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Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products

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Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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Foreword

Technological innovations such as nanotechnology are being developed at such a rapid pace that they present a challenge to health and environmental risk assessment. Because of this rapid innovation, a gap can arise between technological innovations and the development of suitable risk assessment tools and frameworks.

A way to minimise this gap is (a) for industry to try to reduce uncertainties and risks to human and environmental safety, starting at an early phase of the innovation process and covering the whole innovation value chain (the 'Safe(r)-by-Design' concept); and (b) for regulators to anticipate the regulatory challenges posed by innovations such as innovative nanomaterials (NMs) and nano-enabled products, their applications and potential safety issues (Regulatory Preparedness). These two distinct components together form a 'Safe(r) Innovation Approach'.

When facing 'emerging risks' of innovations in nanotechnology and nano-enabled products, the challenge is to make appropriate product development and risk assessment / risk management decisions in the context of present uncertainties. These uncertainties can be reduced by using appropriate frameworks and the development and use of suitable OECD Test Guidelines. Thus, for the identification of potential emerging risks of NMs and nano-enabled products, there is the need to support the development of suitable Test Guidelines, as well as relevant risk assessment tools and frameworks for a Safe(r) Innovation Approach.

Chemical safety is considered a necessary element of sustainability which, as described e.g. by the United Nations Sustainable Development Goals, is a wider concept. Sustainability is not specifically addressed by this document. Nevertheless, some tools pertaining to sustainability assessment, also useful vis-a-vis safety, such as Life Cycle Analysis (LCA) and Socio-Economic Analysis (SEA), are included in the proposed Safe(r) Innovation Approach (SIA).

Based on the considerations mentioned above, representatives from France (INERIS), the Netherlands (RIVM), the European Union (Joint Research Centre of the European Commission), and Industry (Business and Industry Advisory Committee) prepared a project proposal that was presented to the OECDs Working Party on Manufactured Nanomaterials (hereafter WPMN). The WPMN agreed to contribute to the discussion on Safe(r)-by-Design by describing the state-of-the-art frameworks available and initiatives conducted in support of future decision-making when developing more sustainable products, processes and uses. Accordingly, this document is not intended to comment on or replace any existing regulations (especially those to be fulfilled before placing on the market substances or products), nor to circumvent these obligations by a "Safe(r)-by-Design" certificate.

Acronyms

ALARP	As Low As Reasonably Practicable
ANSES	Agence Nationale de sécurité sanitaire de l'Alimentation, de l'Environnement et du Travail (France)
ANSI	American National Standard Institute
AR	Augmented Reality
ASSP	American Society of Safety Professionals
AVICENN	Association de Veille et d'Information Civique sur les Enjeux de Nanosciences et des Nanotechnologies (France)
BfR	Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment - Germany)
BLMs	Biotic Ligand Models (BLMs),
BMU	Bundesministerium für Umwelt, Naturschutz und Nuklear Sicherheit (German Ministry of Environment)
BN	Bayesian Network
BOV	Bewust Omgaan met Veiligheid (Ministry of Infrastructure and Water Management - the Netherlands)
CB	Control Banding
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CEREGE	Centre de recherche et d'Enseignement de Géosciences de l'Environnement (France)
CEPA	Canadian Environmental Protection Act.
COENs	Center of Excellence in Nanotechnology (Thailand)
CPP	Critical Process Parameters
CPSC	Consumer Product Safety Commission (USA)
CQAS	Critical Quality Attributes
CPWR	Center to Protect Workers' Rights (now Center for Construction Research and Training, USA)
DEFRA	Department for Environment Food & Rural Affairs (UK)
DG EPRS	Directorate-General for Parliamentary Research Service (EU)
ECCC	Environment and Climate Change Canada
ECETOC	European Centre for Ecological and toxicology of Chemicals
ECHA	European Chemicals agency
EFP	European Foresight Platform
EFSA	European food safety Authority
EHS	Environmental, Health and Safety
EMA	European Medicines Agency
ENVID	Issues Identification
EPA	Environnemental Protection Agency (USA)
ERGC	European Risk Governance Council
ETA	Event tree analysis
EUON	European Observatory for Nanomaterials
FDA	Food and Drug Administration (USA)
FMEA	Failure mode effects analysis
FNN	Future Nano Needs
FTA	Fault tree analysis
GBP	Granular Biopersistent Particles
GDP	Good Distribution Practices
GMOs	Genetically Modified Organisms
GMPs	Good Manufacturing Practices

HAZAN Hazard Analysis
HAZID Hazard Identification
HAZOP Hazard and operability
HC Health Canada
HSWA Health and Safety at Work Act
ICON International Council on Nanotechnology
INERIS Institut national de l'environnement industriel et des risques
ITF Innovation Task Force (of the European Medicines Agency
IRGC International Risk Governance Council
JRC Joint Research Centre (European Commission)
LCA Life Cycle Analysis
LICARA Life Cycle Approach and Human risk Impact Assessment
LOPA Layer of protection analysis
MAP Monitoring, Analyzing and Positioning
MCA Multi-Criteria Analysis
MFA Material Flow Analysis
MSRA Machine Safety Risk Assessment
MNMs Manufactured Nanomaterials
MTES Ministère de la Transition Écologique et Solidaire (France)
NBM Nanobiomaterials
NEPs Nano-Enabled Products
NFs Nano Fibers
NIA Nanotechnology Industries Association
NIOSH National Institute for Occupational Safety and Health
NMs Innovative Nanomaterials
NNI National Nanotechnology Initiative (USA)
NRGC Nanotechnology Risk Governance Council
NRGM Nano Risk Governance Model
NSC Nano Safety Cluster
NSTDA National Science and Technology Development Agency (Thailand)
OEL Occupational Exposure Levels
OSHA Occupational Safety and Health administration (USA)
PBPK Physiologically Based Pharmacokinetic
PEC Predicted Environmental Concentrations
PPE Personal Protective Equipment
PtD Prevention through Design
(Q)SAR Quantitative Structure-Activity relationship
RA Risk Assessments
RAPEX system Rapid Alert System for dangerous non-food products (EU)
REACH Registration, Evaluation and Authorization of Chemicals (EU)
RIVM Rijksinstituut voor Volkgezondheid en milieuhygiëne (National Institute for Public Health and the Environment, the Netherlands)
RGF Risk Governance Framework
RP Regulatory Preparedness
RRI Responsible Research and Innovation (Norway)
SbD Safer-by-Design, Safe-by-Design or Safety-by-Design
SEA Socio-Economic Analysis
SIA Safe(r) Innovation Approach
SMEs Small and Medium-size Enterprises (SMEs)
STEEPED Social, Technological, Economic, Environmental, Political/legal, Ethical and Demographic
STOA Science Technology Option assessment (Panel for the Future of Sciences and Technology

	- EU)
SUNDS	Sustainable Nanotechnologies Project Decision Support System
TE	Trusted Environment
TLRs	Technology readiness levels
TRA	Target Risk Assessment
TRL	Technology Readiness Levels
TIP	Tire Industry Project
TRWP	Tyre and Road Wear Particles
UBA	Umweltbundesamt (German Environmental Agency)
VR	Virtual Reality
WBCSD	World Business Council for Sustainable Development
WHO	World Health Organization
WRR	Water Resources Research

Executive Summary

This OECD project aims to contribute to the discussion on a 'Safe(r) Innovation Approach' for more sustainable nanomaterials and nano-enabled products. The document presents common working descriptions to ensure a common understanding of concepts such as: Safe(r) Innovation Approach and its elements, Safe(r)-by-Design and Regulatory Preparedness. Then the document compiles existing risk assessment tools, frameworks and initiatives developed for Safe(r)-by-Design. The inventory of risk assessment tools and frameworks should contribute in assisting industry to implement a 'Safe(r) Innovation Approach' for NMs and nano-enabled products. This includes a review of lessons learned from applying existing Safe(r)-by-Design concepts and tools and methods applied in hazard, exposure and risk assessment and management along the innovation value chain. A review of the applicability of the Safe(r)-by-Design concept, based on feedback gained through case studies and existing initiatives was conducted. The constraints and limitations on the applicability of these tools and frameworks were analysed. This information is complemented by an inventory of regulatory strategies for raising awareness and improving decision-making, including foresight, horizon scanning and other methodologies, and of available governance models that incorporate a Safe(r) Innovation Approach and Safe(r)-by-Design concept. The constraints and limitations on the applicability of these strategies and governance models are also outlined. Finally, the document compiles information on regulatory initiatives related to the review of innovative approaches and technologies [(OECD, 2016 and 2015b); (EPRS, 2015), Trusted Environment, pre-consultation processes]. This includes an assessment as to whether these concepts are already integrated into current legislation or guidance.

The document proposes the combination of Safe(r)-by-Design and relevant regulatory strategies for awareness raising and decision making to achieve a Safe(r) Innovation Approach. Accordingly, it supports industrial initiatives in adopting a Safe(r) Innovation Approach with descriptors for a Safe(r) Innovation Approach for NMs and nano-enabled products.

The document is an initial contribution to a growing field that tries to bridge the fast pace of innovations with safety regulations. This OECD project sought to identify commonalities with respect to the Safe(r) Innovation Approach (SIA). SIA combines the Safe(r)-by-Design concept and the Regulatory Preparedness concept. Different initiatives often use slightly different terminology (e.g. Safer-by-Design, Safe-by-Design, Safety-by-Design), while essentially referring to the same concept. To ensure broad inclusion of the different initiatives worldwide, the project opted for the use of 'safe(r)' in its working descriptions. The working descriptions that were developed helped are meant to facilitate the discussion and further promote safe(r) innovation approaches. It can be updated in light of experience gained in the future.

Working Descriptions

1. One of the objectives of this project was to develop a common understanding and working definitions for the Safe(r) Innovation Approach and its elements, the Safe(r)-by-Design and the Regulatory Preparedness concepts. In the course of the project, the "working definitions" aim was modified to "**working descriptions**", which were seen as less formal and concise, and more descriptive.

2. Safer-by-Design (SbD), also named Safe-by-Design or Safety-by-Design, is one of the terms used in different industrial fields and geographical areas to refer to essentially the same concept of reducing the various types of risks of materials, constructions and products at the design stage. The risks addressed range from accidents (e.g. tunnel or occupational safety) to the intrinsic toxicity hazards of chemicals and materials. Some other terms have also been used recently in the field of nanotechnology [e.g. Prevention through Design (PtD), green nanotechnology]. Both of the forms "Safer-by-Design" and "Safe-by-Design" have been used interchangeably at least since the 1990s in e.g. construction industry and road tunnel safety, thus predating the use of the concept in the nanotechnology context, and both forms continue to be used today. The use of the term "safer" rather than "safe" emphasises the unattainability of absolute safety[1,2,3], while the use of "safe" sets a clearer end goal than the ongoing incremental steps suggested by the term "safer".

3. In the context of the safety of nanotechnology, concepts synonymous or closely related to Safe(r)-by-Design (e.g. "safe design") and Regulatory Preparedness ("anticipatory governance") have been discussed in literature since the 2000s. The EU FP7 project NANoREG ["A common European approach to the regulatory testing of nanomaterials"] (2013–2017) developed an elaborate SbD concept (2016)[4] to ensure that while aiming for Safety by Design (i.e. that safety aspects are taken into account throughout the innovation process, particularly in the design phase) the industry also prepares for regulatory requirements for safety, as demonstrated by a safety assessment. The EU Horizon 2020 project NanoReg2[5] ["Development and implementation of Grouping and Safe-by-Design approaches within regulatory frameworks"] (2015–2018) then coupled SbD to the regulatory process for ensuring the safety of novel nanotechnology. This was done by conceptualising Regulatory Preparedness (RP), the readiness of regulators to handle nanotechnology and other innovative technologies[6,7], and by combining SbD and RP into a Safe(r)

[1] Fadeel, 2013. Nanosafety: towards safer design of nanomedicines. Journal of Internal Medicine vol. 274, pp. 578–580, doi: 10.1111/joim.12137

[2] Hjorth et al, 2017. What can nanosafety learn from drug development? The feasibility of "safety by design", Nanotoxicology vol. 11 (3), pp. 305-312, doi: 10.1080/17435390.2017.1299891

[3] Schwarz-Plaschg et al, 2017. Making Nanomaterials Safer by Design? Nanoethics vol. 11, pp. 277–281, doi: 10.1007/s11569-017-0307-4

[4] Noorlander et al, 2016. NANoREG Safe-by-Design (SbD) Concept.

http://www.nanoreg.eu/images/20160602_NANoREG_SbD_concept_final.pdf

[5] http://www.nanoreg2.eu/about

[6] Jantunen et al, 2018. Workshop on Regulatory Preparedness for Innovation in Nanotechnology. EUR 29357 EN, doi: 10.2760/278827, JRC112766

[7] Soeteman-Hernández et al, 2019. Perspective on how regulators can keep pace with innovation: Outcomes of a European Regulatory Preparedness Workshop on nanomaterials and nano-enabled products. NanoImpact vol. 14, 100166, doi: 10.1016/j.impact.2019.100166

Innovation Approach (SIA), conceived to improve safety-related communication and collaboration between industry and regulators[8].

4. In practice, the design process of e.g. nanotechnology requires finding an acceptable balance between various factors including safety, functionality and profitability. Since the desired and the potentially hazardous properties of MNMs both tend to be linked to their reactivity with their surroundings, maximal safety (non-reactivity) would easily render a MNM non-functional and therefore unmarketable[1,3]. Ultimately, the regulatory requirements for safety in various sectors are in place to prevent products that are not safe enough to fulfil certain criteria from reaching the market. The previously mentioned SbD concepts for nanotechnology aim to help industry in deciding whether or not these requirements can be fulfilled while creating a functional and profitable product, and to continue or abandon a research and design process accordingly at any particular stage.

5. RP can be seen as a way of applying the Precautionary Principle in a proactive and time-efficient way: regulators acquire information about a new technology, its characteristics and potential safety concerns early enough while the technology is still in development so that the necessary regulatory tools, such as adapted legislation and appropriate safety assessment methodology, can already be in place when industry is ready to seek any necessary market approval.

6. From the large variety of literature definitions and descriptions of these concepts, this OECD project sought to distil working descriptions with a wide(r) international acceptance and support. The SIA Ad hoc Expert Group reached consensus on the four working descriptions presented in this document in June 2019, and agreed to circulate them to the WPMN, who approved them in September 2020.

7. The European Commission's Joint Research Centre (JRC) accepted to lead the development of working descriptions for the Safe(r)-by-Design concept. In addition to the JRC, experts from France, Germany, the Netherlands, South Africa and United Kingdom expressed their willingness to work on this task.

8. From October to December 2018, in three teleconferences and by e-mail, the Ad hoc group discussed which terms should be defined within this project. The JRC circulated its report "NANoREG harmonised terminology for environmental health and safety assessment of nanomaterials"[9] that presented similar terminology definition work previously performed by JRC. It was emphasised that the definition of even one term requires significant effort in terms of literature research, discussion and decision-making.

9. It was eventually decided that the project's terminology work should focus on Safe(r)(ty)-by-Design, Regulatory Preparedness and Safe(r) Innovation Approach, which were developed as described in section 1 of this report. Additionally, the term “Trusted Environment” was developed with a first description prepared by RIVM, as at drafting the description of Safe(r) Innovation Approach, a need for also describing the concept of Trusted Environment was recognised. In December 2018, the JRC collected and analysed literature definitions and descriptions of these three terms, producing for each an Excel file that lists these definitions (together with the appropriate literature references) and breaks down their various elements and differences in scope and wording.

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[8] Soeteman-Hernandez et al, 2019. Safe Innovation Approach: Towards a future-proof system for innovations. Materials Today Communications vol. 20, 100548, doi: 10.1016/j.mtcomm.2019.100548

[9] Gottardo et al, 2016. NANoREG harmonised terminology for environmental health and safety assessment of nanomaterials. EUR 27808, doi: 10.2788/71213

10. Concept papers concerning Safe-by-Design from the projects NANoREG[5] and ProSafe (Promoting the Implementation of Safe by Design)[10] outline the whole Safe(r) Innovation Approach and therefore formed the basis of the three terms Safe(r)(ty)-by-Design, Regulatory Preparedness and Safe(r) Innovation Approach. Outside of these documents, the starting point for describing Safe(r)(ty)-by-Design was the NANoREG harmonised terminology[9] and the literature documented in it. With Regulatory Preparedness, the similar starting point was the 2018 report of the NanoReg2 Workshop on Regulatory Preparedness for Innovation in Nanotechnology[6], including this workshop's background document and the literature collected for it by RIVM (the Netherlands) on the two closely related concepts "anticipatory governance" and "regulatory preparedness". Additional and more recent literature was searched for on SCOPUS. Regarding the term Safe(r) Innovation Approach, relevant literature was identified by searching for "safe innovation" and "safer innovation".

11. JRC produced draft descriptions of each term and circulated these within the Ad hoc group in January (Safe(r)(ty)-by-Design), February (Regulatory Preparedness) and April 2019 (Safe(r) Innovation Approach). In the meanwhile, RIVM performed a survey among the Ad hoc group in February in order to scope out preferences and interpretations regarding Safe(r)(ty)-by-Design and Regulatory Preparedness. The results of this survey are in Annex 2, detailing the preferences and interpretations on terms.

12. Discussion within the Ad Hoc group regarding the draft terminology took place by e-mail, during teleconferences, and in a face-to-face meeting organised in Paris on 19th February 2019. It was decided that instead of "definitions", the project should aim for "working descriptions" of the selected terminology. Safe(r)(ty)-by-Design raised the most discussion: initially it was suggested that Safe-by-Design, Safer-by-Design and Safety-by-Design should be described separately. However, this was eventually abandoned since these terms are in essence used synonymously in literature, with minor differences in emphasis (safe vs. safer).

13. The draft working descriptions of all four terms, Safe(r)(ty)-by-Design, Regulatory Preparedness, Safe(r) Innovation Approach and Trusted Environment, were discussed and further developed in two teleconferences of the Ad hoc group in May and June 2019, eventually reaching a common understanding and agreement among the group. These working descriptions to the WPMN were refined in following months, and then circulated to the WPMN in October/November 2019 for comments and agreement. Taking into account comments received from Germany, the Netherlands and United Kingdom, the working descriptions could be finalised. The agreed working descriptions are given below.

Safe(r)-by-Design

14. The SbD (Safe-by-Design, Safer-by-Design, or Safety-by-Design) concept refers to identifying the risks and uncertainties concerning humans and the environment at an early phase of the innovation process so as to minimize uncertainties, potential hazard(s) and/or exposure. The SbD approach addresses the safety of the material/product and associated processes through the whole life cycle: from the Research and Development (R&D) phase to production, use, recycling and disposal.

15. For SbD in nanotechnology, three pillars of design can be specified:

I. **Safe(r) material/product**: minimising, in the R&D phase, possible hazardous properties of the nanomaterial or nano-enabled product while maintaining function;

[10] Höhener et al, 2016. ProSafe Safe-by-Design (SbD) Implementation Concept.

https://www.rivm.nl/en/documenten/prosafe-safe-by-design-sbd-implementation-concept-final

II. **Safe(r) production**: ensuring industrial safety during the production of nanomaterials and nano-enabled products, more specifically occupational, environmental and process safety aspects; and

III. **Safe(r) use and end-of-life**: minimising exposure and associated adverse effects through the entire use life, recycling and disposal of the nanomaterial or nano-enabled product. This can also support circular economy.

16. Safety to human health and the environment is always relative rather than absolute. SbD strives for negligible human and environmental safety risks through an acceptable balance between safety, product functionality, and, as far as possible, costs, while meeting any applicable regulatory requirements for human and environmental safety and taking into account how the specific aspects of the innovative material/product may affect safety. In addition, the SbD approach helps to produce the safety-related information and data needed in order to comply with regulatory requirements and effectively communicate on any remaining risks.

Regulatory Preparedness

17. Regulatory Preparedness refers to the capacity of regulators, including policymakers, to anticipate the regulatory challenges posed by emerging technologies such as nanotechnology, particularly human and environmental safety challenges. This requires that regulators become aware of and understand innovations sufficiently early to take appropriate action, and that appropriate regulatory tools are modified or developed as needed. Regulatory Preparedness helps to ensure that innovative materials and products undergo suitable (and if appropriate, adapted) safety assessment before entering the market.

18. Regulatory Preparedness requires dialogue and knowledge-sharing among regulators and between regulators and innovators, industry and other stakeholders. This communication and interaction help regulators to anticipate the need for new or modified regulatory tools, and reduce the uncertainties for innovators and industry associated with the future development of the safety legislation and regulations applicable to emerging technologies.

Safe(r) Innovation Approach (SIA)

19. The Safe(r) Innovation Approach (SIA) combines the Safe(r)-by-Design and Regulatory Preparedness concepts in order to identify and minimize the possible health and environmental risks of innovative materials, products, applications, and processes in a timely manner during the innovation process.

20. SIA addresses regulatory requirements for safety, including any necessary adaptations to cover the specific properties of materials or technologies. SIA thus relies on dialogue between industry and regulators and, as appropriate, other stakeholders. This dialogue ideally starts at an early stage of the innovation process and is facilitated by a Trusted Environment.

Trusted Environment

21. A Trusted Environment (TE) is a physical or virtual space in which industry, innovators and governmental institutions and, as appropriate, other stakeholders can share and exchange knowledge, information and views on new technologies, such as innovative nanomaterials and nano-enabled products. A TE invites trust by ensuring confidentiality and protecting intellectual property. Information-sharing through a TE is motivated by mutual benefit (e.g. reduced uncertainty), and entails some pre-requisites:

a) Appropriate technical conditions that give organisations control over the process of information sharing (anonymity, logging of actions etc.)

b) Juridical certainty to safeguard the information exchange process (non-disclosure agreements, regulations etc.)

c) Clarity and agreement about rules of behaviour on dealing with the obtained information (Code of Conduct).

22. When these requirements are complied with and confidentiality as far as requested by the participants is maintained, a TE stimulates transparency and openness on the exchanged information.

23. Examples of Trusted Environment:

- The European Medicines Agency (EMA), for instance, has an Innovation Task Force and a pre-consultation process which allows the agency to anticipate the regulatory challenges posed by innovations, provides an entry point for promoting innovative technology and methods, contributes towards preparing for regulatory processes and provides a platform for exchange of information between innovators and regulators for the benefit of public health.
- The Food Safety Authority of Ireland also has a working TE where innovators are often in dialogue with regulators for ensuring the safety and clarifying legal uncertainty surrounding the innovative product.

References on Working Descriptions

24. This section present four lists of references used for the development of the working descriptions. As such, there is some overlap between these lists. While each of the publications listed was identified as relevant and studied when developing the description of the term in question, those **in bold** contained useful elements for the eventual descriptions.

Literature for Safe(r) by Design

Accomasso, L., Cristallini, C. and Giachino, C., 2018. Risk Assessment and Risk Minimization in Nanomedicine: A Need for Predictive, Alternative, and 3Rs Strategies. *Frontiers in Pharmacology* 9: 228, DOI: doi: 10.3389/fphar.2018.00228

Adlhart, C., Verran, J., Azevedo, N. F., Olmez, H., Keinänen-Toivola, M. M., Gouveia, I., Melo, L. F. and Crijns, F., 2018. Surface modifications for antimicrobial effects in the healthcare setting: a critical overview. *Journal of Hospital Infection* 99: 239–249, DOI: 10.1016/j.jhin.2018.01.018

Barrick, A., Mouneyrac, C., Manier, N., De Lantivya, L., Jrad, N. and Châtela, A., 2018. Towards the development of a high throughput screening approach for Mytilus edulis hemocytes: A case study on silicon-based nanomaterials. *Marine Environmental Research* 142: 306–318, DOI: 10.1016/j.marenvres.2018.10.014

Bergeson, L. L., 2013. Sustainable Nanomaterials: Emerging Governance Systems. *ACS Sustainable Chemistry & Engineering* 1: 724−730, DOI: 10.1021/sc4000863

Burello, E., 2015. Computational design of safer nanomaterials. *Environmental Science: Nano*2: 454, DOI: 10.1039/c5en00066a

Cobaleda-Siles, M., Guillamon, A.P., Delpivo, C., Vázquez-Campos, S. and Puntes, V.F., 2017. Safer by design strategies. *IOP Conference Series: Journal of Physics: Conference Series* 838: 012016, DOI: 10.1088/1742-6596/838/1/012016

European Agency for Health and Safety at Work (EU-OSHA), 2015. Position Paper 2 Leadership in enabling and industrial technologies: Prevention through Design. https://osha.europa.eu/it/position-paper2-prevention-through-design

Fadeel, B., 2013. Nanosafety: towards safer design of nanomedicines. *Journal of Internal Medicine* 274: 578–580, DOI: 10.1111/joim.12137

Gardini, D., Blosi, M., Ortelli, S., Delpivo, C., Bussolati, O., Bianchi, M. G., Allegri, M., Bergamaschi, E. and Costa, A. L. 2018. Nanosilver: An innovative paradigm to promote its safe and active use. *NanoImpact* 11: 128–135, DOI: 10.1016/j.impact.2018.06.003

Gottardo, S., Quiros Pesudo, L., Totaro, S., Riego Sintes, J. and Crutzen, H., 2016. NANoREG harmonised terminology for environmental health and safety assessment of nanomaterials. EUR 27808, doi: 10.2788/71213

Hale, A., Kirwan, B. and Kjellén, U., 2007. Safe by design: where are we now? *Safety Science* 45: 305–327, DOI: 10.1016/j.ssci.2006.08.007

Hernandez, L. and Noorlander, C., 2016. Towards a harmonised terminology in NanoReg2. Project document, draft.

Hjorth, R., van Hove, L. and Wickson, F., 2017. What can nanosafety learn from drug development? The feasibility of "safety by design", *Nanotoxicology* 11 (3): 305–312, DOI: 10.1080/17435390.2017.1299891

Höhener, K., Höck, J., Lehmann, H.C. and Tãnãsescu, S., 2016. ProSafe Safe-by-Design (SbD) Implementation Concept. https://www.rivm.nl/en/documenten/prosafe-safe-by-design-sbd-implementation-concept-final

Jantunen, P. et al., 2018. Workshop on Regulatory Preparedness for Innovation in Nanotechnology. EUR 29357 EN, DOI: 10.2760/278827, JRC112766

Kraegeloh, A., Suarez-Merino, B., Sluijters, T. and Micheletti, C., 2018. Implementation of Safe-by-Design for Nanomaterial Development and Safe Innovation: Why We Need a Comprehensive Approach. *Nanomaterials* 8: 239, DOI: 10.3390/nano8040239

Leso, V., Fontana, L. and Iavicoli, I., 2018. Nanomaterial exposure and sterile inflammatory reactions. *Toxicology and Applied Pharmacology* 355: 80–92, DOI: 10.1016/j.taap.2018.06.021

Lin, S., Yu, T., Yu, Z., Hu, X., Yin, D., 2018. Nanomaterials Safer-by-Design: An Environmental Safety Perspective. Advanced Materials 30: 1705691, DOI: 10.1002/adma.201705691

López de Ipiña, J.M., Hernan, A., Cenigaonaindia, X., Insunza, M., Florez, S., Seddon, R., Vavouliotis, A., Kostopoulos, V., Latko, P., Duralek P. and Kchit, N., 2017. Implementation of a safe-by-design approach in the development of new open pilot lines for the manufacture of carbon nanotube-based nano-enabled products. *IOP Conference Series: Journal of Physics: Conference Series* 838: 012018, DOI: 10.1088/1742-6596/838/1/012018

Lynch, I., Weiss, C. and Valsami-Jones, E., 2014. A strategy for grouping of nanomaterials based on key physico-chemical descriptors as a basis for safer-by-design NMs. *Nano Today* 9: 266–270, DOI: 10.1016/j.nantod.2014.05.001

Meng, H., Xia, T., George, S. and Nel, A.E., 2009. A Predictive Toxicological Paradigm for the Safety Assessment of Nanomaterials. *ACS Nano* 3 (7): 1620–1627, DOI: 10.1021/nn9005973

Micheletti, C., Roman, M., Tedesco, E., Olivato, I. and F. Benetti, 2017. Implementation of the NANoREG Safe-by-Design approach for different nanomaterial applications. *IOP Conference Series: Journal of Physics: Conference Series* 838, 012019, DOI: 10.1088/1742-6596/838/1/012019

Noorlander, C., Sips, A., Höck, J., Höhener, K. and Lehmann, H.C., 2016. NANoREG Safe-by-Design (SbD) Concept. https://www.rivm.nl/sites/default/files/2018-11/NANoREG%20WP6%20Task%206.2%20Safe%20by%20Design%20concept.pdf

OECD, 2017. Alternative testing strategies in risk assessment of manufactured nanomaterials: Current state of knowledge and research needs to advance their use. Series on the Safety of Manufactured Nanomaterials No. 80, ENV/JM/MONO(2016)63

OECD, 2018. Moving Towards a 'Safer Innovation Approach' for More Sustainable Nanomaterials and Nano-enabled Products: Overview of existing risk assessment tools and frameworks, and their applicability in industrial innovations, Revised project proposal ENV/CHEM/NANO(2017)19/REV2

Ortelli, S., Costa, A. L., Matteucci, P., Miller, M. R., Blosi, M., Gardini, D., Tofail, S. A. M., Tran, L., Tonelli, D. and Poland, C. A., 2018. Silica modification of titania nanoparticles enhances photocatalytic production of reactive oxygen species without

increasing toxicity potential in vitro. RSC Advances 8: 40369, DOI: 10.1039/c8ra07374k

Pagano, L., Maestri, E., Caldara, M., White, J. C., Marmiroli, N. and Marmiroli, M., 2018. Engineered Nanomaterial Activity at the Organelle Level: Impacts on the Chloroplasts and Mitochondria. ACS Sustainable Chemistry & Engineering 6: 12562−12579, DOI: 10.1021/acssuschemeng.8b02046

Rausand, M. and Utne, I. B. 2009. Product safety – Principles and practices in a life cycle perspective. *Safety Science* 47: 939–947, DOI: 10.1016/j.ssci.2008.10.004

Robaey, Z., Spruit, S.L. and van de Poel, I., 2018. The Food Warden: An Exploration of Issues in Distributing Responsibilities for Safe-by-Design Synthetic Biology Applications. Science and Engineering Ethics 24: 1673–1696, DOI: 10.1007/s11948-017-9969-0

Schwarz-Plaschg, C., Kallhoff, A. and Eisenberger, I., 2017. Making Nanomaterials Safer-by-Design? *Nanoethics* 11: 277–281, DOI: 10.1007/s11569-017-0307-4

van de Poel, I., Robaey, Z., 2017. Safe-by-Design: from Safety to Responsibility. *Nanoethics* 11: 297–306, DOI: 10.1007/s11569-017-0301-x

Vlasova, I. I., Kapralov, A. A., Michael, Z. P., Burkert, S. C., Shurin, M. R., Star, A., Shvedova, A. A. and Kagan, V. E., 2016. Enzymatic oxidative biodegradation of nanoparticles: Mechanisms, significance and applications. *Toxicology and Applied Pharmacology* 299: 58–69, DOI: 10.1016/j.taap.2016.01.002

Williams, S., 2018. Network Rail Safe by Design: Buildings and Civils Working Group, UK. *Forensic Engineering* 171 (FE1): 3–11, DOI: 10.1680/jfoen.17.00015

WorkSafe, 2018. Health and Safety by Design: An introduction. https://worksafe.govt.nz/topic-and-industry/health-and-safety-by-design/health-and-safety-by-design-gpg/

Literature for Regulatory Preparedness

Barben, D., Fisher, E., Selin, C. and Guston, D.H., 2007. Anticipatory governance of nanotechnology: Foresight, engagement, and integration. In *The Handbook of Science and Technology Studies*: Third Edition, MIT Press, 979–1000.

Beaudrie, C. E. H., Satterfield, T., Kandlikar, M. and Harthorn, B. H., 2013. Expert views on Regulatory Preparedness for Managing nanotechnologies. *PLOS ONE* 8 (11): e80250, DOI: 10.1371/journal.pone.0080250

Bowman, D. M. and Hodge, G.A., 2008. Governing nanotechnology without governance? *Science and Public Policy* 35(7): 475–487, DOI: 10.3152/030234208X329121

Fuerth, L. S., 2009. Foresight and anticipatory governance. *Foresight* 11(4): 14–32, DOI: 10.1108/14636680910982412

Guston, D.H., 2014. Understanding 'anticipatory governance'. *Social Studies of Science* 44(2): 218–242, DOI: 10.1177/0306312713508669

Hernandez, L. and Noorlander, C., 2016. Towards a harmonised terminology in NanoReg2. Project document, draft.

Hester, K., Mullins, M., Murphy, F. and Tofail, S. A. M., 2015. Anticipatory ethics and governance: towards a future care orientation around nanotechnology. *Nanoethics* 9: 123–136, DOI: 10.1007/s11569-015-0229-y

Hogle, L.F., 2009. Science, ethics and problems of governing nanotechnologies. *Journal of Law, Medicine & Ethics* 37(4): 749–758, DOI: 10.1111/j.1748-720X.2009.00445.x

Höhener, K., Höck, J., Lehmann, H.C. and Tănăsescu, S., 2016. ProSafe Safe-by-Design (SbD) Implementation Concept. https://www.rivm.nl/en/documenten/prosafe-safe-by-design-sbd-implementation-concept-final

Jantunen, P. et al., 2018. Workshop on Regulatory Preparedness for Innovation in Nanotechnology. EUR 29357 EN, DOI: 10.2760/278827, JRC112766

Micheletti, C., Roman, M., Tedesco, E., Olivato, I. and Benetti, F., 2017. Implementation of the NANoREG Safe-by-Design approach for different nanomaterial applications. *IOP Conference Series: Journal of Physics: Conference Series* 838: 012019, DOI: 10.1088/1742-6596/838/1/012019

Noorlander, C., Sips, A., Höck, J., Höhener, K. and Lehmann, H.C., 2016. NANoREG Safe-by-Design (SbD) Concept. https://www.rivm.nl/sites/default/files/2018-11/NANoREG%20WP6%20Task%206.2%20Safe%20by%20Design%20concept.pdf

Nordmann, A., 2014. Responsible innovation, the art and craft of anticipation. *Journal of Responsible Innovation* 1(1): 87–98, DOI: 10.1080/23299460.2014.882064

OECD, 2018. Moving Towards a 'Safer Innovation Approach' for More Sustainable Nanomaterials and Nano-enabled Products: Overview of existing risk assessment tools and frameworks, and their applicability in industrial innovations, Revised project proposal, ENV/CHEM/NANO(2017)19/REV2

Papilloud, C., 2014. Anticipatory governance of nanotechnologies. A conceptual framework. *World Review of Science, Technology and Sustainable Development* 11(1): 71–89, DOI: 10.1504/WRSTSD.2014.062385

Soeteman-Hernández, L. G., Bekker, C., Groenewold, M., Jantunen, P., Mech, A., Rasmussen, K., Riego Sintes, J., Sips, A. J. A. M. and Noorlander, C.W., 2019. Perspective on how regulators can keep pace with innovation: Outcomes of a European Regulatory Preparedness Workshop on nanomaterials and nano-enabled products. *NanoImpact* 14: 100166, DOI: 10.1016/j.impact.2019.100166

Soeteman-Hernandez, L. G., Apostolova, M. D., Bekker, C., Braakhuis, H. M., Dekkers, S., Grafström, R. C., Handzhiyski, Y., Herbeck-Engel, P., Hoehener, K., Jeliazkova, N., Karagkiozaki, V., Kelly, S., Kraegeloh, A., Logothetidis, S., Micheletti, C., Nymark, P., Oosterwijk, T., Sanchez Jiménez, A., Sips, A. J., Sluijters, T., Suarez-Merino, B., Tavernaro, I., van Engelen, J., Wijnhoven, S. W. P. and Noorlander, C. W., 2019b. Safe Innovation Approach: Towards a future-proof system for innovations. *Materials Today Communications* 20: 100548, DOI: 10.1016/j.mtcomm.2019.100548

U.S. Food and Drug Administration, 2011. FDA Strategic Plan: Advanced regulatory science at FDA. https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf

Wender, B. A., Foley, R. W., Guston, D. H., Seager, T.P. and Wiek, A., 2012. Anticipatory governance and anticipatory life cycle assessment of single wall carbon nanotube anode lithium ion batteries. *Nanotechnology Law and Business* 9(3): 201–216.

Literature for Safe(r) Innovation Approach

Hjorth, R., van Hove, L. and Wickson, F., 2017. What can nanosafety learn from drug development? The feasibility of "safety by design", *Nanotoxicology* 11(3): 305–312, DOI: 10.1080/17435390.2017.1299891

Höhener, K., Höck, J., Lehmann, H.C. and Tănăsescu, S., 2016. ProSafe Safe-by-Design (SbD) Implementation Concept. https://www.rivm.nl/en/documenten/prosafe-safe-by-design-sbd-implementation-concept-final

Jantunen, P. et al., 2018. Workshop on Regulatory Preparedness for Innovation in Nanotechnology. EUR 29357 EN, DOI: 10.2760/278827, JRC112766

Micheletti, C., Roman, M., Tedesco, E., Olivato, I. and Benetti, F., 2017. Implementation of the NANoREG Safe-by-Design approach for different nanomaterial applications. *IOP Conference Series: Journal of Physics: Conference Series* 838: 012019, DOI: 10.1088/1742-6596/838/1/012019

Noorlander, C., Sips, A., Höck, J., Höhener, K. and Lehmann, H.C., 2016. NANoREG Safe-by-Design (SbD) Concept. https://www.rivm.nl/sites/default/files/2018-11/NANoREG%20WP6%20Task%206.2%20Safe%20by%20Design%20concept.pdf

OECD, 2018. Moving Towards a 'Safer Innovation Approach' for More Sustainable Nanomaterials and Nano-enabled Products: Overview of existing risk assessment tools and frameworks, and their applicability in industrial innovations, Revised project proposal. ENV/CHEM/NANO(2017)19/REV2

Park, M. V. D. Z., Bleeker, E. A. J., Brand, W., Cassee, F. R., van Elk, M., Gosens, I., de Jong, W. H., Meesters, J. A. J., Peijnenburg, W. J. G. M., Quik, J. T. K., Vandebriel, R. J., Sips, A. J. A. M., 2017. Considerations for Safe Innovation: The Case of Graphene. *ACS Nano* 11: 9574–9593, DOI: 10.1021/acsnano.7b04120

Soeteman-Hernández, L.G., Bekker, C., Groenewold, M., Jantunen, P., Mech, A., Rasmussen, K., Riego Sintes, J., Sips, A. J. A. M. and Noorlander, C. W., 2019a. Perspective on how regulators can keep pace with innovation: Outcomes of a European Regulatory Preparedness Workshop on nanomaterials and nano-enabled products. *NanoImpact* 14: 100166, DOI: 10.1016/j.impact.2019.100166

Soeteman-Hernandez, L.G., Apostolova, M. D., Bekker, C., Braakhuis, H. M., Dekkers, S., Grafström, R. C., Handzhiyski, Y., Herbeck-Engel, P., Hoehener, K., Jeliazkova, N., Karagkiozaki, V., Kelly, S., Kraegeloh, A., Logothetidis, S., Micheletti, C., Nymark, P., Oosterwijk, T., Sanchez Jiménez, A., Sips, A. J., Sluijters, T., Suarez-Merino, B., Tavernaro, I., van Engelen, J., Wijnhoven, S. W. P. and Noorlander, C. W., 2019b. Safe Innovation Approach: Towards a future-proof system for innovations. *Materials Today Communications* 20: 100548, DOI: 10.1016/j.mtcomm.2019.100548

Literature for Trusted Environment

European Medicines Agency (EMA), 2018. "European Medicines Agency Innovation Task Force."
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp

Food Safety Authority of Ireland (FSA), 2017. Personal communication, Karl Macdonald.

Safe(r) Innovation Approach: Risk Assessment Tools, Frameworks and Initiatives related to Safe(r)-by-Design[11]

25. This section presents an inventory of current risk assessment tools and frameworks used for and initiatives to promote Safe(r)-by-Design, in order to collect lessons learned from case studies applying SbD.

26. A survey was developed for establishing such an inventory. The survey was distributed amongst delegations taking part in the WPMN during the period of July–September 2019 (See Annex 3).

27. To this end, the following questions were asked:

- Q1. Are you aware of any 'Safe Innovation' / 'Safe(r) by Design' framework, tool or methodology or more in general on concepts willing to design a product, a production process or the use of a product in a safe condition by its nature?
- Q2. Are you aware of any 'Safe Innovation' / 'Safe(r) by Design' initiatives (lab-scale or industrial case studies) or more in general on concepts willing to design a product, a production process or the use of a product in a safe condition by its nature?
- Q3. Are you aware of any 'Safe(r) Innovation' / 'Safe(r) by Design' framework, tool or methodology that were adapted to emerging technologies (e.g. nanomaterials) or more in general on concepts willing to design a product, a production process or the use of a product in a safe condition by its nature?
- Q4. Are you aware of any 'Safe(r) Innovation' / 'Safe(r) by Design' initiatives (lab-scale or industrial case studies) that were conducted on emerging technologies (e.g. nanomaterials) or more in general on concepts willing to design a product, a production process or the use of a product in a safe condition by its nature?

28. Responses to the questionnaire were received from eight countries, as reported in the Annex 3. In addition, contributing to the inventory of current SbD initiatives, a full presentation of the Tyre Industry Initiative was prepared by BIAC as a detailed case study (see Annex 1). These responses formed the basis of the SbD frameworks and tools inventory database some examples of which are reported in Annex 3. In the following, this inventory will be presented and a review of barriers, constraints and limitations for Safe(r)-by-Design strategies, risk assessment tools, frameworks and initiatives will be discussed.

Classification of Frameworks and Guidelines

29. For this inventory, the Safe(r)-by-Design frameworks and guidelines fulfil the criterion of covering the three pillars discussed in the previous section:

- Safe(r) material/product
- Safe(r) production
- Safe(r) use and end of life

30. In the responses to the questionnaire, more general guidelines concerning project management (such as ISO 21500) or risk management framework (ISO 31000) were also proposed, but they were not considered in this inventory as SbD frameworks. The following examples of frameworks are discussed, because they address the three SbD pillars and in their description provide case studies from which lessons learned can be drawn.

[11] After the approval of the OECD Safe(r) Innovation Approach project proposal in April 2018, the experts from France (INERIS) accepted to lead this task with United Kingdom/IOM as co-lead. Other experts from France, the Netherlands, Switzerland and BIAC offered their support and direct collaboration for the activity.

Guidelines for implementing a safe-by-design approach for medicinal polymeric nanocarriers, NanoBioMat

31. These guidelines were developed in the GoNanoBioMat project (Polymeric NanoBioMaterials for drug delivery: developing and implementation of safe-by-design concept enabling safe healthcare solution.[12]) to implement a Safe(r)-by-Design approach in the context of polymeric nanobiomaterials for drug delivery (Schmutz et al., 2020, and Schmutz and Som, 2019). The SbD approach focuses on addressing human health and environmental safety in the full development phase of nanocarriers (excluding use, disposal, and end-of-life phases). In this context, the proposed SbD approach is an iterative, interdisciplinary process including the following aspects:

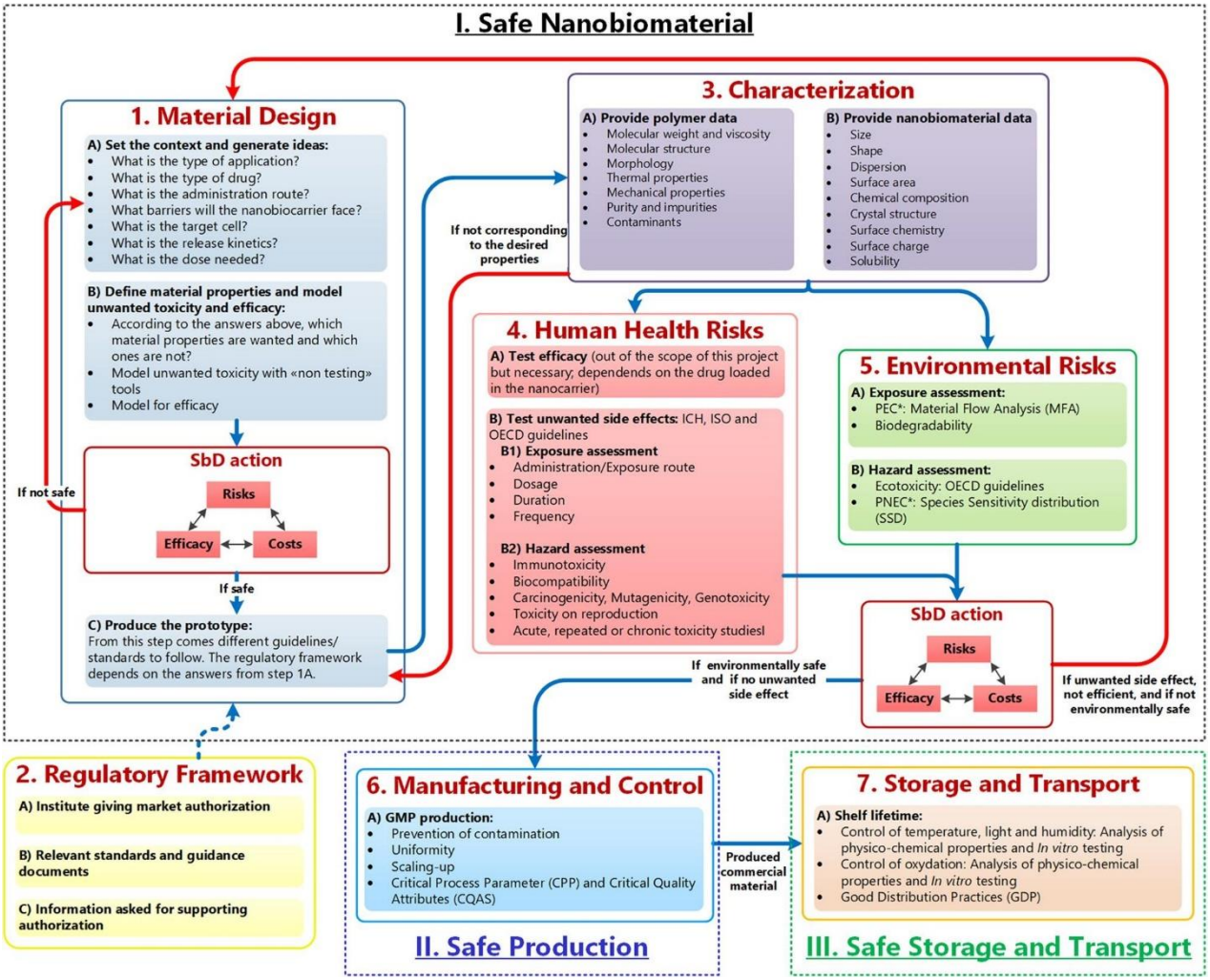
- Safe Nanobiomaterials: designing low-hazard nanocarriers for specific applications by assessing human health and environmental risks early on in the development process.
- Safe Production: manufacturing and control of nanocarriers to ensure their safety and quality.
- Safe Storage and Transport: ensuring the safety and quality of nanocarriers.

32. Impacts of current regulatory frameworks applied in Switzerland and the European Union on products/substances/materials/devices are taken into account within these guidelines. The approach consists of assessing of risk, efficiency and costs at each phase of the nanomaterial development as illustrated in Figure 1.

33. The GoNanoBioMat framework consists of three stages: (1) Safe Nanobiomaterial; (2) Safe Production; and (3) Safe Storage and Transportation, as shown in Figure 1. The GoNanoBioMat SbD approach starts with the designing of Safe Nanobiomaterials (first stage) which entails material design to account for the specification of the materials, their efficacy and safety, and proposing candidates for nanocarriers to be tested through a SbD action in which a decision based on a good balance between safety, efficacy, and costs is made to produce selected Nano-Bio-Material (NBM) prototypes. These prototypes are then characterised and evaluated in terms of human health and the environmental risks. After the Human Health and Environmental risk evaluation step comes a second SbD action which allows the selection of the final candidate in terms of safety, efficacy and cost to be produced in an unscaled way in the manufacturing and control steps (Safe Production - second stage) by applying GMPs to prevent contamination and ensuring good uniformity between batches. After this Safe Production step, the nanocarrier and its encapsulated drug system would go to clinical trial (not treated in this framework) and if successful, a last step regarding Storage and Transport (Third stage) is taken to ensure good (nano)medicine stability during the life cycle.

[12] See https://gonanobiomat.eu

Figure 1. GoNanoBioMat framework



Note: Blue arrows correspond to the flow of polymeric nanobiomaterials as drug delivery systems from design to storage and transport, red arrows are feedback loops used whenever the nanobiomaterial product is unsafe, inefficient or has unwanted side effects, and bullet points represent the methods/tools or endpoints at each step.

NANoREG/ProSafe/NanoReg2 Safe-by-Design concept

34. The EU FP7 NANoREG project developed a Safe-by-Design concept for NMs (Gottardo et al., 2017; Sanchez Jimenez et al. 2020) to achieve identified, reduced and managed uncertainty and risk for innovative materials, products and processes at the time of market introduction. This is complemented by an earlier, increased and improved interaction between innovators and regulatory authorities in Trusted Environments (so-called SAFE HOUSES) to share expertise and knowledge in order to identify uncertainties and potential risks and anticipate the need of new guidance documents for registration or market approval. The document *NANoREG framework for the safety assessment of nanomaterials* (Gottardo et al., 2017); presents definitions, the SbD concept and the basic idea of combining SbD with industrial management processes.

35. The EU H2020 ProSafe project's SbD Implementation Concept was based on the NANoREG SbD concept with the following four main elements:

- The workflows in industrial innovation processes or actor-specific needs

- The Safety Dossier
- The Safety Profile
- Harmonised inventory of SbD protocols, procedures and data

36. The NanoReg2 SbD concept is the outcome of the results of the FP7 NANoREG and H2020 ProSafe projects that have been refined and translated into practice by testing the concept on several industrial case studies (Sánchez Jiménez et al., 2020). The NanoReg2 SbD concept implies the consideration of safety as an integral part of the design process involving functionality and cost. It aims to create safer nanomaterials (NMs), nano-enabled products (NEPs), industrial manufacturing processes and usages. The three pillars underpinning the NanoReg2 SbD concept are:

- **Safe(r) materials and products by design**: This refers to identifying NMs that are less hazardous for humans and the environment, and designing NEPs that, under normal and unforeseeable conditions, do not release free Nano Fibers (NFs) (unless that is a requirement for their performance) to the environment and where the NFs can be recycled at the end of life.
- **Safe(r) use of products**: This consists of evaluating the risks during all uses throughout the product's Life Cycle in order to optimise defined acceptable uses. Building on the first SbD pillar, when a product has been made as safe as is possible, this second pillar will facilitate evaluation and determine any potential restrictions on the use of a specific NEP.
- **Safe(r) industrial production:** This pillar aims to enable better control on the industrial processes along the production chain. The aim is to design processes that eliminate/reduce release of NMs to the workplace and outdoor environment, do not use hazardous chemicals, reduce NM-waste, do not pose a safety hazard (e.g. explosion) and optimise energy consumption.

37. The NanoReg2 concept proposes an implementation process which follows the Stage Gate Innovation Model (Cooper, 2017). The premise of this model is that innovation proceeds along a pathway with stage gates, which are decision points on whether to proceed, stop or adjust the innovation. When initiating an innovation process (Stage 1, in setting up research ideas/business plans about a new NM/NEP, or new processes or usages), safety principles are applied as they are all along the development of the innovation. As the innovation progresses and more information becomes available, more complex risk assessments (RA), Life Cycle Analysis (LCA), and Socio-Economic Analysis (SEA) are carried out. The application of SbD at only later stages of the innovation process is still possible but may require significant and expensive modifications if changes to the existing NM/NEP and/or process are needed to achieve acceptable safety.

38. Based on the Risk/costs/performance analyses at each stage, the company should decide whether to move to the next stage in the innovation process. If a change is required and agreed on, a SbD goal (in terms of risk, cost and performance) should be established and SbD measures (risk reduction methods or procedures) agreed on to achieve this goal.

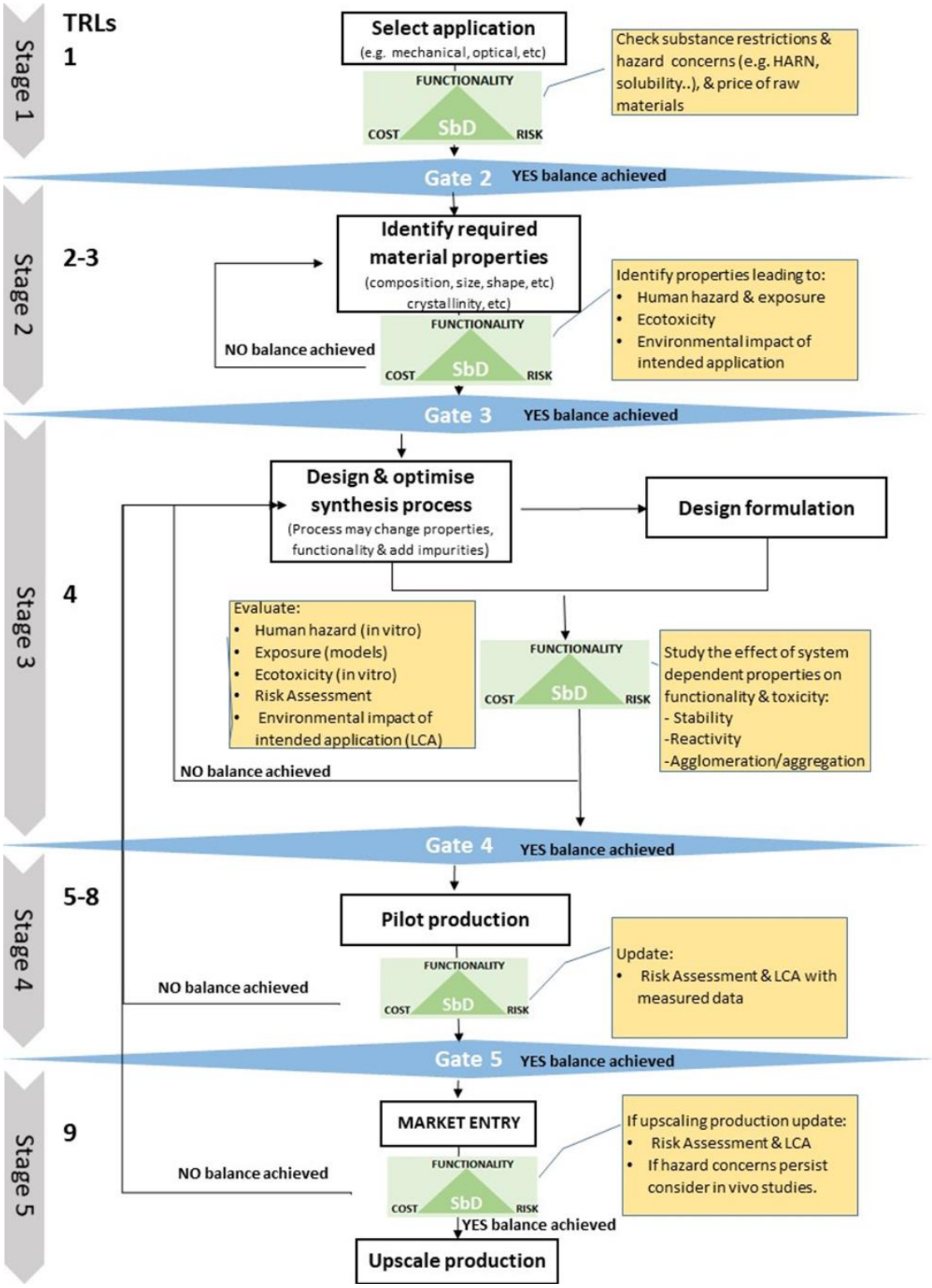
39. Impacts of these product/process-related SbD measures on health, environmental, and safety risks over the life cycle, together with the associated costs and benefits of such measures, should be considered. Once the risk is deemed acceptable, one can move to the next stage. If an acceptable risk cannot be reached, one should consider redesigning the product, the process or its uses.

40. Figure 2 shows a flow chart of the SbD implementation process, starting from when a NM is designed until the market launch. In addition, considerations related to sustainability assessment are also included in Figure 2. The boxes on the sides highlight the main information to take into consideration for the risk assessment. At each stage of the innovation process, risks, functionality and costs are assessed to decide whether to continue, stop or re-design the innovation. Risk

uncertainties are likely to be large at the first stages (low TRLs) of the innovation, and as the innovation evolves, more information is needed to reduce those uncertainties.

41. In some instances, one may want to make safer either the NM (e.g. by modifying the properties responsible for the hazard whilst preserving functionality), the product (e.g. by modifying the matrix to avoid unwanted releases of the NM during use), or the process (e.g. by reducing waste, aerosol releases to the workplace atmosphere). In such cases, SbD can be applied at different technology readiness levels (TRLs), for example at TRL 1–4 for a new product definition and/or formulation and TRL 5–9 for a new/optimised process, as illustrated in Figure 2 (Sánchez Jiménez et al., 2020).

Figure 2. Flow chart for implementation of SbD in the manufacturing of nanomaterials, addressing sustainability considerations.

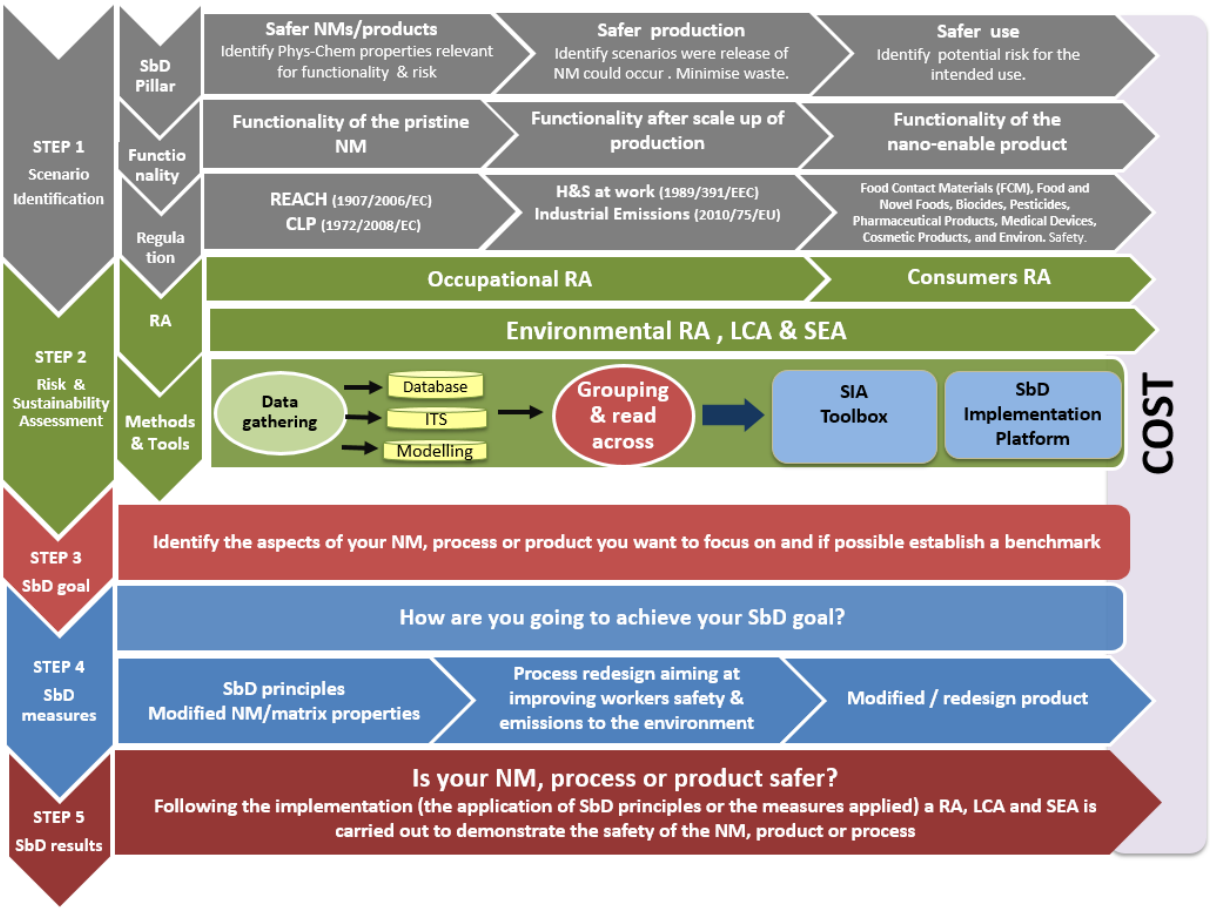


Note: SbD: Safe-by-Design, LCA: Life Cycle Assessment; TRL: Technology Readiness Level (Sánchez Jiménez et al., 2020)

42. Figure 3 shows the steps to follow at each stage to implement the SbD (Sánchez Jiménez et al., 2020).

- Step 1: Scenario identification depending on the three pillars (safety of product, safety of process, and safety of use) on the desired functionality, the development stage of the innovation process and the applicable regulations.
- Step 2: Risk, cost and benefit evaluation including health, environmental impact and safety assessment, LCA and in the later stages SEA with sustainability considerations. This step will help identify where the bottleneck problems are.
- Step 3: SbD Goals are set based on the potential risks identified in the Step 2.
- Step 4: SbD Measures are proposed with their costs.
- Step 5: Proposed SbD measures are tested, and if acceptable, a decision is made on the applicability, benefits and cost of the SbD measure

Figure 3. Step-by-step process for the implementation of SbD along the various stages of the manufacturing of nanomaterials, see Figure 2



Note: RA: Risk Assessment; LCA: Life Cycle Assessment; SEA: Socio-economic Analysis; ITS: Intelligent Testing Strategy; SIA: Safe Innovation Approach (Sánchez Jiménez et al., 2020)

NANOREG2 Case Studies Illustrating the Implementation of SbD

43. The NanoReg2 SbD approach was tested on some industrial case studies, and the results of these case studies are discussed below:

44. GRUPO ANTOLIN[13] is a producer of advanced carbon materials, carbon fibres and graphene derivatives. This case study was oriented on the safety of nanomaterials and their production process. This involved the safety assessment of powder handling systems, identification of point source emissions, and risks for employees and the environment at nanomaterial production stages. Implementation of the outcomes of the industrial case study led to reduced employee exposure through an automated nanomaterial powder handling system and an optimised production process.

45. NANOGAP[14] is a nanomaterial manufacturer producing silver nanowires, and their new nanowires are at the market launch stage. NANOGAP's primary aims was to reduce and recycle its waste, as NANOGAP was losing almost 50% of the silver introduced in the production. NANOGAP's first attempt for waste recycling was not efficient, and hence the process was optimised. SbD implementation for NANOGAP resulted in a reduction of employee exposure and a reduced loss of silver nanomaterial to waste.

46. AVANZARE[15] focused on scaling up the production of graphene in powder form and developing a process for its production in a liquid medium. The first goal was to reduce emissions in the workplace, to reduce waste during synthesis and to create a safe material for end users. Moreover prior to NanoReg2 AVANZARE was producing 8 kg/day, whereas to be competitive, scaling up to 250 kg/day was needed. The SbD process made it evident that the evaluation of risk had to be improved and that information on the exposure to workers was also needed. The measures implemented included the adaptation of the synthesis, recycling during the production, generating the product in a liquid phase and improving local ventilation of the workshop. The outcome was to shift to zero liquid waste and to eliminate the handling of graphene in powder form.

47. HIQ-NANO[16] focused on fluorescent silica nanoparticles and used SbD to replace the cadmium selenide quantum dot, which releases the toxic cadmium ion, with fluorescent dyes. The use of SbD enabled HIQ-NANO to develop a new type of nanoparticle that has fluorescent properties superior to those of the nanoparticles it was previously producing. These new dye-doped, rather than quantum dot-doped, nanoparticles lead to significantly lower environmental impact.

48. DSM[17] had already developed its own SbD approach but was interested in the NanoReg2 approach for a specific consumer application involving the machining of products containing amorphous and crystalline nanosilica in order to get a desired shape of the product, a process that could release nanosilica. DSM sought to investigate the process to determine if there is a release risk and to give advice to its customer. Following the NanoReg2 SbD approach, DSM's experimental testing demonstrated that there were no safety or risk issues.

49. NANOMAKERS[18] produces silicon-based nanomaterials. The focus of the NanoReg2 project was dealing with the final stages of the value chain of large scale customer products. Three nanomaterials with "same end use application" were selected for the study which was based on

[13] http://www.nanoreg2.eu/sites/default/files/Grupo%20Anatolin%20.pdf

[14] http://www.nanoreg2.eu/sites/default/files/Nanogap%20.pdf

[15] http://www.nanoreg2.eu/sites/default/files/Anvazare%20.pdf

[16] http://www.nanoreg2.eu/sites/default/files/HiQ-Nano%20final.pdf

[17] http://www.nanoreg2.eu/sites/default/files/DSM%20Final.pdf

[18] http://www.nanoreg2.eu/sites/default/files/Nanomakers.pdf

four steps: 1) hazards, ecotoxicity, and toxicity; 2) link the physicochemical properties to the main hazard; 3) propose and develop a safer nanomaterial; and 4) evaluate the performance of the safer material. The main benefit was associated with designing new size and particle coating. Specific design of coatings helped to reduce dustiness and explosivity. However, it was not possible to carry out quantitative and robust SEA on this case study due to a lack of data at the early stages of technology development.

TYRE INITIATIVE FROM INDUSTRY

50. In continuity with the OECD report "Nanotechnology and Tyres" (OECD, 2014a), the main tyre manufacturers built the Tyre Initiative for a safe development of new nanomaterials in tyres, which is a consensus between the eleven main tyre producers gathered together (TIP) under the umbrella for the World Business Council for Sustainable Development (WBCSD).[19]

51. The Tyre Initiative, fully described in the Annex 1, addresses the full life cycle of nanomaterials in tyres and contains mainly:

- An engagement by the CEOs of the 11 tyre manufacturing companies to support the Tyre Initiative.
- An analysis addressing challenges and performance expectations in the development of new nanomaterials in tyres.
- An overview of the potential nanomaterial release during the full life cycle of tyres including production, use phase and end of life.
- An assessment of the protection of health and environment by SbD in the case of tyres with new nanomaterials, including technical results on tyre performance, management of EHS information and evaluations to be completed, evolution of legal aspects and management of decision "stop or go" at each stage of each new project.

52. A decisional flow chart is given, starting from R&D and going up to commercialisation of new tyres if any.

53. The reasoning and motivations of the whole SbD approach followed by the tyre industry are explained in the Annex 1 (section 7). It contains:

- The analysis of the background (historic with OECD, interest, challenges, collaboration, consensus…).
- The need of a strong engagement in the SbD approach by each company's top management.
- Since the Research stage and all along the development of each new nanomaterial in tyres, the need to take into account in a realistic manner concerns on risks/uncertainties and consequences.
- The need of decision management "stop or go" at each stage of the new development, stressing the importance to have decision stop if any at the earliest stage.
- The need to take into account any evolution of regulatory aspects.

Lessons Learned from Case Studies in the Implementation of Safe(r)-by-Design Frameworks

54. Lessons learned from case studies in which Safe(r)-by-Design frameworks have been implemented are reviewed below.

[19] The WBCSD is an international organization, which works includes sustainable development for all type of industry. The Tire Industry Project (TIP) s a project of the WBCSD that addresses different issues specific to tyres. For more information see: https://www.wbcsd.org/content/search?searchText=TIP

55. From the implementation of the medicinal polymeric nanocarrier Safe-by-Design framework (NanoBioMat), it was shown that:

- A lack of data on physicochemical properties, pharmacokinetics, exposure and potential environmental hazards does not permit the best choice of a nanomaterial candidate in a risk/benefit balance at the design stage.
- Furthermore, when literature data is used, the toxicological data can be ambiguous due to the variety of methodologies used. This issue stems from the absence of standardised methodologies and guidelines for evaluating the hazards of nanobiomaterials. In such conditions, risk/benefit evaluations are not possible, and the identification of the best candidate at the design stage is not readily feasible.

56. From the implementation of the NanoReg2 SbD framework through industrial case studies, it was shown that the framework can be applied to the three safety pillars (safety of product, safety of process, and safety of use) of the value chain. It also illustrates that safety can be designed for at early stages by:

- Using automation, limiting employee exposure and associated risks (e.g.: of the Grupo Antolin case).
- Modifying the production process to minimise nanomaterial waste, thus having less worker and environmental impacts in the value chain (e.g.: NANOGAP)
- Promoting liquid handling systems rather than powder handling systems for nanomaterials to reduce worker exposure and associated risks, with a high level of reuse (recycling) of liquids to reduce liquid waste (e.g.: Avanzare).
- Promoting nanomaterials that do not release toxic ions (e.g. HiQ-nano)
- Promoting nanomaterials with low and non-toxic emissions during their use (e.g. DSM).
- Designing special nanoparticle coatings that can play the role of a safety barrier (e.g. Nanomakers).

57. It should be noted, however, that these case studies illustrate the difficulty at the conception level of acquiring the necessary data to quantitatively evaluate risks, not only at the early stage gates but also throughout the whole value chain. At the early stages, risk-cost-benefit evaluations are mainly preliminary but are necessary for identifying any further data needed along the development of the innovation.

58. From the implementation of Safety by Design in the Tyre Initiative, the large scale collaboration between the 11 main worldwide tyre producers to implement and successfully develop SbD for nanomaterials in tyres demonstrated that a sectorial industrial approach was a good approach for SbD. This takes into account the specificities of the tyre sector regarding EHS risk, such specificities being in fact similar from one company of the sector to another.

59. The SbD approach of an industrial sector also facilitated the socio-economic evaluation of developing nanomaterials in the sector, as the socio-economic impacts of developing new nanomaterials for tyres was assessed at the sectorial level (OECD, 2014a).

60. In the Tyre Initiative, all tyre companies shared the goal of achieving safe(r) development of new nanomaterials in tyres. The scope of the collaboration on SbD included the management of a safe(r) development of any new materials in tyres, and excluded tyre performance. It is, for example, important to note that each company kept confidential the nanomaterials they are working on and the tyre performance expected. Within this scope, the fact that the participants of the initiative are competitors is not an obstacle for SbD implementation and development.

61. The support given by the CEOs of the eleven companies involved in the tyre SbD project was crucial for applying a SbD approach in the tyre industry. With this support, a clear consensus was obtained between the eleven companies, and SbD was accepted inside each company (see the case study presented in the annex).

62. It was well understood that SbD has to be applied from a very early stage, and even before launching the research. At each step of the progress with a new nanomaterial, information has to be collected and a "stop or go" decision taken. This includes an evaluation of the situation regarding EHS risks in the course of the full life cycle of tyres as well as the evolution of the regulatory situation in the context of the project.

63. It is important to realise that a 'stop' decision has to be taken at the earliest possible stage to avoid wasting time and money on non-viable new nanomaterials projects.

64. An identified difficulty is to get a timely evaluation of risks at each step of the innovation process with a new nanomaterial. To achieve this, testing methods have to be readily available, or if not, the need to develop and implement new methods has to be anticipated at the earliest possible stage. This requires time and resources. Fortunately, co-operation among the 11 tyre producers allowed to share the expertise and the costs for developing new test methods.

65. It is also of high interest to bring any new test methods to the level of published international standard. This validates the new test methods and makes them available to the tyre industry in general as well as to the implementation of new legislation and regulation, if any.

Inventory of Tools for SbD Implementation

Brief overview of the peer-reviewed literature on evaluation of risk assessment tools

66. There are a number of tools available for estimating human hazard and exposure for workers and consumers, with some tools combining both hazard and exposure assessment in a traditional risk assessment (RA) approach for chemicals. Some tools are able to perform the RA along the life cycle of the MNMs.

67. Environmental assessment tools include tools for hazard assessment, risk assessment, material flow analysis, transport and fate assessment of MNMs in different micro-environments and to a lesser extent tools that estimate the uptake of MNMs by different species.

68. Several of these tools have been reviewed against different criteria. Brouwer (2012) evaluated the similarities and differences of six control banding (CB) tools (Precautionary Matrix, ANSES, NanoControl Banding Tool, NanoSafer, Stoffenmanager Nano, IVAM Guidance) for the management of occupational exposures. Brouwer concluded that despite the similarity of the tools (i.e. combining hazard and exposure into control or risk bands, the structure) the applicability domains and the assignment of the hazard and exposure bands show differences that may affect the consistency of the resulting outcomes amongst the various CB tools. Liguori et al. (2016) evaluated the same tools for their applicability in a regulatory context and concluded that Stoffenmanager Nano and NanoSafer include the determinant parameters suggested in ECHA Guidance R.14 and R.14-4, and by the EU-JRC RIP-oN1 and RIP-oN2 projects, and they thereby principally fulfil REACH requirements for exposure assessment.

69. Non nano-specific tools used under the EU regulatory REACH framework (ECETOC TRA, Stoffenmanager 4.0, EASE and CONSEXPO for tier 1) were evaluated as part of the EU FP7 NANEX project. The review concluded that they are not suitable for providing estimates for MNMs since, as they are not calibrated for MNMs, they tend to overestimate exposure (Brouwer et al., 2010)

70. Hristozov et al. (2016) evaluated 48 tools against criteria agreed with stakeholders including nano-specific requirements, life cycle approach, pre-assessment phase, and exposure-driven approach. None of the reviewed tools met all the criteria.

71. Baalousha et al. (2016) reviewed tools focused on environmental risk. The author acknowledged fate models have evolved from substance flow analysis models that lack nano-specific processes to more advanced mechanistic models that (at least partially) take nano-specific processes into account (agglomeration, sedimentation and dissolution), and highlighted that current models require parameterization, calibration and validation with available data, e.g. field data (if available) or experimental data (e.g. aquatic and terrestrial mesocosms), rather than extension into more complex and sophisticated models that include all possible transformation processes.

72. Nowack (2017) discussed the reliability of material flow analysis and environmental fate models and their relevance to the regulatory process. The authors highlight that the available fate models for MNMs are built on concepts already accepted by regulators for conventional chemicals, and therefore those models are likely accepted too. However, they noted the models do not include a validation of PECs (predicted environmental concentrations) by analytical measurements, and recommended that the material flow models should also include information on the material characteristics, e.g. form, size distribution, and if the material has already transformed, since this constitutes very important input information for fate models.

73. Fadeel et al. (2018) reviewed the benefits from emerging technologies, especially omics and high-throughput and/or high-content screening platforms, which coupled with bioinformatics or computational approaches enable the analysis of large amounts of data and the identification of meaningful associations between MNMs characteristics and biological effects. The authors highlighted the importance of high-quality data and concluded that testing of ENMs that have undergone aging or transformation through the life cycle of nano-enabled products is needed, as well as validated in vitro assays based on relevant end-points, that is, in vitro end-points that adequately mirror in vivo outcomes.

74. Brink et al. (2019) discussed the tools and rules for modelling uptake and bioaccumulation of MNMs in invertebrate organisms: biotic ligand models (BLMs), accumulation factors and physiologically based pharmacokinetic models (PBPK models) or biodynamic models. The authors concluded that neither BLMs nor bioaccumulation factors based on measured data can be recommended for modelling the (longer term) bioaccumulation of different forms of nanomaterials. Assumptions underlying these modelling approaches, including the equilibrium theory that relates to the uptake of solutes, are not met in the case of MNMs. Dynamic PBPK modelling approaches are more suitable for nanomaterials.

75. Other reviews have focused on the use of the tools within a regulatory context. Romero-Franco et al. (2017) evaluated the applicability of frameworks based on six decision scenarios that described the most common needs of stakeholders (e.g. manufacturers, regulatory bodies) to arrive at decisions respecting the environmental, health and safety aspects of MNMs. For each of the explored decision scenarios, at least one existing framework was identified as capable of partly meeting the needs of potential decision-making.

76. Oomen et al. (2018) and Trump et al. (2018) reviewed the regulatory relevance of the tools and frameworks. Oomen et al. evaluated risk assessment frameworks and tools according to the OECD criteria for the utility of any regulatory method, protocol, or data set: whether the risk assessment framework is both relevant (to predicting endpoints of interest for regulatory purposes) and reliable (OECD, 2005). The DF4nanoGrouping framework was the only fully elaborated risk assessment framework that transparently and in detail included clear decision criteria, triggers/cut-off values and tools to assess inhalation risks.

77. Sørensen et al. (2019) and Franken et al. (2020) reviewed existing models and tools against criteria agreed with stakeholders on the needs according to the different stages of the value chain.

78. A comprehensive inventory of ready-to-use and publicly available tools for the safety assessment of MNMs was published in 2017 by Jantunen et al. The tools were evaluated for their applicability to SbD in the NanoReg2 context[20].

OECD SIA Inventory of Tools for SbD Implementation

79. For the inventory of frameworks and tools conducted under the OECD SIA project and presented in this report, a selection of tools was reviewed according to their use for SbD, considering the SbD concepts described under the Working Descriptions above.

Selection and classification of tools

a. Human health related tools, including hazard, exposure and risk assessment tools were selected based on previous inventories in recent publications (Hristozov et al., 2016; Jantunen et al., 2017; Sørensen et al., 2020; Franken et al., 2020). Only nano-specific tools available as a functional software tool (either online or as a software package) were included in this review. Dermal exposure tools which were not specifically developed for the risk assessment of MNMs were also taken into account given the scarcity of nano-specific models in this area.

80. The review resulted in 41 tools. The tools identified were classified against the different aspects required for a full implementation of SbD considering the description for SbD. There are three pillars that sustain SbD:

1. Safer materials and products
2. Safer production processes and
3. Safer use and end-of-life of products.

81. To achieve these three pillars, the following health and safety aspects along the material life cycle have to be considered (Table 1).

[20] Document in preparation for submission to NanoImpact led by Llopis.

Table 1. Aspects needing to be considered to achieve safer materials/products, processes and safer use and end-of-life

Safety aspect	Safer material/ product	Safer production	Safer use and end-of-life
Human hazard	X		
Environmental hazard	X		
Worker exposure (chemical hazards)		X	
Worker safety during production (physical hazards)		X	
Releases to the environment during production (outdoor air, liquid & solid waste)		X	
Releases to the environment during product use & end-of-life processes			X
Consumer exposure (incl. professional & industrial use of the final product)			X

82. However, SbD goes beyond the classical risk assessment of combining hazard and exposure. To achieve safer materials, their structure and physico-chemical properties have to be linked to their hazard at the design stage, so that the hazard can be designed out or the least hazardous form with the desired functionality can be taken to the next stage. The implementation of SbD has to be economically viable for the industry, and therefore cost-benefit analysis tools are also required. Furthermore, to assess the overall social benefits of developing SbD products as opposed to non-SbD products, a social impact assessment is necessary.

83. Other aspects considered in the classification of the tools were the exposure route, life cycle stage covered, whether the tool performs a complete life cycle assessment and in the case of Environmental Assessment tools, the environmental compartments covered.

Inventory of models and tools[21]

Table 2. Tools and the different aspects of the SbD definition covered by the models

	Safer NM				Safer production			Safer use						LCA	SEA	Stage Gate
	Human Hazard	Human RA	Environ. Hazard	Environ. RA	Workers exposure	Workers Risk	Process Safety	Consumer Exposure	Consumer RA	Release from products	Flow analysis	Transport & fate	Uptake			
Licara NanoScan	✓	✓	✓	✓	✓	✓		✓	✓					✓	✓	
SUNDS	✓	✓	✓	✓	✓	✓		✓	✓					✓	✓	
Guidenano tool	✓	✓	✓	✓	✓	✓		✓	✓					✓	✓	
Precautionary Matrix for NMs			✓			✓		✓								
ANSES CB Tool for NMs		✓	✓		✓	✓		✓								
Control BandingTool	✓	✓			✓	✓										
Stoffenmanager Nano	✓	✓			✓	✓		✓p	✓p							
Nanosafer CB	✓	✓			✓	✓		✓p	✓p							
SbD Implementation Platform	✓	✓						✓	✓							
NanoRiskCat	✓	✓						✓	✓							
ConsExpo Nano Tool								✓								
QSARs	✓															
NANOSOLUTIONS	✓	✓														
Future Nano Needs - Bayesian network (FNN-BNN)				✓												
CENARIOS® Risk Management and monitoring system		✓		✓		✓										
Golden Egg Check																
US EPA SSD generator			✓													
SSWD			✓													
NanoQSAR model			✓													
NanoQSAR model			✓													
Nanoprofiler			✓													
FINE				✓												
pPERA				✓												
PFMA											✓					
DPMFA										✓	✓					
Lear nano											✓					
SimpleBox4Nano												✓				
NanoFASE: NanoFASE model System												✓				
NanoRelease										✓	✓					
NanoFate												✓				
NanoDuFlow												✓				
Rhone/Rhine Model												✓				
LearNano										✓						
MendNano												✓				
RedNano												✓				
WSM/WASP7												✓				
Rhone/Rhine Model												✓				
GWAVA with water qualtiy module												✓				
Kinetic model/BCF													✓			
Two component efflux/uptake model													✓			
Biodynamic model													✓			

Note: p = professional use

Pillar 1: Safer nanomaterials/nano-enabled products

84. This section discusses tools used to perform human and environmental hazard assessment or the overall risk assessment.

Computational methods to predict hazard

85. There are several computational methodologies available to predict hazard from the physicochemical properties of a material. These methods can be very useful for SbD, although they do not have the added element of predicting functionality. A full review was published by the Nanocomput project (Worth et al., 2017). A brief description is provided below:

[21] In line with the NANoREG project, a ***tool*** is understood as an experimental or computerised procedure used to generate, collect and/or store a certain type of output; whereas a ***model*** is: e.g. an algorithm for predicting exposure/release into the environment or a (Q)SAR application

- **Bayesian methodologies**: these are based on a method of statistical inference in which Bayes' theorem is used to update the probability for a hypothesis as more evidence or information becomes available. Bayesian networks can be applied to hazard identification and ranking of MNMs by capturing the (inter) relationships between the exposure route, the MNM's physico-chemical properties and the ultimate biological effects. Marvin et al. (2017) applied a Bayesian network (BN) construction, parameterisation, and uncertainty analysis to metal and metal-oxide MNMs. The physico-chemical properties used were dissolution, shape, surface area, surface reactivity, particle size, surface coating, surface charge, aggregation and exposure route and the biological effects genotoxicity, neurological effects, immunological effects, cytotoxicity, pulmonary effects, inflammation, central nervous system effects and fibrosis. This BN tool showed high accuracy, with 72% hazard prediction precision in an out-of-sample test, however it is not commercially available. To our knowledge there are no commercially available tools of this type.
- **Q-SARs**: Quantitative Structure-Activity Relationship methods establish relationships between physicochemical properties and the behaviour of MNMs in biological systems. This methodology is well known and applied under REACH (ECHA, 2008a). However, its use for MNMs is still limited due to the lack of data that correlates with the Mode of Action (MOA) or Adverse Outcome Pathway (AOP). The Enalos InSilicoTox Platform[22] holds some tools for the prediction of solubility and TNF (specific NF-kB Induction) Prediction. The OECD has developed a Q-SAR Toolbox to make (Q)SAR technology readily accessible, transparent, and less demanding in terms of infrastructure costs[23].
- **OMIC technologies** and systems biology: OMICs are primarily aimed at the universal detection of genes (genomics), mRNA (transcriptomics: the total mRNA in a cell or organism), proteins (proteomics: the set of all expressed proteins in a cell, tissue or organism) and metabolites (metabolomics: the study of global metabolite profiles in a system (cell, tissue or organism) under a given set of conditions) in a specific biological sample. Systems biology and omics experiments differ from traditional studies, which are largely hypothesis driven or reductionist. The reasoning is that a complex system can be understood more thoroughly if considered as a whole. The strategy is to analyse all data from an experiment to define a hypothesis that can be further tested (Kell et al., 2004). The application of OMICs technologies to nanotoxicology has been hampered by the lack of standard operating procedures for the experimental analysis. However, some studies have used OMICs strategies to successfully predict MOAs (Scala et al., 2018; Pan et al., 2018). Given the large amount of data generated in these studies and the challenges of integrating the data from the different OMICs techniques, sophisticated bioinformatics and dedicated statistics are essential.
- The company OMicX holds several software tools for big biodata analysis and interpretation including ToxFlow (Varsou et al., 2018). However, expert knowledge is required for the use and interpretation of the outputs.

[22] http://www.insilicotox.com/index.php/products/predictive-models-web-services/enalos-insiliconano-platform/

[23] https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

- **INSIdE nano** is a web-based tool (http://inano.biobyte.de/) that highlights connections between phenotypic entities based on their effects on genes. The database behind INSIdE nano is a network whose nodes are grouped into four categories:
  - Nanomaterial exposures
  - Drug treatments
  - Chemical exposures
  - Diseases

86. Currently there are no methods for validating QSARs, but there are some useful principles that are described in OECD Report from the Expert Group on (Q)SARs on Principles for the Validation of (Q)SARs, (OECD, 2004) and OECD Guidance Document 69 on the Validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models (OECD, 2007).

Tools that predict the overall risk or a hazard band

87. **Precautionary Matrix for MNMs**[24]: The Precautionary Matrix helps to assess the need for nano-specific measures ("need for precautions") in connection with synthetic MNMs and applications of these materials for employees, consumers and the environment. In addition, it helps to identify potential sources of risk in the development, production, use and disposal of synthetic nanomaterials. It is based on a limited number of parameters and intended for those situations where data is lacking. Users may carry out their own guided investigations on human exposure, emissions into the environment and the effects of MNMs based on results obtained from the matrix. The tool is not a risk assessment tool.

88. **LICARA NanoScan**[25]: The main goal of LICARA is to develop a structured life cycle approach for MNMs which enables a qualitative evaluation of the benefits and risks associated with new or existing nano-products. It further allows a comparison with the risks and benefits of conventional (non-nano) products. The tool stimulates economic, environmental and social opportunities. This tool is specifically intended for use by SMEs to support them in communicating with regulators, potential clients and investors.

89. **GUIDEnano tool**[26]: The tool guides the user (i.e. industrial nano-enabled product developers) in the design and application of the most appropriate risk assessment and mitigation strategy for a specific product. The tools predicts the overall risk from the nanomaterial along its life cycle. The tool is being improved as part of the H2020 SAbyNA project.

90. **SUNDS**[27] - The Sustainable Nanotechnologies Project Decision Support System: SUNDS is a cloud-based nano-product sustainability assessment Decision Support System. SUNDS supports decisions on the assessment and management of MNMs and nano-enabled products along with their life cycles in industry, regulatory bodies and insurance companies. It applies a two-tiered approach which, on the basis of the supplied information, is able to generate qualitative or quantitative results. The first assessment tier is based on the LICARA NanoScan tool. The second

[24] https://www.bag.admin.ch/bag/en/home/gesund-leben/umwelt-und-gesundheit/chemikalien/nanotechnologie/sicherer-umgang-mit-nanomaterialien/vorsorgeraster-nanomaterialien-webanwendung.exturl.html/aHR0cHM6Ly9uYW5vcmFzdGVyLmJhZ2FwcHMuY2gvcG9ydGFsX2/VuLnBocA==.html?SID=a73736cf632b3b7f1a7dc31a27598b8a

[25] https://www.empa.ch/web/s506/licara

[26] https://www.guidenano.eu/

[27] https://sunds.gd/

assessment tier, based on an adaptation of the authorisation process currently in operation under the EU REACH regulation, allows applying Risk Control (RC) measures and demonstrating adequate control of risk due to a substance's use and that according to the Socio-economic Analysis (SEA), the benefits of using the substance significantly outweigh the societal costs. SEA analyses are based on the triple bottom line approach, which comprises the environmental, economic, and societal 'pillars'.

91. **SbD Implementation Platform**[28]: The SbD Implementation Platform was developed to perform SbD. It helps the user to identify hot spots regarding risks at different stages of the product's life cycle. The platform follows the stage-gate model and produces summary outputs and graphs comparing the results of different control banding tools. The user may also introduce safety thresholds to better understand where they are in terms of risks. The platform contains a repository of guidelines, guidance documents and links to relevant sites.

92. **NanoSafety** Classifier (NANOSOLUTIONS): The Nanosafety Classifier is a computational tool that can predict the environmental and health impact of MNMs based on their characteristics and behaviour. The tool is continuously learning, and the predictions keep improving as new data is fed into it.

93. The **Precautionary Matrix** and **the Licara NanoScan** can be used at the early stages of the value chain when there is not yet a prototype material/product. Their uncertainties are also larger. For later stages when there is more information available, the GUIDEnano tool, SUNDS and NanoSafety Classifier are more suitable, as they produce a quantitative assessment. SUNDS goes further by assessing the societal benefits of incorporating a SbD approach.

Pillar 2: Safer production processes

94. Safer processes imply protection from chemical risks, such as releases of MNMs to the indoor workplace and the outdoor environment (either as solid or liquid waste or to the outdoor air) and from physical hazards such as fire and explosions.

95. Because these hazards have different natures and are subject to different legislation, there is no single tool that can assess them all together. There are tools for assessing the exposure of workers, and tools that deal with the physical safety hazards. The reviewed literature did not include tools that estimate potential releases into the environment taking into account the process parameters.

Tools that cover occupational exposure

96. Several of the risk assessment tools included in this document also include the assessment of the occupational risk of exposure to MNMs during their production:

- Precautionary Matrix for MNMs (qualitative output)
- LICARA NanoScan (qualitative output)
- GUIDEnano tool (quantitative output)
- SUNDs system (quantitative output)

97. There are a number of control banding and risk assessment tools that have been developed specifically to assess the risk of workers and only include risk in occupational settings.

[28] https://temas.taglab.ch/SbDimplementation

98. **ANSES: Control Banding Tool for MNMs**[29]: The control banding tool requires input data, irrespective of the phase of the nanomaterial's life cycle, such as information collected at the workplace through observation of actual work situations, toxicology data, etc. The output data generated by the control banding process will impact other processes of the overall management system defined by the employer.

99. **Control Banding NanoTool**[30]: The tool estimates an emission probability (without considering exposure controls) and severity band and provides advice on engineering controls to use to prevent exposure. It deals with occupational exposures, including domains covering handling of liquids, powders, and abrasion of solids.

100. **Stoffenmanager Nano**[31]: The tool estimates a hazard band and exposure band that are combined in the output as a risk band to qualitatively assess occupational health risks from inhalation exposure to Manufactured Nano Objects (MNO). Risk Management Measures may be selected or included in the Action Plan.

101. **NanoSafer CB**[32]. Online control banding and risk management tool for manufactured MNMs. Hazard assessment and case-specific exposure potentials are combined into an integrated assessment of risk levels expressed in control bands with associated risk management recommendations. The tool can also be used to assess and manage emissions from nanoparticle-forming processes. It uses data on material properties, processes and production facilities to estimate occupational risk. The tool uses the Risk Quotient (i.e. the ratio of an exposure dose to a human effect threshold) to estimate risk deterministically. The tool is capable of estimating exposure from spray processes and it can perform nano-specific Hazard Assessment based on read-across between nanoparticles based on specific material properties and hazard indicators, tested for performance against in vivo experiments.

Tools that cover risks from processing

102. Process safety deals with all the accident scenarios that may be encountered during processing and the possible injuries to workers and damage to the environment. Such scenarios may be triggered by accidental leakages (local and environmental) that could arise from a malfunctioning process, a chemical runaway reaction, self-overheating, a fire or an explosion. To assess the risk of such accidents, one has to know the physicochemical, toxicological and ecotoxicological hazards of the substances involved. This means process starting materials and also their normal and potential accidental transformations in the process. In accident risk analysis, triggering ignition sources (e.g. electrostatic, mechanical or thermal sources) leading to adverse outcomes (release of material, fires, explosion) should be considered with a detailed description of the involved triggering parameters. Presently, this kind of data for MNMs is not available for performing process safety assessment. Moreover, currently few developments on predictive modelling have been made to assess the impact of a massive accidental leak, a process fire or explosion involving MNMs. The information gaps may constitute serious barriers to the development of safe MNMs processes.

103. However, commonly used process risk assessment methodologies, such as PRA, HAZOP, FMEA, BOW-TIE approaches, LOPA, and MSRA that have been developed for processes involving conventional chemicals, can also be used for MNMs. As indicated above, some critical process safety parameters are still unknown. In addition, risk assessment outcomes indicate that

[29] https://www.siatoolbox.com/methods/anses-control-banding-tool-nanomaterials

[30] https://controlbanding.llnl.gov/

[31] https://nano.stoffenmanager.com/Default.aspx

[32] http://www.nanosafer.org/login

for processes involving MNMs, proper design, installation and management of recognized safety barriers (such as explosion venting systems, counter fire actions, catch tanks for runaway reactions) is still lacking. For the development of safe nanomaterial processing, such methods for analysis and barriers need to be developed for MNMs and further standardized. Recognized predictive computational models and tools to design and assess the performances of such barriers are still lacking.

Pillar 3: Tools for safer use and end of life

104. The following tools, previously described, cover exposure assessment to consumers

Tools that cover exposure assessment to consumers

- LICARA NanoScan
- Precautionary Matrix for MNMs
- GUIDEnano tool
- SUNDS -The Sustainable Nanotechnologies Project Decision Support System

105. Additional tools for safer use and end of life are:

106. **NanoRiskCat**.[33] A screening tool for evaluation of exposure and hazard of MNMs integrated into products for professional and private use. It categorises and ranks the possible exposure and hazards associated with a nanomaterial in a product. The primary focus is on MNMs relevant for professional end-users and consumers as well as MNMs released into the environment.

107. **ConsExpo nano**[34]: This tool can be used to estimate inhalation exposure to MNMs in consumer spray products. To run the model, user input on different exposure determinants such as the product and its use, the nanomaterial and the environmental conditions is required. Exposure is presented in different measures. The outcome of the assessment is an alveolar load in the lungs as one of the most critical determinants of inflammation of the lungs is both the magnitude and duration of the alveolar load of a nanomaterial. To estimate the alveolar load arising from the use of nano-enabled spray products, ConsExpo nano combines models that estimate the external aerosol concentration in indoor air, with models that estimate the deposition in and clearance of inhaled aerosol from the alveolar region.

108. **Future Nano Needs - Bayesian Belief Network (FNN-BBN) Shredding Model**[35]. The model is very useful for the exposure assessment of products containing MNMs during shredding (end-of-life), a part of the life cycle where there is little data available. With a Bayesian probabilistic nature in its core, it uses subjective judgement when data is unavailable or scarce while being able to adapt and update risk forecasts as new information becomes available. Its novelty lies in a simplistic approach which combines the material and process variables of the system to determine the probability of number, size, mass and composition of released particles. It is applicable to the shredding of a wide range of nano-enabled products and it aims to reduce the nanomaterial release by using the Safe(r)-by-Design approach. The model works with the Genie 2.1 software- a graphical interface that runs on Windows, OSX and Linux.

[33] http://nanodb.dk/en/nanoriskcat/

[34] https://www.consexponano.nl/

[35] https://www.futurenanoneeds.eu/outputs/fnn-bbn-shredding-model/

Tools that cover Environmental Assessment

109. In this section, we have included tools for risk quantification and tools that estimate some of the aspects required for the environmental risk assessment such as environmental fate, transport, and uptake as well as flow analysis tools. Most of these tools have been reviewed within the OECD project "Compilation of Available Tools and Models for The Assessment of Environmental and Consumer Exposure to MNs" and therefore here are only briefly described.

110. At the time of writing this report, their applicability in SbD had not been demonstrated. Clearly, they can be used to perform risk assessment, which is part of the SbD process. However, it is unknown whether they will be sensitive enough to perceive the difference in risk after the implementation of SbD measures. The fit of these tools to the different stages of the innovation process has been recently reviewed in Sørensen et al. (2018).

111. Two control banding tools evaluating environmental effects were identified: the Precautionary Matrix and the LICARA nanoscan (see description above in para 95 and 96), where more details relevant for the environmental assessment are added below.

112. The **LICARA nanoscan** estimates the potential effect of nanoparticles on the environment by addressing the redox and/or catalytic activity. The stability of the nanoparticles under the relevant environmental conditions is considered based on the half-life of the nanoparticles. The potential emission into the environment is estimated by the volume of nanoparticles present in the marketed products, the physical surroundings of the nanoparticles or carrier material of the nanoparticles in the product as an indicator for the release potential of the nanoparticles and the possible disposal of nanomaterial in different life cycle stages (van Harmelen et al., 2016). The output is a risk band (low, medium or high).

113. For a quantitative risk estimation, the GUIDEnano tool and SUNDS estimate the risk in the environment along the life cycle together with the risk to humans.

114. Other tools that estimate the material flow, fate, transport and uptake/bioavailability are:

115. **SimpleBox4Nano**[36] is a regulatory-relevant multimedia fate model that is specifically fit for use with MNMs. The tool predicts background concentrations of MNMs in air, water, sediment and soil. Designed originally as a research tool, SimpleBox4Nano has proven useful in dedicated environmental fate studies, focused at understanding and predicting environmental fate from fundamental physical and chemical substance properties. It is a screening-level quantitative model that expresses nanoparticle transport and concentrations in and across air, rain, surface waters, soil, and sediment, accounting for nano-specific processes such as aggregation, attachment, and dissolution. The SimpleBox4Nano is a nanomaterial-specific development of the SimpleBox model, which underpins the EU's chemical risk and safety decision-support tool EUSES (European Union System for the Evaluation of Substances). SimpleBox4Nano simulates screening level fate assessments at regional to continental scales. It can also be used to determine the maximum allowed production volume of a specific NP in EU since production volume is linearly correlated with the predicted environmental concentration.

116. **NanoFASE**[37]: This model system performs complex, spatially-explicit simulations at smaller scales. It simulates geographical area(s) as a network of cells. Within each cell, environmental compartments will be linked by transport functions (e.g. sedimentation, deposition, effluent release, soil runoff, biota uptake). Implementation of material flow among cells (e.g. water flow, air movement) enables multimedia transport modelling and fate prediction.

[36] https://www.rivm.nl/en/soil-and-water/simplebox4nano

[37] http://nanofase.eu/

117. **nanoRelease** estimates the annual releases of MNMs from manufacturing, use, and disposal of a product explicitly taking stock and flow dynamics into account. Given the variabilities in key parameters (e.g., service life of products and annual release rate during use), nanoRelease is designed as a stochastic model.

118. **nanoFATE** [38]is a screening-level dynamic multimedia model for predicting concentrations in different environmental compartments at a local scale. The model considers emissions to the air, freshwater, coastal water and different solid compartments and interactions of the nanomaterial and the environment. Ten regions of the USA and Europe can be used to simulate environmental scenarios.

119. **nanoDuFlow**[39] is a spatially resolved hydrological ENP fate model. The model simulates advection, aggregation–sedimentation, resuspension, dissolution and burial for singular ENPs, 5 classes of ENP homoaggregates and 25 classes of heteroaggregates, dynamically in space and time, and uses actual hydrological data of the river, 5 tributaries and a waste water treatment plant effluent.

120. **LearNano**[40] estimates release rates using an LCIA (Lifecycle Inventory Assessment, described in Keller 2013, and Gottschalk 2009) approach. It considers nanomaterial production rates, product applications, treatment plants (WWTP, WIP, etc...) and estimates release rates to environmental compartments such as air, water, soil, including a landfill compartment

121. **MendNano**[41]: This model is used to assess the multimedia environmental distribution of nanomaterials based on a mechanistic description of various intermedia transport and reaction processes. It also allows users to perform rapid "what if" evaluations of the potential environmental implications of ENMs.

122. **RedNano** is a combination of MendNano and LearNano. It is an integrated simulation tool for assessing the potential release and environmental distribution of MNMs based on a life cycle assessment approach and multimedia compartmental modelling coupled with mechanistic intermedia transport processes. The RedNano simulation tool and its web-based software implementation enables rapid “what-if?” scenario analysis, in order to assess the response of an environmental system to various release scenarios.

123. **WSM/WASP7**[42]: This model evaluates the effect of stream dynamics and chemical transformations on the environmental fate of MNMs in a watershed-scale model. The James River Basin portion of the Phase 5.3.2 Chesapeake Bay Watershed Model (WSM) is coupled with EPA water quality modelling suite WASP7 and configured to model NM fate.

124. **Rhone/Rhine Model**: the novelty of this model is that it incorporates spatial variability in environmental conditions in an existing ENP fate model for aquatic environments. The model is parameterised for the Rhine river.

1.1.2. Tools that cover economic aspects of SbD

125. Socio-economic analysis (SEA) has been widely used for helping decision makers and stakeholders in the context of public policies and large-scale infrastructure or industrial projects.

[38] https://pubs.acs.org/doi/abs/10.1021/acs.est.6b05279

[39] https://www.sciencedirect.com/science/article/pii/S0043135415300099

[40] https://nanoinfo.org/learnano/

[41] https://nanoinfo.org/mendnano/

[42] https://pubs.acs.org/doi/10.1021/acs.est.5b01205

SEA goes beyond the mere economic aspect of a product chain value, since it takes into account the societal cost aspects resulting from health and environmental impacts from this chain value. Recently, SEA has been applied to assess economic benefits of new processes and new materials such as nanomaterials in research and development (Boucard and Brignon, 2014).

126. The design of new materials such as MNMs must provide practical and competitive solutions for meeting the objectives of public policy on environment and health This variety of issues to be addressed raises uncertainties for both private and public actors regarding the net benefit of innovative technology investments, i.e. the overall benefits provided to the society when health, environmental impacts and economic costs are considered together. SEA is a valuable tool for establishing the balance between these costs and benefits and providing some clarification on improvement opportunities. Guidelines for the implementation of SEA have been provided by the Organisation for Economic Co-operation and Development (OECD, 2002) and by the European Chemicals Agency (ECHA, 2008b). These guidelines provide a framework for the SEA, but the method must be adapted to the specific needs of each analysis. A range of different methodological tools may be used within SEA. Common methodologies used are: cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and multi-criteria analysis (MCA). These methodologies themselves call upon the use of a number of different analytical techniques (OECD 2002).

127. SEA can only be performed on case studies when enough data on environmental and health impacts have been generated. These data could be provided with the support of Life Cycle Analysis (LCA) and quantitative Risk Analysis (RA) tools. Such data are then coupled to robust industrial economic data (i.e. cost of production, information about market entry of the product) to carry out the SEA.

128. Via case studies, the NanoReg2 project found that quantitative and robust SEAs were not possible to carry out at the early stages of technology development, as data on the nanomaterials at this development stage was not robust enough for decision making. Hence, quantitative SEA is not a suitable tool for assessing a technology at early stages of development. Nevertheless, preliminary qualitative SEA studies can be performed already at early stages to help highlight some of the data needed to carry out a quantitative and robust SEA on the whole value chain.

129. Two operational tools, LICARA Nanoscan and SUNDS, have been identified to address the economic aspects of MNMs. These tools could be useful to have a first look at benefits and costs generated at each stage by the introduction of nanomaterials but cannot yet substitute a complete and robust SEA in the sense of the OECD/ECHA guidelines.

1.2. A review of barriers, constraints, limitations and incentives in the implementation of Safe(r)-By-Design concepts, Regulatory Preparedness and Trusted Environment

130. The fourth aim of the SIA project was to review the barriers, constraints and limitations already identified (or potentially perceived) in the implementation of Safe(r)-by-Design concepts, Regulatory Preparedness and Trusted Environment, as well as the incentives that could possibly contribute to lift (or mitigate) these difficulties.

131. During the OECD SIA workshop held on December 18, 2019 for the stakeholders, an interactive dialogue session was organised via the ‘Mentimeter’ tool to receive feedback from the audience regarding barriers, constraints and limitations to the implementation of SbD, RP and TE, as well as corresponding incentives. The Workshop was attended by 32 delegates, including a few online participants.

132. The major types of barriers identified were:

- Barriers related to resources and costs

- Barriers related to lack of knowledge
- Barriers related to lack of adapted frameworks, guidance and standards, tools, and regulatory organisation
- Barriers related to inadequate regulation
- Barriers linked to insufficient communication, collaboration and open-mindedness
- Barriers specific to SMEs

133. Details on these barriers and corresponding incentives identified during the workshop are summarised below.

Barriers related to resources and costs

134. One probable barrier identified were the possible additional resources needed for the SbD development of nanomaterials compared to that of general chemicals, as well as the possible requirement for additional resources for evaluating such materials. This was expressed in discussions both on "implementation of Safe(r)-by-Design" and "Regulatory Preparedness". On the SbD question, the global cost and possible lack of resources (both in terms of technical equipment and human resources) were emphasised. Additionally, it was noted that SbD for nanomaterials may be particularly time-consuming in implementation, leading to the competitive disadvantage of an increased time-to-market.

135. The specific case of Small and Medium-size Enterprises (SMEs) that could face particular difficulties due to the lack of resources was put forward.

136. In summary, barriers concerning resources can be expressed on two levels:

1) Financial (need for additional technical means and human resources)
2) Extra time to implement SIA with potential competitive disadvantage due to longer time-to-market

1.2.1. Incentives to resolve barrier on resources and costs

137. The main point identified was to allocate resources for SbD for nanomaterials, with particular focus on the benefits of the commercialized product. A second point proposed was to develop structures to help reduce the design cost of the product, the process, and its use to lead to higher profit. Finally, a third point was to provide tax reduction for companies introducing and applying SbD to nanomaterials. Specific funding to support regulators in assisting in this transition was also suggested.

1.2.2. Barriers related to lack of knowledge

138. For SbD (including technical and EHS part), a significant gap between the current level of knowledge and what is estimated to be needed to develop SbD for nanomaterials was highlighted.

139. SbD seems to be complicated, and particularly at the early stage of a project, it requires not-yet-available knowledge.

140. Knowledge enabling an adequate understanding of the health and environmental impacts of nanomaterials was estimated to often be unavailable.

141. It was also emphasised that there are not enough structures for training, education, and producing and sharing information.

142. Barriers concerning lack of knowledge can be summarised as follows:

- Lack of specific knowledge required for the identification of potential problems/issues through SbD
- Lack of specific underlying knowledge and knowhow to implement SbD

Incentives to resolve barriers concerning lack of knowledge

143. A need was identified to address an important lack of education/knowledge on what SbD is; the public and the media lack this knowledge. Different ways to address this were proposed:

- Publish clear and compact guidance,
- Indicate area and cases where SbD is supported,
- Offer training and access to infrastructures.

144. The need to involve more the SMEs was emphasised.

Barriers related to Cultural changes

145. It was strongly emphasised in the comments that the development of SbD for nanomaterials will bring cultural changes, which will not be easy to tackle for key stakeholders, in particular for SMEs.

146. The lack of close collaboration, transparency, and an existing sectoral approach were identified as barriers.

147. The question of how to give innovators legal responsibility regarding the product and its use was raised.

148. The SbD concept has not yet entered the public mindset.

149. Additionally, some manufacturers would benefit from learning more about SbD, thus becoming more likely to adopt it. It was emphasised that there is a lack of information flow from innovators to regulators which, combined with a lack of trust and confidence, makes collaboration difficult.

150. Barriers concerning cultural changes can be summarised as:

- Responsibility of the innovators/manufacturers in SbD not well understood
- Responsibility of people using SbD frameworks/standards or sectorial guidelines not well understood
- SBD not yet known by the general public or by regulators (lack of flow of information), which can lead to lack of trust/confidence

Incentives to resolve barriers concerning Cultural changes

151. It was proposed to establish an international agreement on the SbD concept with support by the national governments. Creating international certificates or rewards for applying SbD was also proposed.

152. Regarding cultural changes in SME, it was proposed to create governmental platforms to provide technical support on SbD to SME.

153. It was suggested to educate the public on the benefits brought about by SbD, for example by promoting some success stories.

Barriers related to frameworks, guidance and standards, tools, regulatory organisation adapted to SbD

154. There was a large consensus on the fact that, for development of SbD on nanomaterials, there are huge gaps between what is estimated to be needed and what is available from current frameworks, guidance, international standards, general and predictive tools (for example, how to practically evaluate decision stop-or-go at early or late stages and how to perform risk assessment, life cycle analysis and socio-economic analysis with predictive tools).

Incentives to resolve barriers concerning frameworks, guidance and standards, tools, regulatory organisation adapted to SbD

- Need of a supportive regulatory environment.
- Development of the normative frameworks.
- The creation of certifications.
- Introduction of SbD in the curricula of technical and scientific studies.

Barriers related to legislation

155. A lack of specific regulatory processes to support SbD for nanomaterials, including a lack of specific legal instruments and associated liabilities, was noted.

156. To date, discussions between regulators and innovators have not been straightforward. For example, creating platforms between regulators and innovators has not yet been seen as an obvious step.

157. The still very limited international regulatory collaboration on SbD for nanomaterials has been cited as a weak point. The risk of over-regulation was also mentioned.

158. On the Regulatory Preparedness (RP) part, a lack of trust and confidence between innovators/manufacturers and authorities was highlighted, and the lack of sufficient flexibility in existing regulatory frameworks to adapt quickly to new products/technology was considered a difficulty. The possibility of an anti-innovation narrative concerning the regulation of emerging technology was raised, as well as a risk of over-regulation.

159. In summary, we observe a lack of concrete legislation to support SbD, but also a concern/fear of over-regulation that could kill innovation.

Incentives to resolve Regulatory barriers

160. The following incentives were identified:

- Develop regulatory requirements and corresponding measures for fulfilling the essential social and environmental aspects of SbD.
- Promote SbD concept beyond OECD, and possibly to the UN.

Barriers linked to communication, collaboration, open-mindedness

161. Trust and confidence were emphasised as key points in all domains, as also the need for a proactive mindset.

162. Barriers related to communication can exist on different levels: Between industry and regulators, between industrial sectors, and between industry and downstream users. These aspects are discussed below.

163. Regarding the communication between innovator/industry and regulators, the information flow from innovators to regulators was considered to be insufficient. A lack of awareness at the regulatory level and the rarity of policy incentives were emphasised. It is also noted that there are usually few or no discussion platforms for regulators and innovators. More generally, there is limited exchange of information on the evolving landscape, potential challenges and solutions provided by industry. It was also emphasised that a conflict between the industry's desire to protect its intellectual property and the regulatory drive for openness and transparency may exist, and that the respective policy goals of regulators and innovators may be often perceived as conflicting rather than mutually beneficial.

164. Regarding the communication between industries, it was noted that a sectoral approach with exchange of information and collaboration between companies of the same sector is not general practice. Competition legislation may re-inforce the lack of communication.

165. It was noted that regarding communication to downstream users, the concept of SbD is not yet in the public mindset and that without a good communication, the trust of the consumers might be limited.

166. In summary, industrial sectors may need specific practices. Sectors are often competitive, which may make the communication difficult. The lack of communication between industry and policymakers, and the lack of a platform between the industry and regulators, are observed. Solutions to this communication barrier are not easy to put in place, and the way to implement them efficiently is still to be devised.

Incentives to resolve barriers linked to communication, collaboration, open-mindedness

- Develop an International Consensus on SbD at high level, e.g. OECD or UN.
- Improve the communication between innovators and regulators by for example establishing open channels or platforms of communication and interaction between industry (R&D) and regulators
- Promote SbD to the general public, e.g. in the media and in civil society, and use success stories for this promotion.

Table 3. Summary of barriers and incentives in SbD implementation

RELATED TO:	BARRIERS TO SbD IMPLEMENTATION	INCENTIVES TO HELP LIFTING BARRIERS TO SbD IMPLEMENTATION
Costs and Lack of Resources	• Additional cost for technical and human resources • Extra time in implementation of SbD	• Allocate resources to enable especially focusing on the benefits of SbD • Develop structures to help design product, process, usages at a reduced price • Provide tax reduction of nanomaterial SbD, specific funding to support regulators to help this transition
Lack of knowledge/ data gaps	• In identification of potential issues/problems brought about by SbD, requiring specific knowledge • Lack of specific underlying knowledge at early stages • Lack of structure for training, education, and information	• Publish clear and short guidance, • Indicate area and cases where SbD is supported, • Offer training and access to infrastructures. • SMEs need to be more involved
Cultural changes	• Responsibility of the innovator/manufacturer in SbD not well understood	• Establish an international agreement on the SbD concept with support of the national governments • Create international certificates or rewards for applying SbD. • Create governmental platforms to provide technical support on SbD to SME. • Educate the public on the benefit brought by SbD, for example by promoting some success stories
Lack of framework, guidance and standards, tools	• Huge gaps between what is needed and what is available from frameworks/guidance • Lack of predictive tools in RA, LCA, and SEA	• Need of a supportive regulatory environment. • Development of the normative activities. • The creation of certifications. • Introduction of SbD in curricula of techno scientific studies.
Inadequate legislation	• Lack of regulatory process to support SbD for nanomaterials, including legal instruments and liabilities • Lack of discussion platform between regulators and innovators	• Develop regulatory requirements and corresponding measures for fulfilling the essential social and environmental aspects of SbD. • Promote SbD concept beyond OECD, and possibly to the UN.
Insufficient communication, collaboration and open-mindedness	• Competitive industrial sectors may render communication difficult between industry and regulator/policymaker	• Develop an International Consensus on SbD at high level. • Improve communication between innovators and regulators by for example establishing open channels or platforms of communication and interaction between industry (R&D) and regulators • Make promotion of SBD in the public, in the media and in civil society and use of success stories.

Anticipatory Governance/Regulatory Preparedness: Inventory of Strategies for Awareness and Decision-Making

Rationale

167. Another aim of this report was to develop an inventory of regulatory strategies for awareness and decision-making including foresight, horizon scans or other methodologies and an inventory of available business and governance models that incorporate a Safe(r) Innovation Approach and Safe(r)-by-Design concept.

168. The Netherlands (RIVM) led the development of this task, together with Canada (Health, Environment and Climate Change) as co-lead and France.

169. Two main publications on Regulatory Preparedness were selected for reviewing (Jantunen et al., 2018; Soeteman- Hernández et al., 2019) because they describe discussions on Regulatory Preparedness for Innovation in Nanotechnology. The discussions took place at the NanoReg2 Workshop, organised by two NanoReg2 partners, the National Institute for Public Health and the Environment (RIVM) and the Joint Research Centre of the European Commission (JRC), and held in Ispra, Italy, 5–6 October 2017, hosted by the JRC. This first Workshop on Regulatory Preparedness for Innovation in Nanotechnology was organised to stimulate the discussion on how regulators can better prepare themselves for the assessment of new and emerging nanotechnologies. During the workshop, more than 60 regulators and risk assessors from the EU and United States of America (USA), representatives of the industry and NGOs discussed how regulators currently deal with innovation, the needs of regulatory risk assessors to prepare for addressing innovations, the tools available and needed to support RP and possible practical barriers. Soeteman- Hernández et al. (2019) highlights the main findings of the workshop, identifying elements of RP needed to anticipate and address the regulatory challenges posed by nanotechnological innovation. The following section describes the outcomes of the workshop and by Soeteman-Hernández et al. (2019). The text has been edited as appropriate for this report.

170. In this workshop, active discussions were held on how regulators currently deal with innovation, the needs of regulatory risk assessors to prepare for addressing innovations, the tools available and needed to support RP and possible practical barriers. The workshop addressed two main topics: 1) the regulatory context and the need for Regulatory Preparedness; and 2) the tools and instruments supporting Regulatory Preparedness. In break-out groups, participants discussed how regulators currently deal with innovations, what they need to be prepared for innovations, what tools are needed to support RP and what the barriers for the implementation of RP in practice are. The outcomes of the workshop fed into the Safe(r) Innovation Approach for nanotechnology, consisting of Safe(r)-by-Design and Regulatory Preparedness, developed by NanoReg2.

171. As a follow-up to the workshop, a survey was developed for establishing an inventory of regulatory strategies for awareness and decision making including foresight, horizon scans and other methodologies, as well as an inventory of available business and governance models. The survey was distributed among OECD Countries (July–September 2019) (See Annex 3). The inventory regulatory strategies for awareness and decision-making were split in the following categories: activities, networks, surveillance and governance.

172. The following questions were asked:

- Q5. Do you know any activities by governments, NGOs or other organisations to gather information about the uses of emerging technologies in products?
- Q6. Do you know any specific networks dedicated to understanding and discussing emerging technologies?

- Q7. Do you know any activities by governments, NGOs or other organisations to gather information about the uses of nanotechnologies in products?
- Q8. Are there any nano-specific pre- marketing surveillance activities in your country?
- Q9. Is there a platform in your country for post-marketing surveillance and adverse effects reporting?
- Q10. Are there any governance models in your country that incorporate 'responsible innovation', 'anticipatory governance' or 'regulatory preparedness' (or a similar concept by another name)?

173. To further consolidate the responses to these questions, a review of barriers, constraints and limitations for anticipatory governance/regulatory preparedness was done during the SIA workshop held on 18 December 2019 at OECD Headquarters, Paris, France. The Workshop was attended by 32 delegates, including some online participants.

Results

Review of the two Publications on Regulatory Preparedness

174. The Workshop on Regulatory Preparedness for Innovation in Nanotechnology served to generate ideas for achieving Regulatory Preparedness (Jantunen et al., 2018)[43]. The following paragraphs describe the outcomes of the issues discussed at the Workshop and the text is based on the Workshop report, edited as appropriate for this report.

175. The participants recognised that while regulators deal with the safety of innovations, few systematic approaches to this work exist. Some innovative products may reach the market before their safety has been appropriately assessed, as illustrated by notifications of unsafe products via RAPEX, the Rapid Alert System for dangerous non-food products[44]. A continuous and proactive combination of interconnected activities was considered to be required for ensuring Regulatory Preparedness. Thus anticipation, e.g. horizon scanning, was seen as important, as was communication between regulators, innovators (industry) and other stakeholders. Regulators need to become aware of innovative products under development in order to ensure that the legislation and methods for safety assessment are available and adequate. Innovators must be aware of regulatory requirements and their likely development. This mutual awareness helps to develop safe products and to avoid delays or other problems in obtaining market approval. Awareness can be achieved through communication, which requires trust, promoted e.g. via Trusted Environments for confidential inquiries and information sharing. Furthermore, regulators need early access to the existing information and data relevant to safety assessment of innovative products in order to provide timely guidance and advice to industry as well as to develop strategies for dealing with uncertainty, e.g. by applying the precautionary principle.

176. Regulatory Preparedness was discussed as part of the SIA, and a "road map" of actions was suggested and outlined.

177. This workshop thus contributed towards the acceptance of implementing Regulatory Preparedness for innovation in nanotechnology through the participation of a variety of stakeholders. This paved the way for better dialogue among stakeholders in a fast economic development cycle, where it is growingly important to quickly identify emerging needs for new approaches to regulatory issues regarding innovation.

[43] Jantunen, P. et al., 2018. Workshop on Regulatory Preparedness for Innovation in Nanotechnology. EUR 29357 EN, doi: 10.2760/278827, JRC112766

[44] https://ec.europa.eu/consumers/consumers_safety/safety_products/rapex/alerts/repository/content/ pages/rapex/index_en.htm

178. The safety of innovations to human health and the environment is primarily addressed through the establishment and enforcement of a regulatory framework, including legal acts and related guidance on implementation. The challenges in ensuring the safety of innovative technologies and products revolve around the lack of knowledge and information about such technologies and products and of existing legislation that applies to them. Knowledge of existing technologies and products may not predict issues of concern introduced by novel technologies and products. Since innovation typically involves an element of surprise, e.g. the particular use/need that the innovation addresses, regulatory authorities may not have sufficient information at their disposal to predict such challenges early enough to effectively address them. A lack of information and preparedness for the regulatory safety assessment of innovative technologies and products can lead either to a delay in an innovative product's introduction to the market, or to an innovative product entering the market before its safety aspects have been appropriately assessed. Delayed market introduction can happen when the product falls under an existing piece of legislation which is not ready to tackle the novel safety aspects of the product; this may also result in no safety assessment. A lack of safety assessment can also occur when no existing legislation explicitly addresses the safety of the product. Obviously factors also need to be in place to ensure product safety, e.g. the science and tools need to be ready to provide a solid foundation for assessing the safety of innovative products. Additionally, the willingness of industry to share their knowledge of the product could be crucial in having a profound understanding of that product, including safety aspects.

How do regulators currently deal with innovations?

General remarks

179. According to the participants, overall, regulators currently have few systematic approaches to dealing with innovations in practice. Typically, innovations were reacted to on a case-by-case basis as they materialise, later resulting in legislation that addresses underlying issues for the future, e.g. the Directive 67/548/EEC[45] that attempts to address hazards of general chemicals in the wake of several examples of disregarded adverse effects of chemicals[46]. The Directive is the first version of legislation addressing dangerous chemicals in general that are currently regulated by REACH[47] [48] [49]. Another example is the Seveso Directive[50] that was agreed in the aftermath of three industrial accidents[51] to prevent similar accidents and ensure information to the general public. In order to avoid unnecessary delay in bringing innovative products to the market but, on the other hand, to properly assess the safety of such products and avoid possible adverse effects on human health and/or the environment, regulators should be able to anticipate future safety assessment needs and prepare for them. One of the challenges is the lack of information connected with innovative products: do hazards and exposures need to be fully known before risks can be predicted and, if

[45] https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX:31967L0548

[46] https://www.eea.europa.eu/publications/environmental_issue_report_2001_22/Issue_Report_No_22.pdf/ view

[47] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32006R1907

[48] https://www.statoquotidiano.it/18/09/2012/indagini-epidemiologiche-17-sin-bibliografia-per-manfredonia/ 99724/

[49] http://www.icheme.org/shop/lpb/2013/major-process-incidents-1-resource-pack/the seveso disaster - an appraisal of its causes and circumstances.aspx

[50] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32012L0018

[51]https://www.icheme.org/communities/special-interest-groups/safety and loss prevention/resources/~/media/Documents/Subject Groups/Safety_Loss_Prevention/HSE Accident Reports/The Flixborough Disaster - Report of the Court of Inquiry.pdf

necessary, reduced to an acceptable level through legislation, and to what extent can the precautionary principle be applied?

180. Interaction between the different actors helps the regulators to anticipate what is coming (and prepare for it) and industry to understand how the regulators handle innovations. Such interaction also promotes the passing of the information needed for safety assessment from innovators to regulators. However, interaction is currently made difficult by both mutual lack of understanding and reluctance by innovators to share information on the science that underpins an innovation, since sharing this information may lead to loss of control of the innovation and the potential financial profit from it.

How regulators become aware of innovations and their risks/hazards?

181. A common starting point for regulators to deal with an innovation is encountering a new type of product about which key information related to safety seems to be missing. The general principle then is to start by gathering information about the innovation: What is it about, and what about it is new and different? Does is fit within the existing safety regulations (and if so, where), or are there significant gaps in the regulations?

182. Awareness may be a result of collaboration e.g. among regulatory bodies, with non-governmental organisations (NGOs) or internationally within the academia, the European Union, the OECD, etc. Also Industry may raise awareness. Another possible source of information leading to awareness is the (legally required) registration of substances or products and their uses by Industry, including requirements of any pre-commercialisation testing or product description, where applicable.

183. As individuals, regulators may attend various sorts of conferences, workshops and meetings (for either experts or stakeholders) in order to become and stay informed of relevant innovations. Systematic screening tools and surveillance systems such as the EU RAPEX system are other means of learning about innovations and upcoming issues.

184. At the institutional level, the current way of dealing with innovations seems to depend largely on the specific sector. For instance, in the thoroughly regulated medical sector, the industry typically approach regulators at an early stage of the innovation process to discuss regulatory matters and minimise the new product's time to market. Some institutions organise regular meetings with the different stakeholders (i.e. policymakers, regulators and industry) for the purpose of discussing innovations.

185. For horizon scanning needs at the level of policy and decision making, the Directorate-General for Parliamentary Research Service (DG EPRS) of the European Commission has developed a guiding framework for technology foresight which aims to cover Social, Technological, Economic, Environmental, Political/legal, Ethical and Demographic (STEEPED) aspects[52].

186. Information is gathered by performing literature searches and by means of calls for data from interested parties. It should be noted that while Industry may have produced data relevant to the safety of the product, the need to protect their intellectual property often makes them reluctant to share it.

187. If the regulators face pressure in the form of e.g. extensive media or public attention, the safety assessment of a certain innovation may be prioritised and stakeholder consultations may be

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http://www.europarl.europa.eu/RegData/etudes/IDAN/2015/527415/EPRS_IDA%282015%29527412_REV1_EN.pdf; http://eusprivienna2017.org/wp-content/uploads/2017/05/ExAB-46-Friedrichs-Evaluating-the-Impact-of-Convergence.pdf

held. However, the amount of media attention that an innovation has attracted may not as such be a good indicator of whether or not its safety actually requires more regulatory attention; it may rather indicate a need for better communication between regulators and the public. Communication with the general public and consulting stakeholders are good practice in innovation processes in general, but consultation is not a fail-proof approach, as seen e.g. in the case of genetically modified organisms (GMOs). The results of such consultations tend to depend on the amount of media interest, which in turn depends largely on what else happens to be competing for this interest at the time.

How regulators assess the risk of innovations?

188. Regulators typically start assessing the safety of innovations when the need arises (the trigger being that it is a regulatory requirement, or missing knowledge or, in some cases, risks/hazards discovered through incidents) and by doing their best with what is available. When several cases of similar new technology have come to light[53], fact-finding and broader discussion takes place. In the meanwhile, the relevant industry can be supported, e.g. through legal information requirements or reports on lessons learnt, with precautionary measures to improve awareness of potential safety issues and provide pragmatic instruments for dealing with them.

189. Also novel types of products require a risk assessment process. In order to understand how to assess the risk of such products, regulators need a fact-finding process (which often involves asking for information from the producer) and in general to "ask more questions". This may be complicated by the lack of clarity on what kind of questions should be asked in each particular case. Regulators can also request and fund research that is aimed at identifying problems from contractors, such as academic institutions and national institutes, and interact with various stakeholders to handle the situation.

190. As an example, many governments started to look relatively early on into the safety issues of nanotechnology and in particular to collect information. OECD's work on the safety of NMs started with governments contacting the OECD to ask how to handle the safety assessment of NMs.

Promoting the safety in innovation

191. Regulators can also influence the safety of innovations by promoting safe technology. In R&D work, exploration is clearly needed. On the other hand, both the occupational safety of the researchers involved and the safety of the eventual products need to be considered, and here the many unknowns of innovative activities are a problem. In publicly funded research, safety measures in the form of SbD or other relevant approaches are generally required; private companies may be less precautionary.

What do regulators need to be prepared for innovations?

General remarks

192. The general regulatory process of dealing with an innovation starts with awareness and passes through the development of the necessary methodology to acquire the information to perform the actual risk (safety) assessment. However, different insights need to be combined in regulatory work, and ideally, the big picture is always looked at: the safety of the innovative product weighed against its contribution to society in e.g. the form of jobs and other benefits that

[53] As illustrated e.g. by the evolution of soaps and detergents, which after 1940 contained increasing amounts of non-biodegradable ingredients, limited in the 1970s by legal requirements concerning biodegradability https://www.sciencedirect.com/science/article/pii/S0304415700000137

the innovation promises to bring; circular economy, life cycle and waste management considerations; and uncertainty in its various forms.

193. It was generally agreed that proactive approaches – looking into the future by e.g. keeping an eye on trends and preparing for it – are better than simply reacting and adapting to information received or results of public consultation, and that more formalised innovation governance and general strategies to follow are needed. The need for communication mainly between Industry and regulators but also with many other stakeholders was emphasised. Adequate resources and the difficulties of prioritisation were recognised as challenges for regulatory work on the safety assessment of innovations. Precautionary measures may be applied to regulate unknowns such as the safety of innovations.

Needs for becoming aware of innovations

194. Becoming aware of innovations that may need the closer attention from regulators requires horizon-scanning activities as well as communication and interaction between regulators, Industry and other relevant stakeholders.

195. Horizon scanning[54] requires both working time and resources. One option is to entrust this work to specific forward-looking regulatory units or task forces, or to units that specifically deal with innovations (this approach is used in the Republic of Korea). While specific tools may facilitate horizon-scanning activities, networking with e.g. R&D activities is also important, and regulators also need to communicate among themselves, discarding excessive compartmentalization mentality.

196. Communication and interaction between regulators and Industry, e.g. in the form of meetings to clarify and improve matters, can become complicated by political issues or be confused with lobbying. An alternative is to organise innovation-themed dialogues between regulators and public funding agencies (about e.g. SbD or funding), and to include one or more organisations representing Industry as the commercial partner through which the companies can submit their ideas or questions. For instance, in Austria, public innovation-promoting agencies and the Chamber of Commerce meet regularly with regulators in a small-scale and informal but effective "brainstorming" approach.

197. Large-scale meetings with different stakeholders are more likely to serve horizon scanning, while smaller and more confidential gatherings can be used to discuss details. While some skepticism over the significance of stakeholder consultation was expressed, it was recognised that stakeholders (e.g. financial actors, insurance companies, NGOs, grass-root organisations, users of the product or occupational organisations) can contribute knowledge, resources and social insight and help to concretise accountability and responsibility concerning the safety of innovative products.

Needs for being able to assess the hazard/risk of innovations

198. Innovation is based on information, and the regulators also need to have access to this information in order to assess the safety of innovative technology and to set priorities. A basic problem is that innovators and regulators do not start from the same knowledge point and they therefore tend to speak a different language. Consequently, regulators need more and better expertise and skills as well as the other necessary resources to deal with innovation properly; this in turn requires political will to invest in developing the regulators' knowledge and skills by providing the budget, capacity and time needed. Of course this needs also to be supported by all

[54] OECD: "a technique for detecting early signs of potentially important developments through a systematic examination of potential threats and opportunities, with emphasis on new technology and its effects on the issue at hand", https://www.oecd.org/site/schoolingfortomorrowknowledgebase/futuresthinking/overviewofmethodologies.htm

actors, e.g. by Industry that could share information early, and by science, which could generate the knowledge required and develop the tools needed for assessing any innovation.

199. In order to cover gaps in the generation of data and information needed for safety assessment of innovations, appropriate test methods may need to be developed, which again requires resources for the relevant experts as well as appropriate prioritisation of the most urgent issues. At the workshop, it was pointed out that metrologists may have a lot to say about analytical and test method development in practical terms (e.g. overall feasibility, choice of units) and about the standardisation of methods, but communication between regulators and metrologists does not currently work well. Regarding chemicals and materials, the use of grouping and read-across and QSAR (quantitative structure–activity relationship) models helps to make efficient use of the existing data and information in safety assessment; however, for new materials, for instance NMs, such techniques may require further development and adaptation to become acceptable in the regulatory context. To look at the big picture of the potential impacts of introducing an innovative product on the market, e.g. socio-economic impact analysis and strategic environmental assessment can be applied. Regarding products that may release a chemical in the environment, population-level biomonitoring and epidemiological data ("cocktail effects") would also come useful.

200. In addition to becoming aware of upcoming innovations as discussed above, regulators also need to receive more extensive, even if yet uncertain, information about these innovations well in advance of intended market launch, preferably straight from the innovators/Industry. Such information includes details such as how the innovation differs from existing products, what the specifications are, details on possible uses (since actual exposure data may not be available yet), and any factors that could be relevant for the assessment of potential adverse outcomes. All in all, open and honest dialogue with Industry that is developing an innovative product is desirable from an early stage, but pre-market notification or registration obligations are stronger instruments than communication; they also balance the responsibility and testing burdens better between regulators (public funding) and Industry (private funding).

201. Regulators need resources and time for going through and properly digesting the available and provided data and information and for considering the options of dealing with each innovation within the existing regulatory framework. An example of real-life difficulties is the case of heat-not-burn tobacco products entering the market; from the regulatory point of view, discussion has been needed on whether they can be placed in an existing regulatory product category (tobacco products) or they need a new category or definition.

202. Legislation concerning safety assessment should be built to be flexible, so that implementation is possible when new types of materials or products appear without a continuous need to change the legal text, which is a time-consuming process for regulators and often seen as an obstacle to innovation by Industry. In order to achieve this, it is crucial that innovators are heard from the beginning of the process of drafting such legislation, although the prevention of conflicts of interest may require that they are involved through an intermediate. In the EU, stakeholders' consultations include representatives of industry associations and are held not only while drafting a legal act but also while its implementation and impact are monitored. "Cross-fertilisation" type learning across different pieces of legislation is also needed, as an innovative application may initially appear in a specific sector (e.g. food) and only later in others (e.g. cosmetics). In the absence of legislation or regulation that properly addresses a particular innovation, it should be possible to require the developers to provide screening-level data for safety assessment.

203. In order to improve communication between regulators and Industry, practical ways to share information and reach reciprocal understanding need to be found. Such dialogue and sharing of information also requires mutual trust: on the one side, the confidentiality of such communication ("use but not disclose") and the intellectual property of Industry needs to be guaranteed by regulators; on the other side, the completeness and validity of the information provided, especially on safety aspects, needs to be ensured by Industry. The required trust takes

time to develop. Ideally, a systematic dialogue allows the regulators to detect in advance whether current regulations need to be adjusted in response to innovative products on their way to the market, and Industry/innovators to respectively detect if safety provisions in regulations are likely to prove a challenge for placing an innovative product on the market.

Tools supporting Regulatory Preparedness

General remarks

204. Certain types of tools, such as dialogue/communication and horizon-scanning activities, had already been recognised in the discussions on the preceding topics, as was the need of Industry for incentives to engage in dialogue and to share data and information that helps to assess and improve the safety of innovative products. There was a strong emphasis on tools for communication. These needs can be served by "Trusted Environments", platforms in which the innovators and Industry feel they can make inquiries and share information with regulators while protecting their intellectual property and financial investments.

Tools for awareness

205. Various kinds of horizon scanning and foresight tools and early warning systems can help regulators to become aware of innovations that require particular attention. However, this also requires identifying indicators or critical factors (triggers) that should draw such attention. While Trusted Environments can encourage innovators/Industry to forewarn regulators of innovative products that may enter the market in the near future and may not be properly covered by current regulations, regulators also need to actively search for such information. Networking (such as visiting the local industry, or exchanges with patent authorities), attending relevant technological conferences and workshops (also technical workshops between innovators and regulators), performing literature searches, utilising tools that scan the internet for emerging subjects or trends, and setting specific task forces for these activities can all serve this purpose. So-called "windtunneling" can be used to create various future scenarios and then test the performance of the existing regulations against them.

206. A type of networking recognised as particularly important was the interaction among regulators or experts from international organisations (e.g. OECD) and different countries (e.g. EU Member States), involving the sharing of experiences and methods. This enables everyone to cast a wider net than can be done within any single country or region and to learn from the experiences of others. In the basic form of such activity, any new type of situation encountered is shared with colleagues, who can then check if they already have the same risk on the table or prepare for encountering it. Such sharing can take place within various types of expert communities as "tour de table" or "lessons learned" exercises. Within the EU, trilateral high-level meetings between ECHA, EFSA and European Medicines Agency (EMA) take place and were recognised as important.

207. Interactions should be regular and can involve individuals or institutions/groups. Different stakeholders can also be involved. Horizon scanning can be performed on general policy level or address risk assessment in a specific field of innovation. As examples of current approaches, in Finland regular meetings involving all stakeholders are held at Ministry level, foresight workshops and stakeholder dialogs (e.g. Nanodialog[55]) are organised in Germany, and France employs a task force.

208. Choosing the appropriate stage in the development of an innovation (e.g. the Technology Readiness Level, TLR) to start communications between regulators, innovators/Industry and other

[55] https://www.bmu.de/en/topics/health-chemical-safety-nanotechnology/nanotechnology/the-nanodialogue/

stakeholders or e.g. request or require entering the product in a registry[56] is not simple. On the one hand, regulators should have adequate warning to prepare for assessing the safety of the innovative product; on the other hand, the innovation should have enough shape to give an idea of what it is and how it is going to be used. Naturally, the information that needs to be provided to regulators should correspond with the stage of the innovation in question.

209. The other half of the SIA concept, SbD, can improve the awareness of innovators of regulatory information requirements and help them both to identify risks of innovative products and to produce the appropriate safety-related information and data at appropriately early stages of the R&D process. The further development and implementation of SbD within Industry and efficient integration with the regulatory safety assessment process is therefore desirable.

Tools for risk assessment or management

210. If possible, regulators should be provided with open access to information related to the safety of innovative products. Whether shared on basis of pre-market obligations (e.g. registration or notification), on "Trusted Environment" type platforms or e.g. in one-on-one meetings between Industry and regulators, such information needs to be relevant, reliable and complete and accompanied by an adequate description of the methods used to generate it (preferably standardised or harmonised). This allows regulators to use this information as a basis for their assessment of the safety of the innovative product (where applicable) or a field of innovation, and helps to develop applicable methodology.

211. The sharing of information and data on innovations also involves complex issues such as which data are actually needed in each case, what methodology should be used to produce it, in what format the data should be provided, and who should have access to which data (involving the practical aspects of data sharing and protection). The idea of an "iTunes shop of studies" was presented for simplifying the process of finding and acquiring access to relevant studies.

212. Prioritisation can be served by tools such as the risk ranking toolbox developed by EFSA for prioritising microbiological risks[57].

213. Best practices guidance on the subject of engaging stakeholders could improve the value of stakeholder consultations. Creating networks of experts on specific topics, e.g. as a database of experts that authorities can use, could be useful for consultations. Such networks can be used for various purposes, though the practical experience to date seems to be that the existing expert networks are not used much.

214. Tools for dealing with innovations that are already on the market or close to their market launch, while sufficient knowledge about their safety is still lacking, depend on the sector; some, such as the medical sector, demand stricter, less flexible safety measures than others. Tools range from applicable guidance to implementing existing regulatory frameworks to developing new legislation. Guidance is fairly easy and quick to change and adapt. The revision of a legal act is challenging and time-consuming but binding for Industry. Implementing safety assessment and risk management requirements for innovative products may entail developing new or adapting existing protocols (e.g. OECD Test Guidelines) and other tools (e.g. control banding tools).

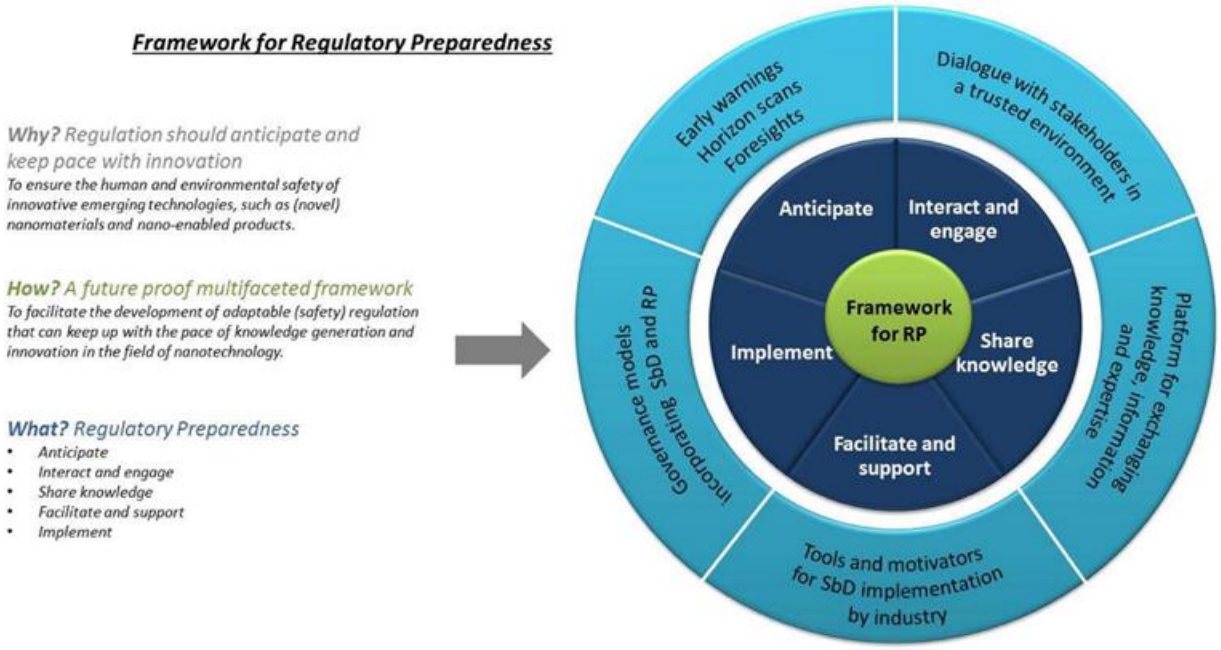
215. Here we provide text from the Soeteman-Hernández et al. (2019a) which, based on the discussions during the Regulatory Preparedness workshop, among others developed a framework for Regulatory Preparedness consisting of five iterative steps: Anticipate, Interact and engage, Share knowledge, Facilitate and support, and Implement (Figure 4). The description below presents

[56] https://www.r-nano.fr/?locale=en

[57] https://www.efsa.europa.eu/en/press/news/150109

the information according to the steps identified (information with dark blue background on figure 4); to some extent that information has also been given in the text above.

Figure 4. Framework for Regulatory Preparedness (RP) for novel nano-technological innovations and the actions needed for its implementation as a part of a Safe(r) Innovation Approach, which is based on a combination of RP and Safe(r)-by-Design (SbD)



Anticipation and associated tools

216. Regulators and policymakers need ways to anticipate the regulatory challenges posed by innovations such as NMs. The tools and approaches identified at the workshop for identifying upcoming issues as early as possible include horizon scans and foresight.

217. Horizon scans and foresight aim to anticipate the long-term implications of emerging technologies by generating scenarios, public debate, and risk analysis and to connect decision-making and governance, resulting in effective policy (Barben et al., 2007; Guston 2007, 2010). Foresight is a systematic and policy-oriented process which actively engages key stakeholders in a wide range of activities that anticipate, recommend and transform technological, environmental, economic, political, social and ethical futures (EFP, 2012). It is supported by horizon scans, which are structured and continuous activities aimed at monitoring, analysing and positioning (MAP) 'frontier issues' relevant for policy, research and strategic agendas. The types of issues mapped by horizon scans include new or emerging trends, policies, products, services, stakeholders, technologies, practices, behaviours, attitudes, 'surprises' (wild cards) and 'seeds of change' (weak signals) (EFP, 2012).

218. Foresight processes are: (i) action-oriented; (ii) participatory (often involving researchers, business people, policymakers and representatives of citizen groups); and they (iii) consider multiple alternative futures (Gurria, 2016; OECD, 2020). The OECD has published several reports on foresight (Allianz, 2005; OECD, 2016a, 2017a, 2018b). In addition, it has developed Technology Foresight Forums, organised by the OECD Committee for Digital Economy Policy, to help identify opportunities and challenges posed by technical developments for the Internet

economy (OECD, 2016b). Strategic foresight leads to better policies that ensure safety and truly benefit the society as a whole.

219. The EU project NANoREG resulted in a proposal for a Foresight System for new NMs and nano-enabled products, presented by Micheletti and Sips (2016). This Foresight System proposes a platform, dedicated to regulators, allowing the assessment of the possible adverse impacts of potential new applications of NMs. The platform identifies Target Applications (TAs) (Micheletti and Sips, 2016) for a preliminary risk assessment approach that includes the definition of qualitative risk hypotheses. The use of Life Cycle Assessment (LCA) or other tools to qualitatively define impacts on health, safety and the environment may complement the preliminary risk assessment. To illustrate how the system works, a case study was developed on the use of graphene in water treatment membranes, as the availability of clean and safe water is a major concern for the future (Micheletti and Sips, 2016).

220. The European Parliament's Science and Technology Options Assessment (STOA) Panel (STOA, 2018) carries out interdisciplinary assessment and provides strategic advice to the European Parliament in the field of science and technology options assessment and scientific foresight. The STOA activities include the European Foresight Platform (EFP), a program supported by the European Commission that aims at building a global network to bring together different communities and individual professionals to share their knowledge about foresight, forecasting and other methods of future studies.

221. The EFP gives information on e.g. current and past foresight projects, conferences, workshops, press articles and other future studies, e.g. the successor of the ForLearn foresight guide (EFP, 2018).

222. We envision a nano-specific European entity, based on the ideas behind the EFP, which can act as a hub for bringing together all horizon scanning and foresight initiatives, including those by the OECD.

Engaging and interacting

223. Dialogue among the different actors of the innovation process is needed for translating the RP concept into practice. This includes knowledge-sharing between policymakers, regulatory risk assessors, industry, NGOs, experts, academia and the society. This dialogue can take place in a Trusted Environment (TE), which allows confidential one-to-one consultations or dialogue between regulators, innovators and other actors (Kraegeloh et al., 2018). At the regulatory level, dialogue and knowledge-sharing among different disciplines and regulatory domains (food, non-food, consumer products, etc.) at various levels (EU, OECD, academic) is desirable for RP. For instance, Germany has organised foresight workshops and stakeholder dialogues (e.g. Nanodialog (BMU, 2018)) for RP.

224. A TE can be regarded as a physical or virtual environment in which industry, universities and other research institutes (innovators) and (semi-)governments (regulators) can openly share and exchange knowledge, information and views on new technologies, such as innovative NMs and nano-enabled products. A TE should stimulate trust, ensure transparency and confidentiality, and protect intellectual property and organisational interests. From the beginning, a TE should clearly state: a) technical requirements for giving organisations control over the process of information sharing (anonymity, logging of actions etc.); b) juridical requirements for safeguarding the information exchange process (non-disclosure agreements, regulations etc.); and c) requirements for clarity and agreement among the participants regarding the rules of behaviour when dealing with the obtained information (code of conduct).

225. A TE that provides clarity on all three aspects stimulates transparency of the information exchanged while maintaining confidentiality as far as required by the participants. In order to

implement the TE, an independent organisation might be established to define and supervise the technical, juridical and behavioural aspects of the TE (including mediation in situations of conflict) and facilitate the organisational aspects, including setting up (virtual) meeting points for the relevant actors along the innovation process. The harmonization of industry's needs for confidentiality with the transparency needs of regulators and other possible stakeholders is a challenge and may be a barrier for engaging industry in dialogue.

226. Examples of existing TEs include the Innovation Task Force (ITF) of the European Medicines Agency, which is a discussion platform for early dialogue with applicants. It allows ITF-EMA to anticipate the regulatory challenges posed by innovations, helps the pharmaceutical industry to prepare for regulatory processes and provides a platform for innovators and regulators to exchange information for the benefit of public health (EMA, 2018). Another example is the EFSA Emerging Risks Exchange Network (EREN), which exchanges information between EFSA and EU Member States on possible emerging risks concerning food and feed (EFSA 2018a). This may also include innovative emerging technologies, such as nanotechnologies, for which a guidance for risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain has been developed (EFSA, 2018b). EFSA recently held a stakeholder workshop on nanoscience and nanotechnology where stakeholders had an opportunity to have open discussions with EFSA and its experts on the new EFSA guidance, focusing on human and animal health issues (EFSA, 2019). The workshop discussed risk assessment challenges such as analytical challenges with physicochemical characterisation, and characterisation and quantification in a food matrix, and oral uptake of nanomaterials. Another example is the Food Safety Authority of Ireland, in whose working TE innovators exchange information with regulators in order to ensure the safety of innovative products and clarify legal uncertainty surrounding them (FSA, 2017).

227. The engagement and interaction of various stakeholders, including researchers, market players, regulators and policymakers (Barben et al. 2007; Guston 2010), support early information exchange. Information can be gathered from a wide range of experts along an NM's life cycle, resulting in increased awareness of and preparation for nanotechnologies (Beaudrie et al. 2013; Michelson 2013).

228. We envision that the interaction between EU agencies can take place at different levels: there can be informal dialogue regarding a general issue relating to nanotechnology, or it can integrated into the overall engagement and interaction process when dealing with specific cases and confidential information.

229. Overall, a TE is seen as a Knowledge and Communication Platform to facilitate the confidential exchanges of information between innovators and regulators.

Share knowledge

230. Knowledge generation in innovation follows an exponential rather than a linear process, resulting rather quickly in the generation of a vast amount of data. As we move towards a circular and learning economy, openness, collaboration, societal interest and digitization, new knowledge-exchange systems are needed. In a Learning Economy (WRR, 2013), information and experience can be transformed into knowledge, skills, behaviours, and attitudes to generate a system of "interaction and exchange". New knowledge-exchange systems are required due to the sheer speed, scope and scale of learning needed to keep up with innovations in e.g. nanotechnology. Anticipation can have a major positive impact on the development of an innovation process. A workable information exchange system requires a platform where information and knowledge can be securely hosted and made accessible to stakeholders as appropriate. An information exchange system can also facilitate a multitude of partnerships and relationships, stimulate collaboration and provide guidance on issues such as safety, scientific and regulatory matters, as well as in innovation and methodologies. For RP to be successful, a system is needed for industry to share knowledge with regulators at an early stage in innovation, e.g. in a TE.

Components of a Knowledge and Communication Platform

231. The OECD recently acknowledged the importance of open science for increasing the efficiency and effectiveness of public investment in science (OECD, 2017b). A critical component in achieving open science is access to research data (generated by publicly funded projects and by industry); this access needs to be sustainable and supported by institutes at national and international levels and coordinated internationally (OECD, 2017b). The OECD Global Science Forum supports the promotion of open data for science, focussing on internationally coordinated data networks, and has identified (OECD, 2017b) principles and policy actions for enabling the establishment and maintenance of effective international data networks. These principles can be translated to components of a Knowledge and Communication Platform for NMs, whereby data networks are shared between international organisations, national authorities, funders and host institutions. Such data networks may cover various data sources, ranging from international projects to industry and data published in the literature. The main recommendations provided by the OECD for a Knowledge and Communication Platform include: 1) common agreement within the data network on the open access to data; 2) common legal and ethical frameworks for sharing different types of research data; 3) recognition of the important role of international data networks for the infrastructure for open science; 4) establishment and development of organisational aspects, such as clearly defined users and data providers, connections to other networks, and roles and responsibilities of all stakeholders; 5) financial support to internationally coordinated data networks through funders and host institutions; 6) clear business models for the networks, including value propositions and measures of success that are relevant to their different stakeholders and will be monitored; and 7) active participation of the funders in relevant international discussions and fora to improve long-term function, support and coordination of data networks (OECD 2017b). We envision, for instance, a Knowledge and Communication Platform for the storage and facilitated exchange of information and knowledge that is fully accessible to regulators and policymakers, while maintaining confidentiality to protect the interests of industry.

232. An example of a common agreement within a data network at the national level is the French Ministère de la Transition Écologique et Solidaire that has recently launched a nano-registry for producers, distributors and professional users of NMs to improve the flow of information to the general public and workers, and to generate additional information for risk assessment (MTES, 2017). For general information sharing at the European level, the European Union Observatory for Nanomaterials (EUON) is an independent and, in principle, unbiased initiative towards a platform for information sharing (ECHA, 2017). Other aspects of this Knowledge and Communication Platform are being addressed in European Union's Horizon 2020 Research and Innovation Programme projects Gov4Nano, NANORIGO, and RiskGONE.

Overcoming methodological hurdles through knowledge sharing

233. The different methodological hurdles encountered when assessing the safety of NMs are numerous. Briefly, the obstacles discussed included:

- In using *in vitro* toxicity test systems for the toxicological evaluation of NMs include interference with read-out systems, inappropriateness of certain *in vitro* tests for NMs (the Ames test may not be suitable for detecting genotoxicity induced by NMs (OECD, 2014b)), cell dosimetry (DeLoid et al., 2014) and the influence of the dispersion method used on the result (Park et al., 2009).

- In using *in vivo* systems, an important issue in interpretation is the derivation of the metrics for a toxic dose of a given NM, since mass and chemical composition, the metrics usually sufficient for general chemicals, may not be adequate for NMs (particles with the same chemical composition can display diverse mass-based toxic doses, depending on e.g. particle size) (Delmaar et al., 2015). Various dose metrics, e.g., particle number, volume,

or surface area, have been suggested, but international consensus is lacking (Delmaar et al., 2015). The OECD programme on Testing and Assessment of Manufactured Nanomaterials tested eleven nanomaterials for up to 59 endpoints, addressing physical-chemical properties, mammalian and environmental toxicity, environmental fate and material safety (Rasmussen et al., 2016). Results indicated that while many existing OECD test guidelines are suitable for NMs, some test guidelines and guidance documents need to be adapted to address NMs specifically, and new ones may be needed for endpoints that are more relevant to NMs (Rasmussen et al., 2016).

234. Many of these methodological hurdles can be addressed more efficiently by networks than by individual organisations acting on their own.

235. The OECD has several nanosafety initiatives, e.g. the Working Party on Manufactured Nanomaterials (WPMN), which promote international cooperation on the human health and environmental safety aspects of manufactured nanomaterials for regulatory purposes (OECD 2018a). The WPMN is a network of regulators and experts working on safety aspects of NMs, including harmonised test guidelines covering nano-specific aspects for subsequent adoption in the OECD Test Guidelines Programme, guidance for safety assessment (for example, on the identification of nano-relevant physical-chemical data, on sample preparation and dosimetry for testing NMs, and on exposure assessment), and integration of NM risk management into existing chemical management practices.

236. Several recent publications on frameworks and decision trees that can help to group NMs for safety assessment purposes are available[58]. In-vitro test protocols have been addressed through European projects such as ProSafe[59], NanoValid (NanoValid, 2018) and NANoREG (NANoREG, 2017). Recent studies have also explored the applicability of toxicogenomics in the safety assessment of NMs, with promising results[60].

237. Currently, many efforts on nanotechnology risk assessment, knowledge, information and needs over various sectors and disciplines (workers, consumers/patients, environmental safety) are fragmented and a system is needed to coordinate, guide and harmonize the data. A key step for unifying the existing efforts is through a Knowledge and Communication Platform. In addition, shared existing data can be more efficiently used for exploration and for confirmation of the applicability of existing and new methods for NMs (including grouping (Oomen 2017; Oomen et al., 2015; Riebeling et al., 2017). Other methods such as the use of toxicogenomics data (Gerloff et al., 2017), QSARs data (Pan et al., 2016; Manganelli and Benfenati 2017)) need to be further developed for the risk assessment of NMs. Further alignment is also needed with activities and guidance by EFSA (EFSA 2018b), ECHA (ECHA 2018, 2019) and European Commission (EC 2009; SCENIHR 2014, 2015) on the risk assessment of NMs. Here we provide the main building blocks towards a system and a Knowledge and Communication Platform that are being addressed in the European Union's Horizon 2020 Research and Innovation Programme projects Gov4Nano, NANORIGO, and RiskGONE.

238. The major results of the workshop are presented in Table 4 and Table 5.

[58] See Gajewicz et al, 2018; Landsiedel et al, 2017; Scott-Fordsmand et al, 2018; Oomen et al, 2017; Oomen et al, 2015; Kuempel et al, 2012; Park et al, 2018; and ECHA, 2019.

[59] See Drasler et al, 2017; Oomen et al, 2018; Sayre et al, 2017; Steinhäuser et al, 2018.

[60] See Williams and Halappanavar, 2017; Rahman et al, 2017; Costa and Fadeel, 2016.

Table 4. Results of workshop discussions

How do regulators deal with innovations?	What do regulators need to be prepared for innovations?	Tools for supporting RP	Barriers for the implementation of RP	Possible solutions to barriers
Reoccurring situation of missing knowledge and unclear what to ask because new technology	Getting better access to information and an equal starting point for industry and regulators (open data, data exchange with patent authorities)	Best practices for engaging stakeholders	IP rights	Incentives to share data
Consult stakeholders or NGOs	Political will to invest in regulator knowledge, skills and working time	Impact assessment for policy prioritization	Lack of political will and resources (priority setting)	More resources
Regulators react as need arises (for instance societal distress)	Resources for horizon scanning	Network of experts	Bureaucracy with projects	Smaller and more agile projects
Implementation of pre-cautionary principle	Dedicated organization to deal with innovations	Dialogue in a trusted environment – 'use but not disclose' policy	SMEs commercially focused	Promoting awareness and making life easier
Request research from university or research institute	Interaction between regulators and industry organizations	Scenario planning (create different scenarios)	Lack of trust	Dialogue in a trusted environment
Evidence-based policy making	Requirement for registering MNMs and transitional SbD requirements before legislation is adopted	OECD or other similar body to prioritize Test Guidelines (TGs) needed for nanomaterials	Lack of regulatory engagement	Commitment of regulators
International collaborations (OECD, EU, academia)	Registry at Member State level (EU compatible)	Tools for measuring value for society (social concern research, forums of consumer views and social impact, customer demands)	Lack of communication between regulatory agencies	Create a platform for regulators to share date in a trusted environment; Feed EU Observatory for nanomaterials (EUON).
RAPEX or other alert systems	Register for products containing nanomaterials in EU market	Infrastructure for data sharing in a trusted environment	Lack of industrial declaration of MNMs	Make declaration of MNMs legally binding (no data, no market)
Focus on uses and not only on substances	Data (screening level data, some interim toxicity data, identification of potential hazardous effects and uses on priority chemicals)	Risk Ranking tools such as those used by EFSA	Lack of enforcement	Facilitate enforcement by creating incentives (social, economic, etc.)
Maintain registries of new substances/products	Epidemiological and population level risk assessment + biomonitoring/cocktail effects (not only assay based)	Foresight and horizon scans	Lack of methods	Develop harmonized and standardized methods for assessing the risk of MNMs
Pre-commercialization testing and product description	Analytical techniques for grouping/QSARs/efficient use of data		Complicated risk assessment tools	User-friendly risk assessment tools
	Learning and cross-fertilization across regulations (multi-domain)		Rigid regulation	Flexible, adaptable and implementable regulations
	Public accountability for risk assessment in a socio-economic analysis			

Source: Soeteman-Hernández et al., 2019a

Table 5. Overview of Regulatory Preparedness workshop findings

Results	Details
The need for a multifaceted agile system consisting of	
Creating awareness	- Horizon scans, internet searches, trend watchers, dialogue with industry
Dialogue with stakeholders in a trusted environment was considered key for achieving RP at various levels	- Interaction at stakeholder level: Dialogue with different stakeholders to translate RP concept into practice including NGOs, experts, academia and society - Trusted environment: one-on-one consultation/dialogue between regulators and innovators - At regulatory level: Dialogue with different disciplines and regulatory domains (food, non-food, consumer products, etc.) at various levels EU, OECD and academia
Knowledge: generation of centralized registry that allows for	- Confidentiality and transparency: develop strategies where there is a balance between maintaining confidentiality yet ensuring transparency
- Data sharing across domains (regulatory) - Industrial open data access	- Registry: aim for obligatory registration of NM and their uses, - Pre-market information: screening level data, some interim tox data, assessing potential hazardous effects and priority checking (based on EFSA presentation) - Open data access
Methodologies: Development of harmonized testing methods specific for new technology in a network (cross domain and industry)	- Overcoming methodological hurdles in networks and not as separate entities - Development of harmonized methods - Explore applicability of new methods including grouping, toxicogenomics, big data
Reflection	- Learning and sharing knowledge across domains and regulations and adapting processes when needed
Other issues	
Costs	- A fair balance of burden between industry and regulators (or public health institutes)
Risk communication	- Maintain society inform as knowledge advances
A dedicated organization or task to deal with new technologies and innovation	- Disseminates the information to other domains and stakeholders

Source: Soeteman-Hernández et al., 2019a

Creating incentives

239. In addition to anticipating, engaging, interacting and sharing knowledge, it is necessary to create incentives to facilitate and support the implementation of RP and SIA. One incentive for facilitating RP implementation might be a SbD index. As part of corporate social responsibility, this index is a label used to create transparency and awareness with regard to SbD. Industry should be rewarded for implementing SbD and an index is one possible way for civil society, regulators and other stakeholders to be aware when a company has implemented SbD. The use of indices to monitor safety, environmental, societal or economic performance indicators might be an effective instrument in stimulating appropriate safety assessment during innovation processes. Examples of such indices include the Dow Jones Sustainability Index (Suzuki et al., 1996a), the Sustainable City Index (Suzuki et al., 1996b) and the Sustainable Society Index (Souliotis et al., 1998). Dialogue (sharing knowledge, engaging and interacting) between industry and regulators is necessary for the development a SbD index that reflects the implementation of SbD in innovation processes. SbD, in turn, helps industry to generate the safety-related information relevant at each step of the innovation process, which both helps industry in their decision-making and can be shared with regulators to mutual benefit.

240. Soft regulation and Good Practices can also facilitate the implementation of the RP concept. For SbD implementation, industry needs to collect and generate nano-specific hazard and/or exposure information early in the innovation process. Codes of conduct and benchmarks, while not legally binding, can be introduced as a first step in addressing the risks of innovations such as nanotechnologies. Research suggests that soft regulation can contribute to responsible nanotechnological development if it is specific enough to meet the needs of the regulated parties, if compliance is supported by financial and professional resources, and if it is embedded in a culture of socially responsible partners, vigilance and adequate adaptation to policy goals, rules, regulatory strategies and tools (Dorbeck-Jung 2011).

Implementation

241. Implementing RP requires the development of new governance models incorporating RP and SbD, which will require effort and investments. Van Asselt and Renn (2011) have defined risk governance as ‘the critical study of complex, interacting networks in which choices and decisions are made around risks and as a set of normative principles which can inform all relevant actors of society how to deal responsibly with risks’. Here a plea for a paradigm shift is made towards a shift in practices.

242. The International Risk Governance Council (IRGC) suggests that for emerging technologies such as nanotechnology, a risk governance framework should be: 1) adaptive (i.e. with flexible risk management strategies that can adapt as new knowledge is generated); 2) collaborative (i.e. information, skills and expertise among different agencies and stakeholders are shared internationally); 3) harmonised (i.e. data, guidelines and reference models are internationally harmonised and validated to generate confidence in safety management); 4) proactive (i.e. it is recognised that innovations evolve at a dynamic speed, and knowledge needs to be constantly updated by sharing and building experience and networks on a global scale); and 5) responsive to human values (i.e. factors such as equality, ethics and privacy are taken into account) (IRGC 2006; Renn and Walker 2008).

243. Other governance models include three primary initiatives such as Safe by Design, improving governance and promoting and streamlining regulatory science for technology are included, in a holistic, multi-criteria approach where the risks, benefits and other issues of nano-enabled products are compared to conventional alternatives (Trump et al., 2018). This comparative

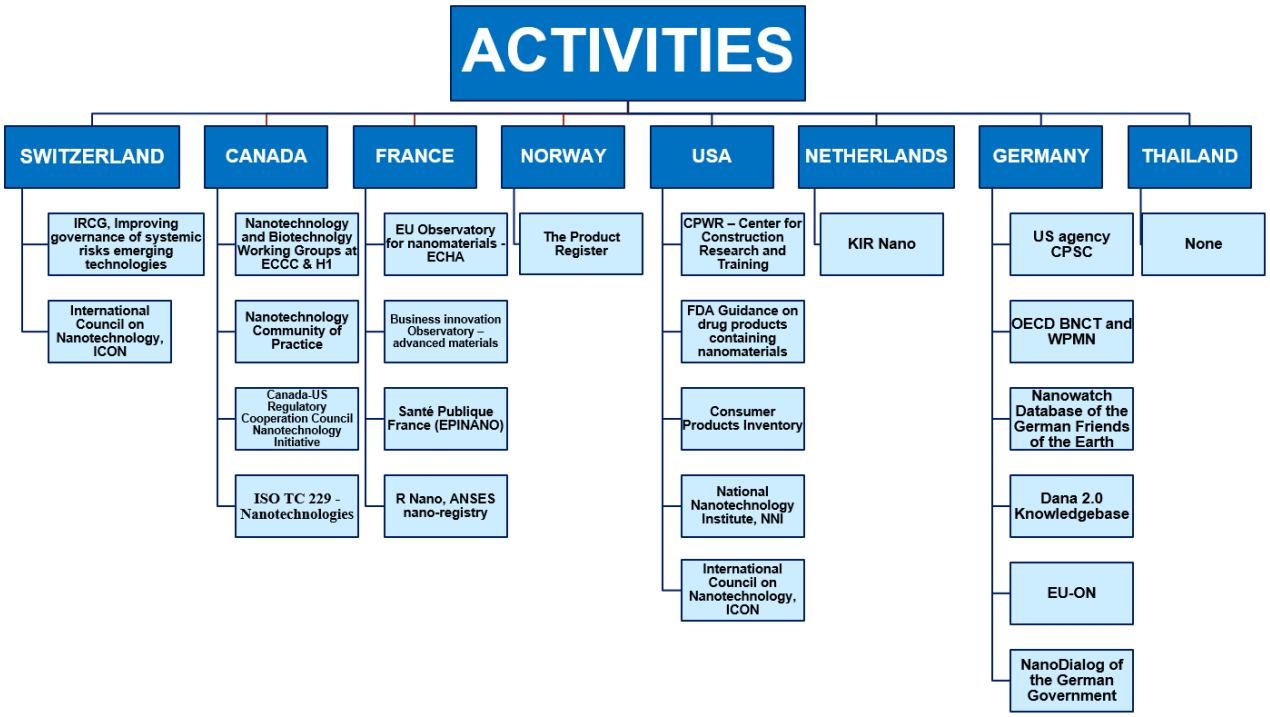
approach might be useful for policymakers and decision makers when evaluating the impact of nanotechnologies to human and environmental health when limited information is available, particularly in the early stages of the innovation process (Linkov et al., 2018). Some studies warn of a global governance gap that is likely to grow unless governments and other stakeholders step up current coordination and cooperation efforts (Falkner and Jaspers 2012). The European Union's Horizon 2020 Research and Innovation Programme projects Gov4Nano, NANORIGO, and RiskGONE are working towards a multi-stakeholder-driven agile operational European Nano Risk Governance system that also includes many additional international partners.

Survey results

244. In addition to reviewing the outcomes of the NanoReg2 workshop , a survey was made to inventory regulatory strategies for awareness and decision making that includes foresight, horizon scans and other methodologies, as well as available business and governance models that incorporate a 'Safe(r) Innovation Approach' and Safe(r)-by-Design concept. Seven delegations responded to the survey: Canada, France, Norway, Switzerland, Thailand, The Netherlands, and the United States.

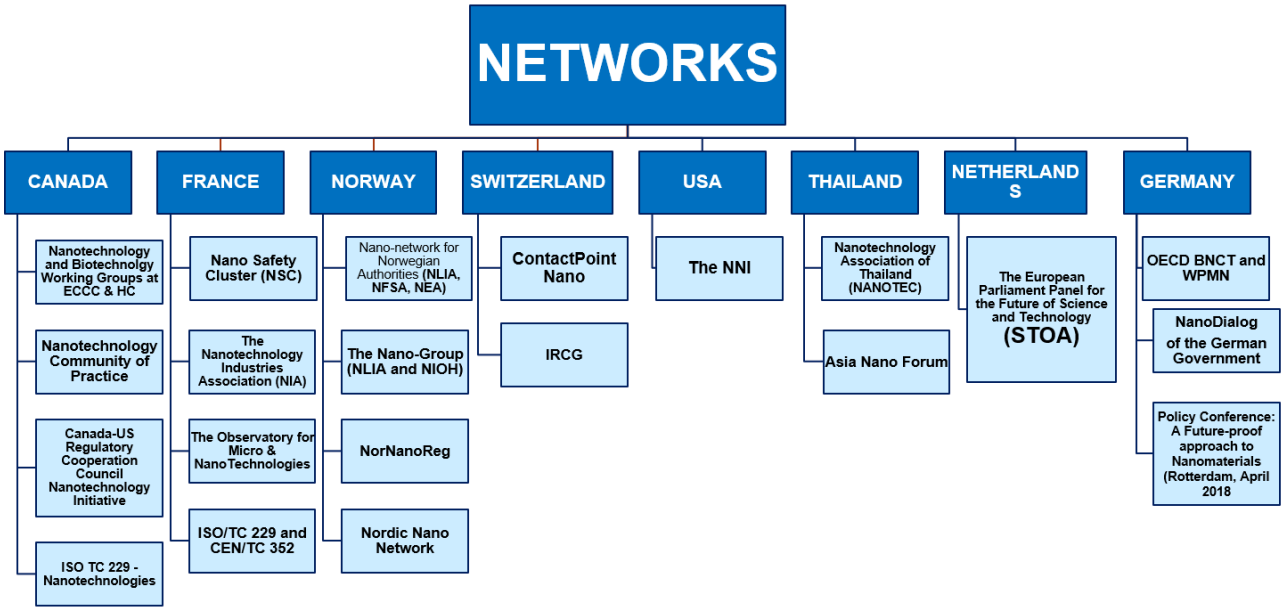
245. The inventory was categorised by Regulatory Preparedness activities, networks, surveillance, and governance. A brief snapshot of the survey responses under each category has been shown schematically in the following sections (Tables 4–5, Figures 5–8).

Figure 5. Regulatory Preparedness activities*



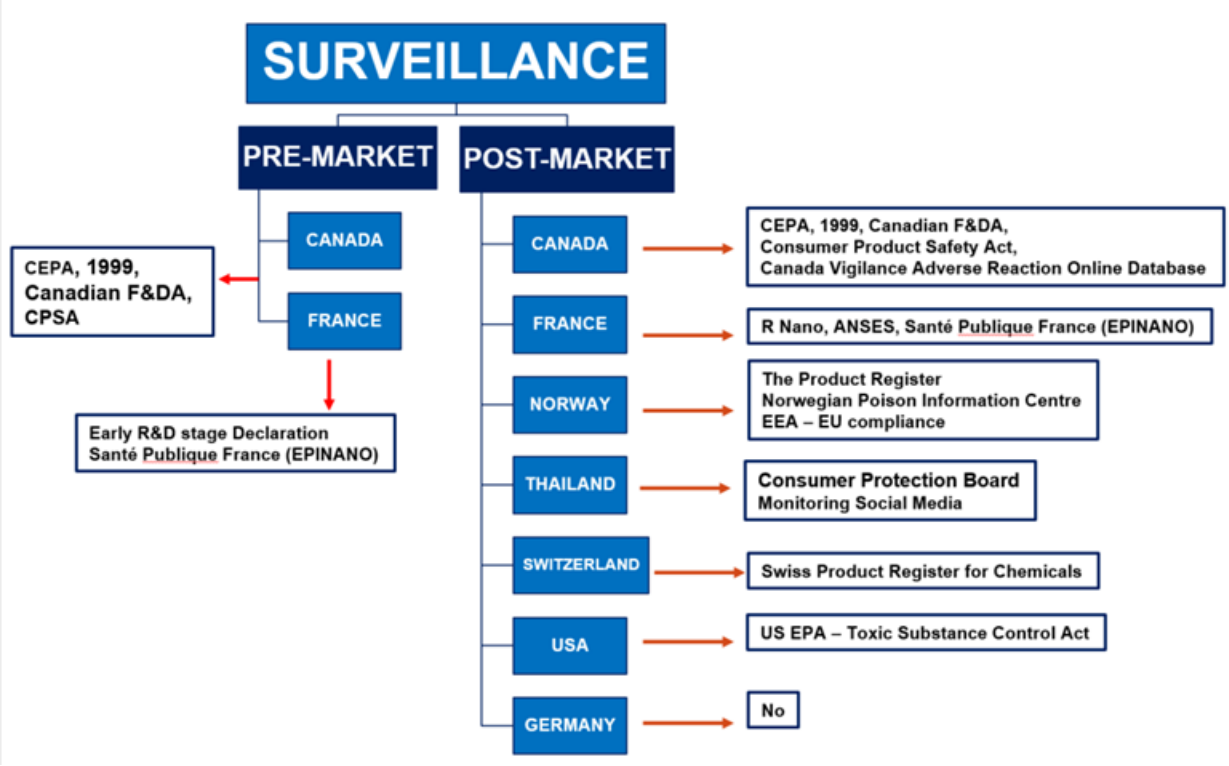
Note: *See Annex 3 for further information on each RP activity.

Figure 6. Overview of Regulatory Preparedness (RP) related Networks*



Note: *See Annex 3 for more information on each network

Figure 7. Surveillance activities for Regulatory Preparedness (RP)*



Note: *See Annex 3 for more information on each surveillance activity.

Figure 8. Governance activities relevant for Regulatory Preparedness (RP)

* See Annex 3 for more information on each governance activity

On-going Horizon 2020 NMBP-13 projects

246. In addition to these governance activities, there are three Horizon2020 NMBP-13 projects: Gov4Nano, NANORIGO and RiskGone (2019–2023), which are all working on developing a new governance system for nanomaterials and towards one Nano Risk Governance Council.

Gov4Nano (https://www.gov4nano.eu/)

247. The Gov4Nano project will develop the first implementation of a future-proof operational Nano Risk Governance Model (NRGM) that addresses the needs of the transdisciplinary field and innovative (and key enabling) character of nanotechnology. It will explore the potential benefit of upcoming tools and approaches such as Findable, Accessible, Interoperable and Re-usable (FAIR) databases, data-hackathons, blockchain technology and implementation of Safe-by-Design to achieve adaptive and resilient risk governance. It will support consensus building, prioritisation and harmonisation of practices amongst stakeholders, with a focus on key aspects for risk governance of nanotechnologies, including risk assessment, risk management, risk perception and risk communication, risk-benefit evaluation, and risk-transfer and the societal desirability of nanotechnology applications. It will include knowledge management and data management, efficiently executed through stakeholder involvement.

248. Gov4Nano will take into account the particulars of different generations of nano-technologies and risk/benefits/public concerns to develop an integrated approach connecting the scientific, regulatory and market layers and the different actors involved from generation of data and knowledge to application in legislation and standards, and propose the basis for efficient and effective risk governance of nanotechnologies. The Gov4Nano project will design and establish a

Nanotechnology Risk Governance Council (NRGC), to create a trustworthy and objective international umbrella for the risk governance of nanotechnologies.

NANORIGO (NANOtechnology RIsk Governance; https://nanorigo.eu/)

249. NANOtechnology RIsk GOvernance aims to develop and implement a transparent, transdisciplinary Nanotechnology Risk Governance Framework and a related Risk Governance Council.

250. NANORIGO will develop and implement a transparent, transdisciplinary and active Risk Governance Framework (RGF) and establish the basis of a related Council (RGC) for manufactured nanomaterials and nano-enabled products. The RGF will be developed through engagement with stakeholders across research, industry, regulation and civil society, and will be based on high-quality scientific data and tools for the physicochemical characterisation of nanomaterials, and the assessment of exposure, hazard and risk for humans and the environment.

RiskGone (https://riskgone.eu/)

251. RiskGone (Risk Governance of Nanotechnology) aims at providing solid procedures for science-based risk governance of nanomaterials, based on a clear understanding of risks and risk management practices.

252. RiskGone will develop new tools or modify existing ones to identify with better certainty the environmental and human health impacts of a number of nanomaterials. These tools and the results of tests using them will then be integrated into the work of a European Risk Governance Council (ERGC), a group of individuals with different areas of expertise on nanomaterials tasked to provide governance decisions on the safety of the specific materials. A risk governance framework, made up of the tools and the ERGC, will be developed to address nanomaterial safety governance in a coherent and scientifically robust way.

Barriers, constraints, limitations and incentives in the building of Regulatory Preparedness and Trusted Environment

253. During the OECD SIA workshop held on December 18, 2019 with the stakeholders, an interactive dialogue session was organised via Mentimeter to receive feedback from the audience regarding barriers, constraints and limitations and the responses are summarised below.

254. The major types of barriers related to RP implementation:

- Barriers related to cost and resources
- Barriers related to rigidity of current regulatory systems
- Barriers related to cultural change
- Barriers related to lack of regulatory organisation adapted for SbD applicability
- Barriers linked to communication, collaboration and change in mind-set

255. Details on these barriers have been summarised in the following paragraphs. It should be noted that one important barrier was not captured in by Mentimeter: that there is no regulatory definition of SbD in the chemicals legislation.

Barriers related to cost/resources

256. Cost/resources was a major barrier named by participants, since RP is time consuming. Regulators are fully occupied by dealing with the current risk assessment issues and do not have resources to address any additional tasks. The lack of human resources, both technical and non-

technical capacity, and support within organisations is lacking. Collecting evidence as to whether an innovation might be a safety risk takes time and financial resources. Finally, the absence of a process for facilitating this, the involvement of regulators is challenging.

Incentives related to cost/resources

257. There is a need to allocate more resources and prioritisation of RP activities among governments and organisations. There is a need for specific funding to support regulators to implement RP activities. Benefits from RP implementation need to be clearly defined at an organisational, national and international level. More resources should lead to a better overview of information on relevant developments that demand attention.

Barriers related to the design of current regulatory systems

258. Currently, there seems to be a lack of awareness that Regulatory Preparedness is needed. The current regulatory systems are not designed to deal with the fast pace of innovations. Finding the right balance between legislation and flexibility to handle the rapid changes of innovation is difficult; however, over-regulation should be avoided. The lack of dialogue between innovators and regulators (in a Trusted Environment) on the evolving innovation landscape hinders addressing potential challenges and solutions in efficiently and supporting SbD strategies.

Incentives related to increasing the adaptivity of current regulatory systems

259. A first step towards adapting current regulatory systems is to establish open channels of communication (Trusted Environments) between industry (R&D) and regulators. This is an incentive for regulators because they gain more information and are aware of new developments which may pose a possible safety risk. This could lead to faster processes and maybe faster time to market. The development of agile regulatory frameworks that include mechanisms for flexibility to adapt to new/emerging products or technologies are needed. Benefits in sharing information in Trusted Environments can be developed through clear regulatory requirements and enforcement for industry (clear roles and conditions).

Barriers related to cultural change

260. In order to facilitate Regulatory Preparedness, a change of cultural- and mind-set is needed. There is a lack of specific processes to support Regulatory Preparedness, including legal instruments to ensure roles and conditions between innovators and regulators are clearly defined. RP is still a new concept for regulators, and there are no processes to facilitate information flow from innovators to regulators in order for them to be prepared for possible challenges of innovations. There is also a lack of trust between innovators and regulators which gets in the way of dialogue. Foresight studies in principle cannot predict risk assessment issues but can give regulators and innovators time to think about what information is needed to address potential safety issues.

Incentives related to cultural change

261. Incentives for a cultural change include better communication and understanding between innovators and regulators and having organisational, national and international consensus on RP/SIA benefits.

Barriers related to lack of a definition of SbD and of regulatory organisation adapted for SbD applicability

262. As SbD is not defined in legislation addressing chemicals, there is no guidance on how to apply SbD. From an innovator's perspective, there is a risk of breach of confidentiality when

sharing information at the early stages of the innovation chain before the product/process has been patented. Regulators need to be sensitive to these issues if Regulatory Preparedness is to be applied. There is no specific regulatory process to facilitate dialogue, protect IP, and there is a need to develop clear legal instruments, the first step being to arrive at a common understanding of SbD in a regulatory context. Potential legal liabilities need to be addressed. A clear overview on how close innovations are to market is lacking, making it difficult to prioritize available resources. There is a need for a global guidance document on SbD, based on an agreed understanding of the concept, to be co-created between innovators, regulators and other important stakeholders. Processes within regulatory organisations need to open to facilitate inter- and intra-organisation information sharing.

Incentives related to lack of a definition of SbD and of regulatory organisation adapted for SbD applicability

263. Capacity building schemes and exercises are needed for regulators to become familiar with SbD. Legal mandates outlining the roles and conditions related to SbD are needed, preferably with international consensus. For regulators, awareness of tools are needed and internationally learning modules are needed to promote SbD consistently in regulatory evolution.

Barriers related to communication, collaboration and open-mindedness

264. Governments need an incentive to want to be prepared for new developments in innovation. There is a lack of a discussion platform or process that facilitates dialogue between innovators and regulators, including a lack of information flow along the innovation chain. There is currently a reactive instead of a proactive mind-set among legislators. The lack of communication and open-mindedness means that governments deal with innovations in a reactive way, i.e. lagging behind the facts.

Incentives related to communication, collaboration and open-mindedness

265. Better communication tools, platform and forms of dialogue are needed to facilitate communication between innovators and regulators. Development of Trusted Environments with clear roles and conditions are needed to protect both innovators and regulators from liabilities and to ensure both innovators and regulators benefit from this process of knowledge exchange.

Barriers related to Trusted Environment

266. There were several barriers mentioned related to Trusted Environments including:

- Difficulties in transparency due to the protection of intellectual property
  - Innovators need to keep their market edge and there is a fear that information may be leaked to competitors
  - IP regimes and related legal arrangements need to be adapted to increase transparency in R&D phase
- Difficulties in convergence
  - There is currently juridical/legal uncertainty with regards to information shared
  - There is a lack of awareness of Trusted Environments by both industry and regulators
  - There is a conflict between industry's desire to protect its intellectual property and the regulatory drive for openness and transparency

- The policy goals of regulators and innovators are often perceived as conflicting rather than mutually beneficial, and this relates to trust and trustworthiness on both sides
- A Trusted Environment is a complex and not well understood process
- There is a lack of clear anticipatory regulatory vision to pave the way

- Difficulties in communication:
  - Inability of regulators to give reliable or useful answers to safety questions
  - More difficult for regulators to reach SMEs
  - Lack of trust from both innovators and regulators
- Difficulties in organisational processes:
  - Lack of formal supporting processes to facilitate Trusted Environments
  - Uncertainty of scope of information sharing; clear roles and conditions are needed
  - Limited time and resources for long processes
  - Presently, there is unclear legal/Intellectual Property Rights/future liability issues
  - Regulators have limited resources to invest in the process. Industry may have too high expectations regarding the benefits of participation

Considerations on limitations/constraints/incentives for Safe(r) Innovation Approach applications, and outlook for future work

Considerations from the NanoReg2 experience

267. The challenges of SIA implementation, as identified by NanoReg2 consortium experts, are summarised here. Implementing a system (SIA) where innovators address safety from the early stages of the innovation process and where regulators are more aware and prepared for innovations is challenging because it requires a change of mind-set from both innovators and regulators. We recommend the following activities for further development:

- raising awareness among innovators and safety regulators/risk assessors for each other's questions and needs;
- stimulate dialogue among innovators and safety regulators/risk assessors on a general level and per case to exchange views, knowledge and information in order to help all stakeholders deal with uncertainties about safety;
- set boundary conditions to secure a trustful environment for dialogues; and integrate nano-specific safety from early phases of innovation onwards in business cases.

268. **For industry/innovators**, there are several challenges and possible barriers for SIA implementation:

- limited resources of SMEs, such as time, money, management processes, equipment, availability of the right personnel, commitment by higher management or, in bigger companies, of local higher management;
- lack of business plans with detailed guidance on how to implement SbD at the operative and strategic processual level including training;
- lack of guidance on how to proceed with operative SbD implementation on the project level; iv) lack of information from supplier, academia or unknown applications/uses, dealers and information availability; and lack of trust for information sharing.

269. **For regulators**, the biggest challenge is to transition from a passive to an active role where the RP concept is put in action. Regulators need to be pro-active in keeping up-to-date with new innovations and via TEs engage with industry for knowledge sharing with regard to how to deal with new developments and limited insight into how nano-specific characteristics influence human and environmental toxicity. Regulators should act proactively and in a timely manner and engage with innovators and policymakers working on innovations (Soeteman-Hernández et al., 2019b).

270. Generating a TE for information sharing is essential for the implementation of SIA. The timely exchange of views between innovators and regulatory risk assessors is essential. The knowledge gap leading to uncertainty of the safety of MNMs and nano-enabled products can be addressed most appropriately and most efficiently by having innovators and regulators share their views, expertise, and ideas on how innovative aspects, such as nano-specific physicochemical characteristics, influence (eco)toxicity. Here, it is vital that input from both regulators and innovators is gathered and the concept of 'learning by doing' to be applied and adapting the process to maintain the information flow. Finding common grounds to address the needs of both innovators and regulations is essential for a successful TE that does not restrict innovation.

271. In order to achieve RP for MNMs and nano-enabled products, a continuous proactive combination of interconnected activities is required. These include being aware of innovations, facilitating dialogue and engagement with stakeholders in a TE, developing knowledge building strategies which include the applicability of soft regulation and setting a New Code of Conduct

which supports SIA. Dedicated organisations or task forces are needed to assess how to deal with innovations and disseminate information across domains and among stakeholders.

272. New business models for industry that support SIA implementation are needed. Industry needs to move towards a proactive business model where there is an investment in knowing the risks of innovations in products and production chain, training suppliers and testing products. Strategic options for managing the risks of chemicals in product and supply chain and creating long-term value by implementing systems to know the risks innovations in products and supply chains are needed.

273. New governance models for regulators that support SIA implementation are also needed. Regulatory risk assessors and policymakers need also to transition to more agile governance models that can easily adapt to new challenges. These models need to be more inclusive involving more stakeholders in the process and allowing for rapid iteration to meet the needs of all stakeholders and society.

274. An information-sharing platform needs to be developed for efficient knowledge sharing. Information is being generated at a dynamic speed but an information-sharing platform is needed for innovators and regulators to have access to up-to-date information. This will ensure partly the robustness of SIA where lessons learned from all the phases of the innovation process are shared to stimulate continuous improvement and ensure trust is sustained. This information-sharing platform would also ensure that information is consolidated in one point of reference. The second component of ensuring robustness of SIA is oversight because it ensures that SbD and RP are implemented and practiced (Soeteman-Hernández et al., 2019b).

Barriers for the implementation of Regulatory Preparedness identified at the Workshop Regulatory Preparedness for Innovation in Nanotechnology (2017)

275. This section is drawn from the report of the workshop on Regulatory Preparedness for Innovation in Nanotechnology held by JRC in Ispra, Italy from 5 to 6 October 2017 (Jantunen et al., 2018), see summary above.

General remarks

276. The identified barriers to implementing Regulatory Preparedness revolve largely around lack of resources, communication, tools, trust or motivation. A clear decision-making framework, confidential and useful two-way communication and straightforward tools with consistent results would help to make the results of the regulatory process more predictable, improving the motivation of the industry to engage.

Identified barriers and proposed solutions

277. Regulators are currently fully occupied and lack time and capacity to look into future challenges. Solving this issue requires the prioritisation of Regulatory Preparedness and political will to grant enough resources (human, technical and financial) for these activities. Policy impact assessment may help policymakers in setting priorities.

278. In the private sector, outside-legal-framework (non-regulatory) safety assessment of novel products may be performed in large companies, but SMEs involved in innovative activities may not have the mind-set or resources to consider safety or regulatory aspects. Particularly the SMEs often focus on the commercial aspects of their products, and a common business model is starting the development process of an innovative product and then selling it to a larger company; at this initial stage of the innovation process, safety may not be a concern that is considered. SMEs may also take significant occupational risks in order to produce a sellable innovation, though the final product as such may very well be safe. Making it easier particularly for SMEs to consider both

occupational and final product safety, the relevant legislation and how regulation is going to evolve (e.g. by actively promoting awareness) can help, and implementing the SbD concept in innovation processes may play a part in this.

279. There are also sectors with little or no current specific regulation and therefore little incentive for the industry to consider the safety aspects of innovations (example: 3-D printing). Since it is in the interest of the industry that their products do not draw negative public attention in the form of safety issues, it should be possible to start discussions with such sectors. Some sectors also lack industry associations able to act as intermediators or facilitators in such discussions, in building trust and in sharing information.

280. Research concerning innovations is generally not risk-focused, and research programmes are rarely focused on regulatory questions, unless this is included in their purpose (e.g. NANoREG, ProSafe). While regulators may request and fund safety-focused research from contractors, project bureaucracy also tends to mean that it takes a long time to set up a research project and then produce the data or information needed. As a remedy, appropriate funding for risk-focused studies should be secured, and smaller projects that are quicker to start and carry through should be considered for answering specific questions.

281. Mistrust among the involved stakeholders covers both intellectual property issues and lack of trust in the information provided by the industry, the methodology used and the robustness of the data obtained. Access to sensitive information is always problematic, particularly if there is no clear incentive for the industry to share this information, e.g. with regulators. As already pointed out, regulators need instruments for requiring certain information from Industry (as e.g. under REACH), but to properly serve Regulatory Preparedness, such information should be received through voluntary communication well before the process to obtain market approval starts. Trust needs to be built up incrementally, ensuring the confidentiality of the communications and the added-value of communication and proper consideration of safety regulations to Industry, while familiarity and a history of safe use improve the confidence of regulators and the public in the safety of a certain innovation. In general, systematic ways of communication are needed.

282. Unclear and/or inapplicable guidance and instructions provided by the authorities are a barrier to Industry producing the required information or data relevant to the safety assessment of an innovation. To solve this issue, regulators need to be able to provide and commit to providing clear and useful guidance, including official answers to questions. Since wider regulatory decisions are necessarily based also on e.g. socio-economic considerations and scientific progress, there are elements of uncertainty in the enforcement and evolution of regulations which can also affect Industry's motivation to engage in dialogue.

Conclusions

283. Demonstrating the validity of the data produced and provided is problematic when there are not yet any agreed standards or validated methods for a particular type of innovative product. The development of TGs and instrumentation and the appropriate validation of protocols require time and appropriate resources for authorities, standardisation organisations and the industry.

Barriers to Regulatory Preparedness identified based on the Workshop on Regulatory Preparedness for Innovation in Nanotechnology[61]

Information and data sharing

284. The barriers identified relate to sharing information and data included a) lack of trust between regulators and industry; b) intellectual property (IP) rights and confidentiality; c) lack of access to information; and d) lack of exchange of information between authorities of different EU Member States and EU agencies. Possible ways to overcome these barriers include creating TEs for dialogue, creating incentives for data-sharing, generating a more equal starting point in terms of knowledge basis for regulators and industry, and forming governance models that allow interagency exchange of data in order to build capacity and share information among regulatory bodies.

Safety regulation

285. The barriers identified relate to safety regulation included the lack of (i) NM-specific test guidelines and methodologies for assessing the safety of NMs; (ii) legislation specifically addressing the safety aspects of innovations such as NMs; and (iii) political motivation and resources for supporting RP. The OECD test guidelines programme and the WPMN are currently developing harmonised test guidelines and methodologies, which process can be accelerated by cooperation and exchange of knowledge. More resources are also needed for developing resilient, adaptive and proactive governance frameworks (WRR, 2013).

286. Safe(r) Innovation Approach (SIA) is a combination of 'Safe(r) by Design' and 'Regulatory Preparedness' concepts, which are to be applied in dialogue with stakeholders in a Trusted Environment, if necessary.

287. The lessons learned from SIA are that it requires:

- A change in culture and mind-set
- Education and promoting actions for awareness
- Guidance on the implementation SbD and regulatory approaches

288. From some case studies on industrial implementation of SIA, we have shown that this concept is at a stage of proof of concept, and there is a need for global guidance to resolve the remaining barriers identified. For Regulatory preparedness, tools are still lacking to help regulators and policymakers anticipate on new challenges posed by innovations.

Considerations for Regulatory Preparedness based on Soeteman-Hernández et al. (2019a) publication

289. The Regulatory Preparedness (RP) concept developed by the EU project NanoReg2 aimed to improve the anticipatory capabilities of regulators and to facilitate the development of (safety) regulation that can adapt to the pace of knowledge generation and innovation regarding new technologies such as NMs and NM-containing products. Regulatory agencies can ease the path for commercialisation of nanomaterials through the acceptance of grouping proposals as outlined in the REACH Guidance for Nanomaterials: The Guidance on Information Requirements on Chemical Safety Assessment (ECHA, 2019). The stepwise strategy for grouping of nanoforms via REACH could lessen the reporting requirements and aid in SbD implementation through the efficient use of existing data, particularly early in the innovation process.

[61] See Soeteman-Hernandez et al. (2019a)

290. Achieving RP for innovations requires a continuous proactive combination of interconnected activities: awareness of innovations, dialogue and stakeholder engagement, knowledge building, methodology enhancement and optimization, soft regulation and reflection, and possibly dedicated organisations or task forces to deal with innovations and disseminate information across domains and among stakeholders. The fair balancing of the financial burden of data generation and safety assessment between industry, regulators and e.g. public health institutes, as well as communication to keep the society informed of advances in knowledge are also important for RP. An important factor in making RP successful is the willingness and openness of industry to start a dialogue at an early stage in the innovation process. TEs play a vital role in the dialogue and knowledge exchange between regulators and innovators while maintaining confidentiality.

291. An inspiring first European RP workshop was the first step in putting the RP concept into practice and bringing together regulators from EU Member States and USA, scientific institutes, industrial partners and NGOs. A framework was found to be needed to support the development of adaptable (safety) legislation in innovative fields such as nanotechnology. Implementation of RP requires the development of new governance models incorporating RP and SbD, which requires effort and investments. The International Risk Governance Council suggests that with respect to emerging technologies such as nanotechnology, a risk governance framework should be adaptive, collaborative, harmonised, proactive and responsive to human values (IRGC, 2006). The multifaceted infrastructure and its actions ('anticipate', 'interact and engage', 'share knowledge', 'create incentives', and 'implement') described in this perspective are a first step towards an agile system of RP that is proactive, vigilant, anticipatory, adaptive, and resilient.

Considerations from the Workshop on Regulatory Preparedness for Innovation in Nanotechnology (Jantunen et al., 2018)

292. Regulatory Preparedness was defined at the workshop as the regulators' timely awareness of innovations and the regulator's actions to check whether present legislation covers all safety aspects of each innovation, including initiating revision of the legislation as appropriate. Achieving Regulatory Preparedness for innovations based on nanotechnology requires a continuous proactive combination of interconnected activities:

- Awareness of innovations: achieved through the use of technology foresight tools, horizon scanning, internet searches, trend-watching, etc. as well as the constant dialogue with stakeholders mentioned below.
- Dialogue: interaction with different stakeholders (Industry, NGOs, experts, academia, etc.), bilateral dialogue between regulators and innovators in Trusted Environments (i.e. platforms in which the innovators and Industry feel they can make inquiries and share information with regulators while protecting their intellectual property and financial investments), and dialogue among regulators representing different disciplines and regulatory domains within e.g. the EU and OECD.
- Knowledge building: gathering information about innovation through registration and pre-market information requirements; open access to safety-relevant data; data sharing across regulatory domains; development of strategies for balancing confidentiality and transparency.
- Methodology enhancement and optimisation: overcoming methodological hurdles in generating safety-relevant data by e.g. networks bridging regulatory domains and Industry, rather than by separate actors; development of harmonised test methods specific for new technologies; exploration of alternative methods, such as grouping and read-across, and new approaches such as toxicogenomics.

- Reflection: learning and knowledge-sharing across domains and regulations, adapting processes as necessary.
- Consideration of additional factors or procedures: potential need for dedicated organisations or task forces to deal with innovations and disseminate information across domains and among stakeholders; fair balancing of the financial burden of data generation and safety assessment between Industry, regulators and e.g. public health institutes; importance of risk communication to keep the society informed of advances in knowledge.

293. In order to implement Regulatory Preparedness for nanotechnology innovations as a part of the Safe(r) Innovation Approach (SIA) pursued by NanoReg2, a "road map" of actions of different time scales and levels of formal acceptance was outlined:

Near-term

- Acceptance of Safe-by-Design (SbD) by regulators:
  - Early engagement of regulators in product design process
  - Industry addresses hazard and exposure concerns early in the product design process
- Establishment of databases for valid (FAIR; Findable, Accessible, Interoperable, Reusable) data
- Establishment of registries of products containing NMs
- Pre-consultations with the industry (individual products)
- Prioritisation of the development of the most needed experimental protocols and guidance

Broader stakeholder meetings

Mid-term

- Development of OECD Test Guidelines for nanomaterials
- Development of other general guidance specific to nanomaterials
- Exploit the EU Nanomedicine Characterisation Laboratory (NCL) as a model for a (nano)innovation network
  - Cooperation between regulators and Industry
  - Protocol development
  - Early screening for the industry (not only medical)
  - Open to Industry use
- Identification of the most promising protocols and methods in development

Formal regulatory developments

- Moving from guidance to legislation
- Where required, shifts in definitions and regulatory requirements for data
- Finalisation of protocols
- Validation and acceptance of alternative methods
- Development of a more effective data generation process that benefits all

- Nano-specific tiered testing or intelligent testing strategies
- Valid protocols for these strategies

References

Allianz, 2005. Small sizes that matter: Opportunities and risks of nanotechnologies. Report in co-operation with the OECD International Futures Programme. https://www.oecd.org/science/nanosafety/44108334.pdf

Baalousha, M., Cornelis, G., Kuhlbusch, T.A.J., Lynch, I., Nickel, C., Peijnenburg, W., vanden Brink, N.W., 2016. Modeling nanomaterial fate and uptake in the environment: current knowledge and future trends. Environ. Sci.: Nano 3, 323–345.

Barben, D., Fisher, E., Selin, C. and Guston, D., 2007. Anticipatory governance of nanotechnology: Foresight, engagement, and integration. In *The Handbook of Science and Technology Studies*, Third Edition, MIT Press, 979–1000.

Beaudrie, C. E. H., Satterfield, T., Kandlikar, M. and Harthorn, B. H., 2013. Expert views on regulatory preparedness for managing the risks of nanotechnologies. PLOS ONE 8 (11): e80250, DOI: 10.1371/journal.pone.0080250

BMU, 2018. Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU): The NanoDialogue. https://www.bmu.de/en/topics/health-chemical-safety-nanotechnology/nanotechnology/the-nanodialogue/

Boucard, P. and Brignon, J., 2014. Socio-Economic Analysis of a Nano-Enabled Technology: Nano-Tio2 Coatings for Solar Panel Efficiency. *4. International Conference on Safe Production and Use of Nanomaterials (Nanosafe 2014)*, Nov 2014, Grenoble, France.

Brouwer D, Gerritsen-Ebben R, van Duuren-Stuurman B, PuijkI, Uzu G, Golanski L, Vaquero C, Gkanis V, Neofytou P van Tongeren M (2010) WP3 report. Occupational Exposure Scenarios 74-wps-reports.

Brouwer, D. H., 2012. Control banding approaches for nanomaterials. *The Annals of Occupational Hygiene*, 56 (5): 506–514, DOI: 10.1093/annhyg/mes039

Cooper R. G., and Edgett S. J. 2017 “Stage Gate Inc.” [Online] Available: https://www.stage-gate.com/

Costa, P. M. and Fadeel, B., 2016. Emerging systems biology approaches in nanotoxicology: Towards a mechanism-based understanding of nanomaterial hazard and risk. *Toxicology and Applied Pharmacology* 299: 101–111.

Delmaar, C. J., Peijnenburg, W. J., Oomen, A. G., Chen, J., de Jong, W. H., Sips, A. J., Wang, Z. and Park, M. V., 2015. A practical approach to determine dose metrics for nanomaterials. *Environmental Toxicology and Chemistry* 34 (5):1015–1022.

DeLoid, G., Cohen, J. M., Darrah, T., Derk, R., Rojanasakul, L., Pyrgiotakis, G., Wohlleben, W. and Demokritou, P., 2014. Estimating the effective density of engineered nanomaterials for in vitro dosimetry. *Nature Communications* 5: 3514.

Dorbeck-Jung, B., 2011. Soft regulation and responsible nanotechnological development in the European Union: Regulating occupational health and safety in the Netherlands. *European Journal of Law and Technology* 2 (3): 1–14.

Drasler, B., Sayre, P., Steinhäuser, K. G., Petri-Fink, A. and Rothen-Rutishauser, B., 2017. In vitro approaches to assess the hazard of nanomaterials. *NanoImpact* 8: 99–116.

EC, 2009. 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. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=SWD:2012:0288:FIN:EN:PDF

ECHA, 2008a. Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals. https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

ECHA, 2008b. Guidance on Socio-Economic Analysis – Restrictions. https://echa.europa.eu/documents/10162/23036412/sea_restrictions_en.pdf/2d7c8e06-b5dd-40fc-b646-3467b5082a9d

ECHA, 2017. European Union Observatory for Nanomaterials. https://euon.echa.europa.eu/

ECHA 2018. How to prepare registration dossiers that cover nanoforms - best practices. http://doi.org/10.2823/128306

ECHA, 2019. Guidance on information requirements and chemical safety assessment. Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals. https://doi.org/10.2823/273911

EFP, 2012. European Foresight Platform supporting forward looking decision making. The role of forward-looking activities for the governance of Grand Challenges. Insights from the European Foresight Platform. http://www.foresight-platform.eu/wp-content/uploads/2012/06/EFP-Publikation-V4_Gesamt.pdf

EFP, 2018. The European Foresight Platform (EFP). http://www.foresight-platform.eu/

EFSA, 2018a. European Food Safety Authority (EFSA) Emering Risks Exchange Network (EREN). https://www.efsa.europa.eu/en/cross-cutting-issues/networks

EFSA, 2018b. Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health. *EFSA Journal* 16(7): 5327, European Food Safety Authority, Parma, DOI: 10.2903/j.efsa.2018.5327

EFSA, 2019. Stakeholder workshop on nanoscience and nanotechnology. https://www.efsa.europa.eu/en/events/event/190401

EMA, 2018. European Medical Agency Innovation Task Force. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp

Fadeel, B., 2013. Nanosafety: towards safer design of nanomedicines. *Journal of Internal Medicine* 274: 578–580, DOI: 10.1111/joim.12137

Fadeel, B., Farcal, L., Hardy, B., Vázquez-Campos, S., Hristozov, D., Marcomini, A., Lynch, I., Valsami-Jones, E., Alenius, H. and Savolainen, K., 2018. Advanced tools for the safety assessment of nanomaterials. *Nature Nanotechnology* 13, 537–543, DOI: 10.1038/s41565-018-0185-0

Falkner, R., and Jaspers, N., 2012. Regulating nanotechnologies: risk, uncertainty and the global governance gap. *Global Environmental Politics* 12: 30–55.

Franken, R. et al 2020. Ranking of human risk assessment models for manufactured nanomaterials along the Cooper stage-gate innovation funnel using stakeholder criteria,

NanoImpact, Volume 17, 2020, 100191, ISSN 2452-0748, https://doi.org/10.1016/j.impact.2019.100191.

FSA, 2017. Food Safety Authority of Ireland. Personal communication by Karl Macdonald.

Gajewicz, A., Puzyn, T., Odziomek, K., Urbaszek, P., Haase, A., Riebeling, C., Luch, A., Irfan, M. A., Landsiedel, R., van der Zande, M. and Bouwmeester, H., 2018. Decision tree models to classify nanomaterials according to the DF4nanoGrouping scheme. *Nanotoxicology* 12 (1): 1–17.

Gerloff, K., Landesmann, B., Worth, A., Munn, S., Palosaari, T. and Whelan, M., 2017. The Adverse Outcome Pathway approach in nanotoxicology. *Computational Toxicology* 1: 3–11.

Gottardo, S. et al., 2016. NANoREG harmonised terminology for environmental health and safety assessment of nanomaterials. EUR 27808, DOI: 10.2788/71213

Gottardo, S. et al., 2017. NANoREG framework for the safety assessment of nanomaterials. EUR 28550 EN, DOI 10.2760/245972.

Gottschalk, F., Sonderer, T., Scholz, R. W. and Nowack, B., 2009. Modeled Environmental Concentrations of Engineered Nanomaterials (TiO2, ZnO, Ag, CNT, Fullerenes) for Different Regions. Environmental Science & Technology 43: 9216–9222, DOI:10.1021/es9015553

Hjorth, R., van Hove, L. and Wickson, F., 2017. What can nanosafety learn from drug development? The feasibility of "safety by design". *Nanotoxicology* 11 (3): 305–312, DOI: 10.1080/17435390.2017.1299891

Gurria, A., 2016. Megatrends to 2050: What better policies for better lives? http://www.oecd.org/about/secretary-general/megatrends-to-2050-what-better-policies-for-better-lives.htm

Guston, D. H., 2007. The Center for Nanotechnology in Society at Arizona State University and the Prospects for Anticipatory Governance. In *Nanoscale: Issues and Perspectives for the Nano Century*, Wiley, 377–392.

Guston, D.H., 2010. The Anticipatory Governance of Emerging Technologies. *Journal of the Korean Vacuum Society* 19 (6): 432–441.

Höhener, K., Höck, J., Lehmann, H. C. and Tãnãsescu, S., 2016. ProSafe Safe-by-Design (SbD) Implementation Concept. https://www.rivm.nl/en/documenten/prosafe-safe-by-design-sbd-implementation-concept-final

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. and Marcomini, A., 2016. Frameworks and tools for risk assessment of manufactured nanomaterials. *Environment International* 95, 36–53, DOI: 10.1016/j.envint.2016.07.016

IRGC, 2006. International Risk Governance Council (IRGC) White paper on nanotechnology risk governance. https://irgc.org/wp-content/uploads/2018/09/IRGC_white_paper_2_PDF_final_version-2.pdf

Jantunen, A.P.K. et al., 2017. NANoREG Toolbox for the Safety Assessment of Nanomaterials. EUR 28676 EN, DOI: 10.2760/332209

Jantunen, P. et al., 2018. Workshop on Regulatory Preparedness for Innovation in Nanotechnology. EUR 29357 EN, doi: 10.2760/278827, JRC112766

Keller, A., McFerran, S., Lazareva, A. and Suh, S., 2013. Global life cycle releases of engineered nanomaterials. *Journal of Nanoparticle Research* 15: 1692, DOI: 10.1007/s11051-013-1692-4

Kraegeloh, A., Suarez-Merino, B., Sluijters, T. and Micheletti, C., 2018. Implementation of Safe-by-Design for Nanomaterial Development and Safe Innovation: Why We Need a Comprehensive Approach. *Nanomaterials* 8 (4): 239.

Kuempel, E. D., Castranova, V., Geraci, C. L. and Schulte, P. A., 2012. Development of risk-based nanomaterial groups for occupational exposure control. *Journal of Nanoparticle Research* 14: 1029.

Landsiedel, R., Ma-Hock, L., Wiench, K., Wohlleben, W. and Sauer, U. G., 2017. Safety assessment of nanomaterials using an advanced decision-making framework, the DF4nanoGrouping. *Journal of Nanoparticle Research* 19 (5): 171.

Liguori, B., Hansen, S. F., Baun, A. and Jensen, K.A., 2016. Control banding tools for occupational exposure assessment of nanomaterials – ready for use in a regulatory context? *NanoImpact* 2, 1–17. DOI: 10.1016/j.impact.2016.04.002.

Linkov, I. T., Benjamin, D., Anklam, E., Berube, D., Boisseasu, P., Cummings, C., Ferson, S., Florin, M. V., Goldstein, B., Hristozov, D., Jensen, K. A., Katalagarianakis, G., Kuzma, J., Lambert, J., Malloy, T., Malsch, I., Marcomini, A., Merad, M., Palma-Oliveira, J., Perkins, E., Renn, O., Seager, T., Stone, V., Vallero, D. and Vermeire, T., 2018. Comparative, collaborative, and integrative risk governance for emerging technologies. *Environment Systems and Decisions* 38 (2): 170–176.

Manganelli, S., and Benfenati, E., 2017. Nano-QSAR Model for Predicting Cell Viability of Human Embryonic Kidney Cells. *Methods in Molecular Biology* 1601: 275–290.

Marvin, H., Bouzembrak, Y., Janssen, E., van der Zande, M., Murphy, F., Sheehan, B., Mullins, M. & Bouwmeester, H.. 2017. Application of Bayesian networks for hazard ranking of nanomaterials to support human health risk assessment. Nanotoxicology. 11. 1-34. DOI: 10.6084/m9.figshare.4585144

Micheletti, C. and Sips, J. A., 2016. NANoREG project Deliverable 6.1: Proposal to monitor innovations in new nanomaterials and their applications. http://www.rivm.nl/en/About_RIVM/Mission_and_strategy/International_Affairs/International_Projects/Completed/NANoREG/deliverables/NANoREG_D6_01_DR_Proposal_to_monitor_innovations_in_new_nanomaterials_and_their_applications.org

Michelson, E. S., 2013. Getting there early: Strategies for seeking policy influence and anticipating nanotechnology's alternative futures. *International Journal of Foresight and Innovation Policy* 9 (2–4): 188–212.

MTES, 2017. Ministère de la Transition écologique et solidaire (MTES), Nano Registry (r-nano). https://www.r-nano.fr/

NANoREG, 2017. A common European approach to the regulatory testing of nanomaterials. https://www.rivm.nl/en/about-rivm/mission-and-strategy/international-affairs/international-projects/nanoreg

NanoValid, 2018. NanoValid: Developing Reference Methods for Nanomaterials http://www.nanovalid.eu/index.php/sops-standard-operating-procedures

Noorlander, C., Sips, A., Höck, J., Höhener, K. and Lehmann, H.C., 2016. NANoREG Safe-by-Design (SbD) Concept. https://www.rivm.nl/sites/default/files/2018-11/NANoREG%20WP6%20Task%206.2%20Safe%20by%20Design%20concept.pdf

Nowack, B., 2017. Evaluation of Environmental Exposure Models for Engineered Nanomaterials in a Regulatory Context. *NanoImpact* 8: 38–47.

OECD, 2002. Technical guidance document in the use of socio-economic analysis in chemical risk management decision making. ENV/JM/MONO(2002)10. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2002)10&doclanguage=en

OECD, 2004. The report from the expert group on (Quantitative) Structure-Activity Relationships [(Q)SARs] on the principles for the validation of (Q)SARs. OECD Series of Testing and Assessment No. 49. ENV/JM/MONO(2004)24. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2004)24&doclanguage=en

OECD, 2005. Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment [ENV/JM/MONO(2005)14]. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono(2005)14.

OECD, 2007. Guidance document on the validation of (Quantitative) Structure-Activity Relationships [(Q)SAR] models. OECD Environment Health and Safety Publications, Series on Testing and Assessment No. 69. ENV/JM/MONO(2007)2. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2007)2&doclanguage=en

OECD, 2014a. Nanotechnology and Tyres: Greening Industry and Transport. OECD Publishing, DOI: 10.1787/9789264209152-en

OECD, 2014b. Genotoxicity of Manufactured Nanomaterials: Report of the OECD Expert Meeting. ENV/JM/MONO(2014)34. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)34&doclanguage=en

OECD, 2016a. Meeting of the OECD Council at Ministerial Level Paris, 1-2 June 2016. Enabling the next production revolution: The future of manufacturing and services- Interim report. https://www.oecd.org/mcm/documents/Enabling-the-next-production-revolution-the-future-of-manufacturing-and-services-interim-report.pdf

OECD, 2016b. OECD Technology Foresight Fora. http://www.oecd.org/sti/ieconomy/oecdtechnologyforesightfora.htm

OECD. 2017a. Meeting of the OECD Council at Ministerial Level Paris, 7-8 June 2017. Enabling the next production revolution: A summary of main messages and policy lessons. https://www.oecd.org/mcm/documents/C-MIN-2017-2015-EN.pdf

OECD. 2017b. Coordination and support of international research data networks. OECD *OECD Science, Technology and Industry Policy Papers* 51, 46 pp, https://doi.org/10.1787/e92fa89e-en

OECD, 2018a. OECD Working Party on Manufactured Nanomaterials. http://www.oecd.org/science/nanosafety/

OECD, 2018b. OECD Science, Technology and Innovation Outlook 2018. http://www.oecd.org/sti/oecd-science-technology-and-innovation-outlook-25186167.htm

OECD, 2020 Strategic Foresight Website, https://www.oecd.org/strategic-foresight/ourwork/

Oomen, A. G., Bleeker, E. A., Bos, P. M., van Broekhuizen, F., Gottardo, S., Groenewold, M., Hristozov, D., Hund-Rinke, K., Irfan, M. A., Marcomini, A., Peijnenburg, W. J., Rasmussen, K., Sánchez Jiménez, A., Scott-Fordsmand, J. J., van Tongeren, M., Wiench, K., Wohlleben, W. and Landsiedel, R., 2015. Grouping and Read-Across Approaches for Risk Assessment of Nanomaterials. *International Journal of Environmental Research and Public Health* 12 (10):13415–13434.

Oomen, A. G., Bleeker, E., Dekker, S., Braakhuis, H., Peijnenburg, W., Lamon, L., Hristozov, D., Gottardo, S., Rauscher, H., Rasmussen, K., Jantunen, P., Quiros Pesudo, L., Wohlleben, W., Jeliazkova, N., Vazquez-Campos, S., Haase, A., Hunt, N., Sanchez-Jimenez, A., Stone, V. and Fernandez, T., 2017. Draft GRACIOUS framework for grouping and read-across of nanomaterials for regulatory risk assessment and safe-by-design (for circulation). https://www.h2020gracious.eu/files/documents/GRACIOUS%20Draft%20framework%20180620%20circulation.pdf

Oomen, A. G., Steinhäuser, K. G., Bleeker, E. A. J., van Broekhuizen, F., Sips, A., Dekkers, S., Wijnhoven, S. W. P. and Sayre, P. G., 2018. Risk assessment frameworks for nanomaterials: Scope, link to regulations, applicability, and outline for future directions in view of needed increase in efficiency. *NanoImpact* 9: 1–13.

Pan L, Lee YM, Lim TK, Lin Q, Xu X (2018) Quantitative Proteomics Study Reveals Changes in the Molecular Landscape of Human Embryonic Stem Cells with Impaired Stem Cell Differentiation upon Exposure to Titanium Dioxide Nanoparticles, Small, 14: 1800190 https://doi.org/10.1002/smll.201800190

Pan, Y., Li, T., Cheng, J., Telesca, D., Zink, J. I. and Jiang, J., 2016. Nano-QSAR modeling for predicting the cytotoxicity of metal oxide nanoparticles using novel descriptors. *RSC Advances* 6 (31): 25766–25775.

Park, M. V., Lankveld, D. P., van Loveren, H. and de Jong, W. H., 2009. The status of *in vitro* toxicity studies in the risk assessment of nanomaterials. *Nanomedicine (London, England)* 4 (6): 669–685.

Park, M. V., Catalan, J., Ferraz, N., Cabellos, J., Vanhauten, R., Vazquez-Campos, S. and Janer, G., 2018. Development of a systematic method to assess similarity between nanomaterials for human hazard evaluation purposes - lessons learnt. *Nanotoxicology* 12 (7): 652–676.

Rahman, L., Wu, D., Johnston, M., William, A. and Halappanavar, S., 2017. Toxicogenomics analysis of mouse lung responses following exposure to titanium dioxide nanomaterials reveal their disease potential at high doses. *Mutagenesis* 32 (1): 59–76.

Rasmussen, K., González, M., Kearns, P., Riego Sintes, J., Rossi, F. and Sayre, P., 2016. Review of achievements of the OECD Working Party on Manufactured Nanomaterials' Testing and Assessment Programme. From exploratory testing to test guidelines. *Regulatory Toxicology and Pharmacology* 74: 147–160.

Renn, O. and Walker, K., 2008. Global risk governance. Concept and practice using the IRGC framework. *International Risk Governance Council Bookseries* vol. 1, Springer Netherlands, Dordrecht.

Riebeling, C., Jungnickel, H., Luch, A. and Haase, A., 2017. Systems Biology to Support Nanomaterial Grouping. *Advances in Experimental Medicine and Biology* 947: 143–171.

Romero-Franco, M.; Godwin, H. A.; Bilal, M.; Cohen, Y. 2017. Needs and challenges for assessing the environmental impacts of engineered nanomaterials (ENMs) Beilstein J. Nanotechnology. 2017, 8, 989–1014. DOI:10.3762/bjnano.8.101

Sánchez Jiménez, A. et al., 2020. Safe by Design implementation in the nanotechnology industry. *NanoImpact* (In press).

Sayre, P. G., Steinhäuser, K. G. and van Teunenbroek, T., 2017. Methods and data for regulatory risk assessment of nanomaterials: Questions for an expert consultation. NanoImpact 8: 20–27.

Scala, Giovanni, Pia Kinaret, Veer Marwah, Jukka Sund, Vittorio Fortino, Dario Greco. 2018. Multi-omics analysis of ten carbon nano-materials effects highlights cell type specific patterns of molecular regulation and adapta-tion. NanoImpact, 11, 99-108 https://doi.org/10.1016/j.impact.2018.05.003

SCENIHR, 2014. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) Opinion on Nanosilver: safety, health and environmental effects and role in antimicrobial resistance. https://ec.europa.eu/health/sites/health/files/scientific_committees/emerging/docs/scenihr_o_039.pdf

SCENIHR, 2015. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) Opinion on the Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices. https://ec.europa.eu/health/sites/health/files/scientific_committees/emerging/docs/scenihr_o_045.pdf

Schmutz, M. and Som, C., 2019. Guidelines for implementing a Safe-by-Design approach for medicinal polymeric nanocarriers, Empa, St. Gallen. https://www.empa.ch/documents/56052/1370048/Guidelines+GoNanoBioMat/925f9053-17be-48c4-a985-6fe73aa98400

Schmutz, M., Borges, O., Jesus, S., Borchard, G., Perale, G., Zinn, M., Sips, A. J. A. M., Soeteman-Hernandez, L. G., Wick, P. and Som, C., 2020. Methodological Safe-by-Design Approach for the Development of Nanomedicines. *Frontiers in Bioengineering and Biotechnology* 8: 258, DOI: 10.3389/fbioe.2020.00258

Schwarz-Plaschg, C., Kallhoff, A. and Eisenberger, I., 2017. Making Nanomaterials Safer by Design? *Nanoethics* 11: 277–281, DOI: 10.1007/s11569-017-0307-4

Scott-Fordsmand, J. J., Amorim, M. J. B. and Sørensen, P. B., 2018. Implementing the DF4 in a robust model, allowing for enhanced comparison, prioritisation and grouping of Nanomaterials. *Regulatory Toxicology and Pharmacology* 92: 207–212.

Soeteman-Hernández, L. G., Bekker, C., Groenewold, M., Jantunen, P., Mech, A., Rasmussen, K., Riego Sintes, J., Sips, A. J. A. M. and Noorlander, C. W., 2019a. Perspective on how regulators can keep pace with innovation: Outcomes of a European Regulatory Preparedness Workshop on nanomaterials and nano-enabled products. *NanoImpact* 14: 100166, DOI: 10.1016/j.impact.2019.100166

Soeteman-Hernandez, L. G., Apostolova, M. D., Bekker, C., Braakhuis, H. M., Dekkers, S., Grafström, R. C., Handzhiyski, Y., Herbeck-Engel, P., Hoehener, K., Jeliazkova, N., Karagkiozaki, V., Kelly, S., Kraegeloh, A., Logothetidis, S., Micheletti, C., Nymark, P., Oosterwijk, T., Sanchez Jiménez, A., Sips, A. J., Sluijters, T., Suarez-Merino, B., Tavernaro, I., van Engelen, J., Wijnhoven, S. W. P. and Noorlander, C. W., 2019b. Safe Innovation Approach: Towards a future-proof system for innovations. *Materials Today Communications* 20: 100548, DOI: 10.1016/j.mtcomm.2019.100548

Sørensen, Sara Nørgaard and Baun, Anders and Burkard, Michael and Dal Maso, Miikka and Foss Hansen, Steffen and Harrison, Samuel and Hjorth, Rune and Lofts, Stephen and Matzke, Marianne and Nowack, Bernd and Peijnenburg, Willie and Poikkimäki, Mikko

and Quik, Joris T. K. and Schirmer, Kristin and Verschoor, Anja and Wigger, Henning and Spurgeon, David J.", 2019 Evaluating environmental risk assessment models for nanomaterials according to requirements along the product innovation Stage-Gate process Environ. Sci.: Nano, ,6, 505-518

Souliotis, V. L., van Delft, J. H., Steenwinkel, M. J., Baan, R. A. and Kyrtopoulos, S. A., 1998. DNA adducts, mutant frequencies and mutation spectra in lambda lacZ transgenic mice treated with N-nitrosodimethylamine. *Carcinogenesis* 19 (5): 731–739.

Steinhäuser, K. G., Sayre, P. G. and Nowack, B., 2018. Reliability of methods and data for regulatory assessment of nanomaterial risks. *NanoImpact* 10: 68–69.

STOA, 2018. The Scientific Foresight Unit (STOA). http://www.europarl.europa.eu/stoa/

Suzuki, T., Hayashi, M., Ochiai, M., Wakabayashi, K., Ushijima, T., Sugimura, T., Nagao, M. and Sofuni, T., 1996a. Organ variation in the mutagenicity of MeIQ in Big Blue lacI transgenic mice. *Mutation Research* 369 (1–2): 45–49.

Suzuki, T., Itoh, T., Hayashi, M., Nishikawa, Y., Ikezaki, S., Furukawa, F., Takahashi, M. and Sofuni, T., 1996b. Organ variation in the mutagenicity of dimethylnitrosamine in Big Blue mice. *Environmental and Molecular Mutagenesis* 28 (4): 348–353.

Trump, B. D., Hristozov, D., Malloy, T. and Linkov, I., 2018. Risk associated with engineered nanomaterials: Different tools for different ways to govern. *Nano Today* 21: 9–13.

van Asselt, M. B. A. and Renn, O., 2011. Risk governance. *Journal of Risk Research* 14 (4): 431–449.

van den Brink, Nico W. and Jemec Kokalj, Anita and Silva, Patricia V. and Lahive, Elma and Norrfors, Karin and Baccaro, Marta and Khodaparast, Zahra and Loureiro, Susana and Drobne, Damjana and Cornelis, Geert and Lofts, Steve and Handy, Richard D. and Svendsen, Claus and Spurgeon, Dave and van Gestel, Cornelis A. M." 2019. Tools and rules for modelling uptake and bioaccumulation of nanomaterials in invertebrate organisms. Environ. Sci.: Nano, 6, 1985-2001

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. and Som, C., 2016. LICARA nanoSCAN - A tool for the self-assessment of benefits and risks of nanoproducts. Environment International 91: 150–160, DOI: 10.1016/j.envint.2016.02.021

Varsou, D-D., Tsiliki, G., Nymark, P., Kohonen, P, Grafström, R., Sarimveis, H. 2018. toxFlow: A Web-Based Application for Read-Across Toxicity Prediction Using Omics and Physicochemical Data. J. Chem. Inf. Model. 2018, 58, 3, 543–549. https://doi.org/10.1021/acs.jcim.7b00160

Williams, A. and Halappanavar, S., 2017. Application of bi-clustering of gene expression data and gene set enrichment analysis methods to identify potentially disease causing nanomaterials. *Data Brief* 15: 933–940.

Worth, A., Aschberger, K., Asturiol Bofill, D., Bessems, J., Gerloff, K., Graepel, R., Joossens, E., Lamon, L., Palosaari, T. and Richarz, A., 2017. Evaluation of the availability and applicability of computational approaches in the safety assessment of nanomaterials: Final report of the Nanocomput project. EUR 28617 EN, Luxembourg, Publications Office of the European Union, JRC106386, DOI: 10.2760/911484

WRR. 2013. The Netherlands Scientific Council for Government Policy (WRR): Towards a learning economy. Investing in the Netherlands' earning capacity. Report no. 90. https://english.wrr.nl/publications/reports/2013/11/04/towards-a-learning-economy

Annex 1. The Tire Industry Initiative: Case Study

294. This annex summarises the outcomes from the Tire Industry Project (TIP)[62]. The TIP project was a project supported by several tires companies (Bridgestone, Continental, Coopertires, Goodyear, Hankook, Kumho tire, Michelin, Pirelli, Sumitomo, Toyo tires, Yokohama), and it was done under the umbrella of the "World Business Council for Sustainable Development" (WBCSD).

1. Background

295. The document "*Nanotechnology and Tyres: Greening Industry and Transport*", published in July 2014 (OECD, 2014b), contained the conclusions of a joint study conducted by the OECD's Working Party on Nanotechnology (WPN) and the Working Party on Manufactured Nanomaterials (WPMN). The document highlighted the potential of new nanomaterials whilst analysing the challenges for their safe and sustainable introduction in the tyre industry. A number of issues related to the use of nanotechnology in mass-market consumer products were explored, using the tyre industry as a case study. The tyre industry was chosen for the project because the environmental challenges and opportunities related to this sector are significant; tires account for 15-30% of a vehicle's fuel consumption and over a billion tyres currently reach the end of their lives each year. To meet these challenges the industry will need to undergo a major transition. By 2030 the number of road vehicles is expected to double, and tyres significantly contribute to the overall environmental impact of the transport sector due to the effect of the rolling resistance of tyres on vehicle fuel consumption, but also due to the high levels of farmed natural resources used such as natural rubber and of synthetic rubber derived from fossil fuels. Besides the need to improve the sustainability of tyres, critical resource requirements show that it is not feasible to service the future demand for tyres using current production methods. The use of new nanomaterials in tyre production could help foster the sustainability of the tyre industry and reduce the environmental impact of vehicles, if the potential environmental, health and safety (EHS) risks of the technology are managed carefully.

296. The OECD 2014 publication described the situation by exploring the status of nanotechnology in tyres, the key drivers of innovation in the tyre industry, and the socio-economic impacts of new nanomaterials in tyre production. The risk assessment and management framework presented in this OECD 2014 document was focused on industrial settings and the protection of workers in tyre manufacturing facilities. However, an initial set of environmental impacts was identified in the context of life cycle assessment of tyres, and a specific section (Chapter 5) provided a first insight as to how a risk management framework could be developed to address the EHS issues potentially raised by nano-enabled tyres.

297. The tyre risk assessment framework has to rely on considerations starting at the early stage of innovation. It should include tire production, storage and transport, and should consider tire uses and address the management of tires at the end of their life. At each stage of a tyre's Life Cycle (innovation, production, storage, transport, use, end of life, recycling), hazard, exposure, safety, and health and environmental effects and on waste management must be addressed. This is in fact

[62] https://www.wbcsd.org/Sector-Projects/Tire-Industry-Project

a 'safer by design to protect health and environment' approach, which should be appropriate for any new nanomaterial.

298. In case of insufficient toxicological information on the fate of nano-additives in tyres, conservative control methodologies are to be developed, which aim to protect health and the environment. Accordingly, a comprehensive risk management framework including relevant risk assessment and recommendations related to best practices is needed.

299. This also benefits tyre manufacturers by allowing them to avoid pursuing the development of products that present potentially unacceptable risks, thus removing unmarketable tyres at an early stage of the development process which is lengthy and expensive (five to ten years are usually required between invention and market introduction), and reducing drastically the costs and time involved for all concerned.

o 2. Engagement of the industry

300. The study, which resulted in the OECD 2014b publication, was originally proposed and supported by the Business and Industry Advisory Committee to the OECD (BIAC) through the Tire Industry Project (TIP) of the World Business Council for Sustainable Development (WBCSD). The goal of TIP is to identify and address potential health and environmental life cycle impacts associated with tyres. The group currently includes eleven tire manufacturing companies representing approximately 65% of the world's tyre manufacturing capacity.

301. The CEOs of the companies involved in TIP welcomed the publication and noted that it highlighted the potential of new nanomaterials, whilst emphasising the challenges for their safe and sustainable introduction in the tyre industry. A 9th October 2015 meeting of the CEOs of TIP member companies saw decisions taken to:

- Encourage the adoption of the "control banding approach for new nanomaterials" (ISO 12901-2) to cover the risk for workers when manufacturing new nanomaterials or using new nanomaterials to produce tyres; and
- Develop a project dealing with the safe management of environmental, health and safety (EHS) issues throughout the life cycle of tyres containing new nanomaterials.
- To achieve safe management of environmental, health and safety (EHS) issues throughout the life cycle of tyres containing new nanomaterials, it is necessary to consider exposure and toxicity of nanomaterials released from tyres during their life cycle. To do this, it is important to develop tools for reliable risk assessment. In practice, the resulting framework described in this annex can be seen as a document, which will complement the OECD 2014b publication to take the product life cycle into account.

302. Safe management of environmental, health and safety (EHS) issues throughout the life cycle of tyres containing new nanomaterials is not limited to a list of nanomaterials available today, but also includes any future nanomaterials.

o 3. Overview of workers protection in tyre conception, industrialisation and production with new nanomaterials

303. According to the state of knowledge, a nanomaterial may exhibit properties, including toxicological properties, which differ from bulk material.

304. Whether in the research, development, industrialization or production stage, the "control banding" approach may overcome the difficulty of incomplete or uncertain toxicological properties in all stages (including for example: shipment, storage, waste treatment, etc.).

305. Control banding is a pragmatic approach which can be used for the control of workplace exposure to potentially hazardous agents with unknown or uncertain toxicological properties and for which quantitative exposure estimations are lacking.

306. Control banding was originally developed by the pharmaceutical industry as a way to safely work with new chemicals that had little or no toxicity information. These new chemicals were classified into "bands" based on the toxicity of analogous and better known chemicals and thereafter safe work practices were described, taking exposure into consideration.

307. The purpose of ISO/TS 12901-2 (Nanotechnologies — Occupational risk management applied to engineered nanomaterials —Use of the control banding approach) is to describe the use of a control banding approach for managing the risks associated with occupational exposure adapted to nanomaterials for which the toxicological information is incomplete. The document:

- Helps businesses and others, including research organisations engaged in the manufacturing, processing or handling of nanomaterials, by providing an easy-to-understand, pragmatic approach for the control of occupational exposures.
- Allows organisations to safely initiate R&D studies without having the full characterisation on toxicology of those new nanomaterials while keeping at a safe level exposure of workers to new nanomaterials for tyres.
- Allows the review of the results of the assessment on the level of protection to be implemented, adaptation of this knowledge on the level of toxicity of new nanomaterials, and aids in the decision to stop development for toxicological reasons if needed.

4. Overview of potential nanomaterials release during the life cycle of tyres

308. A tyre is an intricate construction comprised of many components, they generally include tread, body ply, belt, bead, side wall, and innerliner. The performance requirements of tyre tread mainly focuses on wear resistance, rolling resistance, grip and skid resistance, amongst other criteria (OECD 2014b). Additionally, different tyre components will likely contain different types and amounts of nanomaterial fillers (nanofillers) to enhance different performance requirements. The nanomaterials currently used in tyres are "reinforcing agents". Reinforcement is given by the strong links between the macromolecules of polymer and the aggregates of the fillers. However, fillers have effects on all performances of the tyre such as wear, grip, and rolling resistance (OECD report (2014), pp. 18-20). If a strong link exists between a nanomaterial and a macromolecule of polymer, the nanomaterial no longer exists as such but becomes a composite of polymer modified by a nanomaterial. In this case, the nanomaterial in its original form is unlikely to be released. A nanomaterial will not be released if the link with the polymer material is complete and strong enough, and if this link is not destroyed during any of the phases of the life cycle of the tire.

309. There are two families of nanomaterials currently used by the tyre industry, both are employed as reinforcing agents:

- **Furnace carbon black:** In 1910 furnace carbon black was introduced for the first time in rubber compounds. The unexpected effect was that furnace carbon black allowed to increase the durability of the tyres by a factor of 40. Furnace carbon black is obtained through the incomplete combustion of feedstock from the distillation of crude oil. World production of furnace carbon black is approximatively 10 million tons/year. The size of carbon black agglomerates ranges from 1 to 50 microns, while the aggregates, which are non-divisible, range between 100 to 500 nanometres. The chemical functional groups existing naturally at the

surface of the furnace carbon black generate strong links with the macromolecules of polymer (Figure 0.1).

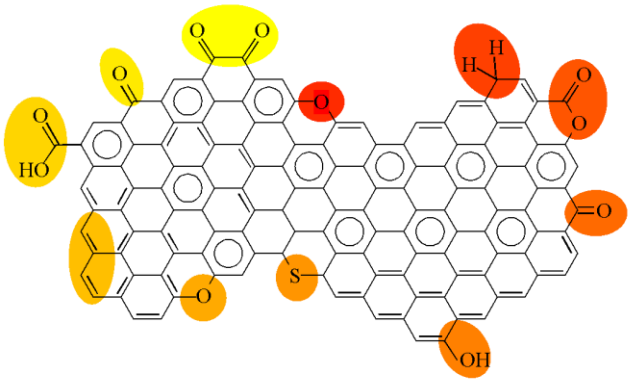


Figure 0.1 Schematic representation of carbon black surface

- **Precipitated amorphous silica**: Silica has been used in tyre tread for the past 20 years to reduce, by decreasing the tyre rolling resistance, the fuel consumption of vehicles and the associated emissions of greenhouse gases (e.g., silica enables a decrease of more than ¼ tonne of CO_2 emissions for each car driving 50000 km (International Symposium on Assessing the Economic Impact of Nanotechnology Washington , 2012), which is a breakthrough achieved without affecting other tyre performance properties). Precipitated amorphous silica is obtained by precipitation of a sodium silicate which is the result of melting sand with sodium carbonate. World production of amorphous silica is approximatively 1.4 million tons, and the tyre industry uses approximately 1/3 of this. The size of precipitated amorphous silica agglomerates ranges between 1 to 50 microns, with non-divisible aggregates of 50 to 300 nanometres. Links between precipitated amorphous silica and macromolecules of polymer are obtained by a chemical agent (silane), which reacts on one side with the silica and on the other side with the macromolecules of polymers (Figure 0.2).

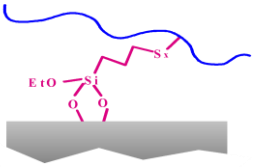


Figure 0.2 Schematic representation of silane linking macromolecule of polymer to amorphous silica

310. Other nanomaterials have been identified for use in tyres, for example, nanoclays which may be added to tyre inner-liners to improve their air retention (Thomas et al. 2010; OECD, 2014).

311. The bonding between nanomaterial and rubber as well as nanomaterial dispersion in the matrix are critical factors that affect the performance of the tyre. These same factors may affect the potential for nanomaterial release from composite material. For example, dispersion of the nanomaterials and bonding with the matrix have been suggested to influence potential for release of nanofillers from composites (Ma et al., 2010; Golanski et al., 2012). The addition of nanomaterials to composites also alters the overall structural integrity of the nanocomposite, which,

in turn, may affect the potential for release of the nanomaterial (Sachse et al. 2013). While the properties of the nanocomposite and nanomaterials themselves can affect their ability to be released, various external stress mechanisms also influence opportunity for nanomaterial release.

312. Presented in Figure 0.3 (Adhikari et al., 2000; Gutowski et al. 2011; OECD, 2014) is the general overview of the life cycle of a tyre. The tyre use is the major stage, the second is end-of-life including recycling.

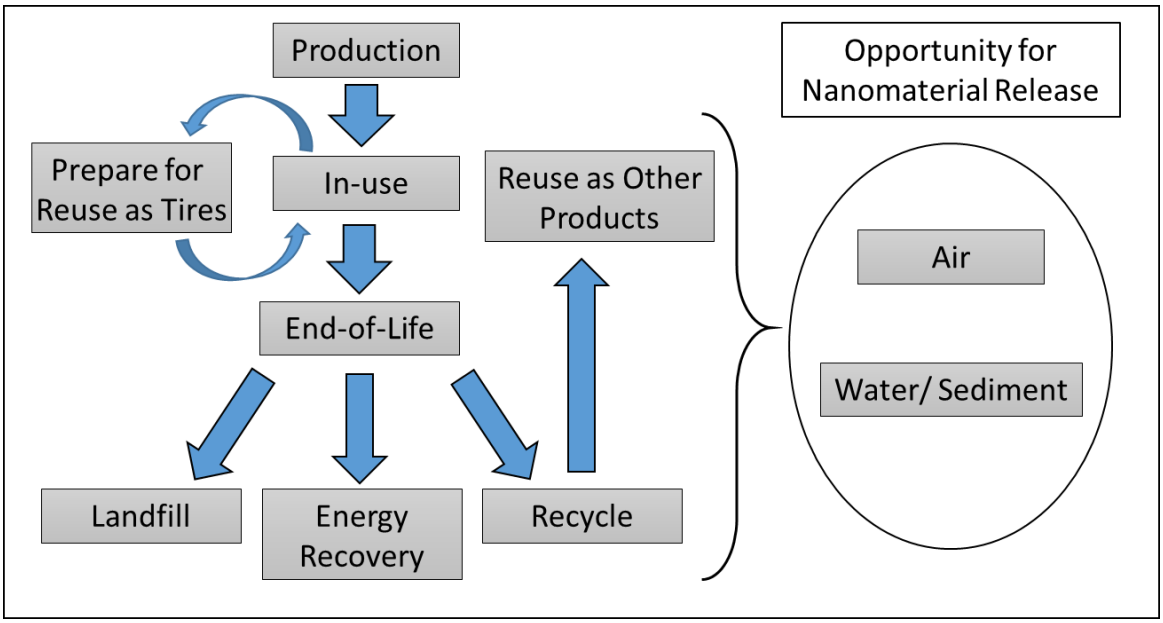


Figure 0.3 Overview of nanomaterial release in tyre use phase

4.1. Release of material is mainly during tyre use phase

313. Based on current knowledge the main release of material during the life cycle of the tyre is in the use phase. This is the consequence of wear of the tyres by friction of the tyre tread to the pavement of the road. The specificity of the particles generated by friction of the tyre tread on the pavement is that they are directly released to the environment. All other possibilities of release to the environment are marginal in comparison with those from the Tyre and Road Wear Particles (TRWP).

314. For more than twelve years, substantial work has been conducted to evaluate the impact of TRWP on human health and the environment, and relevant information related to tyres available on the market has been published. The list of the peer reviewed publications, presentations, conferences and other publications is given in the bibliographic part of this annex. In addition, the analytical methods used in these studies have been accepted by ISO and published, references are also provided in the bibliography.

315. This work can be divided into six topics:

- Physical and chemical characterisation of Tyre and Road Wear Particles (TRWP);
- Evaluation of ecotoxicity of TRWP;
- Evaluation of toxicity by inhalation of TRWP;
- Measurement of contribution of TRWP to pollution of fresh water and fresh water sediment;

- Impact on environment of aging of TRWP; and
- Measurement of contribution of TRWP to PM 10 and PM 2.5 air pollution.

316. In these studies, performed with tyres available on the market (i.e., containing the nanomaterials furnace carbon black and/or precipitated amorphous silica), it was demonstrated that the size of TRWP was mainly between approximatively 10 and 120 microns. (See Figures 0.4 and 15)

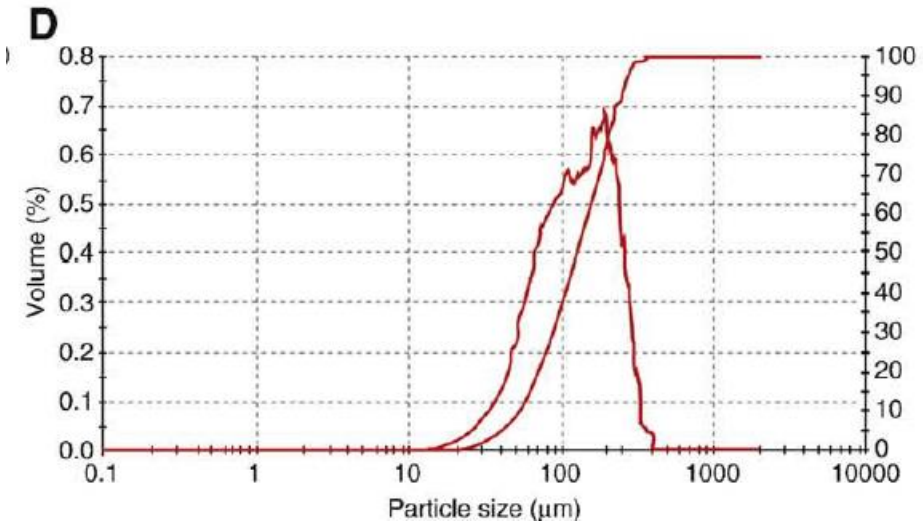


Figure 0.4 Tyre and road wear particles size distribution

Source: Kreider et al. (2010), Physical and chemical characterisation of tyre-related particles: Comparison of particles generated using different methodologies

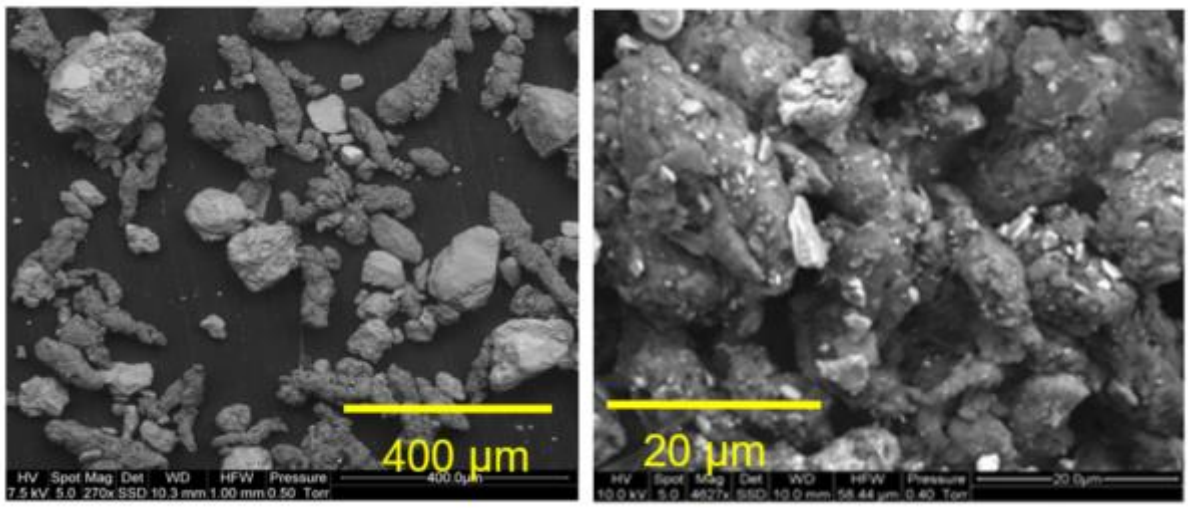


Figure 0.5. TRWP microscopic view

317. ISO/TS22638 describes the generation and collection methodology of pure wear particles from tyres and road surface of pavement, utilising a road simulator in laboratory conditions to avoid unknown contamination which may exist on actual roads.

318. A road simulator at the German Federal Highway Research Institute (Bundesanstalt für Straßenwesen [BASt]) (Figure.0.6) was used to generate and collect the TRWP as described in the literature by Kreider et al (2010).

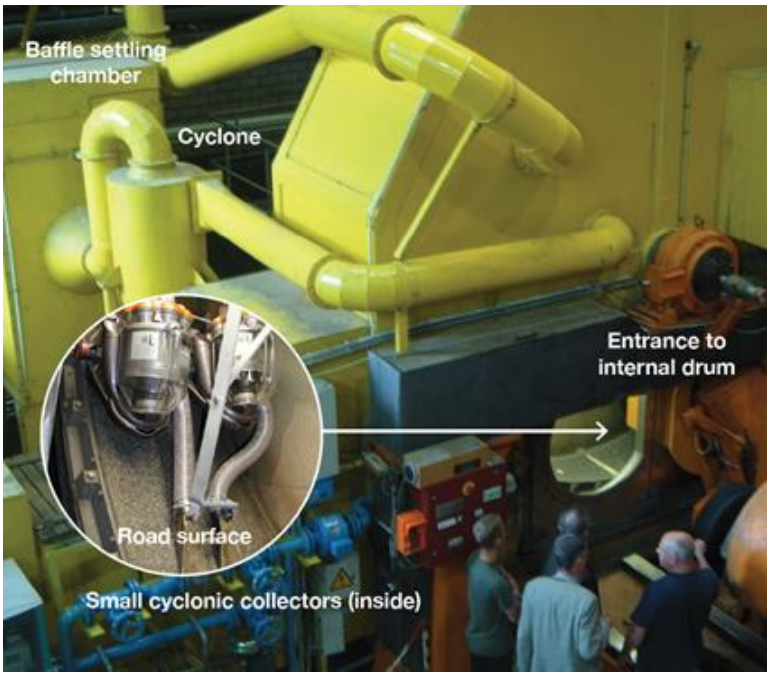


Figure 0.6 Road simulator in BASt

319. The TIP recognised that the road simulator in BASt or other similar internal drum road simulators can generate TRWP physically and chemically similar to those from actual roads.

320. Regarding evaluation of the risk of release of nanoparticles during wear of tyres, an important result was obtained by the Swedish national road and transport research institute (VTI) in collaboration with the University of Lund, the University of Stockholm and the Swedish Environmental Research Institute.

321. The VTI carried out the work on a simulator located in a closed room (Figure 0.7) with tyres available on the market. It was demonstrated that the use of studded tyres generates nanoparticles during wear, but these result from the wear of the road surface, and un-studded tyres emit no significant nanoparticles during their use. (M. Gustafsson et al 2010).

Figure 0.7 Road simulator in VTI

322. In Germany the Ford Forschungszentrum Aachen GmbH, in collaboration with the Bergische Universität Wuppertal. (M.Marcel Mathisse et al 2011) had studied the potential generation of ultrafine particles from the tyre/road interface during real driving. An instrumented crossover Sport Utility Vehicle equipped with summer tyres driving on a regular asphalt road was used to measure particle emissions directly inside the wheel housing during different driving scenarios. The vehicle was equipped with five stainless steel sampling tubes inside the right front wheel housing.

323. Different driving conditions (i.e., straight driving, acceleration, braking, and cornering) were applied. Under normal driving conditions, no substantial nanoparticle concentrations were generated. Under extreme conditions only (i.e., full stop braking, extreme cornering, and racing start) ultrafine particles could be measured with mean particle sizes between 30 nm and 80 nm, where particle formation relates to significant tyre slip.

324. Both studies performed by M. Gustafsson et al and by M. Mathisse et al brought results showing that for tyres today on the market, nanomaterials used in tread are not released into the environment during wear of the tyres in normal usage. However, these results cannot be extrapolated to nanomaterials other than furnace carbon black and precipitated amorphous silica.

325. The different methods used to check the emission of nanoparticles are difficult to apply on a large scale.

326. Methods developed by Gustafsson et al and Mathisse et al do not fully cover the need for industry to have internationally recognised standard methods that can be applied during the development of new nanomaterials that could potentially be hazardous.

327. The methods simulating actual emission of nanoparticles from tyres for different stages of the research and development process are required, especially at the earlier stages, in order to evaluate as soon as possible innovations that can actually cause emission of hazardous nanoparticles during the use phase of a tyre.

328. Development of methods for the identification and evaluation of risk related to the possible emission of nanoparticles during the tyre life cycle are in progress.

4.2 Risk of nanomaterial release during treatment of end of life tyres

4.2.1. End of life tyres (ELT)

329. A tyre is at the end of its life when it can no longer be used on a vehicle (i.e., in certain applications after having been retreaded or regrooved). All tyres including passenger car, truck, airplane, motorcycle, and off-road tyres result in ELTs. However, the majority of ELTs result from car and truck tyres.

Estimated Recovery Rate in % - Recycling and recovery rates for ELT are generally far higher than for most other consumer goods			
Item	Europe	US	Japan
Tyres	92	88	86
Glass	65	22	90
Car batteries	90 (UK)	99	-
Steel containers	63	63	63
Aluminum brewage cans	52	52	92
PET bottles	39	24	66
Paper/cardboard	64	50	66

Table 0.1 Tyre recycling rates (Full Report: Management of End-of-Life tires and Global ELTs Management - A global state of knowledge on collection rates, recovery routes, and management methods .https://www.wbcsd.org/Sector-Projects/Tire-Industry-Project/End-of-Life-Tires-ELTs)

330. Today, over one billion tyres reach the end of their useful lives every year (WBCSD data). Recovering ELT contributes to reduced waste and provides a fuel and material resource that can replace other scarce natural resources. TIP has concluded that cooperation between tyre manufacturers, retailers and governments is essential for ELT to be managed sustainably in the country or the region. Very few tyres are simply abandoned, most are recovered and recycled in the major developed markets. Tyres are one of the most recycled consumer products in well developed markets recovery rates are as high as 85% (Table 0.1).

ELT- Recovery Type of Treatment					
	year	Kilotons of ELT generated by year	Energy recovery Kilotons	Material recovery Kilotons	civil engineering and backfilling Kilotons
USA	2015	3581	1616	1216	297
Europe	2015	3190	1097	1670	122
China	2015	10260	0	5480	0
Japan	2014	863	579	153	1
Mexico	2015	304	118	74	0
Brazil	2015	535	243	243	5
South Korea	2015	266	157	94	0
Canada	2015	395	31	407	0

Table 0.2 ELT type of treatment

(Full Report Global ELTs Management - A global state of knowledge on collection rates, recovery routes, and management methods :https://www.wbcsd.org/Sector-Projects/Tire-Industry-Project/End-of-Life-Tires-ELTs)

331. A large part of this recovery goes toward energy recovery, with material recovery second, and landfilling much lower (Table 0.2).

4.2.2. Energy recovery

332. Tyre Derived Fuel (TDF), one of the leading options for ELTs, is mainly used in cement kilns, but also in thermal power stations, pulp and paper mills, steel mills and industrial boilers. In Europe, the cement sector is the main use of TDF. Tyres have a high energy content and are an equal or better source of energy than many other solid fuels.

333. Various air pollutants may be emitted during the incineration and pyrolysis of tyres (Samuel et al. 2014). When the tyre is decomposed at elevated temperatures, some nanomaterial could be potentially freed from the encapsulating matrix. Some studies have suggested that nanomaterials may be released to the air during incineration and also may be found in the remaining char (Bouillard et al. 2013; Uddin et al. 2016). However, some nanomaterials will no longer exist after the incineration process, (Schlagenhauf et al. 2012; Holder et al. 2013). For example, carbon-based nanomaterials in a tyre may burn during the incineration of tyres. This is not the case for precipitated amorphous silica and may not be the case for some other new nanomaterials based on non-carbon chemistry. Some nanomaterials may melt and thus lose their nano structure.

4.2.3. Material recovery: granulates

334. Granulates are obtained by the shredding or milling of tyres. This is done in factories, and protection of operators can be managed through industrial controls (e.g. Control Banding). The potential for nanomaterial release does depend on the physical and chemical characteristics of the links between the macromolecules of the matrix and the nanomaterial.

335. Tire granulates are used in two principle ways. First, granulates are used as an industrial structure combined as a constituent of new rubber mixes (including for new tyres). This application could grow with the development of a circular economy. In the second application, granulates obtained from ELTs are used in a variety of products including artificial turfs, sport grounds, and play-grounds. For these applications, the question arises about the potential for airborne and

environmental release of new nanomaterials when through the using of the granulate-containing product.

336. ELTs can also be converted into ground or crumb rubber that can then be used for rubber-modified asphalt which contributes, for example, to reduced traffic noise.

4.2.4. Material Recovery: reclaimed rubber

337. Reclaimed rubber is obtained through a post treatment process after shredding or milling of ELTs. It is a chemical/thermal treatment that breaks some chemical links in the polymer itself or on the sulfur crosslink between macromolecules of the polymer.

338. The reclaimed rubber is used as a constituent in new rubber compounds. Reclaimed rubber was used at a large scale in the rubber industry (including the tyre industry) in the middle of the last century but this decreased after the 1970s. Reclaimed rubber could likely find more value within the context of the circular economy development.

339. The production and use of reclaimed rubber are in industrial environments and protection of operators is manageable using existing frameworks like the ISO 12901-2: "Control banding approach."

4.2.5. Landfill, dump, or stockpiled tyres

340. The landfilling, dumping and stockpiling of tyres is decreasing and becoming a marginal ELT management route in industrial countries as recycling and energy recovery are increasingly favoured. (Figure 0.8 and Table 0.3)

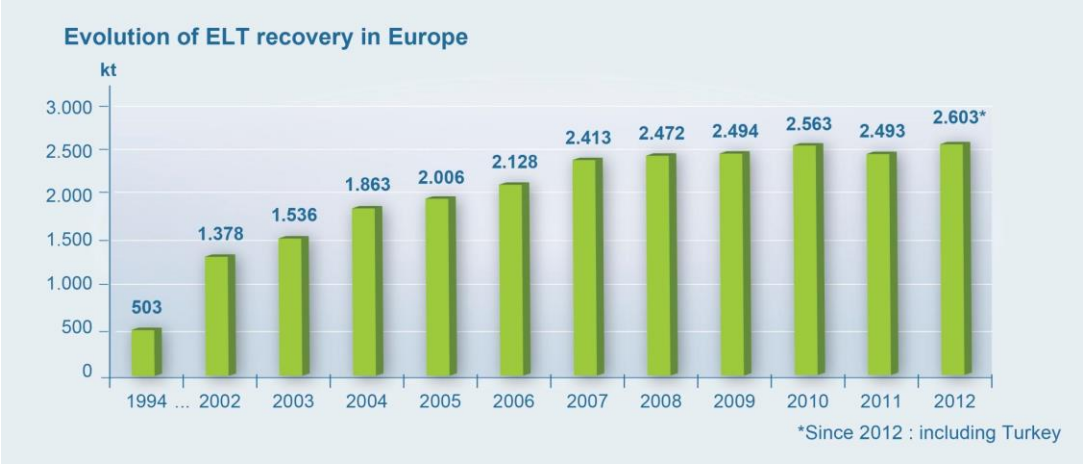


Figure 0.8 ELT recovery in Europe

Sources: Estimates based on data from European Tyre & Rubber Manufacturers' Association

Evolution of recycling and recovery in % of ELT				
	1994	2000	2006	2015
Japan	90	86	85	86
USA	50	70	85	88
Europe	20	50	85	92

Table 0.3 Evolution of recycling and recovery in % of ELT

Sources: Estimates based on data from European Tyre & Rubber Manufacturers' Association

341. The least desirable end-of-life scenario for tyres is to dump, stockpile, or landfill them because this represents a waste of reusable resources and materials, as well as potential environmental impacts (Adhikari et al. 2000; Gransberg et al. 2003). In fact, landfilling and stockpiling have been banned in many countries (Sienkiewicz et al. 2012). The potential for nanomaterial release in landfilling and stockpiling remains uncharacterised (Gualtieri et al. 2005; Wik et al. 2006; Wik 2007).

4.2.6. Civil engineering

342. Whole or shredded tyres are used in a variety of civil engineering projects such as embankments, backfill for walls, road insulation, field drains, erosion control/rainwater runoff barriers, wetlands and marsh establishment, crash barriers, and jetty bumpers. Tyres are excellent materials for such uses because they are lightweight, permeable, good insulators, shock absorbent, noise absorbent, and durable. However, use of ELTs in civil engineering is negligible in comparison with other applications (i.e., Worldwide percentage of ELTs used in civil engineering applications is approximatively 2% of all ELTs).

4.2.7. Life cycle stage of tyre: retread, repair, and regroove

343. When a tyre tread has worn to at or near its limit, it may be possible to retread and/or regroove the tyre and put it back into use. This is done predominantly for some truck tyres. It is done in factories and protection of the operators can be managed with existing industrial controls. Potential for nanomaterial release during retreading and regrooving is not established and may depend on the physical and chemical characteristics of the links between the polymer matrix and nanomaterials.

5. Assessment of the protection of health and environment by design: main points for the case of tyres with new nanomaterials

344. "Safer by design to protect health and environment", (as described in the JRC report 2016 on terminology for EHS assessment of nanomaterials), is applied with the intent that the conditions of production are safe, and that tyres which will be put on the market will not generated unacceptable risk for health or environment during each phase of the life cycle, including at the end of life. Performance has to be assessed together with toxicity and hazard aspects of using new nanomaterials. The goal in development of new nanomaterials use in tyres is not only to consider the technical performances of tyres themselves, for example rolling resistance, wear, grip and durability but also to assess the use of new nanomaterials carefully on the health and environment through the life cycle of tyres. Methods for evaluating tyre performances differs from one company to another and is confidential knowledge that will not be described here.

345. At each stage of the project it is often necessary to review and, if applicable, develop knowledge of the nanomaterial characterisation and analytical methods, complete an evaluation of hazards (human health and environmental), review risk of release, and consider any potential evolution of regulations. It is necessary to decide whether to proceed, stop, or redesign the project depending upon the balance of risks and benefits associated with the new nanomaterial.

346. During the project, the collaboration and information exchange throughout the whole supply chain from nanomaterial suppliers to tyre makers is of paramount importance in order to share experience and appropriately manage exposure scenarios.

347. Note that results and conclusions on one new nanomaterial in one specific part of a tyre may not be extrapolated to other new nanomaterials, or for the same nanomaterial in another part of the tyre.

Key considerations before starting a project on a new nanomaterial for tyres

348. The intention to start a research project with a new nanomaterial or a family of new nanomaterials is in general related to expectations of improved performance, which may pertain to tyre performances (e.g., rolling resistance, wear, grip, and durability), and/or positive societal benefit. Moreover, a tyre company will have to weigh multiple alternative solutions towards achieving the desire goals, and to decide between alternatives. An objective is to use the less hazardous solution possible for the same performance.

349. For the use of new nanomaterials in tyres, EHS information is needed prior to starting the research as well as later during the process of the project. This includes the evaluation, all along the life cycle, of the state of knowledge on human health and environmental hazards for the new nanomaterial, the equivalent bulk material (if relevant), and analogous substances. The gaps between the information available and the information needed should be determined. If applicable, a plan to improve the knowledge on human health and environmental hazards of the new nanomaterial should be considered and reviewed at each stage of the project in parallel with other knowledge improvements.

350. The role of the nanomaterial supplier may be very relevant with regards to their expertise on the design and manufacturing of equivalent bulk materials and/or similar or same nanomaterials already developed for other applications. Any modification regarding the new nanomaterial (physical aspect or others) has to be evaluated at the same time as hazard, functionality, and performance aspects.

351. If it is established that a new nanomaterial presents a low potential hazard, then specific management may not to be needed. However, data gaps may make the assessment challenging, requiring a management scheme around the potential hazard until the data gap has been eliminated.

352. It is important to note that the risk of the release of nanomaterials may differ depending on where the nanomaterials are utilised within the tyre (e.g. tread, inner-liner, side wall), as these uses represent different potentials for exposure.

353. Before starting a project, the risk of nanoparticles emission to the environment throughout the life cycle of the tyre should be evaluated depending on the type of new nanomaterial and its application.

354. It is important that the different scenarios for the potential release of nanomaterials during a tyre life cycle should be documented and updated as the project evolves. This will serve to build the knowledge-base in support of the efficient evaluation of potential exposure.

355. For example, the highest potential for release is when new nanomaterials are used in tyre tread material, because tyre tread wears during the use of the product, which would make it important to consider risk of releasing the new nanomaterials to the environment. However, it

should be noted that if the goal of the project is to improve tyre performance (such as rolling resistance, wear or grip), the nanomaterials will have been incorporated as reinforcing fillers, which means that the nanomaterial will be linked to the macromolecules of the polymer matrix rather than simply being embedded in this matrix. For the design of the new nanomaterial project it is important to know if the new nanomaterial will be completely linked to the macromolecules of the polymer of the rubber mix or not, and to know if the link between the nanomaterial and the macromolecules of rubber is strong enough to withstand wear or fatigue which in the opposite case would cause the release of nanoparticles.

356. Even though tyre wear brings the highest potential for release of nanomaterials, other types of applications and the associated risk of nanomaterial release should be estimated for each application. As a second example, nanoplates may serve an interesting function within inner-liners to improve air retention. In this case, the components containing the nanoplates are inside of the wheel, away from the zone of tread-wear. However, questions remain, for example: How strong is the link between the nanoplates and the rubber of the inner-liner? So during use of the tyre, a question should centre around the fatigue of the inner-liner and whether it will or will not generate release of nanoplates that may be spread when demounting the tyre from the rim or at the stage of recycling an ELT.

357. To evaluate different potential releases of nanomaterials, adapted analytical methods are needed. It should be noted that internationally recognised normative analytical methods to characterise the risk of emission of nanomaterials from tyres do not yet exist. Work is ongoing to explore potential methods.

358. Analytical methods to evaluate if there is a risk of nanomaterial release during the life cycle could include laboratory measurements of cohesiveness between the new nanomaterial and rubber, or by measuring if nanoparticles are released during wear of the tyre under normal driving conditions.

359. If a risk of release exists (especially from the tyre tread), it is helpful to evaluate this early in the project along with the potential toxicity of the new nanomaterial in order to be able to decide whether to continue the project.

360. As usual, knowledge on EHS and exposure aspects should be complemented with the knowledge of the current and potential regulatory status of materials, which may differ from one country to another.

361. Regarding physio-chemical characteristics of nanomaterials, all information is welcome but certain information is particularly important:

- the physical aspect of the new nanomaterial (e.g., nanoparticles, aggregates, agglomerates, nanofibers, nanoplates);
- the size and size distribution;
- the surface chemistry, which may be important to estimate the potential to link the nanomaterials to the polymer matrix;
- the reactivity with other chemicals that may link the nanomaterial to the macromolecules of the polymers;
- the water solubility, which can be important for example, in waste treatment where materials dissolve in water no longer be in nanomaterial form;
- the capacity to burn or to melt completely which may be important for treatment through energy recovery pathways;

- the knowledge on K_{ST} value (defined as the deflagration index of a dust cloud) which may be important for safe handling of raw materials; and
- in case of nanocomposites, the way nanoparticles are embedded (chemical-physically and/or structurally) in the bulk solid, also with reference to all information listed above.

5.1. To be done before initiating research

362. In addition to general information referenced in point 5.0 that has been prepared before starting the project, practical actions can be taken before initiating research like as laboratory study to evaluate the benefit to use in a model or a real tyre rubber compound.

- It is very important before starting to work to have prepared the application of the control banding or another appropriate approach, first for the operators in research, and after for each phase of the project.
- It is also important to check the possibility to reduce exposure by changing the physical aspect (master batch for example) and consider possible use of this physical aspect for next steps while keeping the expected improvement of tyre performance.
- In usual good laboratory practice, special attention should be paid to each of the following points before initiating research:
    - Identify operators who will be working with the new nanomaterial and if needed, complete the training of these operators on the nanomaterial which will be used and on specificity of management of this nanomaterial in tyre application;
    - Implement traceability on the quantity of new nanomaterial;
    - Define the storage conditions for the new nanomaterial;
    - Define the process for treatment of extra quantities of new nanomaterial which were not used in tests along with tracing quantities of unused new nanomaterial;
    - Define adapted rules in case of accidental exposure;
    - Have in place adapted rules for disposal of test compounds containing nanomaterials if a risk is suspected about safety of rubber compounds containing the new nanomaterial; and
    - Check K_{ST} value of the new nanomaterial and apply appropriate risk management procedures to continue use of the materials.
- If information is available showing that the material could pose a high EHS risk, consider stopping project development.

5.2. To be done before initiating development work

363. In addition to the items listed in Section 5.1, the following actions can be taken before initiating development work such as an indoor tyre study or an outdoor tyre study to assess all required performances (for example; dry and wet grip tests, wear tests and, fracture tests) before applying the compound utilising new nanomaterials as the tyre component:

- Apply recommendations from the research phase.
- Update the knowledge on the new nanomaterial hazard and review the EHS plan for addressing any knowledge gaps.
- Review potential evolution of regulations to anticipate new legal obligations.

- Pursue development of analytical methods, mainly those needed for characterisation of release as needed.
- Review and update the scenarios of potential release of nanomaterials throughout the life cycle.
- As soon as possible, perform the first technical evaluation of risk of nanomaterial release during the life cycle of the tyre focusing on most likely scenarios considering the specific use of the material within the product.
- If the links between the nanomaterial and macromolecules of polymer are weaker than required, check the possibility to add a chemical to reinforce these links, and verify improvement in nanomaterial release.
- Establish a preliminary evaluation of possible impact on human health and environment across the product life cycle based on available EHS information and on available information on potential release of nanomaterials during the tyre life cycle.
- Establish a preliminary evaluation of the impact of recycling, repairing and retreading tyres based on the available information on risk of release for each technique.
- To prepare practical organisation of the development stage, it is important to pay attention to the following points:
    - Identity operators who will be working with the new nanomaterial and if needed complete training of these operators on the nanomaterial which will be used, including on the appropriate handling of this nanomaterial in tyre application;
    - Select the most adapted physical aspect for the new nanomaterial (example, use of masterbatch) for the best balance between reduction of exposure by physical presentation and technical performances of tyres;
    - If a decision is made to change physical aspect, also evaluate the risk for operators during preparation of new physical presentation;
    - Evaluate the level of hazard for operators in the development phase and select the right level of protection and put protection in place by applying the Control Banding Approach or another appropriate approach;
    - Define the different options for safe transportation and storage of the new nanomaterial and select the most suitable one for development and industrialization;
    - Define the different available methods for incorporating the new nanomaterial into rubber mixes and identify those which should be the most suitable for development and industrialization, considering the specific risk of nanomaterial release due to the mixing technologies in use, mainly the risk of release in the atmosphere of the workshop;
    - Prepare traceability on quantity of the new nanomaterial for development;
    - Define the process of traceability and treatment of the quantities of each new nanomaterial which was not used during development and do the same for any nano waste;
    - Define safe procedure for cleaning and maintenance of equipment considering the specificities of the mixing operations;
    - Have adapted rules in case of accidental exposure; and
    - If test compounds that contain a new nanomaterial presents a safety risk, put in place adapted rules to safely dispose of test compounds after their testing.

    - If data is not yet available on water solubility, flammability, potential to melt, or KST value characteristics, then work with the nanomaterial producer or conduct research to eliminate data gaps.

- If information is available showing that the material could pose a high EHS risk, consider stopping project development.
- If the project will continue to the development phase, prepare the list of items to check at the end of the implementation phase to facilitate the decision on whether to continue the project. In this context the list should include at minimum points on EHS, potential release (representativeness and capability of critical analytical methods), and regulatory aspects (both current and potential).

5.3. To be done prior to industrialization

364. In addition to the items outlined in Section 5.2, the following actions can be performed prior to industrialization, such as trial production to evaluate the feasibility of mass production and as field tests in limited actual markets:

- Apply recommendations from the development phase.
- Continue to update knowledge on the hazards of the new nanomaterial if needed.
- Review the evolution of regulations to anticipate legal obligations.
- Confirm the evaluation of the impact on the environment during the use of tyres containing the new nanomaterial.
- Confirm the evaluation of the impact on human health generated by the use of tyres containing the new nanomaterial.
- Confirm the evaluation of the potential impacts resulting from the end of life treatment of tyres containing new nanomaterials and define any necessary guidelines for the safe recycling of ELT as needed.
- Define safety restrictions for the repairing and retreading of tyres.
- If necessary, contribute to improve analytical tests on the release of nanomaterials and/or develop complementary tests and improve the evaluation of risk of release of nanomaterials.
- Final update of the scenarios of potential releases of nanomaterials.
- All along production lines (including if it is the case the modification of physical aspect), review the risk management plan and apply appropriate levels of protection for all operators and if possible design processes that prevent release rather than increasing extraction by ventilation.
- Weigh expected benefits and estimated risks to determine whether to continue the project.
- If the project will continue to the industrialization phase, prepare the list of items to check at the end of the phase to facilitate the decision on whether to continue the project.

5.4 To be done prior to mass production and commercialisation

365. In addition to the items to be done in Section 5.3, the following actions can be taken prior to mass production and the marketing of tyres:

- Apply all recommendations from the industrialization phase.
- If tests confirm that nanomaterial is released during the Life Cycle of a tyre, then finalize the state of knowledge on toxicological and ecotoxicological hazards of the new nanomaterial.
- Update knowledge on current and potential regulations.
- Review and validate scenarios for the potential release of nanomaterials.
- Ensure all points of the review checklist have been accepted.

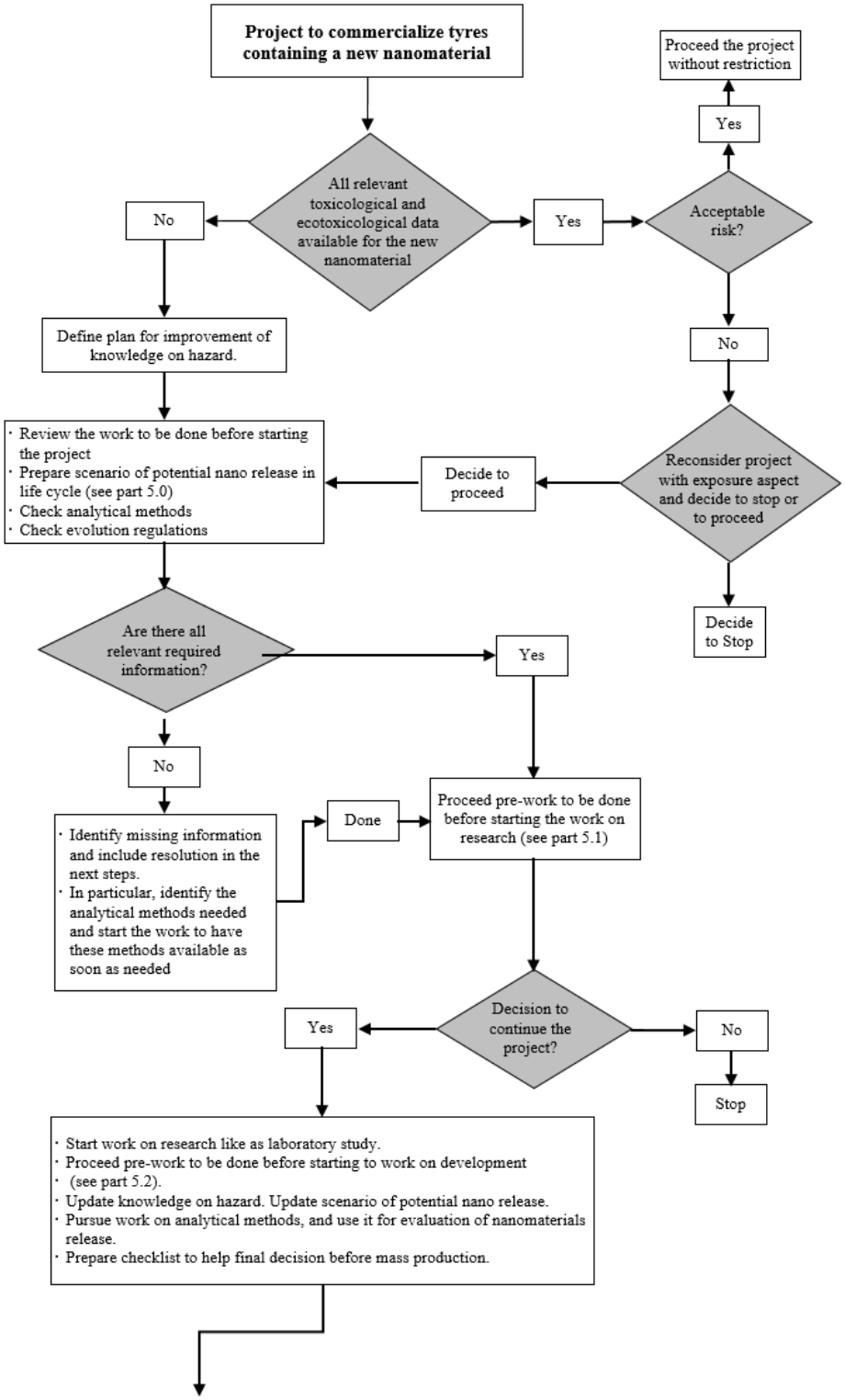
- If specific precautions were identified to promote safe use, ensure they are properly defined, validated and implemented.
- Evaluate the impact of the new nanomaterial during the recycling of used tyres, repairing and re-treading is evaluated for each case and prepare communications on safe handling conditions for operating companies.
- If it is confirmed that the new nanomaterial used in the specific part of the tyre that is targeted, does not generate unacceptable risk to human health or the environment, then mass production and commercialisation of the tyre with the new nanomaterial becomes possible.

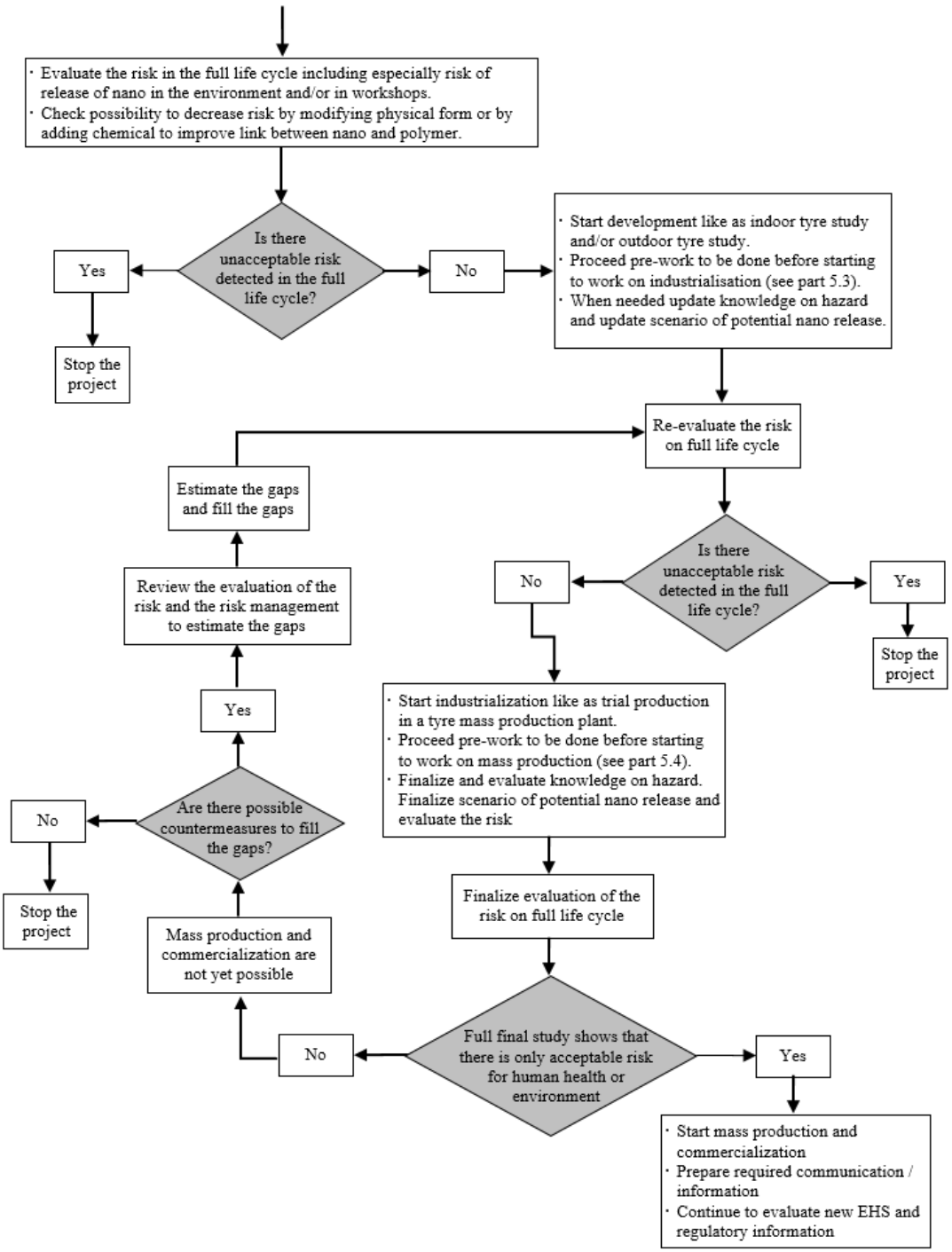
5.5. At commercialisation

366. In addition to the item to be done in Section 5.4 the following actions can or have to be taken prior to commercialisation

- Prepare any communication/information needed for legal requirement if any, and for voluntary information to downstream users.
- Continue to evaluate new EHS and regulatory information for as long as the new nanomaterial is in use
- If any doubt is remaining implement a health surveillance of workers handling nanomaterials.

6. New nanomaterials in tyres: flowchart for "safer by design" approach to protect human health and environment




· Evaluate the risk in the full life cycle including especially risk of release of nano in the environment and/or in workshops.
· Check possibility to decrease risk by modifying physical form or by adding chemical to improve link between nano and polymer.
Is there unacceptable risk detected in the full life cycle?
Yes
Stop the project
No
· Start development like as indoor tyre study and/or outdoor tyre study.
· Proceed pre-work to be done before starting to work on industrialisation (see part 5.3).
· When needed update knowledge on hazard and update scenario of potential nano release.
Re-evaluate the risk on full life cycle
Is there unacceptable risk detected in the full life cycle?
No
Yes
Stop the project
· Start industrialization like as trial production in a tyre mass production plant.
· Proceed pre-work to be done before starting to work on mass production (see part 5.4).
· Finalize and evaluate knowledge on hazard. Finalize scenario of potential nano release and evaluate the risk
Finalize evaluation of the risk on full life cycle
Full final study shows that there is only acceptable risk for human health or environment
Yes
· Start mass production and commercialization
· Prepare required communication / information
· Continue to evaluate new EHS and regulatory information
No
Mass production and commercialization are not yet possible
Are there possible countermeasures to fill the gaps?
No
Stop the project
Yes
Review the evaluation of the risk and the risk management to estimate the gaps
Estimate the gaps and fill the gaps

7. Reasoning followed by the Tyre industry to build its initiative on SIA for development of new nanomaterials

1) Short introduction on the tyre industry initiative

367. The tyre industry initiative included as an annex in the "OECD report on SIA with nanomaterials" is an initiative of the main tyres manufacturers. The content of this initiative was of course agreed to be implemented within these companies. It is the result of a pragmatic work that led to a consensus between the 11 main tyre producers gathered together in the TIP (Tyre Industry Project) under the umbrella for the WBCSD (Word Business Council for Sustainable Development). The TIP is working since 14 years addressing a series of sustainability challenges for the tyre industry in collaboration with several world-class consultants, an advisory panel of world-leading experts, and a number of key industry stakeholders.

368. So the tyre industry initiative presented in this annex is not a document prepared by the OECD but a document provided by industry, as a case on its applicability in an industrial setting.

2) Analysis of the background to build the tyre industry initiative

369. Before deciding to develop the tyre initiative an in-depth evaluation of the background and context was done which did also allowed to define clearly the scoop.

370. The following five key points were identified:

a) All tyre producers are convinced that development of new nanomaterials in tyre should bring a huge breakthrough at a level probably never seen before. This will include not only tyre performances like grip, traction, handling, wear… but also environmental challenges like reducing energy consumption of vehicles, decreasing the need of raw materials, increasing the durability of the tyres.

b) Development of new nanomaterial in tyre bring challenges which are not existing for other new materials like chemicals and polymers. This is mainly linked to the risk of release of nanomaterial in the environment during some steps of the life cycle and another point is the lack of knowledge regarding EHS for new nanomaterials.

c) Even if the type of nanomaterials selected may be different from one tyre company to another, the concerns on how to get a safe(r) development with nanomaterials in tyres are new for all companies. Then it was the opportunity for the members of the TIP to collaborate together in a way which was never done before with the goal to reach a consensus on how to manage in a safe(r) innovation approach the development of new nanomaterials in tyres. This include all steps from concept to mass production and take in account since the beginning the full life cycle of the tyres.

d) Moreover in July 2014 was published the OECD report "Nanotechnology and Tyres, Greening industry and transports". This OECD document highlighted the potential of new nanomaterials whilst analysing the challenges: Status of nanotechnology in tyres, Key drivers of innovation, Socio-economic impacts of new nanomaterials in tyre. Main conclusion were: New nanomaterials in tyre may help to reduce environmental impact of vehicles (Example Reducing vehicles energy consumption), but potential EHS risks have to be managed carefully at each stage of a tyre's Life Cycle (from innovation to end of life). The TIP had welcomed these conclusions and had taken the engagement (approved at CEOs level) to manage this EHS for each development of a new nanomaterial. This led to the Tyre industry initiative document.

e) It was possible to reach a consensus on nanomaterial also because it is for all tyre manufacturers the main large field of innovation regarding new materials in tyres. For the time being outside of development of new nanomaterials they are no others consensus on innovation. They are not often development of new materials in tyres, they are usually specific to only one company and they are treated by the individual classical way to proceed of each company which did of course include EHS concerns.

371. The scoop of the tyre industry initiative is limited on the use of new nanomaterials in tyres and not on other materials (unless this material is directly associated with the use of nanomaterials, example to linking with polymer), and includes the complete tyre life cycle.

3) About the need of an engagement of the top management.

372. To implement, apply and develop the safer initiative approach for any new nanomaterials in tyre, resources are needed. Before starting the project it was first needed to get a strong support from the management. This was especially important in the tyre industry project involving eleven companies, which are competitors.

373. A strong support was given by the eleven CEOs of the companies members of TIP confirmed in a meeting on October 9, 2015.

4) About the need to take in account concerns on risks and uncertainties, and their consequences

374. The SbD (Safe-by-Design, Safe(r)-by-Design, or Safety-by-Design) concept refers to identifying the risks and uncertainties concerning the human and environmental safety at an early phase of the innovation process and then minimizing the uncertainty, the hazard(s) and/or the exposure. The SbD approach addresses the safety of the material/product during the whole life cycle: from the Research and Development (R&D) phase to production, use and recycling or disposal.")

375. In the tyre industry initiative, risk and uncertainties concerning the human and environmental safety are evaluated at a very early phase of the development of each new nanomaterial, and it is specified that EHS information have to be collected and analysed prior starting the research studies. Because most of the new nanomaterials are recent, EHS information have to be completed all along the development in tyres, and contribution of nanomaterial supplier has to be requested.

376. There is the need to define precisely which EHS information are missing and then to complete by performing the toxicologic testing needed. It is needed to have a clear view on EHS for a decision "stop or go" obviously at latest before tyres mass production. Details are giving in the section 5 of this annex and reminded on each phase of the process from 5.1 to 5.3.

377. It is obvious to use the less hazardous solution possible for the same performance, see section 5 of this annex, that means that it is not only needed to select the less hazardous at the beginning but also to follow all information on hazard and to re-evaluate the appropriateness of the project in regard of those new information.

378. Regarding exposure of the workers in each phase research, industrialization and production the tyre industry initiative has decided application of the control banding (more information in Section 3).

379. Regarding risk of exposure during the life cycle of the tyre, it was established by previous studies that the potential risk is by exposure coming from the release of nanomaterials. Type of potential exposures are largely developed with comments in section 4. It is specified in the tyre industry initiative that in each case the potential possibilities of exposure have to be defined as

precisely as possible, tests have to be developed and potential exposure have to be evaluated, this is in sections 5 to 5.4.

5) About the need to take in account evolution of regulatory aspects

380. In the tyre initiative technical improvement and EHS concerns are completed with knowledge of the regulations and evaluation of potential evolution. Those regulations may be on nanomaterials and also on consequences of use of nanomaterials in full tyre life cycle. At the very early stage and all along the process they are reviewed to know and anticipate. All those aspects require dialogue with regulators. It is not forgotten that regulation may differ from one country to another.

6) About the decision to stop or to continue the development of a new nanomaterial in tyre.

381. Before each stage of the development there is a list of key points to be solved and a decision to stop or to continue the development has to be taken (sections 5 to 5.4, and flowchart in section 6). Decision to stop has, for the tyre industry, to be taken at the earliest stage possible and the balance is strongly focused on safety more than on functionality.

382. Cost and time for development of a new nanomaterial in tyre being so high, it has no sense for a tyre company to wait too long to stop a project which may not be safe enough.

7) About commercialisation of tyres with new nanomaterials.

383. It is obvious that tyres to be put on the market have to be safe.

384. At commercialisation step, the tyre industry initiative document plan to prepare any communication/information needed for legal requirement if any, and for voluntary information to downstream users, and to continue to evaluate new EHS and regulatory information for as long as the new nanomaterial is in use

8. References

Adhikari B; De D; Maiti S (2000). Reclamation and recycling of waste rubber. Progress in Polymer Science 25(7): 909-948.

Bouillard JX; R'Mili B; Moranviller D; Vignes A; Le Bihan O; Ustache A; Bomfim JA; Frejafon E; Fleury D (2013). Nanosafety by design: risks from nanocomposite/nanowaste combustion. Journal of Nanoparticle Research 15(4): 1-11.

Gloobal ELTs Management - A global state of knowledge on collection rates, recovery routes, and management methods - https://www.wbcsd.org/Sector-Projects/Tire-Industry-Project/End-of-Life-Tires-ELTs

Golanski L; Guiot A; Pras M; Malarde M; Tardif F (2012). Release-ability of nano fillers from different nanomaterials (toward the acceptability of nanoproduct). Journal of Nanoparticle Research 14(7): 1-9

Gransberg DD; Nash PT; Jayawickrama P; Senadheera S; Sonti K (2003). Evaluate the Use for Scrap Tires in Transportation Facilities

Gualtieri M; Andrioletti M; Vismara C; Milani M; Camatini M (2005). Toxicity of tire debris leachates. Environment international 31(5): 723-730.

Gustafsson M, Blomqvist, G., Lunden, E.B., Dahl, A., Gudundsson, A., Hjort, M., Johansson, C., Jonsson, P., Swietlicki, E. (2010). NanoWear: Nanoparticles from the Abrasion of Tyres and Pavement. VTI report No. 660.

Gutowski TG; Sahni S; Boustani A; Graves SC (2011). Remanufacturing and energy savings. Environmental science & technology 45(10): 4540-4547.

Holder AL; Vejerano EP; Zhou X; Marr LC (2013). Nanomaterial disposal by incineration. Environmental Science: Processes & Impacts 15(9): 1652-1664

ISO 12901-2 Nanotechnologies — Occupational risk management applied to engineered nanomaterials - Use of the control banding approach

International Symposium on Assessing the Economic Impact of Nanotechnology 27-28 March 2012, Washington DC – OECD, US NNI and AAAS. Peters F - Tires and nano materials

JRC Technical Report 2016 "NANoREG Harmonised terminology for environmental health and safety assessment of nanomaterials " Gottardo S, Quiros Pesudo L, Totaro S, Riego Sintes J, Crutzen H.

Kreider ML; Panko JM; McAtee BL; Sweet LI; Finley BL (2010). Physical and chemical characterization of tire-related particles: Comparison of particles generated using different methodologies. Science of the total environment 408(3): 652-659.

Ma P-C; Siddiqui NA; Marom G; Kim J-K (2010). Dispersion and functionalization of carbon nanotubes for polymer-based nanocomposites: a review. Composites Part A: Applied Science and Manufacturing 41(10): 1345-1367.

Managing End of Life Tires (ELT) Full report. https://www.wbcsd.org/Sector-Projects/Tire-Industry-Project/End-of-Life-Tires-ELTs

Marcel Mathissen, Volker Scheer, Rainer Vogt , Thorsten Benter - Atmospheric Environment 45 (2011) 6172-6179 - Investigation on the potential generation of ultrafine particles from the tire-road interface

OECD (2014a), Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models, OECD Series on Testing and Assessment, No. 69, OECD Publishing, Paris, https://doi.org/10.1787/9789264085442-en.

OECD (2014b). Nanotechnology and Tyres, OECD Publishing

Sachse S; Gendre L; Silva F; Zhu H; Leszczyńska A; Pielichowski K; Ermini V; Njuguna J (2013). On nanoparticles release from polymer nanocomposites for applications in lightweight automotive components. Journal of Physics: Conference Series 429: 012046.

Samuel S; Garcia LÁ (2014). Fuel from waste tyres and particulate matter emitted from the process. International Journal of Sustainable Engineering 7(4): 293-306.

Schlagenhauf L; Chu BT; Buha J; Nuesch F; Wang J (2012). Release of carbon nanotubes from an epoxy-based nanocomposite during an abrasion process. Environ Sci Technol 46(13): 7366-7372.

Sienkiewicz M; Kucinska-Lipka J; Janik H; Balas A (2012). Progress in used tyres management in the European Union: a review. Waste management 32(10): 1742-1751.

Thomas S; Stephen R (2010). Rubber nanocomposites: preparation, properties and applications, John Wiley & Sons.

Uddin N; Nyden M (2016). Characterization of nanoparticle release from polymer nanocomposites due to fire. une 13: 15.

Wik A; Dave G (2006). Acute toxicity of leachates of tire wear material to Daphnia magna—variability and toxic components. Chemosphere 64(10): 1777-1784.

Wik A (2007). Toxic components leaching from tire rubber. Bulletin of environmental contamination and toxicology 79(1): 114-119.

9. Suggested Bibliography on Tyre and Road Wear Particles (TRWP)

► The following section includes peer-reviewed publications on studies on tyres and roads wear particles, sponsorised by wbcsd tip (studies performed with tyres available on the market). It is organised by themes:

Physico-chemical characterisation or TRWP (Tyre and Road Wear Particles)

- Physical and chemical characterization of tire-related particles: Comparison of particles generated using different methodologies. M.L. Kreider, J.M. Panko, B.L. McAtee, L.I. Sweet and B.L. Finley (2010), *Science of the Total Environment*, Vol. 408, pp. 652-659
- Use of a Deuterated Internal Standard with Pyrolysis-GC/MS Dimeric Marker Analysis to Quantify Tire Tread Particles in the Environment. K.M. Unice, M.L. Kreider and J.M. Panko (2012), *Int. J. Environ. Res. Public Health*, Vol. 9, pp. 4033-4055

Evaluation of ecotoxicity of TRWP including impact on environment of aging of TRWP

- Acute aquatic toxicity of tire and road wear particles to alga, daphnia, and fish C. Marwood, B. McAtee, M.L. Kreider, R.S. Ogle, B.L. Finley, L. Sweet and J.M. Panko (2011), Ecotoxicology, Vol. 20(8), pp. 2079-2089
- Chronic toxicity of tire and road wear particles to water- and sediment-dwelling organisms J.M. Panko, M.L. Kreider, B.L. McAtee and C. Marwood (2013), Ecotoxicology, Vol. 22, pp. 13–21

- Experimental methodology for assessing the environmental fate of organic chemicals in polymer matrices using column leaching studies and OECD 308 water/sediment systems: Application to tire and road wear particles K.M. Unice, J.L. Bare, M.L. Kreider and J.M. Panko (2015), Science of the Total Environment Vol. 533, pp. 476–487

Evaluation of toxicity by inhalation of TRWP

- Evaluation of potential for toxicity from subacute inhalation of tire and road wear particles in rats M.L. Kreider, M. Doyle-Eisele, R.G. Russell, J.D. McDonald and J.M. Panko (2012), Inhalation Toxicology, Vol. 24(13), pp. 907–917

Measurement of contribution of TRWP to pollution of water and sediment

- Evaluation of Tire and Road Wear Particles in the Seine River Watershed. K.M. Unice, J. Chu, J.M. Panko and B.L. McAtee (2012), Society of Environmental Toxicology and Chemistry / SETAC
- Comparison of Tire and Road Wear Particle Concentrations in Sediment for Watersheds in France, Japan, and the United States by Quantitative Pyrolysis GC/MS Analysis. K.M. Unice, M.L. Kreider and J.M. Panko (2013), Environ. Sci. Technol., Vol. 47, pp. 8138−8147

Measurement of contribution of TRWP to PM 10 air pollution and to PM 2.5 air pollution

- Measurement of airborne concentrations of tire and road wear particles in urban and rural areas of France, Japan, and the United States. J.M. Panko, J. Chu, M.L. Kreider and K.M. Unice (2013), *Atmospheric Environment* Vol. 72, pp. 192-199
- PRESENTATIONS AT CONFERENCES ON TYRES AND ROADS WEAR PARTICLES GIVEN BY CARDNO CHEMRISK - STUDIES SPONSORISED BY WBCSD TIP (Studies performed with tyres available on the market)

Physico-chemical characterisation or TRWP (Tyre and Road Wear Particles)

- Physico-chemical analysis of airborne tire wear particles. J.M. Panko, B.L. McAtee, M.L. Kreider, M. Gustafsson, G. Blomqvist, A. Gudmundsson, L.I. Sweet and B.L. Finley (2009), Eurotox

Evaluation of ecotoxicity of TRWP including impact on environment of aging of TRWP

- Chronic toxicity of tire/road wear particles in sediments to aquatic organisms. C. Marwood, B.L. McAtee, M.L. Kreider, J.M. Panko and B.L. Finley (2010), Society of Environmental Toxicology and Chemistry / SETAC
- Evaluation of Leachate from Tire and Road Wear Particles (TRWP) Upflow Percolation Column Tests. K.M. Unice, J.L. Bare, M.L. Kreider and J.M. Panko (2015), Society of Environmental Toxicology and Chemistry / SETAC

Evaluation of toxicity by inhalation of TRWP

- Effects of Intratracheal Instillation of Tire and Road Wear Particles (TRWP) and Tread Particles (TP) on Inflammation and Cytotoxicity in Rat Lung: A Comparative Toxicity Study. M.L Kreider, J.M. Panko, J.D. McDonald, B.L. McAteea, B.L. Finley and J.C. Seagrave (2009), SOT

- Biological leaching of metals from respirable tire wear particles. B.L. McAtee, M.L. Kreider, J.M. Panko and B.L. Finley (2009), Eurotox
- Effects of Subacute Inhalation Exposure to Tire and Road Wear Particles in Rats M.L. Kreider and J.M. Panko (2012), Eurotox
- Potential for Toxicity on the Cardiopulmonary System from Inhalation of Airborne TRWP M.L. Kreider (2012), Tire tech expo 2012 -Cologne, Germany February 15, 2012

Characterisation and analytical method developed for the studies on TRWP and accepted to be published by ISO:

- ISO 20593: Ambient air — Determination of the mass concentration of tire and road wear particles(TRWP) — Pyrolysis-GC-MS method. Published June 2017
- ISO 21396: Determination of mass concentration of tire and road wear particles (TRWP) in soil and sediments- Pyrolysis - GC/MS method. Published December 2017.
- ISO 22638: Generation and collection of tyre and road wear particles (TRWP) - Road simulator laboratory method – Published July 2018
- ISO 22640: Framework for physical and chemical characterization of tyre and road wear particles (TRWP) – Published July 2018
- ISO 22687: Framework for assessing the environmental fate of tyre and road wear particles (TRWP) - Published August 2018

Annex 2: Results of the Survey on Working Descriptions

Table 0.1. Safe(r)(ty)-by-Design

COUNTRY	ORGANISATION	TERM USED	INTERPRETATION
European Commission	JRC	"SAFE BY DESIGN" refers to satisfying the applicable safety standards, while "SAFER BY DESIGN" emphasizes the relative rather than absolute nature of safety."	"The SbD (Safe-by-Design, Safer-by-Design, or Safety-by-Design) concept refers to identifying and then eliminating, reducing or controlling risks and uncertainties concerning the human and environmental safety of an innovation, starting at an appropriately early phase of the innovation process. The SbD approach addresses the safety of the whole life cycle or value chain of an innovation, including the R&D phase, production, use and disposal. This is reflected in the three pillars of safety: safe design (designing a safe nanomaterial), safe use (of the nanomaterial or nano-enabled product) and safe production (the occupational safety of industrial production). The SbD approach also helps to produce the appropriate safety-related information and data in order to comply with regulatory requirements and effectively communicate the remaining risks.
Canada	HEALTH CANADA	SAFER BY DESIGN "Safer" is in common use for similar initiatives (e.g., "safer chemicals").	"Safer" is used in the context of advancing informed substitution and alternatives assessment: https://www.canada.ca/en/health-canada/services/chemical-substances/consulting-future-chemicals-management-canada/options-advancing-informed-substitution-alternatives-assessment-canada-chemicals-program.html
France	CEREGE	SAFER BY DESIGN	SbD is a strategy to include risk management measures as early as possible in the value. SbD should not impair innovation, and applies to all stages of the value chain i.e. manufacturing, use, disposal/end-of-life
	CEA	SAFE BY DESIGN	Safer by Design indicates it is an iterative process towards more safe products and processes. It could be linked from my own perspective to ALARA principles in risk mitigation. It is not yet built safe according to established (regulated) principles.
Germany	BfR	SAFER BY DESIGN	I am not aware of a gathered German description of SbD, although Germany participated in a number of research project related to the term.
Netherlands	Ministry of Infrastructure and Water Management (via communication with RIVM)	SAFE BY DESIGN, since this represents the long-term ambition of the Ministry of Infrastructure and Water Management	Safe-by-Design seeks to include safety as a design requirement at the earliest stages of product and process development to prevent potential risks for human health and the environment. Interpretation: NL does not have a definition for Safe-by-Design. The Dutch Ministry of Infrastructure and Water Management is however currently looking for frontrunners in the Netherlands to jointly develop the concept of Safe-by-Design. Here we provide the current working description of the Safe-by-design concept presented in a SbD brochure of the

			ministry. Safe-by-Design is one of the strategies that the State Secretary intends to follow in order to prevent risks for human health and the environment.
South Africa	National Institute for Occupational Health/University of the Witwatersrand	SAFE BY DESIGN SAFETY BY DESIGN SAFER BY DESIGN	There are three aspects that need to be considered: 1. The properties of nanomaterials to produce safe nanomaterials (Safe-by-design). 2. The safety of those who are synthesizing these nanomaterials (Safety-by-design). 3. Safer processes taking into account the life cycle of the nanomaterial (Safer-by-design).
Sweden		NA	NA
Switzerland	TEMAS AG	SAFE BY DESIGN	The SbD concept is a methodology, which manages safety/risks regarding products/processes taking into account costs in a way that, at the end, the strategy is economically feasible to industry. The concept is targeted towards nanomaterials, and allows industry to identify, reduce and manage uncertainties about health risks in products and processes to humans and the environment taking into account economic viability.
United Kingdom	DEFRA	Safer by Design	-----
US	*US EPA*	*Safer by Design*	*U.S. EPA who recommended the change from "safe" to "safer" for an understanding of her rationale for the change.* *Essentially it was that "safer" (as incremental) is achievable, whereas "safe" (as absolute) may not ever be.*

Table 0.2. Regulatory Preparedness

COUNTRY	ORGANISATION	TERM USED	INTERPRETATION
European Commission	JRC	Regulatory preparedness	Regulatory Preparedness refers to the capacity of regulators to anticipate the regulatory challenges posed by emerging technologies such as nanotechnology, and to facilitating the development of adaptable (safety) legislation that can keep up with the pace of knowledge generation and innovation regarding MNMs and nano-enabled products. Regulatory Preparedness can be achieved through awareness of innovations through e.g. foresight, trend watching and communication with stakeholders, by gathering information about them through e.g. pre-market information requirements and access to and sharing of data, by the enhancement of methodology for safety assessment, and by the appropriate adaptation of regulatory processes on basis of learning and knowledge-sharing.
Canada	HEALTH CANADA	Regulatory preparedness	I would suggest that the description not be limited to MMMs (as it could apply more broadly).
France	CEREGE	Regulatory preparedness	As proposed definition
	CEA	Regulatory preparedness	As proposed definition
Germany	BfR	Regulatory preparedness	As proposed definition
Netherlands	Ministry of Infrastructure and Water Management (via communication with RIVM)	----	There is no point of view regarding RP from the Dutch ministries
South Africa	National Institute for Occupational Health/University of the Witwatersrand	Regulatory preparedness	As proposed definition
Sweden	-----	------	--------
Switzerland	TEMAS AG	Regulatory preparedness	As proposed definition
United Kingdom	DEFRA	Regulatory preparedness	As proposed definition
US	*US EPA*	Oppose to the term because it implies that governments are currently not prepared	In agreement with definition

Annex 3. Results of the Survey: An inventory of SbD methodologies to help industry to implement a 'Safe(r) Innovation Approach' for MNMs and nano-enabled products.

- This questionnaire was circulated amongst OECD Countries. The responses below were provided in September 2019 by Canada, France, Germany (UBA & BfR), the Netherlands, Norway, Switzerland, the United States, and Thailand

Delegation	Answers + Details	References
Q1. Are you aware of any '*Safe Innovation*' / *'Safe(r) by Design'* **framework, tool or methodology** or more in general on concepts willing to design a product, a production process or the use of a product in a safe condition by its nature?		
Canada	Environment and Climate Change Canada (ECCC) and Health Canada (HC) are supportive of Safe-by-Design (SbD) approach for emerging technologies such as nanomaterials and living organisms (products of biotechnology).	The Safe-by-Design (SbD) approach has been considered and will be adopted, as needed, in a new framework for the risk assessment of manufactured nanomaterials (MNMs) and in updating the framework for the risk assessment of living organism (biotechnology)
France	Prevention through Design: ANSI Standard	**Prevention through design** ANSI/ASSE. (2011). American national standard: Prevention through design: Guidelines for addressing occupational hazards and risks in design and redesign processes (Z590.3-2011) ANSI/ASSE. (2012). American national standard: Occupational health and safety management systems (ANSI/ASSE Z10-2012). See publications **Prevention through design**; mainly targeted towards occupational risks Wilbanks, Lyon, Walline, Ertas, Popov https://www.onepetro.org/journal-paper/ASSE-15-04-46 https://www.onepetro.org/journal-paper/ASSE-16-09-37 https://www.nafe.org/assets/HollywoodEdSeminar/prevention%20through%20design12152014.pdf https://pdfs.semanticscholar.org/18d9/f3306913446768e2d3d930346bd77458a290.pdf Labex Serenade: https://www.cerege.fr/fr/recherche/labex-

Delegation	Answers + Details	References
		serenade
	ISO standard for safety in occupational settings	ISO/TR 12885:2018 Nanotechnologies — Health and safety practices in occupational settings ref. Publications HSE http://www.hse.gov.uk/pubns/ Internet and future networks https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0594:FIN:EN:PDF
Germany (BfR)	Yes	Understanding Pharmaceutical Quality by Design by Lawrence X. Yu, corresponding author Gregory Amidon, Mansoor A. Khan, Stephen W. Hoag, James Polli, G. K. Raju, and Janet Woodcock AAPS J. 2014 Jul; 16(4): 771–783. doi: 10.1208/s12248-014-9598-3 and Medical Device Design for Six Sigma: A Road Map for Safety and Effectiveness By Basem El-Haik, Khalid S. Mekki, 2011 Introduced by Joseph M. Juran in 1992 for pharmaceutical industry.
Germany (UBA)	Sustainable Chemistry - Guide available as well as tool to evaluate products/processes - General terms of chemical safety are used - Based on the long-established concept of green chemistry; UBA guide for sustainable chemistry since 2016; ISC3 established since 2017 Life Cycle Assessment - Various methods are available, most common approaches are listed in ISO 14040:2006 Directive 2009/125/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for the setting of ecodesign requirements for energy-related products	https://www.umweltbundesamt.de/en/topics/chemicals/chemicals-management/sustainable-chemistry Guide: https://www.umweltbundesamt.de/publikationen/guide-on-sustainable-chemicals International Competence centre of sustainable chemistry https://www.isc3.org/en/home.html https://www.iso.org/standard/38498.html https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32009L0125

Delegation	Answers + Details	References
	- European directive - Yes stated in the directive - 2009 for energy related products Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) - European directive - Yes stated in the directive - 2010 for various industrial plants Blue Angel (the German Ecolabel) - Product category specific assessment criteria - Introduced more than 40 years ago Eco labeling Regulation (EC) No 66/2010 of the European Parliament and of the Council of 25 November 2009 on the EU Ecolabel - European regulation - Yes stated in the directive - 2010 for various product categories	https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1439908584691&uri=CELEX%3A32010L0075 https://www.blauer-engel.de/en https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32010R0066 https://www.eu-ecolabel.de/
Netherlands	– NO, but SbD is a long-term ambition of the Ministry of Infrastructure and Water Management. – Safe-by-Design seeks to include safety as a design requirement at the earliest stages of product and process development to prevent potential risks for human health and the environment. – Interpretation: NL does not have a definition for Safe-by-Design. – In June 2018 for nanotechnology, and initiatives are present for chemicals via the Chemicals Innovation Agenda, Biotechnology, and chemical industry via the Sustainable safety 2030 report.	Ministry of Infrastructure and Water Management https://safe-by-design-nl.nl/default.aspx https://safe-by-design-nl.nl/documenten/default.aspx

Delegation	Answers + Details	References
Norway	Safe handling of nanomaterials, guidance given by The Norwegian Labour Inspection Authority WHO has developed guidelines on protecting worker from potential risks of manufactured nanomaterials. NanoReg2 EU Horizon 2020 research project	https://www.arbeidstilsynet.no/tema/kjemikalier/nanomaterialer-og-arbeidsmiljo/rutiner-for-handtering-av-nanomaterialer/, https://www.arbeidstilsynet.no/tema/kjemikalier/nanomaterialer-og-arbeidsmiljo/tre-trinn-for-trygg-handtering-av-nanomaterialer/ https://apps.who.int/iris/bitstream/handle/10665/259671/9789241550048-eng.pdf;jsessionid=BFC97E2916021CD58EAA6245FFCFF61C?sequence=1 http://www.nanoreg2.eu/safe-design
Switzerland	Classification Framework for Graphene-Based Materials	ACS Nano 2017, 11, 9574-9593 Peter Wick, Anna E. Louw-Gaume, Melanie Kucki, Harald F. Krug, Kostas Kostarelos, Bengt Fadeel, Kenneth A. Dawson, Anna Salvati, Ester Vazquez, Laura Ballerini, Mauro Tretiach, Fabio Benfenati,Emmanuel Flahaut, Laury Gauthier, Maurizio Prato, and Alberto Bianco
USA	EPA's Safer Choice program distinguishes products with safer ingredients and encourages innovation in green chemistry, The program coordinates activity between EPA, states and localities, and environmental, labor, and industry groups	http://intranet.epa.gov/opptwork/division/cessd/dfe/index.html
Thailand	NO	NO
Q2. Are you aware of any 'Safe Innovation' / 'Safe(r) by Design' **initiatives (lab-scale or industrial case studies)** or more in general on concepts willing to design a product, a production process or the use of a product in a safe condition by its nature?		
Canada	NO	----------
France	– Nanosmile: Six thematic modules PRECAUTIONS, METROLOGY, HEALTH, ENVIRONMENT, LIFE CYCLE and GOVERNANCE are structured on three levels of knowledge: – NIOSH: National Initiative on Prevention through Design (PtD) – R-Nano.fr: Declaration of Nanomaterials in France – EUON: European Observatory for nanomaterials (linked to ECHA) – DaNa (Dechema) – Nanoportal: Safe handling of Nanomaterials	http://www.nanosmile.org/index.php/en/ https://www.cdc.gov/niosh/topics/ptd/default.html https://euon.echa.europa.eu/ *NanoData (EUON)* Contains data on different products, research projects,

Delegation	Answers + Details	References
	– SweNanosafe: Swedish Nat Platform for nanosafety	publications, patents and companies and helps you to visualise statistics quickly through built-in charts and graphs. The data can also be easily filtered by different sectors and geographic location. The database can be used for example by consumers interested in finding out about products that use nanotechnology. Dana: Information about nanomaterials and their safety assessment- Data knowledge on nanomaterials https://swenanosafe.se/in-english/
Germany (BfR)	Yes	FDA encourages following the principles of quality by design. U. S. Food and Drug Administration. FDA-EMA parallel assessment of Quality-By-Design elements of marketing applications. http://www.fda.gov/Drugs/DrugSafety/ucm365524.htm. Accessed 16 Nov 2013 Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res. 2008;25:781–91. doi: 10.1007/s11095-007-9511-1. Lionberger R, Lee S, Lee L, Raw A, Yu LX. Quality by design: concepts for ANDAs. AAPS J. 2008;10:268–76. doi: 10.1208/s12248-008-9026-7.
Germany (UBA)	Chemical Leasing: Case studies within the framework of chemical leasing award - Contact: Christopher Blum, German Environment Agency	http://www.chemicalleasing.com/ https://www.umweltbundesamt.de/themen/chemikalien/chemikalien-management/nachhaltige-chemie/chemikalienleasing-portaleinstieg#textpart-1
Netherlands	- No - The terms "Safe innovation" and "Safe(r)-by-design" are currently popular in the field of nanotechnology. These terms are used to describe approaches that advocate the consideration of safety aspects already at an early stage of the innovation process of (nano)materials and nanoenabled products.	Park et al. 2017. Considerations for Safe Innovation: The Case of Graphene. *ACS Nano*, 11 (10): 9574-9593 https://pubs.acs.org/doi/abs/10.1021/acsnano.7b04120

Delegation	Answers + Details	References
	- Graphene case study published in 2017. - The Dutch Ministry of Infrastructure and Water Management is currently looking for frontrunners in the Netherlands to jointly develop the concept of Safe-by-Design. Here we provide the current working description of the Safe-by-design concept presented in a SbD brochure of the ministry. Safe-by-Design is one of the strategies that the State Secretary intends to follow in order to prevent risks for human health and the environment. - Several case studies combining SbD and LCA are being funded in academia to obtain lessons learned on how to implement SbD/LCA in an early stage of the innovation process. - In the EU BBI project ReSolve candidate substituents of toluene and NMP are synthesized and immediately assessed for their PBT (CMRS) safety properties; some of the promising candidates are also tested for upscaling potential.	http://resolve-bbi.eu/
Norway	Safe-by-Design - Relevance and added value for Austrian companies (Safe-by-Design Relevanz und Mehrwert für österreichische Unternehmen)	https://www.bionanonet.at/23-projects/completed-projects
Switzerland	Considerations for Safe Innovation: The Case of Graphene	Margriet V.D.Z. Park, Eric A.J. Bleeker, Walter Brand, Flemming R. Cassee, Merel van Elk, Ilse Gosens, Wim H. de Jong, Johannes A.J. Meesters, Willie J.G.M. Peijnenburg, Joris T.K. Quik, Rob J. Vandebriel, and Adrienne J.A.M. Sips
USA	Someone was familiar with a specific case for a carbon material: Considerations for Safe Innovation: The Case of Graphene (2017), which explores the possibilities of safety mechanisms during the stages of the innovation process of graphene Principles of "Design for Safer Nanotechnology" (from Toxics Use Reduction Institute (U Mass) -Emphasis on risk mitigation during incorporation of nanomaterials into products -Provides framework for "design" approaches mitigating risk -"Design" principles include Size, surface, structure Functionalization	https://pubs.acs.org/doi/pdf/10.1021/acsnano.7b04120?rand=wo6urmt1 J Cleaner Prod (2009) https://www.turi.org/content/download/8909/159711/file/SAFER%20Article.PDF

Delegation	Answers + Details	References
	-Provides application examples	
Thailand	NO	NO
Q3. Are you aware of any '*Safe Innovation*' / '*Safe(r) by Design*' **framework, tool or methodology** that were adapted to **emerging technologies** (e.g. nanomaterials) or more in general on concepts willing to design a product, a production process or the use of a product in a safe condition by its nature?		
Canada	NO	----------
France	GuideNano projet Serenade project and the related sub-projects: *SafeTiPaint 1 &2, EcoSun, Snicker, WarmEcoPaint …* NanoLeap project SOPs from NANoREG WP3 (i.e. D3.3, D3.5, D3.6 etc.) RIVM SIA toolox Materials by design: NIST initiatives **Materials by Design :**Cooking Up Innovations with the Materials Genome Initiative	Guide Nano Project - http://www.guidenano.eu/ *Coord. Socorro Vázquez Campos (svazquez@leitat.org)* Labex SERENADE - http://www.labex-serenade.fr/ *Coord. Jerome Rose (rose@cerege.fr)* *Participants: masion@cerege.fr ; simon.clavaguera@cea.fr etc.* NanoLeap Project - http://www.nanoleap.eu/ *Coord. Jose-Luis Valverde (jvalverde@phi4tech.com)* *WP. Leader simon.clavaguera@cea.fr* http://www.nanoreg.eu/ https://www.rivm.nl/en/about-rivm/mission-and-strategy/international-affairs/international-projects/nanoreg http://www.SIAtoolbox.com https://www.nist.gov/featured-stories/materials-design
Germany (BfR)	Yes	See above and U. S. Food and Drug Administration. Quality by design for ANDs: an example for modified-release dosage forms. 2011. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM304305.pdf. CMC Biotech Working Group. A Mab: A case study in bioprocess development. http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=8&ved=0CF8QFjAH&url=http%3A%2F%2Fwww.ispe.org%2Fpqli%2Fa-mab-case-study-

Delegation	Answers + Details	References
		version2.1&ei=f6qIUpXqKuLlsATlioHgDA&usg=AFQjCNH9JB17H4gssCd489dlOwV4xoAmDQ.
Germany (UBA)	Nano-Sustainability Check - Yes - Uses common terms of LCA - 2012 applicable for various sectors/products/applications	https://www.umweltbundesamt.de/publikationen/analysis-strategic-management-of-nanoproducts
Netherlands	- Yes - Yes, see SIA Toolbox website (under NanoReg2 umbrella) - A workable Safe Innovation Approach (SIA) requires tools to support the Safe-by-Design and Regulatory Preparedness concepts in order to address safety aspects timely and minimize uncertainty about health risks to workers, consumers and the environment. - It was introduced in 2018 for nanomaterials.	http://www.SIAtoolbox.com https://www.siatoolbox.com/methods
Norway	The Nordic Council of Ministers has created a free online tool to help small- and medium-sized enterprises (SMEs) register nanomaterials under REACH. The tool is named e-REACHNano which aims to help smaller companies on the regulation of Nanomaterials.	https://ereachnano.dhigroup.com/
Switzerland	1-Precautionary matrix for synthetic nanomaterials (Switzerland) 2-CEN/TC 352 Safe-by-Design concept dedicated for nano scale materials (MNM) and products containing nanomaterials 3-Nanohub (USA)	1-https://www.bag.admin.ch/bag/en/home/gesund-leben/umwelt-und-gesundheit/chemikalien/nanotechnologie/sicherer-umgang-mit-nanomaterialien/vorsorgeraster-nanomaterialien-webanwendung.html 2-Approved by CEN but has not started yet 3-https://nanohub.org/
USA	NIOSH's Prevention thru Design OECD Sustainable Manufacturing toolkit	https://www.cdc.gov/niosh/topics/ptd/default.html https://www.oecd.org/innovation/green/toolkit/aboutsustainablemanufacturingandthetoolkit.htm
Thailand	NO	NO
Q4. Are you aware of any 'Safe Innovation' / 'Safe(r) by Design' **initiatives (lab-scale or industrial case studies)** that were conducted on **emerging technologies** (e.g. nanomaterials) or more in general on concepts willing to design a product, a production process or the use of a product in a safe condition by its nature?		
Canada	----	----
France	SERENADE project NanoLeap project OASIS project	***Environ. Sci.: Nano***, 2017,**4**, 526-538 NanoLeap Project - http://www.nanoleap.eu/ *Coord. Jose-Luis Valverde (jvalverde@phi4tech.com)*

Delegation	Answers + Details	References
	Pilot lines EU funded (FP7, H2020) in nanotechnologies – Safety aspects https://www.eppnetwork.com/ EU Technology infrastructures Ex :Some projects aims at sustainable green energy and electric mobility with a whole value chain analysis	*WP. Leader simon.clavaguera@cea.fr* https://project-oasis.eu/ *WP. Leader jesus.lopezdeipina@tecnalia.com* *Participant josephine.steck@cea.fr* https://eppnetwork.com/files/eppn/post/2018/02/145_d5322fe01c18e2bebd080d7a7b089acd.pdf https://publications.europa.eu/en/publication-detail/-/publication/0df85f8b-7b72-11e9-9f05-01aa75ed71a1/language-en
Germany (BfR)	not known	----------
Germany (UBA)	Within the Nano-Sustainability Check a case study with nanomaterials for cement was investigated	https://www.umweltbundesamt.de/publikationen/analysis-strategic-management-of-nanoproducts
Netherlands	- Yes o Labex SERENADE initiative provides a series of platforms of instrumental tools for the synthesis and risk analysis of nanomaterials and nano-enabled products over their entire life cycle, including design phase. Besides individual operational limitations of these instruments, no overall technical limitations have been addressed by the initiative. Safe by design approach expects that the manufacturers include human and environmental safety considerations since the first steps of design and during the entire production of new-generation nanomaterials. It was conducted in 2012 for nanomaterials. It is applicable to all kinds of nanomaterials and nano-enabled products (including organic or inorganic and under research or commercialized) employed in all industrial sectors (cosmetics, construction, drugs, food additives and packaging, waste recycling etc.). o NANOGENTOOLS provides pre-validated molecular based computational modelling tools for the application	http://www.labex-serenade.fr/safer-ecodesign-research-and-education-applied-nanomaterial-development

Delegation	Answers + Details	References
	of safety-by-design principles. No definition of terms associated. It was conducted in 2016 for carbon based nanomaterials. It is applicable to CNT based nanosensor which is useful for SMEs and suitable for incorporation into regulatory frameworks. o SafeNanoKap assesses the applicability of the Safe-by-Design concept based on the product development of nanomaterials in coffee capsules. The tools used were Life Cycle Mapping and material flow analysis, iterative moderated group interviews with stakeholders, SWOT-analysis, and screening of relevant standards and regulations regarding labour protection, environmental or chemical legislation. Application of the SbD concept should allow identification and minimization of potential, unexpected risks as soon as possible. It was conducted in 2017 for SMEs. The target sector are nanomaterials in food contact materials.	
Norway	NO	NO
Switzerland	See annex on the Tire Industry Initiative	Prepared by the "Tire Industry Project" (TIP : Bridgestone, Continental, Coopertires Goodyear, Hankook, Kumho tire, Michelin, Pirelli, Sumitomo, Toyo tires, Yokohama) under the umbrella of the "World Business Council for Sustainable Development "(WBCSD) Angew.andte Essays DOI: 10.1002/anie.201403335
USA	NO	NO
Thailand	NO	NO
Q5. Do you know any activities by governments, NGOs or other organisations to gather information about the uses of emerging technologies in products?		
Canada	Yes	Emerging technologies such as nanotechnology and biotechnology are regulated by Environment and Climate Change Canada (ECCC) and Health Canada (HC).

Delegation	Answers + Details	References
	Canadian Ministries: ECCC and HC Sectors: ○ food ○ non-food (cosmetics, etc.) ○ workers ○ environment ○ other: Pesticides, Industrial, and Consumer Products Applications	https://www.canada.ca/en/environment-climate-change/services/managing-pollution/evaluating-new-substances/nanomaterials.html https://www.canada.ca/en/health-canada/services/science-research/emerging-technology.html HC and ECCC support research on emerging technologies and provides regulatory oversight of products of emerging technologies to better protect the health of Canadians and the environment. An updated framework for biotechnology and a new framework for manufactured nanomaterials (MNMs) is in-progress. There are specific regulations and schedules for regulating living organisms (products of biotechnology) and a specific schedule for nanomaterials is being proposed. The uses of living organisms and MNMs are part of pre-market risk assessment. https://www.canada.ca/en/health-canada/services/science-research/emerging-technology/nanotechnology/regulating-nanomaterials.html
France	Yes	EU Observatory for nanomaterials - ECHA https://euon.echa.europa.eu/ https://echa.europa.eu/fr/home Business innovation Observatory – advanced materials Observatoire des micro et nanotechnologies. Grenoble https://www.omnt.fr/en/ AVICENN http://veillenanos.fr/ & http://avicenn.fr R Nano, ANSES https://www.r-nano.fr/
Germany (BfR)	Yes, Guidelines for emerging technologies	The US agency CPSC

Delegation	Answers + Details	References
		https://www.cpsc.gov/s3fs-public/Report%20on%20Emerging%20Consumer%20Products%20and%20Technologies_FINAL.pdf Consumer Product Safety Commission; USA Consumer Safety 3D Printers and the printed products; Internet-home based smart technologies; Software as a component part; Wearable products and technologies; New materials, including nanomaterials; Virtual reality (VR) and augmented reality (AR) games; Personal transportation products; High capacity energy storage and energy generation; Robotics, including robotic products to assist older adults; Brain-machine interface/implantable technologies
Germany (UBA)	Yes; for emerging technologies; specific for nanotechnologies; Sector: Food; non-food (cosmetics, etc.); workers and environment OECD BNCT and WPMN Nanowatch Database of the German Friends of the Earth Dana 2.0 Knowledgebase EUON NanoDialog of the German Government	https://www.bund.net/themen/chemie/nanotechnologie/nanoprodukte-im-alltag/nanoproduktdatenbank/ https://www.nanopartikel.info/en/ https://euon.echa.europa.eu/ https://www.bmu.de/en/topics/health-chemical-safety-nanotechnology/nanotechnology/the-nanodialogue/
Norway	(a framework) The Product Register is the official register of hazardous chemicals in Norway, and is administered by the Norwegian Environment Agency. The data is used by the authorities to monitor chemicals, perform risk analyses related to chemical substances, and to deal with acute situations. The duty to declare hazard chemicals to the register is a national regulation and the requirement applies to manufacturers or consumers who manufacture and/or import for occupational or personal use of substances or mixtures classified as hazardous of 100 kg or more per year.	https://tema.miljodirektoratet.no/en/Areas-of-activity1/Chemicals/The-Product-Register/ National legislation (in Norwegian): https://lovdata.no/dokument/SF/forskrift/2015-05-19-541

Delegation	Answers + Details	References
	Information on substances in nanoform Physical data that may be relevant to consider when the chemicals have hazardous properties, must be provided. This includes information about the content of substances on nanoform in the chemical products. Information that is already known by the producer/manufacturer must be provided, and especially if the nanoform has a function in the chemical product. Definition of nanomaterials follows the EU Recommendation 2011/696/EU.	
Switzerland	(For emerging technologies) 1-IRCG, emerging risk (Switzerland) 2-Nanogov/NNI (National Nanotechnology Institute) (USA) 3-ICON (USA)	 1-https://irgc.org/risk-governance/emerging-risk/ 2-www.nsf.gov/crssprgm/nano/ 3-http://icon.rice.edu
USA	University of Virginia and the Pew Institute introduced a nanotechnology based consumer products Inventory CPWR – nanomaterials and construction This project contains information on uses of nanomaterials in construction and an inventory of existing products Nanotechnology: National Nanotechnology Initiative (NNI) gathers and disseminates information about nanotechnology products, development, and research. Guidance for Industry from the Food and Drug Administration on drug products containing nanomaterials.	https://www.nanotechproject.org/cpi/ https://www.cpwr.com/publications/cpwr-updates/nanomaterials-and-construction https://www.nano.gov/ https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-products-including-biological-products-contain-nanomaterials-guidance-industry
Thailand	NO	NO

Delegation	Answers + Details	References
Q6. Do you know any specific networks dedicated to understanding and discussing emerging technologies?		
Canada	Yes	1). Nano and Biotechnology sections at ECCC (Emerging Priorities Division) and Health Canada have working groups to discuss emerging scientific and regulatory challenges associated with risk assessment and risk management of living organisms (products of biotechnology) and MNMs. https://www.canada.ca/en/health-canada/services/science-research/emerging-technology/nanotechnology.html 2). Nanotechnology Community of Practice (an inter-departmental technical group across Government of Canada 3). Canada-United States Regulatory Cooperation Council (RCC)Nanotechnology Initiative 4). International Organization for Standardization Technical Committee 229 - Nanotechnologies
France	Yes	Nanosafety cluster https://www.nanosafetycluster.eu/ Observatoire des micro et nanotechnologies. Grenoble https://www.omnt.fr/en/ Nanotechnology Industries Association http://nanotechia.org/ Nanosafety or advanced materials RU projects
Germany (BfR)	No	
Germany (UBA)	Yes OECD BNCT and WPMN NanoDialog of the German Government Policy Conference: A Future-proof approach to Nanomaterials (Rotterdam, April 2018)	

Delegation	Answers + Details	References
Norway	**1:** Nano-network for Norwegian Authorities. The group's activities focus on the regulatory work on nanomaterials, where the main emphasis is on the development of the field in the EU regulations within the areas of responsibility of the Norwegian Labor Inspection Authority, the Norwegian Food Safety Authority and the Norwegian Environment Agency. This covers issues that include food safety, consumers, the working environment and the external environment. The purpose is to maintain a good network between the Norwegian authorities concerned. **2:** The group for monitoring occupational health related aspects of nanotechnology (The Nano-group). The nano-group continuously obtains new information on health hazards, exposures and prevention of the nanomaterials' potential adverse effects. The group also considers the current working environment legislation and adaptations that are implemented in REACH in order to better regulate working with nanomaterials in Norwegian enterprises. Members of the group are from the Norwegian Labor Inspection Authority and the National Institute of Occupational Health. **3:** The Norwegian research nano network initiative (NorNanoReg). The network is a forum of researchers and scientists that are involved in research on safety and health effects of nanomaterials. The network has been involved in the EU's NanoReg and NanoReg2 projects. **4:** Nordic Nano Network . The aim of the Nordic nanomaterial group is to optimise the efforts of the Nordic countries on ongoing national and EU work on the updating and implementation of legislations for nanomaterials. By coordination of the work the Nordic influence is expected to increase at EU level.	**4:** https://www.norden.org/en/information/subgroups-under-nordic-working-group-chemicals-environment-and-health-nke

Delegation	Answers + Details	References
Switzerland	1-Contactpointnano, SMEs have the possibility to contact this national platform for any question about nanomaterials. There question will then be forwarded to the respective experts. 2-IRCG, emerging risks (Switzerland)	1-https://contactpointnano.ch/ 2-https://irgc.org/risk-governance/emerging-risk/
United States	The NNI also engages in these type of activities including organising, sponsoring, and hosting meetings and webinars on emerging technologies.	https://www.nano.gov/
Thailand	Yes	- Asia Nano Forum - Nanotechnology Association of Thailand - NANOTEC
Q7. Do you know any activities by governments, NGOs or other organisations to gather information about the uses of emerging technologies in products?		
Canada	Yes	1). Nano and Biotechnology sections at ECCC (Emerging Priorities Division) and Health Canada have working groups to discuss emerging scientific and regulatory challenges associated with risk assessment and risk management of living organisms (products of biotechnology) and MNMs. https://www.canada.ca/en/health-canada/services/science-research/emerging-technology/nanotechnology.html
France	Yes	NIA http://www.nanotechia.org/ EU Observatory for nanomaterials - ECHA https://euon.echa.europa.eu/ https://echa.europa.eu/fr/home Observatoire des micro et nanotechnologies. Grenoble https://www.omnt.fr/en/ AVICENN http://veillenanos.fr/ & http://avicenn.fr R Nano, ANSES https://www.r-nano.fr/

Delegation	Answers + Details	References
Germany (BfR)	Yes	The US CPSC is working on this
Germany (UBA)	Yes, see Question 5	
Norway	The Product Register is the official register of hazardous chemicals in Norway (see info in Q5)	https://tema.miljodirektoratet.no/en/Areas-of-activity1/Chemicals/The-Product-Register/
Switzerland	1-INIC (Iran Nanotechnology Innovation Council) 2-Nano Science & Technology Consortium (India)	1-http://en.nano.ir/ 2-http://nstc.in/index.html
United States	NO	NO
Thailand	YES	- Asia Nano Forum - Nanotechnology Association of Thailand - NANOTEC
Q8. Are there any nano-specific **pre- marketing surveillance** activities in your country?		
Canada	Yes	Pre-market assessment of MNMs is mainly by ECCC under the Canadian Environmental and Protection Act, 1999 (CEPA, 1999) and by HC under Canadian Food and Drug Act and Consumer Product Safety Act. This ensures the protection of the environment and health of Canadians.
France	YES	In France, through the French declaration at 100 g/year (small amount used at the early R&D stages). This would constitute some pre surveillance activity R Nano, ANSES https://www.r-nano.fr/
Germany (BfR)	NO	
Germany (UBA)	NO	
Norway	NO	NO
Switzerland	NO	NO
United States	NO	NO
Thailand	NO	NO

Delegation	Answers + Details	References
Q9. Is there a platform in your country for post-marketing surveillance and adverse effects reporting?		
Canada	Yes	Post-market assessment of MNMs is mainly by ECCC under the Canadian Environmental and Protection Act, 1999 (CEPA, 1999) and by HC under Canadian Food and Drug Act and Consumer Product Safety Act. This ensures the protection of the environment and health of Canadians. Health Canada has a Canada Vigilance Adverse Reaction Online Database. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html https://www.canada.ca/en/health-canada/services/consumer-product-safety.html
France	Yes	Yes, also through the French declaration Sutdy of Adverse effects: see ANSES https://www.anses.fr/en
Germany (BfR)	NA	
Germany (UBA)	NO	
Norway	1: Norwegian Poison Information Centre 2: The Product Register is the official register of hazardous chemicals in Norway (see info in Q5) 3: Through EEA Norway follow the EU chemical regulations and enforcement of these.	1: https://helsenorge.no/Giftinformasjon/the-norwegian-poison-information-centre/poison-information 2: https://tema.miljodirektoratet.no/en/Areas-of-activity1/Chemicals/The-Product-Register/
Switzerland	Swiss Product register for chemicals	www.rpc.admin.ch
United States	Under the Toxic Substances Control Act the USEPA has requirements and a voluntary process for gathering data on adverse effects of chemicals in commerce which has included some nanomaterials.	Go to the section on substantial risk notifications for details on how and why this information is reported: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/data-development-and-information-collection-assess-risks
Thailand	YES	- Consumer Protection Board - Social Media

Delegation	Answers + Details	References
Q10. Are there any **governance models** in your country that incorporate 'responsible innovation', 'anticipatory governance' or 'regulatory preparedness' (or a similar concept by another name)?		
Canada	Yes	1). Innovation and Skill Plan of Government of Canada https://www.ic.gc.ca/eic/site/062.nsf/eng/h_00105.html#5 2). The Federal Sustainable Development Strategy (FSDS) 2019-2022 for responsible innovation and sustainable development. https://www.fsds-sfdd.ca/index.html#/en/goals/ Clean Growth Hub: https://www.ic.gc.ca/eic/site/099.nsf/eng/home
France	Precautionary principle – French law General principles for the prevention of risks	*" Lorsque la réalisation d'un dommage, bien qu'incertaine en l'état des connaissances scientifiques, pourrait affecter de manière grave et irréversible l'environnement, les autorités publiques veillent, par application du principe de précaution et dans leurs domaines d'attributions, à la mise en œuvre de procédures d'évaluation des risques et à l'adoption de mesures provisoires et proportionnées afin de parer à la réalisation du dommage. "* PGP : https://www.legifrance.gouv.fr/affichCodeArticle.do?idArticle=LEGIARTI000033019913&cidTexte=LEGITEXT000006072050&dateTexte=20160810
Germany (BfR)	No	-----
Germany (UBA)	YES	
Norway	1: The Norwegian government strategy on Nanotechnology Research and Development for the years 2012-2021 outlines that the main goal is that Responsible Nanotechnology shall give a substantial contribution to Norwegian business development and societal benefits. There are three main national priorities: 1, basic knowledge development. 2, Innovation and commercialisation and 3, responsible technology development.	1: https://www.regjeringen.no/contentassets/5aa4911bcb474c0da4f21d1dcbc47ecb/63867_nanostrategi_web.pdf https://www.forskningsradet.no/om-forskningsradet/programmer/nano2021/

Delegation	Answers + Details	References
	The Norwegian government has, through the Norwegian Research Council, prioritised a Research and Development program on Nanotechnology (NANO2021) which includes Responsible Research and Innovation (RRI) in Health. Projects must, among other things, describe relevant issues related to health, safety and work environment (OSH). This includes issues related to health risks by possible exposure to nanomaterials during the research work and regulations applicable to work with nanomaterials. 2: The Norwegian Labour Inspection Authority guides enterprises in safe handling of nanomaterials.	2: svartjenesten@arbeidstilsynet.no
Switzerland	NO	NO
United States	NO	NO
Thailand	YES	National Nanosafety and Ethic Strategic Plan 2017-2021 Promote awareness, push for policy initiative by regulators, and public access to information