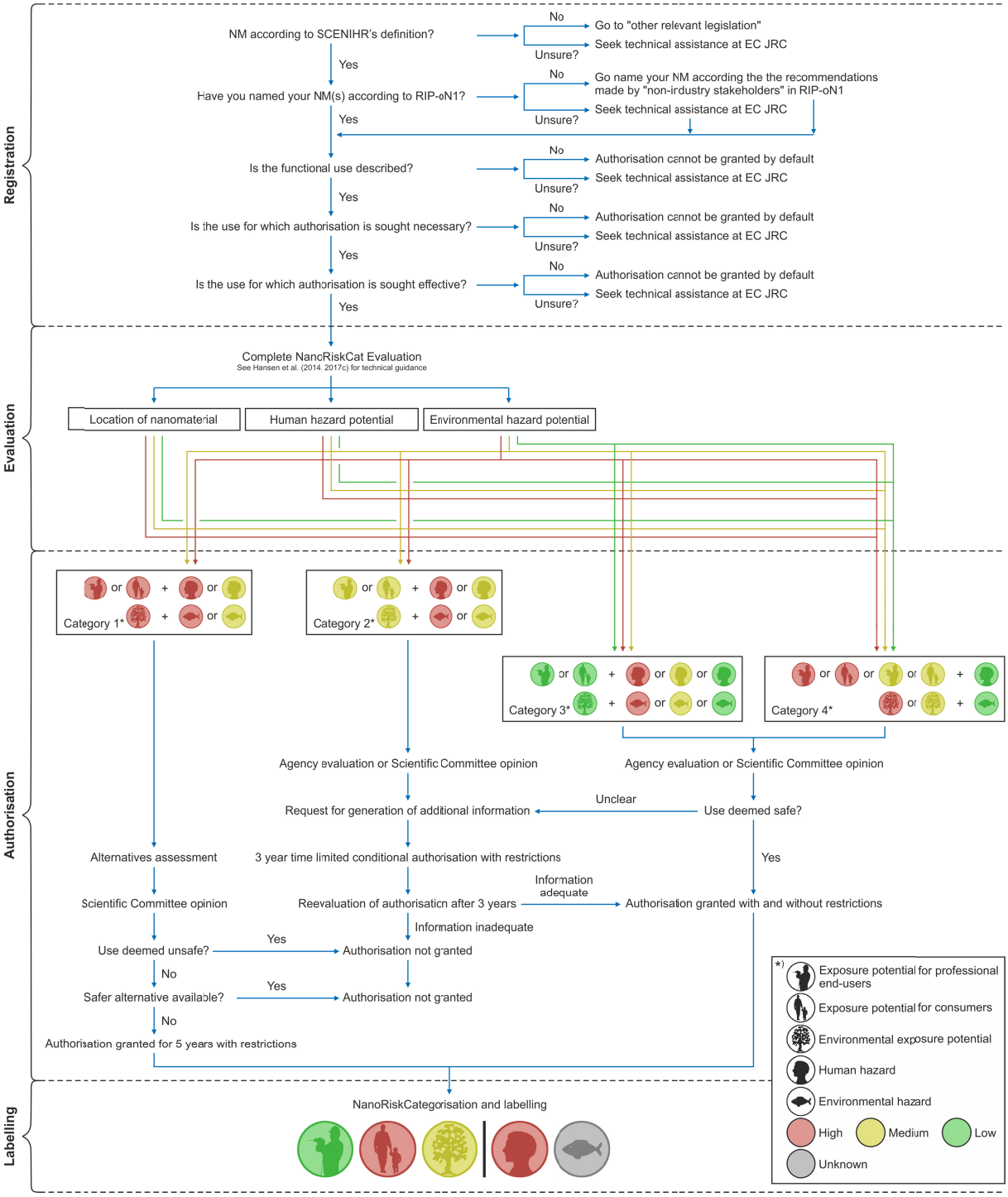


Figure 27: Overall registration, evaluation and authorization process related to information requirements and NanoRiskCat safety evaluation under REACT NOW (From Hansen 2017).

8.1 Scope and definition of NMs in REACT NOW

Similar to the "Nano-patch" proposal by CIEL, ClientEarth and BUND (2012), REACT NOW aims at regulating nanomaterials and shall apply to any use across existing regulations, e.g. food, chemicals, articles, cosmetics. Thus, the scope of REACT NOW is broader than REACH as it is not limited to the manufacturing and import of NMs or NMs in articles.

Under REACT NOW, NMs should be defined according to the proposal made by SCENIHR (2010) and not according to the European Commission's Recommendation 2011/696/EU (Hansen 2017). According to SCENIHR, a material is considered to be a nanomaterial when > 0.15% of the particle number size distribution is < 100 nm, or for dry materials when the volume-specific surface area is > 60 m^2/cm^3 (SCENIHR 2010). This is in contrast to the current situation, for example in the BPR and the proposals made by CIEL, ClientEarth and BUND (2012), Germany (Schwirn et al. 2014) and Sweden (KEMI 2013), as these adheres to the EC definition of a NM. The reason why SCENIHR's definition is preferred here is that there is a serious risk that some NMs will not be captured by the EC definition if a 50% threshold is applied as noted by the Committee on the Environment, Public Health and Food Safety (2014). Furthermore, the very high 50% threshold leaves too much room to manipulate the size distribution. Finally, the EC definition is simply too far away from what manufacturers, developers, scientists and society would normally have perceived as nanomaterials prior to 2011 (Hansen 2017).

8.2 Registration of nanomaterials in REACT NOW

8.2.1 Substance identification and naming of NMs

It is clear that from the EC's attempts to regulate NMs under REACH, their correct and unambiguous identification is essential, and so a distinction between the bulk and nanoforms of a given material need to be specified in REACT NOW (Hansen 2013, 2017). As suggested by member state, NGO and ECHA experts during the RIP-oN1 discussion, it is furthermore clear that nanomaterials cannot be identified solely by chemical composition. Additional main identifiers should be included when identifying and naming nanomaterials (European Commission Joint Research Centre 2011, Hansen 2013, 2017). In contrast to the German dossier-in-dossier proposal (Schröder 2012, UBA, BfR and BAuA 2013, Schwirn et al. 2014), particle size is seen as an "identifier" along with shape, specific surface area and surface treatments, as these are believed to identify a nanomaterial uniquely, influence the properties of the specific NM and govern the risk profile of NMs. In order to distinguish between two nanomaterials, supplementary information is required on:

a) The primary particle size distribution
b) Chemical composition of the functionalisation and/or coating(s), if any are followed by the suffixes "functionalised" and/or "coated"
c) Degree of purity of the core
d) The crystal form(s) of the core, if different forms exist
e) Number of walls and/or layers, if any
f) Chemical composition of the primary nanoparticle core
g) Shape, including the prefix "nano," e.g. nanotubes, nanorods, nanospheres).

It follows that NMs have to be named in REACT NOW with: a) the primary particle size distribution followed by b) the chemical composition of the functionalisation and/or coating(s) followed by <c) degree of purity of the core followed by d) the crystal form(s) of the core, if different forms exist followed by e) number of walls and/or layers, if any followed by f) chemical composition of the primary nanoparticle core followed by g) shape, including the prefix "nano". If one or more of the elements in the generic naming convention described above are not applicable, these should be left out of the name, for instance "25-28 nm ZnO-

coated 95% rutile TiO2 nanospheres." Similarly, for a functionalised and coated nanosubstance for which the primary size distribution varies and for which the shape is spherical, using this naming convention would result in the name "hydroxyl-functionalised AlZr-coated >92.5 % rutile TiO2 nanospheres."

8.2.2 Pre-market obligation to register in REACT NOW

Manufacturers and importers of NMs that fall under SCENIHR's definition of a NM are required to register, prior to their NMs being commercialised in Europe and independent of production volumes (Hansen 2013), as there is evidence from Germany that fewer than 10 kg/year are utilised in activities related to production, use and processing involving nanomaterials (BAuA 2008, CIEL, ClientEarth and BUND 2012). Registration, furthermore, is to be independent of the concentrations of a nanomaterial by weight, e.g. 0.1% w/w in the final product, as their usually low concentration could potentially exclude some nanomaterials from REACT NOW (Franco et al. 2007, Hansen and Baun 2012b). For NMs already on the market, manufacturers and importers should be required to register and fulfil the REACT NOW requirements within a certain time period e.g. six months (Hansen 2017). In REACT NOW, primary particle size distribution, shape (including aspect ratio), specific surface area and surface treatment are considered identifiers and not characterisers, as in the German proposal (UBA, BfR and BAuA 2013). In practice, this means that any variation in the size, shape, surface area and surface of a treated NM that is commercialised in the EU has to be registered separately and put into a separate registration dossier. Although it has been argued that this would lead to "the extreme splitting of similar materials into various substances on their own and that tonnage bands which trigger a registration obligation would not be reached as a consequence" (UBA, BfR and BAuA 2013), not all conceivable combinations of different substances are commercially relevant, and so making registration a prerequisite, independent of production volumes, means that registration obligations will be obligatory even for NMs produced in low volumes. Given the urgency of generating data on nanomaterials, registration fees must be reduced to encourage registration, as suggested by Hansen (2013).

8.2.3 Information requirements in REACT NOW

The information requirements in REACT NOW are related specifically to documenting the identity of the registered NM, its functional use, the specific reason for which authorisation is sought and, finally, to fill out a NanoRiskCat evaluation (see Table 15) (Hansen 2017). The latter includes requirements to provide: 1) accurate physicochemical characterisation, using multiple techniques and taking pros and cons into account, 2) a detailed description of the test material/sample and sample preparation and 3) considerations of the most appropriate/relevant metric following the presentation of several metrics (Hankin et al. 2011, Christensen et al. 2012). Additionally, the registrant has to provide a description of the analytical methods that allow the identification and quantification of the NM in the uses specified in the registration. If the data submitted by the registrant are not satisfactory, they are not allowed to market, import or use NM(s) for a certain time period e.g. 2 years, after which they may re-register the NM and its uses.

Table 15: Overview of information requirements in REACT NOW (From Hansen 2017).

Column 1: standard information required	Column 2: specific rules for adaptation from column 1
1. Registration and NM identity	
1.1 Primary size distribution	
1.2 Analytical methods used and their applicability in regard to primary size distribution	
1.3 Chemical composition of the primary nanoparticle core	
1.4 Analytical methods used and their applicability in regard to chemical composition	
1.5 Degree of purity of the core	
1.6 Analytical methods used and their applicability in regard to determining the degree of purity of the core	
1.7 Crystal form(s) of the core	
1.8 Analytical methods used and their applicability in regard to determining crystal form(s)	
1.9 Shape, including the prefix "nano," e.g. nanotubes, nanorods, nanospheres, and number of walls and/or layers, if any	
1.10 Analytical methods used and their applicability in regard to shape	
1.11 Surface chemistry	
1.12 Analytical methods used and their applicability in regard to surface chemistry	
2. Uses of NMs	
2.1 Relevant uses of NM	
2.2 Location of the NM for each use	
2.3 Mass concentration for each use	
3. Functional need and necessity	
3.1 Function of the NM for each specific use	
3.2 Necessity of the NM for each specific use	
4. Effectiveness	
4.1 Minimum mass concentration at which use is effective on each occasion 4.1.1 Justification for the selected concentrations for each use has to be provided and based on data and information in the form of laboratory studies, field test data, etc.	
4.2 Analytical methods used and their applicability in regard to measuring effectiveness for each use	
4.3 Method of application, if known, to influence effectiveness 4.3.1 Specification of NM concentration-effectiveness relationship	
4.4 Known limitations on effectiveness, e.g. specific environmental or other conditions or the presence of other substances for each use	

Table 15 continued: Overview of information requirements in REACT NOW (From Hansen 2017).

5. Human health	
5.1 HARN	5.1 The study does not need to be conducted if there is scientific evidence proving HARN
5.2 Bulk CLP	5.2 The study does not need to be conducted if: - NM is a HARN
5.3 Acutely toxicity	5.3 The study does not need to be conducted if: - NM is a HARN - NM has a bulk CLP classification
5.4 Genotoxicity and mutagenicity	5.4 The study does not need to be conducted if: - NM is a HARN - NM has a bulk CLP classification - NM is acutely toxic - There is scientific evidence proving that the - NM is genotoxic and mutagenic
5.5 Carcinogenicity	5.5 The study does not need to be conducted if: - NM is a HARN - NM has a bulk CLP classification - NM is acutely toxic - There is scientific evidence proving that the NM is carcinogenic
5.6 Respiratory toxicity	5.6 The study does not need to be conducted if: - NM is a HARN - NM has a bulk CLP classification - NM is acutely toxic - There is scientific evidence proving that the NM causes respiratory toxicity
5.7 Cardiovascular toxicity	5.7 The study does not need to be conducted if: - NM is a HARN - NM has a bulk CLP classification - NM is acutely toxic - There is scientific evidence proving that the NM causes cardiovascular toxicity
5.8 Neurotoxicity	5.8 The study does not need to be conducted if: - NM is a HARN - NM has a bulk CLP classification - NM is acutely toxic - There is scientific evidence proving that the NM causes neurotoxicity

Table 15 continued: Overview of information requirements in REACT NOW (From Hansen 2017).

5.9 Reproductive effects in humans and/or laboratory animals	5.9 The study does not need to be conducted if: - NM is a HARN - NM has a bulk CLP classification - NM is acutely toxic - There is scientific evidence proving reproductive effects in humans and/or laboratory animals
5.10 Organ-specific accumulation	5.10 The study does not need to be conducted if: - NM is a HARN - NM has a bulk CLP classification - NM is acutely toxic - There is scientific evidence proving accumulates in specific organs

6. Environment

6.1 Bulk CLP	
6.2 Aquatic toxicity 6.2.1 Short-term toxicity testing on invertebrates 6.2.2 Growth inhibition study aquatic plants (algae preferred)	6.2 The study does not need to be conducted if: - NM has a bulk CLP classification
6.3 Freshwater tests for degradation	6.3 The study does not need to be conducted if: - NM has a bulk CLP classification - NM has a LC50 < 100 mg/L
6.4 Bioaccumulation	6.4 The study does not need to be conducted if: - NM has a bulk CLP classification - NM has a LC50 < 100 mg/L - NM has a $T_{1/2}$ < 40 day
6.5 Scientific review in regard to: dispersive or long-range transport, ecosystem effects and novelty	6.5 The study does not need to be conducted if: - NM has a bulk CLP classification - NM has a LC50 < 100 mg/L - NM has a $T_{1/2}$ < 40 day - NM has a BMF > 0.1

In order to take into account that the test methods currently used were originally developed for soluble chemicals and might not be applicable to nanomaterials (Hansen et al. 2017a, b), a range of measures should be taken to ensure that the tests performed meet the information requirements are indeed tailor-made to investigate the (eco)toxicological effects of NMs.

Most importantly, nanomaterial dispersion stability should be measured using multiple characterization methods and the pros and cons of these methods should be clearly described. The dissolved fraction should furthermore be characterized over time and for various test concentrations, covering the setup for the aquatic toxicity test conducted (Hansen et al. 2017a). When it comes to algal growth inhibition tests, the impact of shading must be accounted for and, for bioaccumulation tests, trophic transfer has to be considered as both exterior bound and/or accumulated nanomaterials in prey organisms will be available for predator organisms with nanomaterials (Hansen et al. 2017a). These aspects regarding dispersion, dissolution, shading and bioaccumulation have been highlighted in the draft updates of the guidance that ECHA provides and hence, these can be used by the registrant in regard to living up to the REACT NOW requirements. However, a number of aspects have been pointed out by Hansen et al. (2017a) that should furthermore be taken into account. For nanomaterials, which dissolve substantially and are composed of elements known to be hazardous to the aquatic environment, a short-term 3h pulse exposure may be applied instead of the commonly used 48 h exposure. In regard to algae at least two endpoints should be determined: one being algal growth rate inhibition or carbon-assimilation and another being subtler effects to the individual algal cells, such as membrane damage and oxidative stress (Sørensen 2016).

In cases were NPs dissolve over time in media, one acute toxicity test should be conducted using a freshly prepared suspension of NPs in test medium, and one test should be conducted using an aged suspension where NPs are added to the media 1-3 days prior to testing, depending on the shelf life of the media (Sørensen and Baun 2015). This aging step may increase or decrease toxicity and the lowest EC50 value obtained should be used in REACT NOW.

Similarly, two tests are required on crustaceans for each endpoint as toxicity has been observed to be feeding dependent and the reporting on food abundance in all tests is required. One of the tests has to be with low food availability that follows the OECD TGs (for instance OECD guideline 211) and one with three times the amount applied in the low food abundance scenario (Mackevica et al. 2015). Finally, uptake and depuration of ENPs in test organisms has to be determined for each commercialized functionalization of the nanomaterials (Hansen et al. 2017a).

8.2.4 Is there a reasonable functional use and a technological need?

The third and fourth aspects to be addressed in REACT NOW are similar to the requirements that currently exist in EU food legislation (EP and the Council 2008a, Commission 2011) and relate to whether there is a reasonable functional use of the NM in the product and if the application of the NM and nanoproduct is useful and necessary (Hansen 2017).

For many applications of NMs, at least for consumer products, it is often unclear why NMs were used for other than commercial purposes (e.g. product branding). As noted by Hjorth et al. (2017b), it may be easiest in such cases simply to avoid using a given NM if it

serves no necessary function or is completely redundant. Hence, in order to obtain authorisation, the registrant has to describe the purpose of using NM(s) and the functional use of NM(s) in the applications for which they seek authorisation, as well as provide information necessary to verify that the proposed use does not mislead the consumer and that it has advantages and benefits for the consumer (EP and the Council 2008a). Functional use being defined as the why and how the NM is used (Tickner et al. 2015). Furthermore, verification has to be provided that there is a reasonable functional and technological need that cannot be achieved by other economically and technologically practicable means, such as in the case of EU regulation on food additives.

8.2.5 Is the use for which authorisation is sought usable and effective?

A fifth aspect to be addressed in REACT NOW is whether the application of the NM is to be considered usable and does what the producer claims, as well as whether the NM can be expected to be effective in the concentrations used and/or released during use (Hansen 2017). Usability is not only limited to the effectiveness, for instance, of biocidal active substances and products, but it also covers "the extent to which a product can be used by specified users to achieve specified goals with effectiveness" (ISO 1998). However, it is especially relevant for NM and biocidal products and biocidal applications, as it has been reported that minimum inhibitory concentrations of bacteria are magnitudes higher than the total NM released (Mackevica et al. 2016b).

Inspired by the requirement to document efficacy under the BPR, the effectiveness of NMs should be described and specified for each use and method of application, if the latter does indeed influence effectiveness (ECHA 2014). This includes specifying the concentration-effectiveness relationship of the NM and the possible existence of a threshold concentration for the desired effect. Furthermore, justification for the selected concentrations for each use has to be provided and based on data and information in the form of laboratory studies, field test data, etc. Moreover, the registrant must demonstrate that the NM is effective and suitable for its intended use when applied according to its instructions. The use concentration should ideally be the minimum effective concentration under real conditions for the respective service life, taking into account all relevant parameters that affect efficacy. Any known limitations on effectiveness should be specified, including possible factors that may reduce efficacy, for instance hot, cold or humid environments, or the presence of other substances, in addition to as an explanation as to the reasons for these limitations (ECHA 2014).

In order to enhance the quality and image of products based on nanotechnology, and to protect consumers' rights, the agency should set up a system for certifying nanoproducts, similar to the one currently implemented since 2004 by the Industrial Development Bureau, Ministry of Economic Affairs in Taiwan (Mackevica et al. 2016a). Authorisation should only be granted to uses of NMs that are considered good enough for a specified level after tests have to be completed by qualified and verified laboratories validating the claims made by manufacturers regarding the particle size and chemical constitution of the nanomaterials and their advertised efficacy (Hsu 2006). Hence, under the proposed regulatory framework REACT NOW, it is mandatory to disclose and report the use of NMs, and it is illegal to advertise and market products as "nano" when they do not contain nanomaterials. The

purpose of this strict regulation is to avoid confusion and protect the rights of consumers while also preventing "bad products from driving out good ones in a market glutted with nanoproducts of different quality" (Taiwan Nanotechnology Industry Development Association 2007, Industrial Development Bureau 2016).

8.3 Evaluation and safety evaluation in REACT NOW

A key component of REACT NOW is the safety evaluation used to lay the foundation for decisions about when authorisation should be given, and so it is suggested to employ NanoRiskCat to evaluate NMs and their uses (Hansen et al. 2014, 2017c, Hansen 2017).

As mentioned earlier, existing legislation relies heavily on chemical risk assessment, but this has repeatedly been found to have a number of limitations when it comes to nanomaterials despite a decade of EHS research into adapting chemical risk assessments. For instance, Syberg and Hansen (2016) have pointed out that chemical risk assessment has a series of limitations, such as the fact that hazard identification, hazard characterisation and exposure assessment are highly data- and resource-intensive, and overall, they seem inadequate for informing policymakers in a timely manner about the complex health and environmental risks of nanomaterials, if not in the short term then most definitely in the long term. It has furthermore been argued that chemical risk assessment has a tendency to pack a wealth of information into a single number, thereby ignoring any nuances and richness.

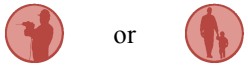
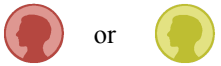
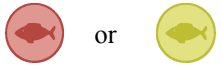
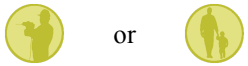
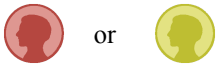
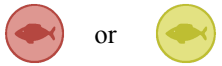
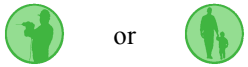
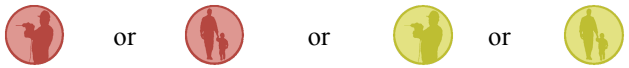
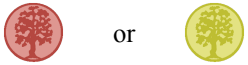
We do not know enough to say that nanomaterials are safe in quantitative terms, but there is evidence that some are certainly hazardous, depending on their particle characteristics, how they are applied and how humans and the environment are exposed to them. There is so much uncertainty about the hazards and exposure of NMs that any kind of quantitative risk characterisation and risk assessment does not make sense.

As under REACH, the burden is on industry and it is up to the registrant to provide information in REACT NOW and fill out a NanoRiskCat evaluation for their NM and its specific uses. For guidance on how to fill out a NanoRiskCat evaluation, see Hansen et al. (2014, 2017c) and The Nanodatabase (2017) for numerous examples of how this can be done. In REACT NOW, the registrants are asked to fill out and report the human hazard and environmental hazard profiles first and subsequently the exposure profiles of the specific uses for which they seek authorisation. The agency is subsequently required to evaluate critically their submitted information as well as the NanoRiskCat evaluation completed by the registrant. Specifically, the agency has to ensure that the data used to fill out the NanoRiskCat evaluation are specifically relevant to the NM subject to the registration. When evaluating the information submitted by the registrant, the agency should rely on the approach developed by Hartmann et al. (2016) rather than Klimisch et al. (1997).

8.4 Authorisation and Categorisation

The generated NanoRiskCat safety evaluation can be divided into four overall categories, each of which includes a human health category as well as an environmental category (see Table 16).

Table 16. Overall NanoRiskCat categories based on the NanoRiskCat evaluations

Category	Outcome of NanoRiskCat Exposure potential evaluation	Outcome of the NanoRiskCat hazard potential evaluation
1 Human		combined with 
1 Environment		combined with 
2 Human		combined with 
2 Environment		combined with 
3 Human		combined with 
3 Environment		combined with 
4 Human		combined with 
4 Environment		combined with 

Depending on the outcome of the NanoRiskCat evaluation, manufacturers and importers of NMs and producers of NM products might have to seek authorisation to market or use specific NMs in specific applications. In REACT NOW, authorisation can only be given for specific uses of NMs and nanoproducts that are deemed necessary and obtaining general authorisation to use a given NM for several unspecified applications is not possible. The same goes for uses of NMs and products that are deemed unnecessary, as suggested by Baun et al. (2009).

For uses of NMs that have a NanoRiskCat evaluation that falls into category 1 in Table 16, meaning that they have a red professional end-user and/or consumer exposure profile combined with a red human health hazard profile, the registrant should be required to complete an Alternatives Assessment and the agency shall be required in REACT NOW to seek opinion on safe use from the European scientific committee of relevance, i.e. EFSA when it comes to food applications, SCCS when it comes to cosmetics and SCENIHR for all other applications. Similarly, for uses of NMs that have a red environmental exposure profile combined with a red environmental hazard profile, an Alternatives Assessment should be completed, and the agency should ask the Scientific Committee of Health and Environmental Risks (SCHER) for an opinion about safe use (Hansen 2017).

It is important to underline that although the use of a given NM or a nanoproduct might be assigned an unfortunate combination of red hazard and exposure profiles, it does not imply that there is necessarily a risk of using the given product, as the actual concentrations used in it might be too low to cause adverse effects when used (Hansen et al. 2014, 2017c).

As under the Novel Food regulation and the European regulation on cosmetic products, scientific committees should give their opinion within six months on the safety of a nanomaterial for specified uses upon receiving a request from the agency. In their opinion, and in their evaluation of the information submitted by the registrant as well as the Alternatives Assessment, aspects such as necessity of applied uses, the use of personal protection equipment for professional end-users, the possibility of skin penetration for consumer applications and actual NM concentration in the final product could be taken into consideration. Furthermore, as in the regulation concerning novel foods and novel food ingredients, possible effects on vulnerable groups of the population should be taken into consideration, by verifying that the most up-to-date test methods have been used to assess safety and highlighting uncertainties and limitations, where relevant.

It is possible that products that have an all-red colour profile according to the NanoRiskCat, e.g. in the use of TiO2 in sunscreens, will be deemed safe to use by the scientific committees. In such cases, authorisation should be granted, but only if the specific use under consideration is deemed necessary. Here, it is furthermore important to note that especially the hazard evaluations in NanoRiskCat should be re-evaluated continuously in light of the published scientific literature as well as independent scientific expert evaluations (Hansen et al. 2014, 2017c).

NM uses deemed not to be safe by the scientific committees, e.g. dispersive uses of HARN, indoor consumer uses of spray products with NMs associated with respiratory toxicity, should not be granted authorisation and should not be given permission to be marketed in Europe. The same goes for NMs and their uses that have one or more grey

exposure or hazard profiles in the NanoRiskCat evaluation, as this means that the registrant has not fulfilled the REACT NOW information requirements (Hansen 2017).

For all other combinations of exposure and hazard profiles, i.e. NanoRiskCat categories 2-4, the agency can ask for an opinion from the scientific committees of relevance on a case-by-case basis. As a general rule, authorisation should only be given for specific professional end-user and consumer applications, if they have a green human health hazard profile combined with a green professional end-user exposure profile and consumer exposure profile, respectively. The same goes for uses that are expected to lead to environmental exposure – that they should only be granted authorisation if the NM in question has a green environmental hazard profile. Should the agency or the scientific committees have questions about the safety of the NM and its specific use, they can request additional information, which must be generated within 3 years, during which time conditional authorisation may be granted (Hansen 2017).

For combinations of yellow exposure and hazard profiles, e.g. a yellow consumer exposure profile combined with a yellow human hazard potential or a yellow environmental exposure profile combined with a yellow environmental hazard profile, conditional authorisation is possible for a time-limited period, such as for 3 years, during which time the agency should ask the registrant to generate additional information (Hansen 2017).

Overall, this means that a NM and a nanoproduct can be granted authorisation for specific professional end-user applications but not be granted authorisation when it comes to consumer uses. Similarly, a product would be granted authorisation under the condition that there is no environmental exposure throughout the life cycle of the product and this has been and can be documented (Hansen 2017).

8.5 Alternatives Assessment

REACH requires an Alternatives Assessment for substances of very high concern for which registrants seek authorisation (ECHA 2011). Broadly speaking, the use of Alternatives Assessments may help guide decisions when one potentially more toxic material or substance may be substituted by a less toxic alternative (Baun et al. 2009). According to Geiser et al. (2015), a "chemical Alternatives Assessment is a process for identifying, comparing and selecting safer alternatives to chemicals of concern (including those in materials, processes, or technologies) on the basis of their hazards, performance, and economic viability". The blueprint for a Alternatives Assessment can be structured around three overall steps: 1) scope, 2) assessment and 3) selection and implementation, according to Geiser et al. (2015), whereas Jacobs et al. (2016) work with six standard AA components: 1) hazard assessment, 2) exposure characterisation, 3) life cycle impact considerations, 4) technical feasibility, 5) economic feasibility assessment and 6) decision-making (i.e. how trade-offs among alternatives are evaluated and resolved) (Geiser et al. 2015, Jacobs et al. 2016, Malloy et al. 2016).

In REACT NOW, an Alternatives Assessment is required for uses of NMs that have 1) a red professional end-user and/or a consumer exposure profile combined with a red human health hazard profile and/or 2) a red environmental exposure profile combined with a red environmental hazard profile (Hansen 2017). This means that registrants have to identify candidate alternatives that will achieve the same purpose or function served by the chemical

of concern for a given application, evaluate and compare alternatives and the NM of concern based on a range of human and environmental health endpoints at critical life cycle points (e.g. manufacturing, use, disposal), and evaluate and compare technical and economic feasibility characteristics (OECD 2013, NRC 2014, Jacobs et al. 2016, Hjorth et al. 2017b). More than a dozen Alternatives Assessment frameworks have been published over the last decade by academic institutions and by non-governmental and governmental organisations, and in REACT NOW, the registrants have to follow the National Academy of Sciences' framework for Alternatives Assessment (NRC 2014) (see Figure 28), in which the focus should be on e.g. functional substitution, and not just on NM substitution (Tickner et al. 2015, Hjorth et al. 2017b). In a study by Hjorth et al. (2017b), the overall applicability of Alternatives Assessment for nanomaterials was tested when it comes to manufacturing processes and products, and it was concluded that Alternatives Assessment is appropriate for nanomaterials, though some adaptations are required (Hjorth et al. 2017b). Specifically, it was recommended 1) that the hazard comparison should be based primarily on results of actual toxicity tests (including high-throughput testing) rather than on hazard extrapolations from inherent physicochemical properties, 2) that the intrinsic exposure potential is considered as part of the comparative assessment process because there are distinct physicochemical properties as well as use characteristics that will distinguish which alternative (nano or bulk chemical) is fundamentally safer and, finally, 3) that the normal hazard assessment module might fail to differentiate between different alternatives incorporating nanomaterials, because it may not account adequately for the differences in toxicity among similar materials with slightly different properties (Hjorth et al. 2017b). In their Alternatives Assessment, registrants will have to document how they consider these and related aspects.

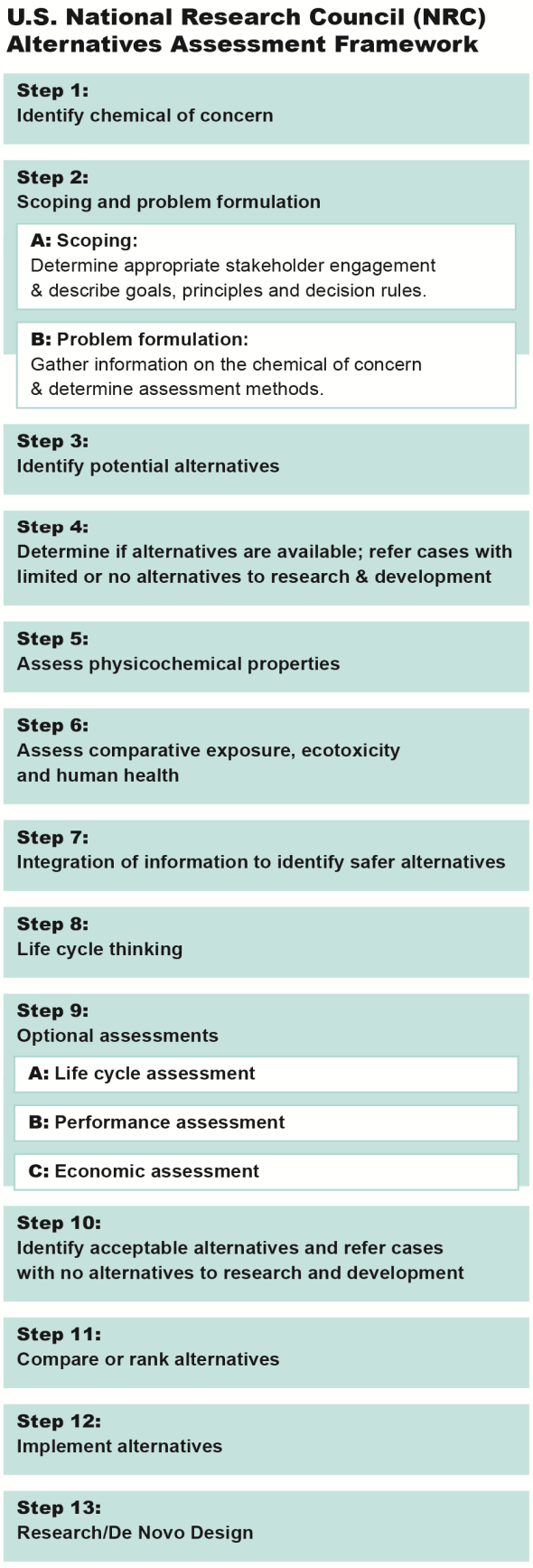


Figure 28: US NRC Alternatives Assessment framework (From Hjorth et al. 2017b)

8.6 Restriction of NMs and the use of NMs in products in REACT NOW

Under certain specific circumstances, NMs and their uses which fall under categories 1-4, can be granted authorisation with restrictions (Hansen 2017). This could, for instance, be focused on restricting dispersive uses of nanomaterials for those which fulfil the criteria for authorisation and for which dispersive uses that cannot be ruled out throughout the life cycle of the nanomaterials exist. When it comes to restriction, all options are available to decision-makers; for example, they can request the use of various engineering controls, impose restrictions/authorisations and introduce product-specific category restrictions (OECD 2016a).

8.7 Adequate labelling using the outcome of the NanoRiskCat evaluation

For chemicals, classification and labelling have to be performed for all substances registered in REACH, and the same goes for NMs in REACT NOW (Hansen 2017). Using the methodology outlined in Hansen et al. (2014, 2017c), the outcome of the NanoRiskCat evaluation in the form of the use sentence and the five coloured bullets should be used as a label (Hansen 2017). As in the case of cosmetics and the BPR, the label should be clearly visible and visibly indicated on all commercialised products, either on the product itself or in the list of ingredients with the name of the material followed by the word "nano" in brackets (e.g. TiO2 [nano], silver [nano]). The HH- and EE- sentences should be included beneath the label, just as the H sentence is for chemicals under the CLP (ECHA 2016e).

In order to ensure that specific labelling requirements do not mislead the consumer (EU food legislation), claims about the tag "nano" should only be allowed if certified by an independent entity such as the European Commission Joint Research Centre.

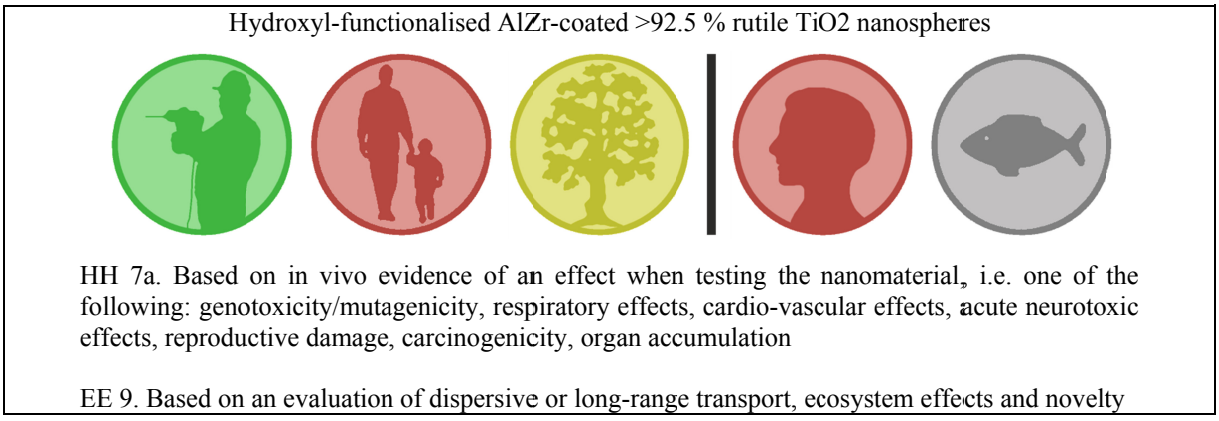


Figure 29: Hypothetical example of a nanoproduct label under REACT NOW

8.8 Administrative responsibility and technical assistance to be provided in REACT NOW

To ensure the proper implementation of REACT NOW and consistency in its daily operations, as well as those of the BPR, REACH and the CLP, responsibility for the daily operations of REACT NOW should fall under ECHA, just as REACH, BPR and the CLP currently do (Hansen 2017). Non-technical support should be provided through the publishing of various newsletters, agency guidance documents on determining various nanomaterial characteristics, (eco)toxicological testing and monitoring, the establishment of a website for stakeholders to exchange information and firm-to-firm dialogue and, finally, the

establishment of a publically available and searchable NM and NM product database (Hansen 2010, Hansen and Baun 2012b). The NM database should include information provided as part of the registration and could be structured similar to the Nanowerk Nanomaterial Database (Nanowerk 2016), though it should also include the NanoRiskCat human health and environmental hazard profile of the NM and the HH and EE sentences. In regard to the NM product database, the agency could find inspiration in how The Nanodatabase is structured and run.

Technical expertise is required in a lot of places in REACT NOW, especially when it comes to fulfilling information requirements. In order to assist registrants and especially SMEs in regard to gathering and/or generating the data and information they need in order to fulfil the information requirements technical assistance should be provided as part of REACT NOW (Hansen 2013, 2017). Given the nature of such a task, this requirement could fall under the jurisdiction of an entity such as the European Commission Joint Research Centre. Specifically, this entity would be responsible for providing confidential technical assistance on aspects related to the registration of NMs, such as whether a given NM falls under the SCENIHR definition used in REACT NOW, how to describe functional use, how to document technical needs and, finally, how to complete tests dismissing or validating the claims made by manufacturers regarding the particle size, advertised efficacy and chemical constitution of the nanomaterials in their products (Hansen 2010, 2013, 2017, Mackevica et al. 2016a). The current Nano Mark System, implemented by the Industrial Development Bureau, Ministry of Economic Affairs in Taiwan in 2004 for certifying nanoproducts, could be used as an inspiration for certification activities for which such an entity would be responsible under REACT NOW, whereas the Massachusetts Toxics Use Reduction Institute (TURI) could be a model for how to provide research, education, technical guidance and support to small and medium-sized companies (Hansen and Rejeski 2008, Mackevica et al. 2016a).

8.9 Opportunities and weaknesses of REACT NOW

Although REACT NOW provides a number of opportunities there are weaknesses that are important to be aware of. Very often, these are not clear-cut opportunities or weaknesses, but rather issues of a dual nature in the sense that they can be perceived as opportunities or strengths from one perspective or under one set of circumstances and as weaknesses from another perspective or under another set of circumstances.

One of first notable strengths of REACT NOW is that its scope covers production and all applications of NMs and that it is not limited to the manufacturing and import of NMs or in articles. This creates the opportunity to have one single regulatory framework for all uses on NMs and thus to ensure consistency across different pieces of EU legislation.

SCENIHR's definition of NMs is preferred in REACT NOW as there is a serious risk that some nanomaterials and uses of nanomaterials will not be captured by the EC definition if a 50% threshold is applied as noted by the Committee on the Environment, Public Health and Food Safety (2014). The SCENIHR definition, however, has several of the same limitations as the EC definition when it comes to operationalization, e.g. lack of validated standard methods to determine size and size distribution. These limitations can still not be avoided in REACT NOW – however technical and non-technical support is provided in

REACT NOW in order to assist especially SMEs in determining whether their materials are a nanomaterial or not. Similarly, having no volume registration threshold ensures that REACT NOW err on the side of caution as more materials that will be defined as nanomaterials, in comparison to the EC definition, and would subsequently have to go through the registration and safety evaluation process.

Another prominent strength of REACT NOW is the unambiguous identification and naming of NMs and the fact that any variation in size, shape, surface area and surface of a treated NM that is commercialised in the EU has to be registered separately and put into a separate registration dossier. This will eliminate current confusion about whether nanomaterials should be considered different from their bulk counterpart, and the possibility of tonnage bands, which trigger a registration obligation, would not be reached. This provides regulatory clarity.

The fact that any variation in the size, shape, surface area and surface of a treated NM that is commercialised in the EU has to be registered separately in REACT NOW could lead to what has been called "the extreme splitting of similar materials into various substances on their own" (UBA, BfR and BAuA 2013). Whether this is a weakness of REACT NOW what will eventually materialize itself is not quite clear as not all conceivable combinations of different nanomaterials and surface treatments are or should be commercially relevant in the first place. REACT NOW requirements to provide justification of necessity, functional need and effectiveness should also ensure that not all conceivable combinations of different nanomaterials will be registered.

It is unclear at the moment, how the current information and testing requirements are to be applied to risk assess nanomaterials in many pieces of EU legislation e.g. REACH and the BPR. It is furthermore unclear how the information and data submitted by the registrant will eventually be evaluated and used by regulators. In REACT NOW, the information requirements are related specifically to documenting the identity of the registered NM, its functional use, the specific reason for which authorisation is sought and, finally, to filling out a NanoRiskCat evaluation. This reduces uncertainty about why the information requirements have to be fulfilled, which tests have to be completed and how the information and data provided by the registrant will eventually be evaluated and used. The information requirements are furthermore tiered in such a manner that no more information has to be generated once the human health and/or environmental hazard potential have been established.

It is moreover, clear how the NanoRiskCat safety evaluation provides the foundation for evaluating when and under which conditions authorization can or is to be given or not given. Logical and easy to comprehend labelling requirements and guidance are provided.

When it comes to the evaluation aspect of REACT NOW, a clear tool for completing the safety evaluation of NM and its specific uses is provided in the form of NanoRiskCat, which again has been applied on more than 2,000 products. As mentioned in 7.3, NanoRiskCat has both some opportunities and some weaknesses that may transcend into REACT NOW. For instance, the exposure assessment in NanoRiskCat is arguably quite crude and does not consider the concentration of nanomaterials in the product nor how much of the materials, users are actually exposed to. Many of the nanomaterials subjected to the NanoRiskCat evaluation in The Nanodatabase have received a red human health and/or

environmental hazard profile, which could indicate that the approach suggested in NanoRiskCat is overly precautionary, which again would influence the authorisation process in REACT NOW. Here it is, first of all, important to note that the reasons for why the different nanomaterials receive a red colour code vary, and hence that there is not one single determinant that makes all materials go "red." (Hansen et al. 2014, 2017c). Secondly, the fact that a given nanomaterial has gotten a red human health and/or environmental hazard profile does not necessarily mean that the use of the nanomaterial will eventually be restricted. It simply means that the registrant has to complete an Alternatives Assessment and that the information provided by the registrant is to be subject to an expert evaluation by the Scientific Committees. Thirdly, even if REACT NOW is precautionary, there is evidence that precautionary environmental health regulation does not hamper innovation (EEA 2013, Hansen and Tickner 2013, Hansen and Gee 2014).

In REACT NOW, details are provided on how to complete the information requirements using tests that are tailored to investigate the ecotoxicological effects of NMs, however such detailed guidance still might have to be further developed in regard to human health. For nanomaterials that are not HARN, CLP classified or acute toxic, NanoRiskCat furthermore requires a holistic assessment of carcinogenic, respiratory, cardiovascular, reproductive effects, etc. in humans and/or laboratory animals. But limited guidance is provided in regard to how to complete this holistic assessment in Hansen et al. (2014, 2017c).

Having to explain the functional uses and providing justification for the technological need that cannot be achieved by other economically and technologically practicable means is not something that producers, importers and downstream-users are used to in regard to the regulation of chemicals and technological development (Hansen and Gee 2014). It is, however, a well-established practice in EU food legislation though guidance on how to provide this justification is limited in the technical guidance provided by EFSA, and there seems to be a need to further develop such guidance.

Registrants of active substances have a lot of experience with evaluation and providing documentation of the effectiveness under the BPR, which again will go a long way in regard to addressing the REACT NOW requirements to establish whether the application of the NM is to be considered usable, fulfils what the producer claims, and whether the NM can be expected to be effective in the concentrations used and/or released during use.

As said, Alternatives Assessment plays a prominent role in the authorization process of REACT NOW, however also Alternatives Assessment still has some elements that need to be developed further when it comes to nanomaterials. For instance, which intrinsic hazard properties to take into consideration and how to combine hazard evaluation with intrinsic exposure consideration (Hjorth et al. 2017b). Guidance of how to complete Alternatives Assessments for various uses of nanomaterials should be prepared

Authorisation should only be granted to uses of NMs that are considered to fulfil a specified level, after tests have been completed by qualified and verified laboratories validating the claims made by manufacturers regarding the particle size, structure, shape and chemical constitution of the nanomaterials and their advertised efficacy. However, what this "specified level" is supposed to be and how it can be determined will have to be a future challenge for the risk assessment research.

9. Conclusion and recommendations

This doctoral thesis summarises the research that I have been involved in since 2009 with regard to the regulation and risk assessment of nanomaterials, specifically in relation to: 1) mapping current uses of nanomaterials in Europe, 2) understanding the limitations of existing legislation and 3) addressing the restraints of risk assessment and alternatives when it comes to nanomaterials. The outcome of this research has led me to conclude that the fact that nanomaterials are covered by the scope of existing legislation will not be enough to ensure the protection of human health and the environment and that we need a new regulatory framework tailored for NMs and their applications.

The research regarding current uses of NMs clearly shows not only that the diversity of applications is immense, but also that we lack information and lack of access to information about key pieces of data such as production volumes, the identity of the NMs in various consumer products and concentrations used. It is furthermore clear that release from consumer products is to be expected and that environmental exposure will occur, although we do not understand the properties that govern the environmental fate and behaviour of NMs. Overall, this hampers our ability to complete any kind of meaningful risk assessment when it comes to NMs.

Despite recent revisions, carried out in order to take the specific properties of nanomaterials into account, many pieces of existing regulatory frameworks hold a vast amount of weaknesses such as, for instance, unclear definitions of key terminology when it comes to nanomaterials, threshold values and information requirements not tailored to the nanoscale, lack of metrological and characterisation tools and (eco)toxicological methods and data, as well as lack of occupational and environmental exposure limits.

Initiatives that looked promising in the past included developing working definitions of nanomaterials, collecting existing data and product information, addressing data gaps in the field of (eco)toxicology, establishing best practices in regard to worker, health and safety protection and initiating public discussion about nanotechnology (Hansen 2010). However, the prospects of these initiatives have faded over the course of the past half-decade, as we seem to have become distracted along the way – attributable in part to bureaucratic inertia and in part to influential views that research jeopardises innovation and that regulation is bad for business (Hansen et al. 2008b, Hansen et al. 2013b). For instance, we have several NM definitions that have been hard to operationalise, and we still do not have an overview of what is produced, what is used, how much it is used and why it is used in the EU. Additionally, we still lack a fundamental understanding of how nanomaterials interact with living systems and how to assess the relevant end-points for nanomaterial toxicity, and we still have a paucity of usable data on the environmental hazards of nanomaterials. Moreover, we still lack test methods that would enable the safety assessment of numerous novel nanomaterials, and the public is not better informed or more engaged in the discussion about the benefits and risks of nanomaterials, and how they should be regulated than they were a decade ago.

Many of the initiatives that have been taken are focused on collecting data but without making it mandatory for manufacturers and importers to provide this information and without making it clear how these data will eventually lead to the completion of risk assessments and how the limitations of risk assessment are to be overcome. It is furthermore unclear how the results of a risk assessment will lead to transparent risk management measures and how these

will be implemented and evaluated (Hansen 2010).

Overall, it seems that governments and decision-makers in the EU are currently relying too heavily on nanomaterials falling under the scope of various pieces of existing legislation, e.g. REACH, which again are crumbled by our inability to: 1) develop an operational NM definition, 2) accept that NM properties are fundamentally different compared to bulk materials and should be considered identifiers and not characterisers and 3) complete a meaningful chemical risk assessment of nanomaterials (Hansen 2010, Syberg and Hansen 2016). Additionally, as noted by representatives of the European Commission at a 2014 OECD Expert Meeting on Categorisation of Manufactured Nanomaterials, the lack of specific risk management tools for assessing NMs means that case-by-case assessment is needed. Case-by-case assessment, on the other hand, is becoming increasingly difficult, due to the sheer quantity of current nanomaterials and new ones constantly being created. NMs are furthermore also difficult to regulate, due to a lack of information, their complexity and a regulatory framework tailored to chemicals rather than manufactured materials (Laursen, 2014 cited in OECD 2016a).

One of the key limitations identified relates to our lack of ability to complete meaningful risk assessments of NMs at this point in time. Several alternatives have been proposed, and based on an analysis of 50 of these as well as several reviews, I conclude that although there are several tools available that can be applied throughout the life cycle of a NM, each of them has a distinct weakness, especially in regard to regulatory relevance. Overall, these tools seem to be less prone in the final risk evaluation to the vulnerability of one or more of the preceding steps regarding hazard identification, hazard characterisation and exposure assessment. Only NanoRiskCat, developed by Hansen et al. (2014), was found to entail key elements that have subsequently been used in this thesis to develop a regulatory framework tailored to NMs. NanoRiskCat seems to be the only safety evaluation tool that has been designed to support regulatory decision-making and which is REACH- and CLP-oriented – and it has already been applied on products including NMs.

Given the cross-cutting nature of nanotechnology and nanomaterials, as well as the current pace of development, the challenges and limitations identified in the analysis of the revisions that have been implemented for existing legislation when it comes to NMs and an analysis of the proposed revisions, I conclude that it would be more effective to implement a new, authoritative and prescriptive regulatory framework tailored specifically to nanomaterials.

I therefore propose the adoption of a framework called Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW). Key elements of REAT NOW are presented in this thesis including when nanomaterials have to be registered, information requirements, how authorities are to evaluate submitted information, when authorisation to produce and use NMs should be granted/denied based on an overall assessment of the functional use, the necessity of NM use for which authorisation is sought, the effectiveness of the NM use and, finally, a NanoRiskCat evaluation and an Alternatives Assessment.

It may seem premature to implement a proposal like REACT NOW that is fundamentally different, taking into consideration that it ends up with semi-qualitative conclusions and no quantitative estimations about risks. I would, however, argue that we have

many of the pieces needed in order to set up a whole new legislation framework for NMs. REACT NOW puts them together and provides a flexible and holistic framework that is able to provide timely decision support before the risks of nanomaterials have materialised. In addition, REACT NOW is inspired by existing amended regulations as well as proposed new legislative revisions by EU member states and NGOs, and it further introduces key missing elements developed over the past seven years at DTU Environment e.g. NanoRiskCat for NMs and Alternatives Assessment.

We do not have all the answers to the scientific questions currently in circulation and which are relevant to raise, but we do know enough to start asking producers and importers to provide EHS information about the nanoform that they produce and/or use in their products. With REACT NOW we can provide them with some guidance on how to submit this information and which methods to use, how they should go about explaining the opportunities and weaknesses of their methods, and how they have used a multifaceted approach. We also know how to evaluate the applicability of the submitted information, and we have clear ideas about how the information itself and its quality can be assessed and evaluated and subsequently can provide the basis of an authorisation procedure.

That is why I urge regulators to initiate REACT NOW, before it is too late. We are entering a phase in the development of nanotechnology where the early hype about the benefits of this mind-blowing technology is over. Initially, concerns raised about the adverse impact of nanomaterials have been very loud, but they are slowly quietening down and we can now expect 15-20 years of univocal EHS research that will not provide definitive answers (see Lawless et al. 1977, EEA 2001, 2013).

That is why it is urgent now to react and to implement REACT NOW, to ensure public health and to protect the environment from the potential risks of nanomaterials.

10. List of references

1. Aitken, R.A, Bassan, A., Friedrichs, S., Hankin, S.M., Hansen, S.F., Holmqvist, J., Peters, S.A.K., Poland, C.A., Tran, C.L. 2011. Specific Advice on Exposure Assessment and Hazard/Risk Characterisation for Nanomaterials under REACH (RIP-oN 3) Final Project Report. Document reference RNC/RIP-oN3/FPR/1/FINALBrussels: European Commission. Available: http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon3.pdf

2. Anastas, P., Davis, M. 2010. August 2010 BOSC nanomaterial case studies workshop review letter report. US Environmental Protection Agency Office of Research and Development, Board of Scientific Counselors (BOSC).

3. ANEC/BEUC. 2015. List of Nanotech. http://www.beuc.eu/publications/2013-00141-01-e.xls (Accessed 13-08-2015).

4. ANSES 2010. Development of a specific control banding tool for nanomaterials. Maisons-Alfort: French Agency for Food, Environmental and Occupational Health Safety (ANSES).

5. Arts, J.H.E., Hadi, M., Keene, A.M., Kreiling, R., Lyon, D., Maier, M., Michel, K., Petry, T., Sauer, U.G., Warheit, D., Wiench, K., Landsiedel, R., 2014. A critical appraisal of existing concepts for the grouping of nanomaterials. Regulatory Toxicology & Pharmcology 70: 492–506.

6. Arvidsson, R., Furberg, A., Molander, S. 2016. Review of screening risk assessment methods for nanomaterials. Report no. 2016:12. Gothenburg: Department of Energy and Environment Division of Environmental System Analysis Chalmers University of Technology.

7. Aschberger, K., Rauscher H., Crutzen, H., Rasmussen, K., Christensen, F.M., Sokull-Klüttgen, B., Stamm, H. 2014. Considerations on information needs for nanomaterials in consumer products. European Commission Joint Research Centre Institute for Health and Consumer Protection.

8. Azoulay, D. 2012. Just Out of REACH. Center for International Environmental Law. Available: http://www.ciel.org/Publications/Nano_Reach_Study_Feb2012.pdf (Accessed 22-08-2016).

9. BAuA. 2008. Exposure to nanomaterials in Germany, Results of the corporate survey of the Federal Institute for Health and Safety (BAuA) and the association of the chemicals industry (VCI) using questionnaires. Federal Institute for Health and Safety (BAuA).

10. Baun, A., Hansen, S.F. 2008. Environmental challenges for nanomedicine. Nanomedicine 2(5): 605-608.

11. Baun, A., Hartmann, N.B., Grieger, K.D., Hansen, S.F. 2009. Setting the Limits for Engineered Nanoparticles in European Surface Waters. Journal of Environmental Monitoring 11: 1774-1781.

12. Bergeson, L.L., Hutton, C.N. 2016. EC Denies 2014 Petition Seeking EU-Wide Ban on Nanoparticles. Available: http://nanotech.lawbc.com/2016/07/ec-denies-2014-petition-seeking-eu-wide-ban-on-nanoparticles/ (Accessed 12-12-2016).

13. Biocidal Products Committee 2014. Opinion on a request according to Article 75(1)(g) of Regulation (EU) No 528/2012 HeiQ AGS-20 ECHA/BPC/ 001/ 2014. Available: http://echa.europa.eu/documents/10162/21680461/bpc_opinion_heiq_ags-20_en.pdf (Accessed 02-12-2016).

14. BIPRO and RPA 2014. Study to Assess the Impact of Possible Legislation to Increase Transparency on Nanomaterials on the Market. Brussels: DG Enterprise and Industry, European Commission.

15. Boholm, M., Arvidsson, R. 2016. A Definition Framework for the Terms Nanomaterial and Nanoparticle Nanoethics 10:25-40.

16. Boldrin, A., Hansen, S.F., Baun, A., Hartmann, N., Astrup, T.F. 2014. Environmental exposure assessment framework for nanoparticles in solid waste. Journal of Nanoparticle Research 16:2394 DOI 10.1007/s11051-014-2394-2.

17. Bolyard, S.C., Reinhart, D.R., Santra, S., 2013. Behavior of engineered nanoparticles in landfill leachate. Environmental Science & Technology 47(15):8114-8122.

18. Bondarenko, O., Juganson, K., Ivask, A., Kasemets, K., Mortimer, M., Kahru, A., 2013. Toxicity of Ag, CuO and ZnO nanoparticles to selected environmentally relevant test organisms and mammalian cells in vitro: a critical review. Archives of Toxicology 87:1181–1200.

19. Bouillard, J., Vignes, A. 2014. Nano-Evaluris: an inhalation and explosion risk evaluation method for nanoparticle use. Part I: description of the methodology. Journal of Nanoparticle Research 16(2): 1-29.

20. Bowman, D.M., Calster, G.v., Friedrichs, S. 2009. Nanomaterials and regulation of cosmetics. Nautre Nanotechnology 5:92

21. Brinch, A., Hansen, S.F., Hartmann, N.B., Baun, A. 2016. EU Regulation of Nanobiocides: Challenges in Implementing the Biocidal Product Regulation (BPR). Nanomaterials 6:33. DOI:10.3390/nano6020033.

22. Broomfield, M., Hansen, S.F., Pelsy, F. 2016 Support for 3rd regulatory review on nanomaterials – environmental legislation. Brussels: European Commission DG Environment.

23. Brouwer, D.H. 2012. Control banding approaches for nanomaterials. Annals of Occupational Hygiene 56(5):506-514.

24. BSI 2007. Guidance on the Labelling of Manufactured Nanoparticles and Products Containing Manufactured Nanoparticles. PAS 130:2007. London: British Standards Institution.

25. BUND 2010. BUND veröffentlicht Datenbank mit über 200 Nano-Produkten. Available: http://www.bund.net/nc/presse/pressemitteilungen/detail/zurueck/pressemitteilungen/artikel/bund-veroeffentlicht-datenbank-mit-ueber-200-nano-produkten/ (Accessed: 30-10-2015).

26. BUND 2015. Nanoproduktdatenbank. Available: http://www.bund.net/nc/themen_und_projekte/nanotechnologie/nanoproduktdatenbank/produktsuche/ (Accessed 13-08-2015).

27. Buxton, L. 2016. Switzerland plans reform of nano regulation Revision to include specific registration requirement for nanomaterials. Chemical Watch 12 August, 2016. Available: https://chemicalwatch.com/48982/switzerland-plans-reform-of-nano-regulation#utm_campaign=48930&utm_medium=email&utm_source=alert (Accessed 12-12-2016).

28. Bühler Partec. 2010: Media releases: Bühler Partec's risk management system certified. Available: http://www.buhlergroup.com/global/en/about-buhler/media/media-releases/ details-buehler-partecs-risk-managementsystem-certified.htm?title=B%C3%BChler +Partec%C2%B4 s+risk+management+system+certifie (Accessed 03-11-2010).

29. Canis, L., Seager, T., Linkov, I. 2010. Application of stochastic multiattribute analysis to assessment of single walled carbon nanotube synthesis processes. Environmental Science & Technology 44(22):8704–8711.

30. CCA. 2008. Small Is Different: A Science Perspective On The Regulatory Challenges of the Nanoscale. Ottawa: The Council of Canadian Academies.

31. Chaudhry, Q., Blackburn, J., Floyd, P., George, C., Nwaogu, T., Boxall, A., Aitken, R. 2006. A Scoping Study to Identify Gaps in Environmental Regulation for the Products and Applications of Nanotechnologies. London: Department for Environment, Food and Rural Affairs.

32. Chemical Watch 2011. Nanosilver producers refute German institute's warning. Global Business Briefing May 2011 Chemical Watch.

33. Chemical Watch 2012. Which way now for nanomaterials and REACH? Global Business Briefing July/August 2012 Chemical Watch.

34. Chemical Watch 2014a. Belgium to implement nanomaterials register in 2016. Chemical Watch 12 February 2014.

35. Chemical Watch 2014b. Dancet asks EU Commission to speed up nano work pleads for resource flexibility. Chemical Watch 4 December 2014.

36. Christensen, F.M., Aschberger, K., Gottardo, S., Hartmann, N., Micheletti, C., Rauscher, H., Riego Sintes, J., Sokull-Klüttgen, B., Vegro, S., Fabrega Climent, J., Falck, G., Kloslova, Z., Quinn, B., Sumrein, A. 2012. NANO SUPPORT Project Scientific technical support on assessment of nanomaterials in REACH registration dossiers and adequacy of available information AA N°07.0307/2010/581080/AA/D3 between DG Environment (DG ENV) and the Joint Research Centre (JRC) Final Report on analysis and assessment (Task I, step 3&4&5) and options for adapting REACH (Task II, step 1). Available: http://ec.europa.eu/environment/chemicals/nanotech/pdf/jrc_report.pdf (Accessed 11-11-2016).

37. CIEL, ClientEarth and BUND. 2012. High time to act on nanomaterials. A proposal for a "nano patch" for EU regulation. CIEL, ClientEarth and BUND. Available: http://www.ciel.org/wp-content/uploads/2014/10/Nanopatch_EU_Nov2012.pdf (Accessed 20-12-2016).

38. Committee on the Environment, Public Health and Food Safety 2014. Report Plenary sitting on the proposal for a regulation of the European Parliament and of the Council on novel foods (COM(2013)0894 – C7-0487/2013 – 2013/0435(COD)). Available: http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-%2f%2fEP%2f%2fNONSGML%2bREPORT%2bA8-2014-0046%2b0%2bDOC%2bPDF%2bV0%2f%2fEN (Accesed 09-12-2016).

39. Commission 2011. Commission Regulation (EU) No 234/2011 of 10 March 2011 implementing Regulation (EC) No 1331/2008 of the European Parliament and of the Council establishing a common authorisation procedure for food additives, food enzymes and food flavourings. Official Journal of the European Union L64/15 - L 64/24.

40. Commission of the European Communities 2008a. Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee Regulatory Aspects of Nanomaterials [Sec(2008) 2036] Com(2008) 366 Final. Brussels: Commission of the European Communities.

41. Commission of the European Communities 2008b. Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Official Journal of the European Union. L 142/1 - 142/739.

42. Commission of the European Communities 2008c. Commission Regulation (EC) No 987/2008 of 8 October 2008 amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annexes IV and V. Official Journal of the European Union L 268/14- L 268/19.

43. Commission of the European Communities 2009. Commission Regulation (EC) No 450/2009 of 29 May 2009 on active and intelligent materials and articles intended to come into contact with food. Official Journal of the European Union L 135/3- L 135/11.

44. Cornelissen, R., Jongeneelen, F., van Broekhuizen, F., van Broekhuizen, F., 2011. Guidance working safely with nanomaterials and products, the guide for employers and employees. Available: http://www.industox.nl/Guidance%20on%20safe%20handling%20nanomats&products.pdf (Accessed 04-03-2017).

45. Council of the European Union 2016. Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009. Available: http://data.consilium.europa.eu/doc/document/ST-9364-2016-REV-3/en/pdf (Accessed 14-11-2016).

46. CPI 2015. Consumer Product Inventory. Project of Emerging Nanotechnologies. Available: http://www.nanotechproject.org/cpi/ (Accessed 13-08-2015).

47. Cornelissen, R., Jongeneelen, F., van Broekhuizen, P., van Broekhuizen, F. 2011. Guidance Working Safely with Nanomaterials and nanoproducts - the Guide for Employers and Employees. Version 1.0. Amsterdam, the Netherlands: IVAM.

48. CSF 2015. Nanotechnology in Food. Center for Food Safety. Available: http://salsa3.salsalabs.com/o/1881/p/salsa/web/common/public/content?content_item_KEY=14112. (Accessed 30-10-2015).

49. Dale, A. L., Lowry, G. V., Casman, E. A. 2013. Modeling nanosilver transformations in freshwater sediments. Environmental Science & Technology 47:(22):12920-12928.

50. Davies, J.C. 2006. Managing the Effects of Nanotechnology. Washington, DC: Woodrow Wilson International Centre for Scholars. Available: www.nanotechproject.org/file download/30 (Accessed 25-06-2006).

51. Davis, J.M. 2007. How to assess the risks of nanotechnology: Learning from past experience. Journal Nanoscience & Nanotechnology 7(2):402–409.

52. Davis, J.M., Wang, A., Sharkin, J.A. et al. 2009. External Review Draft Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and in Topical Sunscreen. EPA/600/R-09/057. July 2009 National Center for Environmental Assessment Office of Research and Development U.S. Environmental Protection Agency Research Triangle Park, NC

53. Dekkers, S., Oomen, A. G., Bleeker, E. A. J., Vandebriel, R. J., Micheletti, C., Cabellos, J., Janer, G., Fuentes, N., Vázquez-Campos, S., Borges, T., Silva, M. J., Prina-Mello, A., Movia, D., Nesslany, F., Ribeiro, A. R., Leite, P. E., Groenewold, M., Cassee, F. R., Sips, A. J. A. M., Dijkzeul, A., van Teunenbroek, T., Wijnhoven, S. W. P. 2016. Towards a nanospecific approach for risk assessment. Regulatory Toxicology and Pharmacology 80:46-59.

54. ECHA 2009. Guidance in a Nutshell Chemical Safety Assessment. Helsinki: European Chemicals Agency. Available: https://echa.europa.eu/documents/10162/13632/nutshell_guidance_csa_en.pdf/8fe6c700-fae0-45de-809a-dfae85485c25 (Accessed 09-12-2016).

55. ECHA 2010. Guidance on information requirements and chemical safety assessment Chapter R12 Use descriptor system Version: 2 March 2010. Available: http://echa.europa.eu/documents/10162/13632/information_requirements_r12_en.pdf. (Accessed 05-06-2013).

56. ECHA 2011. Guidance on the preparation of an application for authorization ECHA-11-G-01-EN. Helsinki: European Chemicals Agency.

57. ECHA 2012a. Guidance on information requirements and chemical safety assessment Appendix R7-1 Recommendations for nanomaterials applicable to Chapter R7a - Endpoint specific guidance. Helsinki: European Chemicals Agency.

58. ECHA 2012b. Guidance on information requirements and chemical safety assessment Appendix R7-1 Recommendations for nanomaterials applicable to Chapter R7b - Endpoint specific guidance. Helsinki: European Chemicals Agency.

59. ECHA 2012c Guidance on information requirements and chemical safety assessment Appendix R7-2 Recommendations for nanomaterials applicable to Chapter R7c - Endpoint specific guidance Helsinki: European Chemicals Agency.

60. ECHA 2012d. Guidance on information requirements and chemical safety assessment, Chapter R. 15: Consumer exposure estimation. version 2.1 Available: http://echa.europa.eu/documents/10162/13632/information_requirements_r15_en.pdfAccessed 02-12-2015).

61. ECHA 2014. Guidance on the Biocidal Products Regulation Volume II: Efficacy Part A: Information Requirements Version 1.1 November 2014. Helsinki: European Chemicals Agency. Available: https://echa.europa.eu/documents/10162/15623299/bpr_guidance_ir_part_vol_ii_part_a_en.pdf/5f332775-9cf7-4bb6-880f-c9d6b5f67de7 (Accessed 24-11-2016).

62. ECHA 2016a. Silicon dioxide (as a nanomaterial formed by aggregates and agglomerates). Available: http://dissemination.echa.europa.eu/Biocides/factsheet?id=1449-18, Accessed 14-03-2016 (Accessed 02-12-2016).

63. ECHA 2016b. Silver adsorbed on silicon dioxide. http://dissemination.echa.europa.eu/Biocides/factsheet?id=1448-09 (Accessed 02-12-2016).

64. ECHA 2016c. Ongoing guidance consultations. Available: https://echa.europa.eu/da/support/guidance/consultation-procedure/ongoing-reach (Accessed 22-08-2016).

65. ECHA 2016d. Guidance on Appendix 4: Recommendations for nanomaterials applicable to the Guidance on Registration Draft (Public) Version 1.0 May 2016. Helsinki: European Chemicals Agency. Available: https://echa.europa.eu/documents/10162/22334052/appendix_reg_nano_draft_for_peg_en.pdf/faab274d-5aaa-4c5c-b484-3de9719da66a (Accessed 02-12-2016).

66. ECHA 2016e. Guidance on Labelling and Packaging Version 2.0 - September 2016. Available: https://echa.europa.eu/documents/10162/13562/clp_labelling_en.pdf (Accessed 02-12-2016).

67. ECHA 2016f. Guidance on Information Requirements and Chemical Safety Assessment, Helsinki: European Chemicals Agency, Finland.

68. ED & DuPont 2007. Nano Risk Framework. Environmental Defense and DuPont.

69. EEA 2001. Late Lessons from Early Warnings: The Precautionary Principle 1896–2000. Copenhagen: European Environmental Agency.

70. EEA 2013. Late Lessons from Early Warnings: Science, Precaution, Innovation. Copenhagen: European Environment Agency.

71. EFSA 2009. The Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety. The EFSA Journal 958: 1-39.

72. EFSA 2010. Database of guidance on different toxicity end-points, risk assessment methodologies and data collection related to food, feed, animal health and welfare and plant health. EFSA Journal 8(3):1518. 1-86.

73. EFSA 2011. Endorsed For Public Consultation Draft Scientific Opinion Guidance On Risk Assessment Concerning Potential Risks Arising From Applications Of Nanoscience And Nanotechnologies To Food And Feed. Parma: EFSA Scientific Committee, European Food Safety Authority.

74. EFSA 2012. Application of the definition on nanomaterial to food and feed. Parma. EFSA Scientific Committee Unit. Available: https://www.efsa.europa.eu/sites/default/files/assets/corporatenanotechnology121003.pdf (Accessed 22-08-2016).

75. EFSA 2014. Statement on the safety assessment of the substance silicon dioxide, silanated, FCM Substance No 87 for use in food contact materials. EFSA Journal 12(6):3712. Available: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3712/epdf (Accessed 02-12-2016).

76. EFSA 2016a. Scientific opinion on the re-evaluation of silver (E 174) as food additive EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)2,3. EFSA Journal 14(1):4364. Available: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4364/epdf (Accessed 02-12-2016).

77. EFSA 2016b. Scientific Opinion on the re-evaluation of titanium dioxide (E 171) as a food additive. EFSA Journal 14(9): 4545. Available: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4545/epdf (Accessed 02-12-2016).

78. EP and the Council 2006. Regulation (EC) No. 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. Official Journal of the European Union L 396:1-849.

79. EP and the Council 2008a. Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. Official Journal of the European Union L 354: 16–33.

80. EP and the Council 2008b. Regulation (EC) No 1331/2008 of the European Parliament and of the Council of 16 December 2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings. Official Journal of the European Union L 354:1–6.

81. EP and the Council 2009a. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. Official Journal of the European Union L 342/59 -209.

82. EP and the Council 2009b. European Parliament and of the Council. Commission Regulation EC No 761/2009 of 23 July 2009 amending, for the purpose of its adaptation to technical progress, Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Official Journal of the European Union L 220: 1–94.

83. EP and the Council 2011a. Directive 2011/65/EU of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment. Official Journal of the European Union L 174: 88–110.

84. EP and the Council 2011b. Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. Official Journal of the European Union L 304, 22.11.2011, p. 18–63

85. EP and the Council 2012a. Regulation EU No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products. Official Journal of the European Union L 167: 1–123.

86. EP and the Council 2012b. Directive 2012/19/EU of the European Parliament and of the Council of 4 July 2012 on waste electrical and electronic equipment (WEEE). Official Journal of the European Union L 197: 38-71.

87. EP and the Council 2013. Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. Official Journal of the European Union L 226:1-17.

88. EP and the Council 2015. Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. Available: http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1449760581954&uri=OJ:JOL_2015_327_R_0001 (Accessed 22-08-2016).

89. European Commission 2004a. Nanotechnologies: a Preliminary Risk Analysis on the Basis of a Workshop. European Commission, Brussels.

90. European Commission 2004b. Communication from the Commission Towards a European Strategy for Nanotechnology. Brussels: European Commission Research DG. Available: https://cordis.europa.eu/pub/nanotechnology/docs/nano_com_en_new.pdf (Accessed: 02-12-2016).

91. European Commission 2011a. Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food Text with EEA relevance. Official Journal of the European Union L 12/1 - L 12/89.

92. European Commission 2011b. Commission Decision of 24 June 2011 on establishing the ecological criteria for the award of the EU Ecolabel to lubricants. Official Journal of the European Union L 169/28 - L 275/39.

93. European Commission 2011c. Commission Recommendation of 18 October 2011 on the definition of nanomaterials (2011/696/EU). Official Journal of the European Union L 275/38 - L 275/40.

94. European Commission 2012a. Communication from the Commission to the European parliament, the council and the European Economic and Social Committee Second Regulatory Review on Nanomaterials SWD(2012) 288. COM(2012) 572 final. Brussels: European Commission.

95. European Commission 2012b. Commission Staff Working Paper Types and uses of nanomaterials, including safety aspects accompanying the Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee on the Second Regulatory Review on Nanomaterials SWD(2012) 288 final. Brussels: European Commission.

96. European Commission 2013a. Commission Regulation (EU) No 209/2013 of 11 March 2013 amending Regulation (EC) No 2073/2005 as regards microbiological criteria for sprouts and the sampling rules for poultry carcases and fresh poultry meat. of the European L 68/19- L 68/23.

97. European Commission 2013b. Public consultation relating to the REACH Annexes on Nanomaterials. Available: http://www.industriall-europe.eu/Sectors/Chemical-BM/2013/Nano-ques1.pdf (Accessed 22-08-2016).

98. European Commission 2016. Inception Impact Assessment Possible amendments of Annexes to REACH for registration of nanomaterials. Available: http://ec.europa.eu/smart-regulation/roadmaps/docs/2014_env_013_nanomaterials_en.pdf (05-05-2017).

99. European Commission 2017. Catalogue of nanomaterials used in cosmetic products placed on the EU market Version 1 (31.12.2016). Available: http://ec.europa.eu/docsroom/documents/24521 (05-08-2017).

100. European Commission Joint Research Centre 2011. REACH Implementation Project Substance Identification of Nanomaterials (RIP-oN 1). Available: http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon1.pdf (Accessed 02-12-2016).

101. European Parliament 2009. European Parliament legislative resolution of 24 March 2009 on the proposal for a regulation of the European Parliament and of the Council on cosmetic products (recast) (COM(2008)0049—C6-0053/2008—2008/0035(COD)). 2009. Available: http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P6-TA-2009-0158+0+DOC+XML+V0//EN (Accessed 23-11-2009).

102. European Parliament 2014. Novel foods: MEPs call for moratorium on nano-foods and labelling of cloned meat. 25-11-2014. REF.: 20141125IPR80424. Available: (Accessed 22-08-2016).

103. Fleury, D., Fayet, G., Vignes, A., Henry, F., Frejafon, E. 2013. Nanomaterials Risk Assessment in the Process Industries: Evaluation and Application of Current Control Banding Methods. Chemical Engineering Transactions 31:949-954

104. FOEN 2010. Swiss Federal Office for the Environment (FOEN). Workplace safety is first priority. 2010. Available: http://www.bafu.admin.ch (Accessed 04-11- 2010).

105. France 2014. Evaluation of active substances Assessment Report Synthetic amorphous silicon dioxide (Rentokil Initial) Product-type 18 (Insecticide) March 2014 RMS: FRANCE. Available: https://circabc.europa.eu/sd/a/b8085681-e864-4ceb-ae41-4d652d295322/Synthetic%20amorphous%20Silicon%20dioxide%20(assessment%20report%20as%20finalised%20on%2013.03.2014).pdf (Accessed 02-12-2016).

106. Franco, A., Hansen, S.F., Olsen, S.I., Butti, L. 2007. Limits and Prospects of the "Incremental Approach" and the European Legislation on the Management of Risks related to Nanomaterials. Regulatory Toxicology & Pharmacology 48:171–183.

107. Fransman, W., Verbist, K., Stuurman, B., Vink, S., Heussen, H., Brouwer, D., van Niftrik, M. 2010. Stoffenmanager nano 1.0: an online control banding tool for the prioritization of risks related to working with manufactured nano objects. Nanosafe 2010 conference in Grenoble, France.

108. Froggett, S.J., Clancy, S.F., Boverhof, D.R., Canady, R.A. 2014. A review and perspective of existing research on the release of nanomaterials from solid nanocomposites. Particle Fibre Toxicology 11:17-8977–11-17.

109. Führ, M., Hermann, A., Merenyi, S., Moch, K., Moller, M. 2006. Legal appraisal of nanotechnologies, Existing legal framework, the need for regulation and regulative options at a European and national level. Final Report. Umweltbundesamt. Available: https://www.umweltbundesamt.de/sites/default/files/medien/publikation/long/3480.pdf (Accessed 12-12-2016).

110. Ganzleben, C., Pelsy, F., Hansen, S.F., Corden, C., Grebot, B., Sobey, M. 2011. Review of Environmental Legislation for the Regulatory Control of Nanomaterials. Brussels: Milieu Ltd.

111. Ganzleben, C., Hansen, S.F. 2012a. Environmental Exposure to Nanomaterials – Data Scoping Study. Service Contract No.07.0307/2011/610874/ETU/D.3. Brussels: Milieu.

112. Ganzleben, C., Hansen, S.F. 2012b. Nanomaterials as priority substances under the Water Framework Directive. European Journal of Law and Technology 2:38-45.

113. Geiser, K., Tickner, J., Edwards, S., Rossi, M. 2015. The Architecture of Chemical Alternatives Assessment Risk Analysis 35(12): 2152–2161.

114. Gellert, R., Mantovani, E., De Hert, P., Dolez, P. 2015. The EU Regulation of Nanomaterials: Smoother or Harder? The Precautionary Tool Chest as the Basis for Better Regulating Nanomaterials. Nanoengineering: Global Approaches to Health and Safety Issues. Elsevier. p.339-373.

115. Genaidy, A., Sequeira, R., Rinder, M., A-Rehim, A. 2009. Risk analysis and protection measures in a carbon nanofiber manufacturing enterprise: An exploratory investigation. Science of the Total Environment 407:5825–5838.

116. Gottschalk, F., Nowack, B., Lassen, C., Kjølholt, J., Christensen, F. 2015. Nanomaterials in the Danish environment. Modelling exposure of the Danish environment to selected nanomaterials. Environmental project No. 1639, 2015 Copenhagen: Danish Environmental Protection Agency.

117. Gridelet, L., Delbecq, P., HervÉ, L., Boissolle, P., Fleury, D., Kowal, S. Fayet, G. 2015. Proposal of a new risk assessment method for the handling of powders and nanomaterials. Industrial Health 53(1): 56-68.

118. Grieger, K.D., Hansen, S.F., Linkov, I., Baun, A. 2012. Environmental Risks of Nanomaterials: Review and evaluation of Frameworks. Nanotoxicology 6(2):196-212

119. Groso, A., A. Petri-Fink, A. Magrez, M. Riediker, and T. Meyer. 2010. Management of nanomaterials safety in research environment. Particle and Fibre Toxicology 7(40):1-8.

120. Hankin S.M., Peters S.A.K., Poland C.A., Foss Hansen S., Holmqvist J., Ross B.L., Varet J. and Aitken R.J. 2011. Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH (RIP-oN 2) – Final Project Report. Document reference RNC/RIP-oN2/FPR/1/FINAL. Brussels: Eurropean Commission. Available: http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon2.pdf

121. Hansen, S.F., Larsen, B.H., Olsen, S.I., Baun, A. 2007. Categorization framework to aid hazard identification of nanomaterials. Nanotoxicology 1:243-250.

122. Hansen SF, Michelson E, Kamper A, Borling P, Stuer-Lauridsen F, Baun A. 2008a. Categorization framework to aid exposure assessment of nanomaterials in consumer products. Ecotoxicology 17:438–447.

123. Hansen SF, Maynard A, Baun A, Tickner JA. 2008b. Late lessons from early warnings for nanotechnology. Nature Nanotechnology 3:444–447.

124. Hansen SF, Rejeski D. Applying the chemical policy options to emerging technologies and materials: adaptations and challenges. In: Tickner JA, Torrie Y, eds. Options for State Chemicals Policy Reform: A Resource Guide. Lowell: Lowell Center for Sustainable Production, University of Massachusetts; 2008. Available at: http://sustainableproduction.org/downloads/OptionsforStateChemicalsPolicyReform.pdf (Accessed February 18, 2008).

125. Hansen, S.F., Tickner, J.A. 2013. The Precautionary Principle and false alarms. In David Gee et al. (Eds.). Late lessons from early warnings: science, precaution, innovation. European Environment Agency Available: http://www.eea.europa.eu/publications/late-lessons-2

126. Hansen, S.F. 2010. A global view of regulations affecting nanomaterials. WIRES: Nanomedicine and Nanobiotechnology 2(5): 441-449.

127. Hansen, S.F., Alstrup-Jensen, K., Baun, A., 2011. NanoRiskCat – a conceptual model for risk classification of nanomaterials. Environmental Project No. 1372 2011. Danish Environmental Protection Agency.

128. Hansen, S.F., Baun, A. 2012a. When Enough is Enough. Nature Nanotechnology 7: 409-411.

129. Hansen, S.F., Baun, A. 2012b. European regulation affecting nanomaterials – review of limitations and future recommendations. Dose Response 10(3): 364-383.

130. Hansen, S.F. 2013. The European Union's chemical legislation needs revision. Nature Nanotechnology 8, 305–306.

131. Hansen, S.F., Nolde Nielsen, K., Knudsen, N., Grieger, K.D., Baun, A., 2013a. Operationalization and application of "early warning signs" to screen nanomaterials for harmful properties. Environmental Science: Processes & Impacts 15:190-203

132. Hansen, S.F., Maynard, A., Baun, A., Tickner, J.A., Bowman, D.M. 2013b. Nanotechnology — early lessons from early warnings. Gee et al. (Eds.). Late lessons from early warnings: science, precaution, innovation. European Environment Agency Available: http://www.eea.europa.eu/publications/late-lessons-2

133. Hansen, S.F., Brinch, A., 2014. The biocides market for nano actives. Chemical Watch 67: 8-9

134. Hansen, S.F., Gee, D. 2014. Adequate and anticipatory research on the potential hazards of emerging technologies: a case of myopia and inertia? J Epidemiol Community Health doi:10.1136/jech-2014-204019

135. Hansen, S.F., Jensen, K.A., Baun, A. 2014. NanoRiskCat: A conceptual tool for categorization and communication of exposure potentials and hazards of nanomaterials in consumer products. Journal of Nanoparticle Research 16(1):2195 DOI 10.1007/s11051-013-2195-z.

136. Hansen, S.F. 2015. The challenges of ecotox testing of nanomaterials and the BPR. Chimica Oggi - Chemistry Today 33(3):78-79.

137. Hansen, S.F., Baun, A. 2015. DPSIR and Stakeholder Analysis of the Use of Nanosilver. NanoEthics 9(3): 297-319.

138. Hansen, S.F. 2016. The Emergence of Nanorisk-Immunity. Frontiers of Nanoscience and Nanotechnology 2(3): 131-134.

139. Hansen, S.F., Heggelund, L.R., Besora, P.R., Mackevica, A., Boldrin, A. and Baun, A., 2016. Nanoproducts–what is actually available to European consumers? Environmental Science: Nano 3(1):169-180.

140. Hansen, S.F. Sørensen, S., Skjolding, L.M., Hartmann, N., Baun, A. 2017a. Revising REACH technical guidance on information requirements and chemical safety assessment for engineered nanomaterials for aquatic ecotoxicity endpoints – recommendations from the EnvNano project. Environmental Science Europe 29:14 DOI 10.1186/s12302-017-0111-3.

141. Hansen, S.F., Hjorth, R., Skjolding, L.M., Bowman, D.M., Maynard, A., Baun, A. 2017b. A Critical Analysis of the Environmental Dossiers from the OECD Sponsorship Programme for the Testing of Manufactured Nanomaterials. Environmental Science: Nano 4: 282 – 291.

142. Hansen, S.F., Jensen, K.A., Baun, A. 2017c. Erratum to: NanoRiskCat: a conceptual tool for categorization and communication of exposure potentials. Journal of Nanoparticle Research. 19:236. DOI 10.1007/s11051-017-3909-4.

143. Hansen, S.F. 2017. React now regarding nanomaterial regulation. Nature Nanotechnology 12: 714-716.

144. Hartmann, N.B., Skjolding, L.M., Hansen, S.F., Kjølholt, J., Gottschalck, F., Baun, A. 2014. Environmental fate and behaviour of nanomaterials New knowledge on important transformation processes Environmental Project No. 1594, 2014. Copenhagen: The Danish Environmental Protection Agency.

145. Hartmann, NB, Lützhøft, HCH, Ågerstrand, Baun, A., 2016. A transparent method to assess the regulatory adequacy of ecotoxicity studies of nanomaterials – relevance and reliability revisited. NanoImpact. DOI: 10.1016/jimpact.2017.03.004.

146. Hauri, J.F., Niece, B.K. 2011. Leaching of silver from silver-impregnated food storage containers. Journal of Chemical Education 88:1407–1409.

147. Heggelund, L., Hansen, S.F., Astrup, T.F., Boldrin, A. 2016. Semi-quantitative analysis of solid waste flows from nano-enabled consumer products in Europe, Denmark and the United Kingdom – Abundance, distribution and management. Waste Management 56 :584-592.

148. Hjorth, R., Holden, P., Hansen, S.F., Colman, B.P., Grieger, K., Hendren, C.O. 2017a. The role of alternative testing strategies in environmental risk assessment of engineered nanomaterials. Environmental Science: Nano 4: 292-301.

149. Hjorth, R., Hansen, S.F., Jacobs, M., Tickner, J., Ellenbecker, M., Baun, A. 2017b. The Applicability of Chemical Alternatives Assessment for Engineered Nanomaterials. Integrated Environmental Assessment and Management 13(1):177-87.

150. Howard, C.V., de Jong, W. 2004. Concept note on a hazard trigger algorithm as a potential prioritization tool for use by regulators. In: Nanotechnologies: a preliminary risk analysis on the basis of a workshop organized in Brussels on 1–2 March 2004 by the Health and Consumer Protection Directorate General of the European Commission. Brussels: European Commission, 35-36. Available: http://ec.europa.eu/health/ph_risk/documents/ev_20040301_en.pdf (Accessed 16-04-2013).

151. Hristozov, D.R., Gottardo, S., Critto, A., Marcomini, A. 2012. Risk assessment of engineered nanomaterials: a review of available data and approaches from a regulatory perspective. Nanotoxicology 6(8):880-898.

152. Hristozov, D.R., Zabeo, A., Foran, C., Isigonis, P., Critto, A., Marcomini, A., Linkov, I. 2014. A weight of evidence approach for hazard screening of engineered nanomaterials Nanotoxicology 8:1: 72-87.

153. Hristozov, D.R., Zabeo, A., Foran, C., Isigonis, P., Critto, A., Marcomini, A., Linkov, I. 2014. A weight of evidence approach for hazard screening of engineered nanomaterials. Nanotoxicology 8(1): 72-87.

154. Hristozov, D., Gottardo, S., Semenzin, E., Oomen, A., Bos, P., Peijnenburg, W., van Tongeren, M., Nowack, B., Hunt, N., Brunelli, A., Scott-Fordsmand, J.J., Tran, L., Marcomini, A. 2016. Frameworks and tools for risk assessment of manufactured nanomaterials. Environment International. DOI: 10.1016/j.envint.2016.07. 016.

155. Hsu, A. 2006. Taiwanese government launches nanoproduct certification system. Taiwan Journal. February 17, 2006. http://www.taiwantoday.tw/fp.asp?xItem=23198&CtNode=451 (Accessed June 2016).

156. Hund-Rinke, K., Baun, A., Cupi, D., Fernandes, T.F., Handy, R., Kinross, J.H., Navas, J.M., Peijnenburg, W., Schlich, K., Shaw, B.J., Scott-Fordsmand, J.J. 2016. Regulatory ecotoxicity testing of nanomaterials—proposed modifications of OECD test guidelines based on laboratory experience with silver and titanium dioxide nanoparticles. Nanotoxicology 10(10): 1442-1447.

157. Hund-Rinke K, Herrchen M, Schlich K, Schwirn K, Völker D (2015) Test strategy for assessing the risks of nanomaterials in the environment considering general regulatory procedures. Environmetnal Science Europe 27:1–12.

158. Höck, J., Hofmann, H., Krug, H., Lorenz, C., Limbach, L., Nowack, B., et al., 2008. Guidelines on the Precautionary Matrix for Synthetic Nanomaterials version 1.1. Available: http://www.temas.ch/WWWTEMAS/temas_homepage.nsf/vwRes/Spiegel_053/$FILE/Guidelines+on+the+Precautionary+Matrix+for+Synthetic+Nanomaterials+June+09.pdf (Accessed 02-12-2016).

159. Höck, J., Epprecht, T., Hofmann, H., Höhener, K., Krug, H., Lorenz, C., et al., 2011. Guidelines on the Precautionary Matrix for Synthetic Nanomaterials version 2.1. Available: http://www.temas.ch/wwwtemas/temas_homepage.nsf/vwRes/NanoSR26/$FILE/Wegleitung_e.pdf (Accessed 02-12-2016).

160. Höck, J., Epprecht, T., Furrer, E., Gautschi,M., Hofmann, H., Höhener, K., et al., 2013. Guidelines on the Precautionary Matrix for Synthetic Nanomaterials [Internet]. Federal Office of Public Health and Federal Office for the Environment version 3.0. Available: http://www.bag.admin.ch/nanotechnologie/12171/12174/index.html?lang=en&download=NHzLpZeg7t,lnp6I0NTU042l2Z6ln1ad1IZn4Z2qZpnO2Yuq2Z6gpJCHd3x9g2ym162epYbg2c_JjKbNoKSn6A-- (Accessed 02-12-2016).

161. Industrial Development Bureau 2016. NanoMark, Product Information. Industrial Development Bureau, Ministry of Economic Affairs, Taiwan. Available: http://www.nanomark.org.tw/Eng/Product/product.asp (Accessed 02-12-2016).

162. IRGC 2005. Risk governance: Towards an integrative approach. Geneva: International Risk Governance Council.

163. IRGC 2007. Nanotechnology risk governance: Recommendations for a global, coordinated approach to the governance of potential risks. Geneva: International Risk Governance Council.

164. IRGC 2009. Appropriate Risk Governance Strategies for Nanotechnology Applications in Food and Cosmetics. Geneva: International Risk Governance Council.

165. ISO 1998. Ergonomic requirements for office work with visual display terminals (VDTs) -- Part 11: Guidance on usability. ISO 9241-11:1998. Available: http://www.iso.org/iso/catalogue_detail.htm?csnumber=16883 (Accessed 02-12-2016).

166. Jacobs, M.M., Malloy, T.F., Tickner, J.A., Edwards, S. 2016. Alternatives assessment frameworks: research needs for the informed substitution of hazardous chemicals. Environmental Health Perspectives 124:265–280.

167. Jensen, K.A., Saber, A.T., Kristensen, H.V., Liguori, B., Jensen, A.C.Ø., Koponen, I.K., et al. 2016. NanoSafer version 1.1: A web-based precautionary risk assessment and management tool for manufactured nanomaterials using first order modeling (in preparation).

168. Jones, P. 2012. OECD says existing test methods are apt for nanomaterials. Chemical Watch. Available: https://chemicalwatch.com/12310/oecd-says-existing-test-methods-are-apt-for-nanomaterials (Accessed 02-12-2016).

169. Jones, P. 2013. 2013 deadline sees only four nano registrations. Chemical Watch. Available: https://chemicalwatch.com/15076/2013-deadline-sees-only-four-nano-registrations (Accessed 09-11-2016).

170. Juganson, K., Ivask, A., Blinova, I., Mortimer, M., Kahru, A. 2015. NanoE-Tox: New and in-depth database concerning ecotoxicity of nanomaterials. Beilstein J. Nanotechnol. 6: 1788–1804.

171. KEMI 2013. Draft proposal for a regulation on nanomaterials. Swedish Chemical Agency. Available: http://www3.kemi.se/Documents/Forfattningar/Reach/Draft-proposal-regulation-nanomaterials.pdf (Accessed 02-12-2016).

172. Kjølholt, J., Gottschalk, F., Brinch, A., Holten Lützhøft, H-C., Hartmann, N.B., Nowack, B., Baun, A. 2015. Environmental assessment of nanomaterial use in Denmark. Copenhagen: The Danish Environmental Protection Agency.

173. Klaine, S.J., Koelmans, A.A., Horne, N., Carley, S., Handy, R.D., Kapustka, L., Nowack, B., von der Kammer, F. 2012. Paradigms to assess the environmental impact of manufactured nanomaterials. Environmental Toxicology & Chemistry 31(1):3-14.

174. Klimisch, H.J., Andreae, M., Tillmann, U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regulatory Toxicology & Pharmacology 25: 1–5.

175. Kristensen, H.V., Hansen, S.V., Holm, G.R., 2010. Nanopartikler i arbejdsmiljøet: Viden og inspiration om håndtering af nanomaterialer. Available: http://nanosafer.i-bar.dk/media/Nanopartikler_i_arbejdsmiljoet_samlet.pdf (Accessed 15 March, 2017).

176. Larsen, P.B., Christensen, F., Keld, C., Jensen, A., Brinch, A., Mikkelsen, S.H., 2015. Exposure assessment of nanomaterials in consumer products. Environmental Project No. 1636. Copenhagen: Danish Environmental Protection Agency.

177. Lawless, E.W. 1977. Technology and Social Shock, Rutgers University Press, New Brunswick/New Jersey.

178. Liguori, B., Hansen, S.F., Baun, A., Jensen, K.A. 2016. Control banding tools for occupational exposure assessment of nanomaterials - Ready for use in a regulatory context. NanoImpact 2: 1–17.

179. Linkov, I., Satterstrom, F., Steevens, J., Ferguson, E., Pleus, R. 2007. Multi-criteria decision analysis and environmental risk assessment for nanomaterials. Journal of Nanoparticle Research 9: 543-554.

180. Linsinger, T. Roebben, G., Gilliland, D., Calzolai, L., Rossi, F., Gibson, N., Klein, C. 2012. Requirements on measurements for the implementation of the European Commission definition of the term "nanomaterial" EUR 25404. Luxembourg: European Commission Joint Research Centre

181. Lynch, I., 2015. Compendium of Projects in the European NanoSafety Cluster. European Commission 2015 Edition. European Commission. Available: http://www.nanosafetycluster.eu/uploads/files/pdf/2016_NSC_Compendium.pdf (Accessed 09-12-2016).

182. Lövestam, G., Rauscher, H., Roebben, G., Sokull-Klüttgen, B., Gibson, N., Putaud, J.-P., Stamm, H. 2010. Considerations on a Definition of Nanomaterial for Regulatory Purposes. EUR 24403EN. Luxembourg: European Commission Joint Research Centre.

183. Mackevica, A., Skjolding, L.M., Gergs, A., Palmqvist, A., Baun, A. 2015. Chronic toxicity of silver nanoparticles to Daphnia magna under different feeding conditions. Aquatic Toxicology 161:10–16.

184. Mackevica, A. 2016. Release of nanomaterials from consumer products and implications for consumer exposure assessment. PhD Thesis October 2016. Kgs. Lyngby: DTU Environment Department of Environmental Engineering Technical University of Denmark

185. Mackevica, A. and Hansen, S.F., 2016. Release of nanomaterials from solid nanocomposites and consumer exposure assessment– a forwardlooking review. Nanotoxicology 10(6), 641-653.

186. Mackevica, A., Besora, P.R., Brinch, A., Hansen, S.F. 2016a. Current uses of nanomaterials in biocidal products and treated articles in the EU. Environmental Science: Nano 3: 1195-1205.

187. Mackevica, A., Olsson, M.E., Hansen, S.F. 2016b. The release of silver nanoparticles from commercial toothbrushes. Journal of Hazardous Materials, 322(Part A):270–275.

188. Mackevica, A., Olsson, M.E. and Hansen, S.F., 2016c. Silver nanoparticle release from commercially available plastic food containers into food simulants. Journal of Nanoparticle Research, 18(1), 1-11.

189. Malloy, T.F., Zaunbrecher, V.M., Batteate, C. 2016. Advancing Alternative Analysis: Integration of Decision Science. Environmental Health Perspectives DOI: 10.1289/EHP483

190. Maynard, A.D., Aitken, R.J., Butz, T., Colvin, V.L., Donaldson, K., Oberdörster, G., Philbert, M.A., Ryan, J., Seaton, A., Stone, V., Tinkle, S.S., Tran, L., Walker, N., Warheit, D.B. 2006. Safe Handling of Nanomaterials. Nature 444: 267-269.

191. Maynard, A. 2016. Why I'm suffering from nanotechnology fatigue. Slate September 27, 2016. Available: http://www.slate.com/articles/technology/future_tense/2016/09/why_i_m_suffering_from_nanotechnology_fatigue.html (Accessed 10-12-2016).

192. Mikkelsen, S.H., Hansen, E., Christensen, T.B., Baun, A., Hansen, S.F., Binderup, M-L. 2011. Survey on basic knowledge about exposure and potential environmental and health risks for selected nanomaterials. Environmental Project No. 1370 2011. Copenhagen: Danish Ministry of the Environment. Danish Environmental Protection Agency.

193. Mueller, N., Nowack, B. 2008. Exposure Modeling of Engineered Nanoparticles in the Environment. Evironmental Science & Technology 42:4447–4453.

194. NanoSafer. Copenhagen: Industriens Branchearbejsmiljø. Available: http://www.nanosafer.org (Accessed 02-12-2016).

195. Nanoscale Science Engineering and Technology Subcommittee, The Committee on Technology, National Science and Technology Committee 2004. The National Nanotechnology Initiative Strategy Plan December. Arlington, VA: National Nanotechnology Coordination Office.

196. Nanowerk 2016. Nanomaterials Database, http://www.nanowerk.com/nanomaterial-database.php (Accessed 02-12- 2016).

197. NIOSH 2006. Approaches to Safe Nanotechnology: An Information Exchange with NIOSH. Washington, D.C.: Department of Health And Human Services Centers for Disease Control and Prevention National Institute for Occupational Safety and Health.

198. NRC 2014. A framework to guide selection of chemical alternatives. Washington (DC): National Research Council, National Academies.

199. O'Brien, N. J., Cummins, E. J. 2011. A Risk Assessment Framework for Assessing Metallic Nanomaterials of Environmental Concern: Aquatic Exposure and Behavior. Risk Analysis 31(5): 706-726.

200. Oberdorster G, Oberdorster E, Oberdorster J. 2005. Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles. Environmental Health Perspective 113: 823-839.

201. OECD 2008. Series on the safety of manufactured nanomaterials number 6 list of manufactured nanomaterials and list of endpoints for phase one of the OECD testing programme, ENV/JM/MONO 13 (2008). Paris: Organisation for Economic Co-operation and Development.

202. OECD 2009a. Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials. OECD Environment, Health and Safety Publications. ENV/JM/MONO2009/21. Paris: Organisation for Economic Co-operation and Development.

203. OECD 2009b. Guidance Manual for the Testing of Manufactured Nanomaterials: OECD's Sponsorship Programme; First Revision. OECD Environment, Health and Safety Publications. ENV/JM/MONO(2009)/20/REV. Paris: Organisation for Economic Co-operation and Development.

204. OECD 2010. Preliminary Guidance Notes on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials. ENV/JM/MONO(2010)25. Paris: Organisation for Economic Co-operation and Development.

205. OECD 2012. Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials. ENV/JM/MONO2012/40. Paris: Organisation for Economic Co-operation and Development.

206. OECD 2013. Current landscape of alternatives assessment practice: a meta-review. Series on Risk Management No. 26. Paris: Organisation for Economic Co-operation and Development.

207. OECD 2016a. Categorisation of manufactured nanomaterials workshop report Series on the Safety of Manufactured Nanomaterials No. 66. ENV/JM/MONO(2016)9. Paris: Organisation for Economic Co-operation and Development.

208. OECD 2016b. Six years of OECD work on the safety of manufactured nanomaterials, http://www.oecd.org/env/ehs/nanosafety/Nano%20Brochure%20Sept%202012%20for%20Website%20%20(2).pdf (Accessed 10 June 2016).

209. OECD 2016c. OECD chemical studies show way forward for nanomaterial safety, http://www.oecd.org/chemicalsafety/nanosafety/news-nanomaterial-safety.htm, (Accessed 10 June 2016).

210. OECD, 2016d. Nanomaterials in Waste Streams: Current Knowledge on Risks and Impacts. Paris: Organisation for Economic Co-operation and Development. Available online, last accessed 23/5-2016: http://www.oecd-ilibrary.org/environment/nanomaterials-in-waste-streams_9789264249752-en

211. Ostiguy, C., Riediker, M., Triolet, J., Troisfontaines, P., Vernez, D. 2010. Development of a specific control banding tool for nanomaterials. French Agency for food, environmental and occupational health and safety (ANSES).

212. Owen, R., Handy, R. 2007. Formulating the problems for environmental risk assessment of nanomaterials. Environmental Science & Technology 41:5582–5588.

213. Oziel, C. 2017. ClientEarth files complaint over EU cosmetics nano inventory. Chemical Watch Available: https://chemicalwatch.com/58020/clientearth-files-complaint-over-eu-cosmetics-nano-inventory (Accessed 07-08-2017).

214. Paik, S.Y., Zalk, D.M., Swuste, P., 2008. Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. Annals of Occupational Hygiene 52(6):419-428.

215. Park B, Donaldson K, Duffin R, Tran L, Kelly F, Mudway I, Morin J-P, Guest R, Jenkinson P, Samaras, et al. Hazard and risk assessment of a nanoparticulate cerium oxide-based diesel fuel additive—a case study. Inhalation Toxicology 20:547–566.

216. Patel, T., Telesca, D., Rallo, R., George, S., Xia, T., Nel, A. 2013. Hierarchical Rank Aggregation with Applications to Nanotoxicology. Journal of Agricultural, Biological, and Environmental Statistics 18(2): 159-177.

217. Paun, C. 2013a. Belgium notifies EU Commission of nano register plan. Chemical Watch 10 July 2013. Available: https://chemicalwatch-com.globalproxy.cvt.dk/15632/belgium-notifies-eu-commission-of-nano-register-plan?q=Belgium%20notifies%20EU%20Commission%20of%20nano%20register%20plan (Accessed 30-10-2015).

218. Paun, C. 2013b. French nanomaterials register receives 3,400 declarations. Chemical Watch 12 December 2013. https://chemicalwatch-com.globalproxy.cvt.dk/17530/french-nanomaterials-register-receives-3400-declarations?q=French%20register.

219. Paun, C., Chynoweth, E. 2014. Denmark launches consumer product register for nano. Chemical Watch 26 June 2014. Available: https://chemicalwatch-com.globalproxy.cvt.dk/20265/denmark-launches-consumer-product-register-for-nano?q=Belgium%20notifies%20EU%20Commission%20of%20nano%20register%20plan; https://www.retsinformation.dk/Forms/R0710.aspx?id=163367 (Accessed 30-10-2015).

220. Paun, C. 2015. EU nanomaterials register looks unlikely Not a good way to provide information to consumers, EU Commission says. 11 December 2014. https://chemicalwatch.com/22241/eu-nanomaterials-register-looks-unlikely?q=nano%2C%20unlikely (Accessed 30-10-2015).

221. Peijnenburg, W. J. G. M., Baalousha, M., Chen, J. et al. 2015. A Review of the Properties and Processes Determining the Fate of Engineered Nanomaterials in the Aquatic Environment. Critical Reviews in Environmental Science and Technology 45: 2084–2134.

222. PEN 2015. Updates. Project of Emerging Nanotechnologies. Available: http://www.nanotechproject.org/cpi/about/updates/ (Accessed 30-10-2015).

223. Quik, J.T.K., Vonk, A.I., Hansen, S.F., Baun, A., Van De Meent, D. 2011. How to assess exposure of aquatic organisms to manufactured nanoparticles? Environment International 37(6):1068-77.

224. Rauscher, H., Roebben, G., Amenta, V., Boix Sanfeliu, A., Calzolai, L., Emons, H., Gaillard, C., N. Gibson, N., Linsinger, T., Mech, A., Quiros Pesudo, L., Rasmussen, K., Riego Sintes, J., Sokull-Klüttgen, B., Stamm, H. 2014. Towards a review of the EC Recommendation for a definition of the term "nanomaterial" Part 1: Compilation of information concerning the experience with the definition, Eds. H. Rauscher, G. Roebben. JRC Scientific and Policy Report, EUR 26567 EN. Luxembourg: European Commission Joint Research Centre

225. Rauscher, H., Roebben, G., Boix Sanfeliu, A., Emons, H., Gibson, P., Koeber, R., Linsinger, T., Rasmussen, K., Riego Sintes, J., Sokull-Kluettgen, B., Stamm, H.,. 2015. Towards a review of the EC Recommendation for a definition of the term "nanomaterial": Part 3: Scientific-technical evaluation of options to clarify the definition and to facilitate its implementation. Eds. H. Rauscher, G. Roebben. Luxembourg: European Commission Joint Research Centre. Availbale: http://bookshop.europa.eu/is-bin/INTERSHOP.enfinity/WFS/EU-Bookshop-Site/en_GB/-/EUR/ViewPublication-Start?PublicationKey=LBNA27240 (Accessed 02-12-2016)

226. Riediker, M., Ostiguy, C., Triolet, J., Troisfontaine, P., Vernez, D., Bourdel, G., et al., 2012. Development of a Control Banding Tool for Nanomaterials. Journal of Nanomaterials doi:10.1155/2012/879671.

227. Roberts, G. 2016. Commission rejects idea of EU nano register. Chemical Watch. Available: https://chemicalwatch.com/45776/commission-rejects-idea-of-eu-nano-register

228. Robichaud, C.O., Tanzil, D., Weilenmann, U., Wiesner, M.R. 2005. Relative risk analysis of several manufactured nanomaterials: An insurance industry context. Environmental Science & Technology 39(22): 8985–8994.

229. Rocks, S., Pollard, S., Dorey, R., Levy, L., Harrison, P., Handy, R. 2008. Comparison of risk assessment approaches for manufactured nanomaterials. United Kingdom Department for Environment, Food and Rural Affairs.

230. Roebben, G., Rauscher, H., Amenta, V., Aschberger, K., Boix Sanfeliu, A., Calzolai, L., Emons, H., Gaillard, C., Gibson, N., Holzwarth, U., Koeber, R., Linsinger, T., Rasmussen, K. Sokull-Klüttgen, B., Stamm, H. 2014. Towards a review of the EC Recommendation for a definition of the term "nanomaterial" Part 2: Assessment of collected information concerning the experience with the definition, JRC Scientific and Policy Report, EUR 26744 EN, Eds. G. Roebben, H. Rauscher. Luxembourg: European Commission Joint Research Centre.

231. Romero-Franco, M., Godwin, H.A., Bilal, M., Cohen, Y. 2017. Needs and challenges for assessing the environmental impacts of engineered nanomaterials (ENMs). Beilstein Journal of Nanotechnology 8: 989-1014.

232. Sass, J., Heine, L., Hwang, N. 2016. Use of a modified GreenScreen tool to conduct a screening-level comparative hazard assessment of conventional silver and two forms of nanosilver. Environmental Health 15:105. DOI 10.1186/s12940-016-0188-y

233. Savolainen, K., Backman, U., Brouwer, D., Fadeel, B., Fernandes, T., Kuhlbusch, T., Landsiedel, R., Lynch, I. & Pylkkänen, L. (2013). Nanosafety in Europe 2015-2025: Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations Nanosafety in Europe Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations. Available: http://www.etp-nanomedicine.eu/public/news-events/news-archive-1/nanosafety-in-europe-2015-2025-towards-safe-and-sustainable-nanomaterials-and-nanotechnology-innovations (Accessed 02-12-2016).

234. SCCNFP 2002. Updated basic requirements for toxicological dossiers to be evaluated by the SCCNFP Revision 17 december 2002. The scientific committee on cosmetic products and non-food products intended for consumers. Brussels: European Commission http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out185_en.pdf (Accessed 02-12-2016).

235. SCCS 2012a. OPINION ON Zinc oxide (nano form) COLIPA S 76 . Luxembourg: European Commission http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_103.pdf

236. SCCS 2012b. Guidance on the safety assessment of nanomaterials in cosmetics. Luxembourg: European Commission http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_005.pdf

237. SCCS 2013. MEMORANDUM on "Relevance, Adequacy and Quality of Data in Safety Dossiers on Nanomaterials". Luxembourg: European Commission http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_142.pdf

238. SCCS 2014a. Addendum to the opinion SCCS/1489/12 on Zinc oxide (nano form) COLIPA S76 Luxembourg: European Commission http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_137.pdf

239. SCCS 2014b. Opinion on Titanium Dioxide (nano form) COLIPA n° S75 Luxembourg: European Commission http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_136.pdf

240. SCCS 2015a. OPINION on Carbon Black (nano-form) Luxembourg: European Commission http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_144.pdf

241. SCCS 2015b. Opinion on Silica, Hydrated Silica, and Silica Surface Modified with Alkyl Silylates (nano form). Luxembourg: European Commission http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_175.pdf

242. SCCS 2015c. OPINION ON 2,2'-Methylene-bis-(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) (nano form) Luxembourg: European Commission Submission III. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_168.pdf

243. SCCS 2016a. Opinion on additional coatings for Titanium Dioxide (nano form) as UV-filter in dermally applied cosmetic products. Luxembourg: European Commission. Available: https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_202.pdf (Accessed 12-12-2016).

244. SCCS 2016b. Opinion on Hydroxyapatite (nano). Luxembourg: European Commission. Available: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_191.pdf (Accessed 12-12-2016).

245. SCENIHR 2005. Opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies. Brussels: European Commission. Available: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf (Accessed: 09-11-2016).

246. SCENIHR 2007. 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. Brussels: European Commission Health & Consumer Protection Directorate-General. Available: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_010.pdf (Accessed: 09-11-2016).

247. SCENHIR 2009. Opinion on: Risk assessment of products of nanotechnologies. Brussels: European Commission. Available: http://ec.europa.eu/health/archive/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf.

248. SCENIHR 2010. Scientific Basis for the Definition of the Term "Nanomaterial". Brussels: European Commission. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_030.pdf

249. SCENIHR 2014. Opinion on Nanosilver: safety, health and environmental effects and role in antimicrobial resistance. Brussels: European Commission. Available: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_039.pdf (Accessed: 09-11-2016).

250. Schröder, F. 2012. Nano and REACH - On-going activities in Germany. CASG Nano 8 Item 7-1 DE activities.

251. Schwirn, K., Tietjen, L., Beer, I. 2014. Why are nanomaterials different and how can they be appropriately regulated under REACH? Environmental Sciences Europe 26:4. Available: http://www.enveurope.com/content/26/1/4 (Accessed 09-11-2016).

252. Seager, T.P., Linkov, I. 2008. Coupling multicriteria decision analysis and life cycle assessment for nanomaterials. Journal of Industrial Ecology 12(3):282–285.

253. Shatkin, J.A. 2008. Nanotechnology: Health and environmental risks. 1st ed. Boca Raton, FL: CRC Press.

254. Shatkin, J.A. 2009. Investigating the life cycle risks of a nanomaterial in a coating using nano LCRA. Society for risk analysis annual meeting, Symposium M4-I, Baltimore, December 7.

255. Shatkin, J.A., Kim, B. 2015. Cellulose nanomaterials: life cycle risk assessment, and environmental health and safety roadmap. Environmental Science: Nano 2: 477-499.

256. Shinohara N, Gamo M, Nakanishi J (2009). Risk assessment of manufactured nanomaterials. Kawasaki, National Institute of Advanced Industrial Science and Technology, Research Institute of Science for Safety and Sustainability.

257. Som, C., Nowack, B., Krug, H.F., Wick, P. 2012. Toward the Development of Decision Supporting Tools That Can Be Used for Safe Production and Use of nanomaterials. Accounts of Chemical Research 46(3):863–872.

258. Standing Committee on Biocidal Products 2011. Standing Committee on Biocidal Products, Assessment ReportCopper (II)HydroxideProduct-type 8 (Wood preservatives) September 2011 France. http://dissemination.echa.europa.eu/Biocides/ActiveSubstances/0016-08/0016-08_Assessment_Report.pdf (Accessed June 2016).

259. Stone, V., Hankin, S., Aitken, R., Aschberger, K., Baun, A., Christensen, F., Fernandes, T., Hansen, S.F., Hartmann, N.B., Hutchinson, G., Johnston, H., Micheletti, G., Peters, S., Ross, B., Sokull-Kluettgen, B., Stark, D., Tran, L. 2010. Engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES). 2010. Available: http://nmi.jrc.ec.europa.eu/project/ENRHES.htm (Accessed 01-02-2016).

260. Stone, V., Johnston, H.J., Balharry, D., Gernand, J.M., Gulumian, M. 2016. Approaches to Develop Alternative Testing Strategies to Inform Human Health Risk Assessment of Nanomaterials. Risk Analysis 36(8):1538-50.

261. Syberg, K., Hansen, S.F. 2016. Environmental risk assessment of chemicals and nanomaterials - The best foundation for regulatory decision-making? Science of the Total Environment 541: 784–794.

262. Sørensen, S. 2016. Aquatic toxicity testing for hazard identification of engineered nanoparticles. PhD thesis DTU, Denmark, 2016.

263. Sørensen, S.N., Baun, A. 2015. Controlling silver nanoparticle exposure in algaltoxicity testing A matter of timing. Nanotoxicology 9:201–209.

264. Taiwan Nanotechnology Industry Development Association 2007. Nano Mark. http://www.tanida.org.tw/Eng/Mark/ (Accessed 01-06-2016).

265. Tervonen, T., Linkov, I., Figueira, J., Steevens, J., Chappell, M., Merad, M. 2009. Risk-based classification system of nanomaterials. Journal of Nanoparticle Research 11: 757-766.

266. The Nanodatabase 2017. The Nanodatabase. Available: www.nanodb.dk (Accessed 15-01-2017).

267. Tickner JA, Schifano JN, Blake A, Rudisill C, Mulvihill MJ. 2015. Advancing safer alternatives through functional substitution. Environmental Science & Technology 49:742–749.

268. TüV SüD 2008. Certification standard CENARIOS. Munich:TüV SüD Industrie Service GmbH. Available: http://www.tuev-sued.com/uploads/images/1219824286015340810363/CENARIOS_Zertifiziergrundlage_e.pdf (Accessed 09-12-2016).

269. UBA, BfR, BAuA 2013. Nanomaterials and REACH - Background Paper on the Position of German Competent Authorities 30 January 2013. Available: http://www.bfr.bund.de/cm/349/nanomaterials-and-reach.pdf (Accessed 09-12-2016).

270. US EPA 2009. External review draft nanomaterial case studies: Nanoscale titanium dioxide in water treatment and in topical sunscreen. Research Triangle Park, NC: National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency. Report No. EPA/600/R-09/057.

271. US EPA 2010a. Nanomaterial case study: Nanoscale silver in disinfectant spray (external review draft). Washington DC: US Environmental Protection Agency. Report No. EPA/600/R-10/081.

272. US EPA 2010b. Nanomaterial case studies workshop: Developing a comprehensive environmental assessment research strategy for nanoscale titanium dioxide. Workshop summary for the EPA Board of Scientific Counselors, 29–30 September 2009. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Division Office of Research and Development, US Environmental Protection Agency. Report No. EPA/600/R-10/042.

273. van Duuren-Stuurman, B., S. R. Vink, K. J. M. Verbist, H. G. A. Heussen, Brouwer, D. H. Kroese, D. E. D., Van Niftrik, M. F. J., Tielemans, E., Fransman, W. 2012. Stoffenmanager Nano Version 1.0: A Web-Based Tool for Risk Prioritization of Airborne Manufactured Nano Objects. Annals of Occupational Hygiene 56(5): 525-541.

274. van Harmelen, T., Zondervan-van den Beuken, E. K., Brouwer, D. H. , Kuijpers, E., Fransman, W., Buist, H. B., Ligthart, T. N., Hincapié, I., Hischier, R., Linkov, I., Nowack, B., Studer, J., Hilty, L., Som, C. 2016. LICARA nanoSCAN - A tool for the self-assessment of benefits and risks of nanoproducts. Environment International 91: 150-160.

275. Leeuwen, C.J. van, Vermeire, T.G. (Eds.). Risk Assessment of Chemicals: An Introduction Second Edition. Dordrecht: Springer.

276. Vance, M. E., Kuiken, T., Vejerano, E. P., McGinnis, S. P., Hochella, M. F., Jr., Rejeski, D. and Hull, M. S. 2015. Nanotechnology in the real world: Redeveloping the nanomaterial consumer products inventory. Beilstein Journal of Nanotechnology, 6, 1769-1780.

277. Vogelezang-Stoute, E. 2014. Regulating uncertain risks of new technologies: Nanomaterials as a challenge for the regulator. In M. Peeters and R. Uylenburg (Eds.) EU Environmental Legislation Legal Perspectives on Regulatory Strategies. Cheltenhan: Edward Elgar. pp. 211-232.

278. von Goetz, N., Fabricius, L., Glaus, R., Weitbrecht, V., Gunther, D., Hungerbuhler, K. 2013. Migration of silver from commercial plastic food containers and implications for consumer exposure assessment. Food Additives and Contaminants 30:612–620.

279. Walser, T., Limbach, L.K., Brogioli, R., et al. 2012. Persistence of engineered nanoparticles in a municipal solid-waste incineration plant. Nature Nanotechnology 7, 520–524.

280. WHO. 2013. Nanotechnology and human health: Scientific evidence and risk governance. Report of the WHO expert meeting 10–11 December 2012, Bonn, Germany. Copenhagen, WHO Regional Office for Europe.

281. Wickson, F., Hartmann, N. I. B., Hjorth, R., Hansen, S. F., Wynne, B., Baun, A. 2014. Balancing scientific tensions. Nature Nanotechnology 9: 870-870.

282. Wiesner, M.R., Lowry, G.V., Jones, K.L., Hochella, J., Michael, F., Di Giulio, R.T., Casman, E., Bernahardt, E.S. 2009. Decreasing uncertainties in assessing environmental exposure, risk, and ecological implications of nanomaterials. Environmental Science & Technology 43:6458–62.

283. Wijnhoven, S.W.P., Peijnenburg, W.J.G.M., Herberts, C.A., Hagens, W.I., Oomen, A.G., Heugens, E.H.W. Roszek, B., Bisschops, J., Gosens, I., Van De Meent, D., Dekkers, S., De Jong, W.H., van Zijverden, M., Sips, A.J.A.M., Geertsma, R.E. 2009. Nano-silver – a review of available data and knowledge gaps in human and environmental risk assessment. Nanotoxicology 3(2):109–138.

284. Wijnhoven, S.W.P., Oomen, A.G., Sips, A.J.A.M., Bourgeois, F.C., te Dorsthorst, G.J.P.M., Kooi, M.W., Bakker, M.I. 2010. Development of an inventory for consumer products containing nanomaterials. Final Report 070307/2010/580587/SER/D3. Available: http://ec.europa.eu/environment/chemicals/nanotech/pdf/study_inventory.pdf (Accessed 29-10-2015).

285. Zalk, D.M., Paik, S.Y., Swuste, P. 2009. Evaluating the control banding nanotool: A qualitative risk assessment method for controlling nanoparticle exposures. Journal of Nanoparticle Research 11:1685–1704.

286. Zalk, D., Paik, S.Y. 2016. Risk Assessment Using Control Banding, 2nd Edition. In Gurumurthy Ramachandran (Ed.): Assessing Nanoparticle Risks to Human Health, 2nd Edition. Elsevier Inc. pp.121-152.

287. Zainzinger, V. 2015. "Anomalies" in notifications behind nanomaterials inventory delay Cosmetics industry confused by different national rules, lack of test methods. 5 March 2015. Available: https://chemicalwatch.com/23044/anomalies-in-notifications-behind-nanomaterials-inventory-delay?q=nano%2C%20inventory (Accessed 13-08-2015).

288. Zuin S, Micheletti C, Critto A, Pojana G, Johnston H, Stone V, et al. 2010. Weight of evidence approach for the relative hazard ranking of nanomaterials. Nanotoxicology 5: 445-458.

289. Öko-Institut. 2010. Legal feasibility study on the introduction of a nanoproduct register. Freiburg, Institute for Applied Ecology. Available: http://www.bmu.de/files/pdfs/allgemein/application/pdf/bericht_nanoproduktregister_en_bf.pdf (Accessed 30-10-2015).

11. Appendix: Published peer reviewed journal papers

1. Baun, A., Hartmann, N.B., Grieger, K.D., Hansen, S.F. 2009. Setting the Limits for Engineered Nanoparticles in European Surface Waters. Journal of Environmental Monitoring 11: 1774 – 1781.
2. Hansen, S.F. 2010. A global view of regulations affecting nanomaterials. WIRES: Nanomedicine and Nanobiotechnology 2(5): 441-449.
3. Ganzleben, C., Hansen, S.F. 2012. Nanomaterials as priority substances under the Water Framework Directive. European Journal of Law and Technology 2: 38-45.
4. Grieger, K.D., Hansen, S.F., Linkov, I., Baun, A. 2012. Environmental Risks of Nanomaterials: Review and evaluation of Frameworks. Nanotoxicology 6(2): 196-212.
5. Hansen, S.F., Baun, A. 2012. When Enough is Enough. Nature Nanotechnology 7: 409-411.
6. Hansen, S.F., Baun, A. 2012. European regulation affecting nanomaterials – review of limitations and future recommendations. Dose Response 10(3): 364-383.
7. Hansen, S.F. 2013. The European Union's chemical legislation needs revision. Nature Nanotechnology 8: 305–306.
8. Hansen, S.F., Nolde Nielsen, K., Knudsen, N., Grieger, K.D., Baun, A., 2013. Operationalization and application of “early warning signs” to screen nanomaterials for harmful properties. Environmental Science: Processes & Impacts 15: 190-203.
9. Boldrin, A., Hansen, S.F., Baun, A., Hartmann, N., Astrup, T.F. 2014. Environmental exposure assessment framework for nanoparticles in solid waste. Journal of Nanoparticle Research 16:2394 DOI 10.1007/s11051-014-2394-2.
10. Hansen, S.F., Gee, D. 2014. Adequate and anticipatory research on the potential hazards of emerging technologies: a case of myopia and inertia? Journal of Epidemiology and Community Health doi:10.1136/jech-2014-204019.
11. Hansen, S.F., Jensen, K.A., Baun, A. 2014. NanoRiskCat: A conceptual tool for categorization and communication of exposure potentials and hazards of nanomaterials in consumer products. Journal of Nanoparticle Research 16(1): 2195 DOI 10.1007/s11051-013-2195-z.
12. Hansen, S.F., Jensen, K.A., Baun, A. 2017. Erratum to: NanoRiskCat: a conceptual tool for categorization and communication of exposure potentials. Journal of Nanoparticle Research. 19:236. DOI 10.1007/s11051-017-3909-4.
13. Wickson, F., Hartmann, N. I. B., Hjorth, R., Hansen, S. F., Wynne, B., Baun, A. 2014. Balancing scientific tensions. Nature Nanotechnology 9: 870-870.
14. Hansen, S.F., Baun, A. 2015. DPSIR and Stakeholder Analysis of the Use of Nanosilver. NanoEthics 9(3): 297-319.
15. Syberg, K., Hansen, S.F. 2016. Environmental risk assessment of chemicals and nanomaterials - The best foundation for regulatory decision-making? Science of the Total Environment 541: 784–794.

16. Brinch, A., Hansen, S.F., Hartmann, N.B., Baun, A. 2016. EU regulation of nanobiocides: challenges in implementing the Biocidal Product Regulation (BPR), Nanomaterials 6(2), 33. doi:10.3390/nano6020033.
17. Hansen, S.F. 2016. The emergence of nanorisk-immunity. Frontiers of Nanoscience and Nanotechnology 2(3): 131-134.
18. Hansen, S.F., Heggelund, L.R., Besora, P.R., Mackevica, A., Boldrin, A., Baun, A. 2016. Nanoproducts – What is actually available to European consumers? Environmental Science: Nano 3(1): 169-180.
19. Heggelund, L.R., Hansen, S.F., Astrup, T., Boldrin, A. 2016. Semi-quantitative waste flow analysis of nano-enabled products in Denmark and the United Kingdom – Abundance, distribution and treatment. Waste Management 56: 584-92.
20. Liguori, B., Hansen, S.F., Baun, A., Jensen, K.A. 2016. Control banding tools for occupational exposure assessment of nanomaterials - Ready for use in a regulatory context. NanoImpact 2: 1–17.
21. Mackevica, A., Besora, P.R., Brinch, A., Hansen, S.F. 2016. Current uses of nanomaterials in biocidal products and treated articles in the EU. Environmental Science: Nano 3: 1195-1205.
22. Mackevica, A., Hansen, S.F. 2016. Release of nanomaterials from solid nanocomposites and consumer exposure assessment – A forward-looking review. Nanotoxicology 10(6): 641-653.
23. Mackevica, A., Olsson, M.E., Hansen, S.F. 2016. Silver nanoparticle release from commercially available plastic food containers into food simulants. Journal of Nanoparticle Research 18: 5 DOI 10.1007/s11051-015-3313-x
24. Mackevica, A., Olsson, M.E., Hansen, S.F. 2016. The release of silver nanoparticles from commercial toothbrushes. Journal of Hazardous Materials, 322(Part A): 270–275.
25. Hansen, S.F., Hjorth, R., Skjolding, L.M., Bowman, D.M., Maynard, A., Baun, A. 2017. A critical analysis of the environmental dossiers from the OECD sponsorship programme for the testing of manufactured nanomaterials. Environmental Science: Nano 4: 282 – 291.
26. Hansen, S.F. Sørensen, S., Skjolding, L.M., Hartmann, N., Baun, A. 2017. Revising REACH technical guidance on information requirements and chemical safety assessment for engineered nanomaterials for aquatic ecotoxicity endpoints – Recommendations from the EnvNano project. Environmental Science Europe 29:14 DOI 10.1186/s12302-017-0111-3.
27. Hjorth, R., Hansen, S.F., Jacobs, M., Tickner, J., Ellenbecker, M., Baun, A. 2017. The applicability of chemical alternatives assessment for engineered nanomaterials. Integrated Environmental Assessment and Management 13(1):177-87.
28. Hansen, S.F. 2017. React now regarding nanomaterial regulation. Nature Nanotechnology 12: 714-716.

Please note that the published peer reviewed journal papers are not included in this web version but can be obtained from electronic article databases e.g. via www.orbit.dtu.dk or on request from DTU Environment, Technical University of Denmark, Bygningstorvet, Building 115, 2800 Kgs. Lyngby, Denmark, info@env.dtu.dk.

Steffen Foss Hansen is Associate Professor in Regulatory Engineering at the Technical University of Denmark, Department of Environmental Engineering (DTU Environment). He has a Master Degree in Technological and Socio-Economic Planning from Roskilde University and a Ph.D. from DTU Environment. He teaches courses in 1) Nanotechnology and the Environment and 2) Environmental Management and Ethics whereas his research activities focuses on 1) how science and engineering can best be used in regulatory settings in situations pervaded by scientific uncertainty and complexity and 2) risk analysis, regulation and governance of nanotechnologies, and the applicability of decision-making tools.

DTU Environment is one of the largest university departments in Europe specialising in water, environmental engineering and sustainability. The department is working to develop new environmentally friendly and sustainable technologies and disseminate this knowledge to society and new generations of engineers. DTU Environment has around 180 employees of more than 30 nationalities. Focus is on water resources engineering, urban water systems, water technology, residual resource engineering, atmospheric environment and environmental chemistry.

DTU Environment
Department of Environment Engineering
Technical University of Denmark

Bygningstorvet, buildning 115
2800 Kongens Lyngby
Denmark

Phone: +45 4525 1600
e-mail: info@env.dtu.dk
www.env.dtu.dk

ISBN 978-87-93478-84-8