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Nanotechnologies — Nanomaterial risk evaluation

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TECHNICAL REPORT

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Nanotechnologies — Nanomaterial risk evaluation

Nanotechnologies — Évaluation des risques associés aux nanomatériaux

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

In exceptional circumstances, when a technical committee has collected data of a different kind from that which is normally published as an International Standard ("state of the art", for example), it may decide by a simple majority vote of its participating members to publish a Technical Report. A Technical Report is entirely informative in nature and does not have to be reviewed until the data it provides are considered to be no longer valid or useful.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO/TR 13121 was prepared by Technical Committee ISO/TC 229, *Nanotechnologies*.

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Introduction

This Technical Report is intended for use in all countries, regardless of whether they have legal or regulatory schemes that address manufactured nanomaterials.

This Technical Report might be useful to those who believe that legal compliance alone is not sufficient for adequate product stewardship or risk management. Organizations should be aware of the regulatory requirements applicable to nanomaterials (and materials generally), and that implementing the process described in this Technical Report does not necessarily mean that the organization will be in compliance with all applicable legal requirements. This Technical Report is not a legal or regulatory compliance guidance document aimed at satisfying the specific legal or regulatory requirements of any particular jurisdiction. Such guidance should be sought from the appropriate regulatory authorities.

This Technical Report is intended primarily for organizations that manufacture or process nanomaterials, or manufacture, process or distribute products that contain manufactured nanomaterials. However, governmental authorities, professionals, and members of the public might also find this information useful.

NOTE This Technical Report is based on the Nano-Risk Framework, an approach created by the Environmental Defense Fund and DuPont. For further details, see http://www.nanoriskframework.org.

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Nanotechnologies — Nanomaterial risk evaluation

1 Scope

This Technical Report describes a process for identifying, evaluating, addressing, making decisions about, and communicating the potential risks of developing and using manufactured nanomaterials, in order to protect the health and safety of the public, consumers, workers and the environment.

While the overall product stewardship and risk management process set forth in this Technical Report is not unique to nanomaterials, it supplements recognized approaches by providing, where possible, a focus on information and issues specific to nanotechnologies. It offers guidance on the information needed to make sound risk evaluations and risk management decisions, as well as how to manage in the face of incomplete or uncertain information by using reasonable assumptions and appropriate risk management practices. Further, it includes methods to update assumptions, decisions, and practices as new information becomes available, and on how to communicate information and decisions to stakeholders.

This Technical Report suggests methods organizations can use to be transparent and accountable in how they manage nanomaterials. To that end, it describes a process of organizing, documenting, and communicating what information organizations have about nanomaterials. This includes acknowledging where information is incomplete, explaining how information gaps were addressed, and explaining the rationale behind the organization's risk management decisions and actions.

2 Symbols and abbreviated terms

ADME: Absorption, distribution, metabolism, and excretion

AIChE: American Institute of Chemical Engineers

BAF: Bioaccumulation factor

BCF: Bioconcentration factor

CAS: Chemical Abstract Service

CBI: Confidential business information

CNT: Carbon nanotube

COSHH: Control of Substances Hazardous to Health

CVD: Chemical vapour deposition

DEFRA: U.K. Department for Environment Food and Rural Affairs

EEC: European Economic Community

EHS: Environmental health and safety

EPA: U.S. Environmental Protection Agency

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GHS:	Globally Harmonized System of Classification and Labelling of Chemicals
HPV:	High production volume
HSE:	U.K. Health and Safety Executive
ILSI:	International Life Sciences Institute
ISO:	International Organization for Standardization
IUR:	Inventory Update Rule
LCA:	Lifecycle assessment
LOAEL:	Lowest observed adverse effect level
NAICS:	North American Industrial Classification System
NGO:	Non-governmental organization
NIOSH:	U.S. National Institute for Occupational Safety and Health
NCI-NCL:	U.S. National Cancer Institute's Nanotechnology Characterization Laboratory
nm:	Nanometer
NNI:	U.S. National Nanotechnology Initiative
NOM:	Natural organic matter
NPPTAC:	U.S. National Pollution Prevention and Toxics Advisory Committee
NTP:	U.S. National Toxicology Program
OECD:	Organization for Economic Co-operation and Development
OPPTS:	U.S. EPA Office of Pollution, Prevention, and Toxic Substances
OSHA:	U.S. Occupational Safety and Health Administration
R&D:	Research and development
REACH:	Registration, Evaluation, Authorisation and Restriction of Chemicals (EU)
ROS:	Reactive oxygen species
SETAC:	Society for Environmental Toxicology and Chemistry
SIDS:	Screening information data set
SME:	Small/medium enterprise
TiO_2:	Titanium dioxide
TSCA:	U.S. Toxic Substances Control Act
WHO:	World Health Organization

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3 Summary of the process described in this Technical Report

This Technical Report focuses on manufactured nanomaterials that might exhibit novel properties and consist of particles or physically discrete entities that, in their primary, non-aggregated form, are typically at or below 100 nanometers (nm) in one dimension (e.g. nanoplates), two dimensions (e.g. nanofibres), or three dimensions (e.g. nanoparticles). This process is focused primarily on manufactured nanomaterials as they are used in industrial, chemical, manufacturing, and consumer applications, and on the potential risks associated with releases of nanomaterials at some point in their lifecycles. Where a product, process or material contains manufactured nanomaterials, it might not be the nanomaterial component that poses the most significant risk. Accordingly, the focus in this Technical Report on nanomaterials is not intended to suggest that risk management be limited to the evaluation of the nanomaterial component of materials or products.

Step 1. Describe materials and applications

The first step is to identify and describe the manufactured nanomaterials being evaluated and their intended uses or functions (including potential benefits). The organization might also identify analogous materials (i.e. similar materials that are not in the nanoscale and applications) that might help address data gaps.

Step 2. Material profiles

The second step describes a process to develop three sets of “profiles” of (1) the manufactured nanomaterial's physical and chemical properties; (2) inherent environmental, health and safety hazards, and (3) potential human and environmental exposures throughout the nanomaterial's lifecycle. All three profiles work together; for example, exposure information might suggest which hazards are most important to investigate, or vice versa. Similarly, the nanomaterial's properties might suggest which hazard or exposure scenarios are most likely. The profiles of the nanomaterial's hazards and exposures might also include information about the material's potential to reduce hazards or exposures in comparison with the materials they are intended to replace.

The process of developing these profiles should also include identifying and prioritizing data gaps, and deciding how to address such gaps (e.g. by collecting additional data or, in the place of the missing data, using “reasonable worst case assumptions” or values).

Step 3. Evaluate risks

In this step, the information from the profiles is evaluated to identify and characterize the nature and magnitude of the risks (i.e. combination of hazards and exposure) presented by particular manufactured nanomaterials and their anticipated applications.

Step 4. Assess risk management options

Here, the organization evaluates how to manage the risks identified in Step 3 and recommends a course of action. Options might include materials substitution (e.g. using a safer material), product or process modifications, engineering controls, protective equipment, and risk communication.

Step 5. Decide, document, and act

In this step, appropriate to the product's stage of development, the organization decides whether or in what capacity to continue development and production of the nanomaterial (or the process or product using the nanomaterial). The organization documents those decisions and their rationale, and might share appropriate information with relevant stakeholders, both internal and external. The organization might decide that further information is needed and take action to gather it.

Step 6. Review and adapt

Through regularly scheduled reviews, as well as reviews triggered by specific events, the organization might update the risk evaluation, ensure that risk management systems are working as expected, and revise or improve those systems in response to new information (e.g. new hazard data) or new conditions (such as new or altered exposure patterns).

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Implementing the process

This process is intended to be implemented flexibly, and does not suggest a “one-size-fits-all” approach. Different organizations, depending on their size and structure, and the legal jurisdictions in which they operate, might have different ways of implementing this process or parts of this process. How it is implemented will depend in part on the organization's position in a nanomaterial's lifecycle. For example, organizations that develop and manufacture nanomaterials for sale as primary products in diverse applications might adopt a broader perspective than organizations that purchase specific nanomaterials for a narrow set of applications. Cooperation and timely information exchange between nanomaterials' suppliers and their customers will be important to effective risk identification and management.

Implementation will be influenced by the nature and degree of regulation of manufactured nanomaterials. While implementing this process does not necessarily ensure compliance with applicable laws, organizations should be aware of and comply with applicable legal requirements, and understand that such requirements might be frequently changing as nanotechnologies develop.

Organizations are encouraged to integrate the elements of this process into their existing product development, product stewardship or supply-chain management processes, occupational health and safety, or quality management (e.g. ISO 9001) or environmental management (e.g. ISO 14001) systems.

Recognizing that most organizations have limited resources, this process suggests approaches or assumptions that can be used to simplify implementation. For example, organizations might use “reasonable worst case scenarios” (e.g. assume that a material is hazardous and implement appropriate worker protection, risk management or engineering protocols), thus potentially decreasing the need (and cost) for generating new hazard or exposure information. Organizations are also encouraged to use existing information and seek information up and down the supply chain about the nature and intended uses of the nanomaterial(s).

Specific individual or individuals (e.g. a team or committee) in the organization should have the defined responsibility for the implementation of this process. In most cases, the responsible person(s) will be someone who already has responsibility for product development. Equally important is the input and participation from individuals who are involved in technical product development, business development and marketing, manufacturing, and legal compliance, frequently in “cross-functional” teams.

Ideally, the team will include professionals competent (whether by education, experience, or a combination of the two) in risk assessment, toxicology, environmental fate, occupational safety and industrial hygiene. However, many organizations might not have the resources to include such staff. It might be necessary to rely on publicly-available literature, engage appropriate outside experts (e.g. hiring consultants such as industrial hygienists or risk assessors, or partnering with university researchers), or participate in consortia to share resources and expertise (where allowed by applicable laws).

Organizations may also choose to include external stakeholders in some or all of the process of implementing the steps set forth in this Technical Report.

This process may be incorporated into or paired with an organization's management and compliance systems to ensure its execution. That system may be an existing product development or product-stewardship process, quality, environmental or occupational health and safety management system, or a new system. The key point is to ensure that responsible and accountable individuals should see to it that the implementation in fact occurs. Moreover, in keeping with the iterative nature of the process, these individuals should also ensure that it is revisited on a periodic and as-needed basis.

The Output Worksheet (Annex F) is meant to facilitate the collection, evaluation, management, and communication of data. The Worksheet provides a template for organizing all information collected during the process, capturing overall evaluations of that information, and recording management decisions on how to act on it. The Worksheet can also be used as the basis for sharing information and decisions with stakeholders[1)].

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1) Case studies using the Nano Risk Framework created by Environmental Defense Fund and DuPont can be found at http://www.nanoriskframework.org.

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4 Describe materials and applications

4.1 General

The first step is to describe the manufactured nanomaterial(s) and its intended uses[2]. Accurately describing nanomaterials is important, as changes in composition (e.g. surface coatings) might have a substantial effect on the biological behaviour of the materials. Accurate identification is also essential for comparing research results obtained with the same materials at various locations. This description should be sufficient to guide development of the more detailed profiles of the nanomaterial's properties, and its hazard and exposure potential, at various lifecycle stages such as manufacture, use (including maintenance and servicing) and end-of-life. This description should allow the organization's decision makers and interested stakeholders to become familiar with the material, how it might change over time or in different conditions, and its reasonably foreseeable applications.

Much of the information necessary for this step might already be in the possession of the developer, manufacturer or supplier of the nanomaterial, or be available in the literature. An end user might be able to obtain relevant information from its suppliers or the nanomaterial's developer[3]. The information obtained should be reviewed for accuracy and completeness (which might require the assistance of experts).

The lifecycle of a product system involving nanomaterials encompasses all the processes and activities that occur from initial extraction or creation of the material (or its precursors) from the earth to the point at which any of the nanomaterial's residuals are returned to the environment[4]. Organizations should consider both *established* and *reasonably anticipated* activities or processes to which the nanomaterial might be subject over its lifecycle (either intended or unintended).

A formalized lifecycle assessment (LCA) methodology of nanomaterial product systems is not necessary, nor the associated consideration of all material and energy inputs and outputs that LCA typically entails. Rather, the relevant processes and activities throughout the lifecycle of a nanomaterial (or its predecessor or successor materials) should be identified and evaluated to determine whether they carry the potential for the release of, or exposure to, the nanomaterial or any of its derivatives.

Because knowledge of each application might reside downstream of the primary nanomaterials producer, communication up and down the supply chain is necessary to understand the material's potential uses and end-of-life options.

The lifecycle profile helps identify the different organizations (typically, commercial entities) that might be involved in decisions about nanomaterials. While the material manufacturer typically decides on or influences activities (such as workplace-safety practices) “within its four walls,” such decisions can profoundly affect the options available to the other actors in the supply chain. For instance, a decision to use a toxic heavy metal in a product might ultimately compromise the safety of, or limit the disposal or recycling options for that product at the end of its service life.

Organizations' place in the life cycle will affect the breadth and depth of their analyses. A developer and manufacturer of a nanomaterial intended for a potentially broad range of uses should typically undertake a comprehensive and wide-ranging analysis. On the other hand, an end-user that is planning on purchasing a single nanomaterial for use in a single product aimed at a narrow market might conduct a much more focused analysis.

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2) The development and use of nanomaterials can arise in the context of the creation of new products, or the enhancement of or modifications to existing products. Accordingly, the process described in this Technical Report is not limited to new product development.

3) The expectation that this information will generally already be in the possession of the developers is shared by some regulatory agencies. See: National Pollution Prevention and Toxics Advisory Committee [NPPTAC], A Federal Advisory Committee to the U.S. Environmental Protection Agency. Overview Document on Nanoscale Materials, November 22, 2005; Consultation on a Proposed Voluntary Reporting Scheme for Engineered Nanoscale Materials, United Kingdom Department for Environment Food and Rural Affairs [DEFRA], March 2006.

4) ISO 14040 and ISO 14044 provide detailed guidance on LCA.

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4.2 Materials descriptions

The physical and chemical description of the manufactured nanomaterial should include chemical composition (including impurities), surface composition, physical structure, physical form, concentration, size (or surface area) distribution, solubility, and aggregation and agglomeration state. An organization should also identify the nanomaterial's sources and the manufacturing processes in which the organization uses (or plans to use) the nanomaterial, and review the literature on its known relevant uses. More guidance on identifying the physical properties of nanomaterials is provided in Clause 6 of this Technical Report.

4.3 Materials sourcing

Describe the source of the inputs used to manufacture the nanomaterials (if you are a developer or manufacturer) or the source of the nanomaterials (if you are a processor or end-user). This includes transport from points of acquisition to the point of processing or use. This information is relevant for determining whether there is potential exposure to nanomaterials at these stages, or if the specific sources of the starting materials influence the composition, properties, or behaviour of the resulting nanomaterial (e.g. by affecting the extent of impurities). Relevant reference materials[5)] should also be identified, as well as “incumbent materials” that might be replaced by the nanomaterial, and bulk counterparts (that is, larger, non-nanoscale materials with the same chemical composition as the nanomaterial).

4.4 Manufacturing

Three substages, materials manufacture, product fabrication, and packaging, are typically involved in the transformation of source materials into a nanomaterial to be delivered to end-users. The degree of detail and relevance of each of these descriptions will depend in part on the evaluating organization's stage in the life cycle.

1) *Materials Manufacture*. Describe the activities involved in converting a source material into a form that can be used to fabricate a finished product. The production of intermediate chemicals or materials is normally included in this category, as is their transport. For example, carbon nanotubes (CNTs) can be produced by several techniques, including arc discharge, laser ablation, chemical vapour deposition (CVD), or high-pressure carbon monoxide (HiPco), each of which can produce nanomaterials with particular characteristics. Since each process can yield a distinct combination of products, it is important that their associated processes, the differences between them, and the differences between the resulting products, be identified.

2) *Product Fabrication.* Describe the use or processing of manufactured nanomaterials to create a product. That product might be an intermediate or component of a larger product, a product intended for industrial or commercial uses, or a consumer product. For example, purification of CNTs, their incorporation into matrices (e.g. to form a polymer nanocomposite), and their preparation for final or intermediate use (e.g. by means of grinding and smoothing operations), or incorporating nanomaterials into a coating, would all be activities in this substage of the lifecycle profile.

3) *Packaging.* Describe the processes that package an intermediate or finished product. Although these activities might change the location or physical configuration of a product, they do not involve a transformation of materials. Packaging CNT-containing polymer pellets for distribution to automotive-parts producers, for example, or packaging molded parts for distribution to end-product manufacturers (or to retail or repair facilities), would be included in this substage.

4.5 Distribution

Describe the transportation modes (e.g. truck, rail, air, marine) that are used throughout the product or service system to deliver a manufactured nanomaterial(s) (or a product containing the nanomaterial(s)) to users (e.g. industrial, commercial, retail, or direct to consumer, such as through internet sales).

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5) In ISO Guide 30:1992, reference materials are defined as follows: “Material or substance, one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials.”

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4.6 Use/reuse/maintenance

Describe the intended or reasonably likely uses of the manufactured nanomaterial(s) (or the product containing the nanomaterial(s)) relevant to the organization conducting the evaluation. The reasonably anticipated conditions of use will differ among industrial, professional or consumer uses. For example, the conditions of use in the pharmaceutical or medical device sectors are likely to be more highly controlled than consumer uses. The description of the use may include the improved product performance characteristics that are anticipated to be related to the use or incorporation of nanomaterial(s) (e.g. improved strength/weight ratio, increased efficiency or efficacy, etc.). The description should also take into account activities such as storage, wear and tear, weathering and other conditions of degradation or failure, maintenance, repair, and replacement.

4.7 End of life/recycle/waste management

This describes what occurs after the product or nanomaterial as served its intended purpose and will enter either a new product system (through reuse or recycling) or its end-of-life (through the waste-management system). Post-use possibilities such as recycling, composting, landfills, disposal through wastewater systems (for example, down-the-drain disposal of a personal care product containing nanomaterials), and incineration, and associated distribution, should be considered. If recycling or re-use is a reasonably anticipated option, consideration should be given to whether the “new” uses will be different from the originally anticipated uses.

4.8 Questions to ask regarding the nanomaterial

The following questions and suggestions should help to guide the creation of the basic descriptions of the nanomaterial and its applications (noting that each question might not be relevant to every organization):

4.8.1 Questions to ask regarding the description of nanomaterials

— What is the stage of development (lab scale, pilot, demonstration, commercial, etc.) of this nanomaterial?

— Briefly describe the source of the nanomaterial. Is it manufactured in-house or purchased?

— If purchased, who produces the nanomaterial?

— How is the nanomaterial manufactured?

— How and in what form is it transported to your facility(ies)?

— Is there a larger-sized, or bulk, version of this nanomaterial in commerce?

— What other nanomaterials exist that are similar to this one?

— How long has this nanomaterial, or a similar nanomaterial, been in commerce?

— What are sources of additional information on this nanomaterial?

4.8.2 Questions to ask regarding the description of applications

— What are the known or intended uses of the nanomaterial based on a literature review?

— What are the expected or intended applications of this nanomaterial, (noting especially differences from the uses of incumbent and non-nanomaterial forms of the material).

— Are these uses new compared to any that are already represented in the literature?

— Why is the material being manufactured and used in the nanoscale range, as opposed to other sizes?

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— How will you (and your employees or contractors) be handling, using or processing the nanomaterial?

— How will the nanomaterial be handled when received by downstream processors? By end- users?

— In what form will the nanomaterials be present in final products?

— Will the nanomaterials be agglomerated or bound in a matrix in the final product? If so, describe.

— Will the nanomaterial be used by a large number of downstream users? In what form will it be when it is so used?

— How much of the nanomaterial will be present in the intended products? What types and sizes?

— What volume of nanomaterials will be used on an annual basis?

— What new or different application benefits does this nanomaterial offer compared to existing alternatives for the same application?

— What are the other potential applications of this nanomaterial?

— Are there applications for this nanomaterial that intentionally will not be pursued?

— How will the nanomaterials or products be handled and disposed of, post-use?

5 Profiles of the nanomaterials' properties, hazards and exposures

5.1 General

5.1.1 Introduction

This part of the process includes describing the nanomaterial's physical and chemical properties, its inherent hazards, and the exposures associated with its lifecycle. This introduction provides an overview about the data sets associated with these profiles, and what steps can be taken when one does not have all of the desired data. The accurate and complete identification of the manufactured nanomaterials (see Clause 5) is essential to the accuracy of these profiles.

5.1.2 The use of data sets

“Data sets” have been outlined for each of the three main categories of information -physical/chemical properties, hazard, and exposure potential (see Annexes A, C and E for more detailed information on the data sets). Data sets collect those types of data that are deemed by technical professionals to be necessary for the adequate characterization and use of chemicals[6)]. The data sets serve as a reference point for the type and amount of information that should be addressed by the time of a product's commercial launch, and can be used for screening purposes in early stages of product development.

To the extent that there are national or regional legal requirements applicable to the data that must be developed and submitted if a nanomaterial is to be placed on the market or distributed in commerce, those requirements must be met.

6) Data sets are used in other programs that promote or require hazard-data development for chemicals, such as the screening information data set (SIDS) program of the Organization for Economic Co-operation and Development (OECD). Annex G describes some of the sources from which the data sets in this Technical Report were derived.

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The data sets are not meant to represent a comprehensive assessment or full toxicological profile of a given nanomaterial. Rather, they are designed to cover the kinds of data that might be required to provide a reasonable balance between an adequate characterization of properties, hazards, and exposure, and a practical strategy for the development of nanomaterials. The strategies outlined in Annexes A to E represent several current approaches for achieving those goals.

It might not be necessary in every case to generate all of the data called for in the data sets. For example, where data are sufficient to rule out a particular route of exposure, the user will not likely pursue hazard evaluations specific to that route. Similarly, one might elect not to pursue certain elements of the data set, or one might need to develop more information than is called for in the data set, depending on the expected uses of a nanomaterial or its stage of development.

These data sets are expected to be dynamic; that is, they will need to be revised as more information is developed or published on nanomaterials' risks and as other efforts to refine appropriate risk-assessment and risk-management approaches are developed or made public.

5.1.3 Use of default values and assumptions

Developing the data sets will typically begin with a survey of existing literature to obtain the characterization, hazard and exposure data necessary for an adequate assessment of risk. However, there might be “gaps” in the literature such that the data sets cannot be completed. It might not be feasible or appropriate, especially at the early stages of product development, to perform new tests on nanomaterials in order to complete the data sets. In these situations, the literature-based data might nonetheless be sufficient to allow initial decisions to be made based on sound (and documented) expert judgment. Where the literature does not support such judgments, one can use “reasonable worst-case” default values or assumptions in the absence of testing and a complete data set, and before commercialization.

“Reasonable worst-case” default *assumptions* can be useful in the absence of complete data, as they allow a risk characterization or a preliminary assessment to be conducted for estimating, in a reasonable worst case, the risks that a nanomaterial might pose. For example, if no data exist on the fate of a nanomaterial discharged to a sewage treatment plant, one could assume that none or very little of the nanomaterial is degraded and most of it is discharged in effluent. That is, the environment gets the full dose. Such assumptions are sometimes used by regulatory agencies as inputs to exposure models when measured data are unavailable[7)]. The more data or information on analogous situations is available, the more one can adjust assumptions from a “reasonable worst case” to less conservative assumptions. The factual and analytical predicates for any such assumptions should be transparently described. Further, reasonable worst case scenarios generally do not include speculative or highly improbably assumptions.

“Reasonable worst-case” default *values* can be derived from several sources, such as data available on analogous bulk toxic materials (i.e. non-nanoscale materials that have the same or similar chemical structure as the subject nanomaterial) or non-manufactured nanoparticles. For example, one could manage a nanomaterial as if it were as toxic as a related toxic bulk material for which the toxicity is well understood[8)]. It might also be possible to “bridge” or “read across” from data that exists for a similar material (discussed below). If there are no data on the related bulk materials, reasonable worst-case values might come from assignment to the highest-level tier in an existing classification system. For example, one could manage a nanomaterial as if it possessed characteristics of reproductive toxicity sufficient to classify it as a Category 1 substance (known or presumed human reproductive or developmental toxicant) under the UN's Globally Harmonized System for Classification and Labeling[9)].

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7) See, e.g. U.S. EPA's New Chemicals Program homepage, http://www.epa.gov/oppt/newchems/index.htm.

8) The nano-scale form of a bulk material may exhibit different properties and thus different hazards than are present in the bulk material. One should not assume, for example, that the nano-scale form of a non-toxic bulk product will not be toxic.

9) United Nations, Globally Harmonized System of Classification and Labelling of Chemicals (GHS), 2005, http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html.

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It is not intended that default values and assumptions be taken as characterizations of the actual toxicity or exposure to a nanomaterial or even to indicate any presumption of toxicity or exposure potential (or lack thereof). Rather, they are meant to allow an assessment to be conducted even in the absence of such data and experience. As new data and experience with nanomaterials accumulate, these values or assumptions can be updated or supplanted with more specific information.

While it is expected that, in general, a full set of data will be used to assess potential lifecycle risks by the time of commercial launch, some organizations could by choice or necessity not generate the recommended data. In this case, default values and assumptions (or values or assumptions based on transparently-described data or information from analogous situations) should provide a margin of safety to workers and other potentially exposed populations and environments. As additional data are generated, risk-management decisions more specific to the nanomaterials being commercialized might be possible.

It is important, however, that in cases in which an organization has relied on assumptions rather than data to develop risk evaluations and to drive risk management decisions and practices, the organization should clearly describe why they were made, and why the organization believes them to be reasonable. This is information that may be shared with key stakeholders.

5.1.4 Evaluating data quality

Evaluating, documenting, and communicating the quality, sufficiency, and uncertainty of data are integral parts of the decision-making process[10]. Basing decisions on scientifically sound and defensible information, identifying uncertainty, and maximizing transparency increases the integrity and credibility of the process. An assessment of the degree of confidence in the data should be made and carried along with the data themselves. A method that has been used internationally is the Klimisch score for evaluating the validity of data[11]. However, this approach does not fully take into account the characterization of nanomaterials as part of the study design of a toxicity study. Where additional data will likely be needed to complete the risk evaluation, that fact should be noted, as should the intention that as additional data become available, the assessment will be updated.

5.2 Develop physical/chemical properties profile

This part of the process identifies and characterizes the nanomaterial's physical and chemical properties, including property changes, throughout the lifecycle identified in the first step of the process. This knowledge is critical to the correct handling of the nanomaterial, anticipating its behaviour when interacting with its surroundings, and to assessing the ultimate fate and behaviour of the nanomaterial in the environment.

The nature of the nanomaterial must be understood not only in the “free form” but also, appropriate to the stage of development, its characteristics after subsequent aggregation, processing, incorporation with or into other materials, during use (including maintenance and servicing), ultimate fate, potential reuse/recycling, or release (during or after its service life) in the form of waste. The extent of variations in the properties, including those resulting from differences in manufacturing, processing, and specific applications, should also be noted. Similarly, the properties of the nanomaterial should be compared to those of the corresponding non-nanomaterial forms of the material, where appropriate, to determine the nature and extent to which the properties are different.

Any anticipated changes in relevant physical and chemical properties across the lifecycle of the nanomaterial should be noted. For these reasons, it might be necessary to characterize the nanomaterial at multiple points of the life cycle, unless there is good reason to expect that the nanomaterial will remain unchanged.

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10) U.S. EPA has developed guidelines and provides training to facilitate the evaluation of data quality. EPA 2006. Quality Management Tools — Data Quality Assessment, http://www.epa.gov/quality/dqa.html.

11) Klimisch HJ, Andreae E and Tillmann U (1997). A systematic approach for evaluating the quality of experimental and ecotoxicological data. Reg.Tox. and Pharm. 25:1-5. The “Klimisch score” was developed as a scoring system for data reliability, particularly for ecotoxicity and health studies. See Chapter 3 (data evaluation) of the OECD Manual For Investigation Of HPV Chemicals (2009).

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Any physical and chemical properties from the data-set list (see Annex A) that remain unknown, as well as any additional physical and chemical properties that the organization deems important, should be highlighted and documented for further investigation. The order of collection of the missing data should then be prioritized, test methods defined, and testing completed as needed. Data on physical and chemical properties beyond the data set need only be gathered if they are deemed relevant to determining the fate, behaviour, hazard, or exposure potential, and subsequently to determining the risks, associated with the nanomaterial or nanomaterial-containing product. Any decision that filling in the gaps on particular physical or chemical properties in the data set is not necessary should be explained and documented.

5.3 Develop hazard profile

5.3.1 Introduction

In this step, information is gathered and integrated into a hazard profile that characterizes the nanomaterial's potential intrinsic health, environmental, and safety hazards over the entire lifecycle. As part of this procedure, the needs for additional data are determined and prioritized, and actions are taken to fill those data needs or to develop default assumptions. Two approaches to collecting health hazard data are presented in Annexes B and C. Environmental hazard and fate data sets are described in Annexes D and E.

Maximizing the quality and completeness of the hazard profile is fundamental to considering an application's risks. Of course, certain intrinsic hazard endpoints might be relevant to only specific routes of exposure. If particular routes of exposure are not reasonably likely to occur based upon an evaluation of a nanomaterial's life cycle, then the hazards associated with such a route of exposure become less relevant. Therefore, there is an iterative relationship between the hazard and exposure analyses. For example, information that there might be significant occupational or public exposures to “free” nanomaterials should be taken into account in planning the hazard evaluation.

Scientifically valid hazard data might not always be available for a particular nanomaterial. Therefore professional judgment might be needed in order to conduct realistic evaluations of the potential hazards. End users of nanomaterials should request relevant hazard data from their suppliers. Manufacturers and suppliers should take steps to obtain that hazard data and provide it to end users

If suppliers are not able to provide such information, end users should seek alternative suppliers who can provide that information, undertake to collect the information on their own or, if they elect to use the nanomaterial without relevant hazard information, should take a precautionary approach to handling it.

The organization may also choose to develop a “matching set” of health and environmental hazard data for any “incumbent” materials that the nanomaterials might be replacing. This information would be relevant to the risk evaluation and risk management steps (i.e. decision makers and interested stakeholders might consider relevant the relative hazards of the target nanomaterials and the materials that might be replaced).

5.3.2 Testing issues

At this time, a number of *in vivo* and *in vitro* methods have been used to evaluate the toxicity of manufactured nanomaterials, but most have not been validated for this purpose. Many stakeholders wish to reduce dependence on mammalian toxicity testing and develop reliable, reproducible and predictive tests using *in vitro* assays and tests involving lower-order animals. Organizations are encouraged to use preferentially alternative validated toxicity testing methods that avoid the use of animals as, over time, these methods are further tested and developed and their performance characteristics proven to be useful.

“Tiered” or “phased” testing organizes groups of tests according to increasing levels of complexity, specificity, and expense. *See* Annex B. Ideally, the initial tiers of testing should have a very high ability to predict toxicity in humans and ecosystems, with subsequent, more resource-intensive tiers employed only to confirm positive results or determine mechanisms or other aspects of toxicity needed to eliminate, reduce or manage toxic risks.

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The current ability of *in vitro* tests to screen for potential toxicity of nanomaterials with a high degree of predictive accuracy is limited, and the accuracy of *in vivo* tests for these purposes is also limited. An integrated testing system comprised of both *in vitro* and *in vivo* test systems is suggested, with initial tiers of *in vitro* tests used to provide preliminary insights into potential toxicity rather than definitive assurance of the presence or absence of toxic hazards[12]. This allows developers to align hazard testing strategies with product development.

At early stages of product development, organizations might only conduct early phase testing – simpler, faster, and cheaper screening tests that might identify nanomaterials with greater probability for toxicity or other risks. This early screening data, combined with early assessment of the technical and business prospects for the nanomaterial or product being developed, can help inform decisions on whether and how to continue product development. Where early phase screening tests suggest likely significant toxicity or other hazards, organizations are encouraged to seek ways to “engineer out” the risks through changes in the material or the way it will be used.

As a nanomaterial or product gets closer to market launch, organizations should apply the more complex and specific tests (which are usually more expensive) of later tiers or phases to more precisely assess the potential hazards a nanomaterial or product might present. By the time a product or nanomaterial reaches commercial launch, the information from all tiers or phases should have been addressed.

Different organizations may choose different timing and triggers to move from one tier of testing to another, but the tiers described below can be applied to the typical stages of product development. For example, an organization might apply Tier 1 testing during the research and development stage, move to Tier 2 testing if and when the nanomaterial or product moves to a prototype stage, apply Tier 3 testing as they prepare for test marketing, and complete Tier 4 as they move to manufacturing scale-up prior to commercial launch.

In some cases, uncertain results from one Tier of tests might result in a decision to use higher stage tests earlier than planned to resolve the uncertainties. In any case, the data sets and tiered test plans that are relevant to the organization's planned activities should be addressed (either through data, sound professional decisions based on existing literature, “reasonable worst case” values or assumptions where there are significant data gaps, or controls) by the time of product launch so that the user can make reasonably sound conclusions about potential risks.

5.3.3 Use of “bridging information”

When an organization has limited specific hazard data for a nanomaterial, one way to evaluate that nanomaterial is to extrapolate or “bridge” (or “read across”) to another nanomaterial for which there exists robust hazard data for a specific type of endpoint of interest (e.g. pulmonary toxicity). The two nanomaterials may be entered into a toxicological evaluation, with the well-characterized nanomaterial serving as a “reference” for the nanomaterial of interest for which limited data exists. In most cases, the test that was conducted was a shorter, simpler test than what would be needed for a more thorough understanding of the specific type of toxicity endpoint under consideration for the nanomaterial of interest[13].

Rigorous guidance on multi-factor approaches to bridging, or “read across”, for conventional chemicals, have been developed by OECD and various regulatory agencies[14]. The strength of the bridging strategy is dependent on a number of factors, including: robust data on the “reference” nanomaterial from more thorough

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12) Oberdorster et al, “Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy,” Particle and Fibre Toxicology, October 2005, http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1260029; Warheit, David B., Borm, Paul J. A., Hennes, Christa & Lademann, Jürgen (2007). Testing Strategies to Establish the Safety of Nanomaterials: Conclusions of an ECETOC Workshop. Inhalation Toxicology, 19 (8), 631-643. Retrieved March 20, 2009, from http://www.informaworld.com/10.1080/08958370701353080.

13) An example would be bridging from markers of pulmonary inflammation in a short-term test to pulmonary fibrosis on a chronic assay.

14) OECD: http://appli1.oecd.org/olis/2007doc.nsf/linkto/env-jm-mono(2007)28. U.S. EPA has also done extensive work on this topic. http://www.epa.gov/chemrtk/pubs/general/categuid.htm.

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toxicity tests, and evidence that supports the relevance of the “reference” nanomaterial to the new nanomaterial, particularly with respect to its potential mechanisms of toxicity. Where such relevance can be established, bridging studies might provide useful insights into the new nanomaterial's relative ability to cause a particular type of hazard through mechanisms shared with the well characterized “reference” nanomaterial[15)]. Bridging and read-across criteria for nanomaterials have not yet been developed. However, the physical and chemical characteristics of nanomaterials will play an important role in developing such criteria. When conducting read-across, the user should determine that the “reference” or “surrogate” nanomaterial has as many of the properties of size, size distribution, crystallinity, surface reactivity, etc. in common with the nanomaterial of interest as possible.

The results of bridging are not as reliable as actually performing thorough toxicity and epidemiological studies on the nanomaterial of interest, and it might not be possible at this time to bridge across endpoints and different mechanisms for nanomaterials. Nevertheless, appropriate bridging studies might provide a preliminary screen when evaluating the same or closely related toxicological effects for a newly developed nanomaterial or when making small modifications to an existing nanomaterial.

Nanomaterials pose unique challenges compared to conducting read-across for conventional chemicals. For example, similarity of two conventional materials' chemical structures alone is considered by some to be a sufficient basis for read-across. But the properties and potential hazards of nanomaterials are frequently assumed to be related to other factors besides chemical structure (i.e. the unique properties of nanomaterials are frequently size-dependent, rather than dependent on chemical structure). Hence, a more conservative approach to read-across for nanomaterials is recommended[16)].

5.3.4 The process of creating the hazard profile

For each lifecycle stage, as appropriate to stage of development:

— *Use existing data.* An initial literature review on the usual, non-nanomaterial form of the manufactured nanomaterial, as well as on any variations or impurities that arise as a result of sourcing, industrial processing, or environmental/biological transformation, is performed. Existing data should be evaluated using a “weight-of-evidence” approach, along with exposure information, to determine whether additional information is needed for making a hazard assessment.

— *Prioritize data needs*. Where data needs (i.e. gaps) are identified, determine (and explain) how best to address them. For example, information from the physical/chemical properties profile and exposure profile might be useful in prioritizing data gaps in the hazard profile. Key considerations include the most likely modes of release and routes of exposure, the nature of the nanomaterial expected to be released or to which exposure might occur, the expected magnitude of release or exposure (e.g. number of exposed individuals, spatial and temporal extent), as well as the resources needed (and available) for testing the product. All decisions on data needs, the justifications for those decisions, and the means used to compensate for missing data elements should be documented in the Output Worksheet. In some jurisdictions, there are mandatory data sets established by law for the registration of chemical substances, including nanomaterials.

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15) This strategy has been used in studies where toxicity assessments for a new ultrafine TiO_2 particle were conducted and compared to toxicity assessments for two other types of TiO_2 and a control. See Warheit DB, Webb TR, Reed KL, Frerichs S, and Sayes CM. “Pulmonary toxicity study in rats with three forms of ultrafine-TiO_2 particles: Differential responses related to surface properties.” Toxicology 230: 90-104, 2007, Nov 10, 2006.

16) First, read-across should be limited to identical or closely related endpoints. Second, it should only be applied when there are data available for the nanomaterial of concern from a short-term or mechanistic test for a given endpoint, and those data indicate that it responds similarly to a well-characterized substance subject to the same test. In these cases, bridging may appropriately be used to predict that the nanomaterial would also respond similarly to the way the well-characterized substance performed in a related, but more robust test. As more data is generated regarding specific nanomaterials, the use of read-across could potentially be expanded. For more information on the use and limitations of read-across strategies, see “Practical Guide 6: How To Report Read-Across and Categories, (ECHA 2009).

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