SRI LANKA STANDARD 12002:2012
ISO/TR 13121:2011

NANOTECHNOLOGIES – NANOMATERIAL RISK EVALUATION

SRI LANKA STANDARDS INSTITUTION

Sri Lanka Standard
NANOTECHNOLOGIES – NANOMATERIAL RISK EVALUATION

SLS 12002:2012
ISO /TR 13121:2011

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This standard does not purport to include all the necessary provisions of a contract.

Sri Lanka Standard
NANOTECHNOLOGIES – NANOMATERIAL RISK EVALUATION

NATIONAL FOREWORD

This standard was approved by the National Mirror Committee on Nanotechnology and authorized for adoption and publication as a Sri Lanka Standard by the Council of the Sri Lanka Standards Institution on 2012.01.22.

This Sri Lanka Standard is identical with **ISO/TR 13121:2011** Nanotechnologies – Nanomaterial risk evaluation, published by the International Organization for Standardization (ISO).

TERMINOLOGY AND CONVENTIONS

The text of the International Standard has been accepted as suitable for publication, without any deviation as a Sri Lanka Standard. However, certain terminology and conventions are not identical with those used in Sri Lanka Standards. Attention is therefore drawn to the following:

a) Wherever the words “International Standard” appear referring to this standard they should be interpreted as “Sri Lanka Standard”.

b) The comma has been used throughout as a decimal marker. In Sri Lanka Standards, it is the current practice to use a full point on the baseline as the decimal marker.

Wherever page numbers are quoted, they are “ISO” page numbers.

CROSS REFERENCES

Corresponding Sri Lanka standards for International Standards listed under references in **ISO /TR 13121:2011** are not available.

SLS 12002 : 2012

TECHNICAL REPORT

ISO/TR 13121

First edition
2011-05-15

Nanotechnologies — Nanomaterial risk evaluation

Nanotechnologies — Évaluation des risques associés aux nanomatériaux

Reference number
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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*.

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.

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

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

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).

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)].

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

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.

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.”

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?

— 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.

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.

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).

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.

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.

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).

— *Define protocols and conduct appropriate testing*. Once existing information has been reviewed and data gaps have been identified, specific test protocols needed to complete the hazard profile should be selected. Possible sources for test protocols include those listed by International Life Sciences Institute[17)] and by the U.S. National Cancer Institute[18)]. Two possible approaches to developing these data sets are contained in Annexes B and C. All such data generated and resulting decisions, as well as their justifications, should be documented in the Output Worksheet.

— *Characterize hazard.* Information based on existing literature is combined with any new data generated and entered into the Output Worksheet. A profile of the known hazard information on the nanomaterial, including comparisons to reference, bulk, and incumbent materials, is then generated. Ultimately, the key product of this step should be a formal hazard characterization, available by the time of commercial launch. Even then, the profile will not be truly final; it might have to be updated thereafter as new information warrants.

5.4 Develop exposure profile

5.4.1 Introduction

This step identifies and characterizes the potential for human and environmental exposures across the full lifecycle of the product system involving the subject manufactured nanomaterials. As noted above, this information is not only important to the ultimate evaluation and management of risk, it is also an important input to designing the hazard evaluation process, reflecting the iterative nature of the process described in this Technical Report.

Potential exposures might occur in two ways: when an opportunity arises for an organism to come into direct contact with a nanomaterial, or when a nanomaterial is released into a medium (e.g. air, water, soil, sediment) or used in a product that might lead to such contact. Exposure may be followed by actual entry into the organism via intake (inhalation or ingestion) or uptake (dermal penetration or absorption though other exposed tissue, such as the eye).

Regarding consumer usage, the nature of the nanomaterial-based product may lead to various routes of exposure. For example, if the nanomaterial is a component in a spray-product formulation, release from the spray can cause emissions into the ambient air and subsequent inhalation into the lungs or dermal penetration through the skin. To provide another example, if the nanomaterial is ultimately intended to go down the drain, e.g. it is part of a cleaning product, water might be the primary medium for exposure and dermal penetration and ingestion is possible. Ingestion might occur directly, through contact with the water into which the product has been discharged, or even by eating food that has been in contact with the water. Furthermore, direct contact with residuals (left after the cleaning product is used) is a potential route of exposure.

Organizations should take into account how the nanomaterial is incorporated into their product, since that might affect whether, how and the nature of any nanomaterials that have the potential to be released. For example, a nanomaterial may be part of a coating such that exposure potentials are limited (e.g. to releases from weathering, grinding). Further, the use of nanotechnology or nanomaterials in the manufacture of a product does not necessarily mean that the final product contains nanomaterials.

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17) 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.

18) See Assay Cascade of the Nanomaterial Characterization Laboratory of the National Cancer Institute (http://ncl.cancer.gov/working_assay-cascade.asp).

5.4.2 The process of developing the exposure profile

5.4.2.1 Overview

For each lifecycle stage, as appropriate to phase of development and the planned activities of the organization:

— *Assess the potential for releases of manufactured nanomaterials.* All known or reasonably anticipated processes or uses involving the nanomaterial or nanomaterial-containing product should be evaluated for the potential to cause exposure from direct contact or releases to the environment.

Because risk management and control measures affect exposure during manufacturing, answers to the following questions should be obtained when developing an exposure profile at the occupational level:

— What are the routes or opportunities for occupational exposure to nanomaterials?

— What engineering controls (e.g. dust collection, containment) are in place and how are they performing?

— What personal protection equipment (e.g. specific filter cartridge, glove type) is in use?

— What procedures (including housekeeping, decontamination of spills or releases, changing of filter systems, recycling, waste management and disposal methods) are in place to minimize exposure?

— How effective are the engineering controls and protection equipment with regard to the particular nanomaterial under consideration?

For both human and environmental exposures, the mechanisms of potential exposure should be identified. For example, are there potential exposures to nanomaterials associated with the intended use of the material or product, will exposures only be likely in servicing or repair situations (e.g. grinding, drilling, welding), or are there specific end-of-life scenarios that might create exposures (e.g. exposure to acidic liquids in a landfill, causing nanoscale materials to leach into groundwater)? Further, nature of the nanoscale materials that might be released in any particular scenario is also relevant.

Each medium into which a release is expected to occur should be “mapped.” That is, all known fates (e.g. transformations or transfers to other media) are identified. In this way, it is possible to determine what is not known about pathways, routes of exposure, dose, and other relevant factors. Acquiring information proceeds along two lines: human-exposure and environmental-exposure potentials (though the two can be related). The following types of questions should be considered when assessing potential for human exposure:

— What are the potential routes of human exposure (e.g. inhalation, ingestion, and eye or dermal penetration)? What mechanisms or activities might cause releases that could result in exposure?

— Are nanomaterials present in a consumer product? If yes, in what form are they present? Under conditions of intended or reasonably anticipated use, what are the potential routes of exposure (if any)?

— If nanomaterials are released to water, what is the use of the water (e.g. recreational, drinking, agricultural)?

— Can the nanomaterials be present in the ambient air or surfaces of the workplace, home, and other locations where people could be exposed? How?

— What sensitive populations (e.g. children, elderly persons) could be exposed? Under what conditions?

When investigating environmental-exposure potential, consider these questions:

- What are the potential routes of entry into the environment (e.g. air, water, soil, sediment, and biota)? Under what conditions might the nanoscale materials enter the environment?
- How does the nanomaterial partition in the environment (that is, how does it distribute itself between air, water, soil, sediment, and biota)?
- What are the potential exposure pathways?
- Does the nanomaterial degrade or transform in the environment? How? Where?
- What is the ultimate environmental fate of the nanomaterial and does it accumulate in particular "environmental sinks"?
- Will the nanomaterial persist in the environment in a bioavailable form?
- Based on the above environmental-fate information, what are the populations (e.g. avian, aquatic, benthic, or terrestrial species) that might be exposed? How?
- What is the bioaccumulation potential?
- What is not known about the nanomaterial's environmental fate and how could such unknowns best be addressed?

— *Prioritize data needs.* Where data gaps exist, determine how best to address them. 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), and the resources needed for testing the product. Depending upon the situation, it might be possible to exclude certain exposure pathways. All decisions on data needs, the justifications for those decisions, and the means used to compensate for missing data elements should be documented and recorded in the Output Worksheet (see Annex F).

— *Develop and implement a plan to address data needs.* After reviewing the questions described above and identifying and prioritizing the critical unknowns, a plan should be developed to fill the data gaps (or explain why data gaps are not or do not need to be filled, and how they are being otherwise addressed in lieu of data). The information sources, technical experts, and budgetary resources for meeting the most critical data needs first should be identified.

— *Characterize exposure*. The primary output from this step is an exposure characterization (a summary and synthesis of the gathered exposure information) available by the time of commercial launch and updated thereafter as changes in use or exposure information warrant. The exposure characterization includes:

- A statement of purpose, scope, level of detail, and the approach used in the assessment, including key assumptions.
- Estimates of exposure and dose by pathway, both for individuals and populations
- Evaluation of the overall quality of the assessment and the degree of confidence in the exposure estimates and conclusions drawn

5.4.2.2 Guidance on obtaining exposure information

— **Manufacturing**

  — Number and locations of manufacturing sites.

  — Current and expected annual production volumes of nanomaterials.

  — Industrial functions (e.g. adhesive, coloring agent) of the nanomaterial.

  — Stage of development (e.g. R&D, pilot scale, commercial scale).

  — Percentages of production volume for each planned industrial function of the nanomaterial.

  — Physical form(s) of the nanomaterial as it leaves the organization's possession, along with the associated percentage of production volume.

  — Maximum concentration of the nanomaterial in each industrial function as it leaves the organization's possession.

  — Description of manufacturing methods.

  — Number of employees working with the nanomaterial at the site of manufacture or import.

  — Types of employees, handling practices, and occupational and environmental containment and control equipment used to mitigate exposure potential.

— **Processing**

  — Description(s) of industrial processing or use operations involving nanomaterials at downstream sites.

  — Approximate number of processing and commercial-use sites.

  — The functions of the nanomaterial during the processing or use operations.

  — The percentage of production volume, number of sites, and number of workers associated, whether for processing or use, with each industrial-function combination.

  — Estimated number of employees working with the nanomaterial at sites where the substance is used or processed.

  — Types of employees, handling practices, and environmental containment and control equipment used to mitigate exposure potential.

— **Use**

  — Commercial or consumer product types (e.g. paints and coatings, soaps, and detergents) in which the nanomaterial is used or might be present.

  — Amount (and concentration) and nature of the nanomaterials used or present in commercial or consumer products, and how they are present in the article (e.g. coatings, agglomeration state, etc.).

  — The percent of production volume associated with each commercial or consumer use.

  — Locations of use (e.g. in manufacturing sites, in homes, outdoors)

- Frequency of use of the products containing nanomaterials.
- Use patterns (e.g. description of products or applications and how they are used).
- Numbers of commercial users (including workers) working with the nanomaterial and consumers using the product.
- Indication of whether the products are intended for use by children or other sensitive populations
- Indication of whether the nanomaterial is intended for release during use, or can reasonably be anticipated to be released, during use, repair, maintenance or disposal. If so, what are the mechanisms, magnitude, frequency, duration, and mode (e.g. to air) of the expected release?
- Indication of whether there is potential for exposure to the nanomaterial in the product through inhalation, ingestion, skin absorption, or ocular uptake.
- Required or recommended controls for use (e.g. training, engineering controls, personal protective equipment).
- Recovery/recall techniques (e.g. in case of misuse or new hazard data).

— **Distribution/storage**

- Methods of delivery of nanomaterial or nanomaterial-containing products to customers.
- Type of packaging and labeling utilized.
- Methods of storage by producer and by customers.

— **Waste from manufacturing/processing**

- Reasonably anticipated releases, specified in terms of physical form, magnitude, frequency, duration, and media, from manufacturing, processing, transportation, and waste management
- Expected recycling or disposal methods for manufacturing waste and off-specification nanomaterials.
- Nature and concentrations of the nanomaterial in each waste stream.

— **Post use management**

- Describe potential disposal, recovery, reuse and recycling methods for the products containing or using nanomaterials.
- Describe possible exposures (human and environmental) associated with these methods.

5.4.2.3 Guidance for exposure measurements/monitoring

Methods should be implemented to gather exposure-profile information on nanomaterials, covering detection, sampling, and monitoring. The monitoring program should be designed to focus on key uncertainties and target end-points identified in the other steps of this process[19)].

a) Workplace Monitoring:

1) Until methods for measuring worker exposure to airborne nano-objects are more fully developed, the following measurements should be considered:

i) Mass concentration.

ii) Nano-object-number concentration.

iii) Nano-object-size distribution.

iv) Surface area.

v) Particle characterization.

2) Measurements should be taken before processes are started in order to create an adequate baseline against which to assess potential increases in airborne concentrations that result from nanomaterial handling (recognizing that there remain significant technical challenges in accurately doing so). Worker-exposure air-monitoring data in particular should be collected to establish pre-manufacture concentrations (mass and particle number), and then again after operations have commenced. The data should include short-term exposure levels, maximal measured concentrations, and eight-hour time-weighted averages for workers with the highest potential exposures.

3) Based on the manufacturing and handling processes employed, a sampling strategy should be developed that takes into account spatial and temporal variability, locations of anticipated maxim concentration, presence of potentially exposed workers, and availability and performance of engineering controls and safe-handling practices.

4) In order to assess the efficacy of the control measures, exposure monitoring data should be collected, whenever possible, both before and after the installation of engineering controls aimed at reducing exposures.

5) Engineering estimates of nanomaterials released from accidents and spills within workplaces should also be made where feasible, with results recorded (particularly of maximum concentrations).

6) Workplace settings associated with the repair and maintenance, waste handling, reclamation and recycling of nanomaterials (or products containing nanomaterials) should also employ an appropriate monitoring and sampling strategy, with measurements obtained prior to and during operations.

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19) Much of the content of this section reflects recent guidance contained in the ISO/TR 12885, *Health and Safety Practices in Occupational Settings Relevant to Nanotechnologies*, as well as the information contained in National Institute of Occupational Safety and Health, Approaches to Safe Nanotechnology: An Information Exchange with NIOSH, available online at www.cdc.gov/niosh/topics/nanotech/safenano/. See also: ISO/TR 27628, *Workplace atmospheres — Ultrafine, nanoparticle and nano-structured aerosols — Inhalation exposure characterization and assessment*; Maynard, A. D. and Kuempel, E. D., "Airborne nanostructured particles and occupational health," *Journal Of Nanoparticle Research* (2005) 7(6):587-614 (basic information on exposure monitoring). Online, available: http://www.springerlink.com/content/700q5022523342j4/fulltext.pdf.

b) Environmental releases from manufacturing, processing, storage, transport, or waste handling

1) In processes and operations involving manufactured nanomaterials, gaseous emissions (e.g. from air ventilation and exhaust systems), waterborne discharges (e.g. to wastewater treatment), and solid wastes should be routinely monitored for the presence of the nanomaterials being processed, etc.. In order to assess the efficacy of the containment and control measures, data should be collected before and after the installation of engineering controls.

2) For points of potential fugitive or non-routine releases, engineering calculations of potential releases should be performed where feasible.

3) Engineering estimates of nanomaterials released from accidents and spills involving manufacturing, processing, storage and waste-handling facilities and transport containers/vehicles should be conducted, with results on associated maximum air and liquid concentrations recorded.

4) Further monitoring or measurements, including field simulations and actual measurements of environmental concentrations, could be triggered by initial monitoring data or new toxicity information.

c) Consumer use and post use

1) For any applications during use or post-use stages of the lifecycle that can be anticipated to lead to releases to the air, water, soil, or sediment, or to deposition onto surfaces, simulations, calculations or modeling based on reasonably anticipated use patterns (including wear, degradation, maintenance or repair) should be performed. Full characterization of nanomaterials that might be released, including particle-size distribution and other dose-relevant parameters, should also be conducted. For airborne releases, maxim and time-weighted average concentrations (mass and number) should be modeled.

2) Where uses might involve direct skin contact with nanomaterials, the evaluation should provide estimates of dose, frequency, and duration of application, including an evaluation of factors such as dermal uptake and absorption, as well as ingestion (e.g. hand-to-mouth contact).

3) Where applications might involve the actual or potential presence of nanomaterials in, or migration to, food or water, organizations should provide measured or calculated nanomaterial concentration data under reasonably anticipated conditions of consumer use.

6 Evaluate risks

6.1 General

This step in the process is the assessment of risk, taking into account the data collected to create the physical/chemical properties, and hazard and exposure profiles. Depending on the stage of development and availability of relevant hazard and exposure data, the risk analysis might result in qualitative, semi-quantitative, or fully quantitative estimates of the nature, likelihood, and magnitude of effects on human health and the environment[20)]. Ideally, the early recognition of potential risks, at all stages of the product life cycle, will provide better opportunities for risk mitigation and management. There is a considerable amount of literature extent on how to conduct risk evaluations, and this text is not intended to suggest a novel approach to this topic. Rather, it applies well-known risk assessment principles to the challenges related to nanomaterials.

20) Separately from good risk management practices, regulations may require an organization to evaluate the risks of a chemical substance. For example, under REACH, Chemical Safety Reports must be created for chemical substances place on the EU market in annual quantities exceeding 10 tonnes.

6.2 The risk evaluation process

— *Review hazard and exposure profiles.* Review the hazard and exposure profiles in anticipation of integrating their contents. In order to facilitate this process, relevant information from the profiles can be organized in the Output Worksheet (see Annex F).

— Match exposure situations with hazards and compare potential exposure levels to published or derived effect levels, where available. For each exposure situation identified in the product lifecycle, the relevant routes of exposure and potential receptors (e.g. workers, children, elderly persons, specific ecosystems) should be identified. All hazard data relevant to those routes of exposure or receptors are then assembled, and the effects levels associated with each hazard endpoint should be identified. Safety factors may be applied to these effect levels, as appropriate, and then compared to the potential magnitude of exposures

— Evaluate (quantifying, where possible) the nature, magnitude, and likelihood of identified potential risks. In cases where there are insufficient hazard or exposure data to do a full quantitative assessment of risks, a qualitative assessment of available data can be done, especially at early stages of product development. But as the nanomaterial is nearing commercialization, these alternative, qualitative, or semi-quantitative methods should no longer be relied upon; rather, adequate hazard or exposure profiles should be as complete as practically possible by this time.

— Where there is a decision to be made regarding alternative materials and processes, the comparative risks of each should be taken into account (i.e. the risks associated with the nanomaterial should not be singled out to the exclusion of the risks associated with either incumbent or competing new materials).

— *Evaluate uncertainty in the risk assessment.* If the data are sufficient for conducting a quantitative risk assessment to generate a risk value, then the application of uncertainty factors (also sometimes called assessment factors or margins of safety) should be considered to account for uncertainty. In the absence of adequate data, the risk assessment will be qualitative. In such cases, assumptions and default values should be conservative (meaning to err on the side of caution by assuming a “reasonable worst case”).

— *Assess potential for and consequences of changes in material and applications.* It might be appropriate to take into account a variety of potential situations that might alter the likelihood, nature, or magnitude of potential risks[21)]. Examples could include changes in the supplier of nanomaterials which might cause subtle changes in the properties of the product at some stage of the lifecycle; or shifts from applications with very little exposure potential (such as industrial catalysts) to ones with higher exposure potential (such as hazardous waste cleanups). While such changes cannot always be foreseen, the questions should be asked, as the answers could have significant impact on potential risks. In any event, the “review and adapt” element of the process is intended to encourage organizations to regularly address the possibility and consequences of relevant changes.

— *Identify knowledge gaps.* In the course of evaluating risks, there will likely be significant gaps in knowledge of exposure, or hazard, or both. Careful consideration during the development of the nanomaterial profiles should lead to identification of data needs for known and reasonably anticipated exposure and risk scenarios. These can then be prioritized for further data development. For example, a plastic additive containing nanomaterials might pose little exposure risk until or unless the plastic starts to degrade. It might be difficult in early developmental stages to sufficiently characterize the nature of the degraded material, but this goal can be prioritized for further study prior to commercialization.

21) There are a variety of methods and tools for doing this, including but not limited to failure analysis and scenario planning. For more information on these tools, see the following references: UK HSE (Health & Safety Executive) Risk Management Home Page http://www.hse.gov.uk/risk/index.htm American Institute of Chemical Engineers (AIChE) — Center for Chemical Process Safety. Technical Guidelines and Publications. http://www1.lvs.dupont.com/SHE/psm&fire/process/training/reference_materials/aiche_ccps_publications.pdf.

— Develop a plan to fill data needs or identify “reasonable worst-case” values, assumptions, and scenarios for use as benchmarks in risk management. If the data are insufficient at this point for adequately assessing potential risks in specific scenarios developed in the lifecycle exposure profile, decisions should be made regarding the data gaps. For example: should the missing data be generated now; how necessary is the missing data; or should the next steps be informed instead by the use of “reasonable worst-case” values, assumptions, and scenarios that can subsequently serve as benchmarks for control and mitigation efforts? Scenarios are a combination of data and assumptions to create situations that are reasonably foreseeable. The purpose of considering scenarios is to enable the team to consider what risk management measures could be needed. As the product nears commercialization, priority should be given to completing the data sets for relevant hazard and exposure profiles; in that way, the scenarios are based as much as possible on real data.

7 Assess risk management options

Risk management comprises actions for managing and reducing the identified potential risk to humans and the environment from a process or product, in this case, a nanomaterial-containing process or product. The risk management assessment should provide information sufficient for determining how best to pursue practices, conduct processes, and safely produce, use, and ultimately dispose of or recycle the product.

Specialists in safety, occupational health, and environmental science, along with business managers familiar with the product and application, as well as those who know the applicable legal requirements, should be involved in this process. The outputs of this process are the actions, if necessary, to reduce and control risks from known and reasonably anticipated activities associated with the product's or nanomaterial's raw-material sourcing, manufacturing processes, transportation, expected uses, and disposal, recycling, or reuse pathways. The scope of this effort depends on where the organization is in the nanomaterial's life cycle. For example, it is often not practical for an end-user to reduce or control the risks associated with the raw-material sourcing of their suppliers.

Results of this assessment process might include material substitution, product or process modifications, engineering or management controls, warning labels, or decisions to change or abandon the product. The current consensus in the literature for risk management is that the hierarchy of “most effective to least effective” controls is the following: 1) elimination, substitution, or reduction of the material, process, or condition that presents the hazard; 2) engineering controls; 3) warnings; 4) training, procedural, and administrative controls; and 5) personal protective equipment.

This Technical Report does not prescribe specific risk management actions, which need to be decided on a case-by-case basis. The aim of this Technical Report is instead to provide guidance for achieving a performance-based level of risk management. There are many sources of information that provide additional knowledge, guidance, and tools to guide risk management for nanomaterials[22)]. Users should consult these references and consider adopting their recommendations, as appropriate, to particular nanomaterials, applications, and conditions.

22) These references, while not exhaustive, provide an overview (based on the current state of knowledge) of available options for risk management that could be applicable to nanomaterials. Health and Safety Executive — United Kingdom Information Note: Nanotechnology http://www.hse.gov.uk/pubns/hsin1.pdf; Health and Safety Executive — United Kingdom, COSHH (Control of Substances Hazardous to Health) — Achieving Control http://www.hse.gov.uk/coshh/control.htm; German Federal Institute for Occupational Safety and Health (BAuA) and German Association of the Chemical Industry (VCI), “Guidance for handling and use of nanomaterials at the workplace” (August 2007); ASTM International — ASTM E2535-07, “Standard Guide for Handling Unbound Engineered Nanoparticles in Occupational Settings” (October 2007); U.S. National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, “Approaches to Safe Nanotechnology — Managing the Health and Safety Concerns Associated with Engineered Nanomaterials (March 2009).

The risk management process includes the following elements, all based upon the evaluation of risk discussed above:

— *Determine needed levels of protection.* Control measures should be commensurate with the identified risk. Decisions should be based on existing health, safety and environmental legal requirements and standards, and on the effectiveness of the chosen control method in reducing exposure to below the level determined acceptable in the risk evaluation (or lower, if so indicated by management)[23)]. These decisions need to be made for each stage of the product lifecycle, and they should be based on the risk evaluation.

  Elements to consider for the decision process could include a formal management policy that states a commitment to minimizing potential exposures to the nanomaterial; relevant safety, health, and existing environmental exposure requirements standards; and well-developed risk-assessment information. In addition, reasonable professional judgment should be exercised, based on the nanomaterial used, conditions of use, control measures implemented, exposure assessments, and the knowledge and experience of the users. For example, handling nano-objects incorporated or fixed in a polymer might reduce the potential for skin and inhalation exposure, whereas a mixing operation with nano-objects in a non-fixed state (e.g. a powder) will pose an increased potential for skin, ocular and inhalation exposure. A user might decide, therefore, that working with nanoparticles fixed in a polymer would require less restrictive levels of protection (e.g. general ventilation, goggles, and gloves), while working with nanoparticles in a dry-mixing operation would require higher levels of protection (e.g. engineering controls).

— *Review of controls for reducing identified risks* . This phase of the process is a formal and ongoing review of current risk management practices relevant to the manufacturing process, the product itself, and the transportation and use of the product. Measurement of exposures should be undertaken where appropriate and practical to inform the assessment of controls. The review should also take into account the following: safety, health, environmental goals, policies, and procedures; applicable legal requirements; safe-handling practices; suppliers; product distribution and transportation; customer use and misuse of the product; and recycling and waste management[24)]. Issues that can be considered, or questions that can be asked, include:

  — Substitution. Can the hazards be reduced or eliminated by changing the nanomaterials, chemistry, or process variables (taking into account the degree of risk posed by substitutes and the incumbent materials)?

  — Engineering issues. For example, are local exhaust/ventilation systems effective at capturing airborne nanoparticles and are they being maintained and performing according to specifications?

  — Administrative issues. For example, are hand-washing and other good-hygiene practices required prior to leaving the work area where nanomaterials are processed?

  — Personal-protection equipment issues. For example, are respirators that are effective at capturing nanomaterials available, are workers trained in their use, and are they being properly used?

  — Communication. Is hazard and safe-handling information shared with those who have a need to know (e.g. through Safety Data Sheets, training, supply-chain communications)?

  — Are procedures communicated to customers in order to inform them on how to safely use, dispose of, or recycle the product, and manage environmental, health, and safety risks?

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23) Many practitioners will be familiar with this approach as the ALARA principle (“As Low As Reasonably Achievable”). See http://www.ilpi.com/msds/ref/alara.html.

24) These questions could be asked in the context of an organization's formal occupational health and safety management system, if it has one.

- Do labels, other safety-information communications, and packaging used by the organization indicate the extent of harm that could result from reasonably foreseeable misuse and comply with applicable legal requirements (e.g. national or regional requirements based on the United Nations' Global Harmonized System)?

— *Determine best risk management options.* Once the above steps have been performed, the adequacy of existing risk management options, and the need to enhance or supplement them, must be evaluated. In that way, the user may determine whether the risks posed by a given product at any particular stage of its lifecycle should be managed. The selected risk management options should adequately address existing and potentially new exposure scenarios.

The decision process is guided by the management objectives of manufacturing products that can be safely used, and minimizing unintended exposures across the products' lifecycles. The process should include: implementation of procedures to achieve the expected level of protection; facilities and equipment improvements for containment control; and the availability of supporting equipment and other resources. Organizations should also consider whether there are needs for customer and distributor training; communications to guide customers on safe use, disposal, recycling, environmental control, and permitting recommendations; and first-aid and medical recommendations for overexposure. In the end, the organization should be able to credibly document that the risk management measures chosen will adequately address the identified risks.

— *Develop a plan for risk management*, which includes monitoring, compliance, and reporting. The plan is a means of determining and documenting (as well as verifying, through the implementation of a written audit protocol) that appropriate and effective systems are in place for managing a product's safety, health, and environmental risks throughout its lifecycle. The plan should identify and address key uncertainties. The documentation of the plan provides a foundation for communicating the current risk management program and considering whether future changes to the program may be warranted.

8 Decide, document and act

8.1 General

Earlier steps in this process involve the compilation (typically, by the project leader or the product steward) of needed environmental, health, and safety information and assessments. In this step of the process, the organization reviews those compilations, analyzes the options, makes decisions, documents the analyses and decisions, and takes appropriate actions.

The scope of information that is considered and the composition of the review team should be appropriate to the stage of the project. Early-stage developments, for example, might have limited information to consider and small review teams, while late-stage developments might generate substantial amounts of information and require more diverse qualifications and more senior membership in the review team.

Organizations might wish to involve outside stakeholders in the review and decision making process, when appropriate, as early in the process as possible. Involving additional perspectives can result in more complete and effective reviews and anticipate potential concerns that might not be identified within the organization. A more transparent approach might enhance the broader acceptance of nanotechnologies and nanomaterials.

The deliberations of the review team might produce a number of outputs, including:

— A decision to move ahead on, terminate, or redirect or modify the development, manufacture, use, or sale of the product or application involving manufactured nanomaterials.

— If moving ahead or redirecting, identification of specific actions to be taken.

— Assignment of a “product steward” (if not already assigned).

— Specification of (along with rationale for) additional data to be collected, including how, by whom and when this would be done.

— Endorsement of assumptions used in place of data; or recommendations for review and revision of assumptions.

— Final implementation timeline for the risk management, monitoring, and compliance processes.

— Determination of an agreed-upon product-review cycle, including the timing and conditions for the next review.

— Documentation of the review team's decisions and its recommended actions.

— A plan to communicate this information, as appropriate, across the organization and to other stakeholders.

The following is a description of the key steps an organization should take in the review and decision making process. Organizations that already have product development processes should integrate these steps into such processes, and do not need to create special review processes for manufactured nanomaterials.

8.2 Assemble a cross-functional decision-making review team

The size and composition of the review team will depend on the nature of the organization involved, the scope of the overall effort, and the stage of development. Ideally, the team will include a broad cross-section of relevant viewpoints, including technical, manufacturing, workforce, business, and legal perspectives. The organization may also choose to include participants from outside the organization, such as members from the supply or value chain of the product under consideration (e.g. suppliers, customers), consultants, financiers, or knowledgeable experts from academia or consulting firms.

The review team should include individuals that, together, have the competence, based on education, training and experience, to understand, evaluate and make decisions about the information that is gathered pursuant to this process, including:

— The nanomaterials and technology being contemplated, including the life cycle of the material and related products;

— The human health and environmental exposures, hazards and risks associated with the contemplated course of action;

— How the nanomaterials or products containing them are intended to be manufactured, marketed and used;

— The applicable environmental, product safety and occupational safety legal requirements; and

— How the nanomaterials will be handled by and in the organization, including any occupational safety or environmental measures

Ideally, the team will include persons with knowledge and experience in risk assessment, toxicology, environmental fate, and industrial hygiene. Many organizations might not have all of the necessary competencies on staff. One option is to engage outside experts to meet these needs (e.g. hiring consultants or partnering with university researchers), which can be more efficient than having such individuals on staff full-time. Additionally, the creation of consortia could function to share resources to ensure that these areas of expertise are covered (taking appropriate notice of potential restrictions established by competition law).

8.3 Review information

Review the information that was collected and evaluated regarding the risks associated with development, manufacture, use, reuse/recycling, and disposal of the nanomaterial, and the options to lessen, control or eliminate such risks. Different perspectives, reflecting different organizational roles, will likely surface, which collectively should aid in the determination of whether additional information or action is needed.

8.4 Consider business, legal, and stakeholder issues

Examples include emerging regulations, public perceptions, worker perspectives, liability concerns, potential for design changes to reduce risk, and the potential benefits (including any reductions in risks) associated with the use of the nanomaterial.

Particularly important is attention to public, consumer and worker safety perspectives. It is prudent to understand these issues early in the product-development cycle so that lines of communication are open and relevant information can be factored in.

8.5 Determine who is responsible for implementing recommended actions

An individual (who ideally should have already been assigned during the previous steps) should be identified who is responsible to follow through on the recommendations of the review team (or the decisions of senior management) to ensure that they are implemented. Frequently, the responsibility for taking specific actions contained in the recommendations might be scattered in various functions (e.g. product design, occupational safety, marketing).

8.6 Based on these inputs, decide whether and how to proceed

Possible outcomes of the review team's deliberations include

— Acceptance of the tentative recommendations as presented to the team and implementation of the project

— Provisional acceptance, with specified additional information required

— Provisional hold or suspension of the project, with specified additional information required

— Redirection of the project

— Termination of the project.

In the case of provisional acceptance, provisional hold, or redirection, the review team should list criteria that must be met, or hurdles to overcome, for the revised project to proceed.

8.7 Determine additional data needs and initiate data collection, as necessary

These data could include physical and chemical property data, hazard data, exposure data, or risk management information. Staff involved in the product development must then obtain this information to present to the review team.

8.8 Establish and implement appropriate risk management, monitoring, compliance, and communication processes

If the project and plan for risk management, monitoring, compliance, and reporting are approved and moved forward, mechanisms, including those related to accountability, should be established to ensure that the plan is properly executed. The monitoring program should be designed to focus on key areas of uncertainty or risk.

The decisions made and the bases for those decisions should be documented. This documentation should describe the technical results of the risk evaluation and risk management assessment, and summarize decisions relevant to future development or commercialization of the product. The results of all studies, regardless of the conclusions they support, should be included in the documentation. All assumptions should be clearly described. Advantages and limitations of each test, measurement, model, or estimate employed should be identified, and residual uncertainty caused by the nature or source of the data, as well as data gaps and potential biases, should be noted.

Documentation allows those not present at the meetings to understand the decision-making process, its outcomes, and the resulting actions. The documentation can also serve as a transparency tool for informing stakeholders (e.g. customers, the public, workers, government agencies, nongovernmental organizations) that potential risks have been identified and addressed and that necessary risk management measures are in place.

The organization must decide who will have access to such documentation. For example, consistent with most occupational hazard communication programs, information relevant to occupational exposures, hazards, risks and controls (including the rationales for such controls) should be communicated and made available to workers who research, develop, or manufacture the product (e.g. through safety data sheets and training), and that appropriate feedback mechanisms are in place to address worker concerns.

As products move into commercialization, organizations should consider making relevant information available to a broader range of stakeholders[25)]. Organizations may choose to create a publicly available report that summarizes relevant information or decisions, create documents for specific audiences in order to facilitate ease of understanding, or provide selected stakeholders with relatively open access to a broad range of documentation. Organizations should be prepared to respond to requests from stakeholders for more detailed information, and should also be prepared to demonstrate to stakeholders that the risks associated with their materials or products have been identified and are being appropriately controlled.

While a transparent decision-making process is important for credibility with certain external stakeholders, it is also recognized that users have a need to protect legitimate confidential business information (“CBI”) to prevent competitors from gaining an unfair commercial advantage based on the nanomaterial developers' efforts. A balance should be struck between providing transparency to encourage public trust and withholding CBI to protect investments and intellectual property[26)]. In certain cases, it might be desirable to have a responsible independent third party examine the CBI to validate conclusions to outside stakeholder groups. Where CBI has been withheld in stakeholder reports, this should be noted. Organizations should consider the possibility of providing a non-proprietary description of the sensitive information (e.g. a description of the type and class of material that does not reveal its exact chemical composition).

In order to gain shared awareness of the risks and precautions, it might be beneficial that users provide as much summary information as possible without compromising CBI. The summary should be sufficient to allow the reader understand the user's risk management decisions, given the potential risks of the nanomaterial.

The Output Worksheet included in the Annex F (or a variation thereof) should be used as a means of summarizing the information that the team considered, the assumptions it made, the risk management decisions it came to, and the rationales behind those choices.

Because the state of knowledge about risks associated with manufactured nanomaterials is rapidly developing and changing, it is recommended that organizations make new data publicly available, especially as they apply to human health and environmental hazards, environmental fate and transport, physical hazards, and exposure. Publication in peer-reviewed journals might provide the most credibility for such findings.

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25) Some “downstream” communication may be required by law. For example, suppliers of manufactured nanomaterials are typically obligated to provide safety data sheets to their customers, and certain legal regimes, such as the EU's Regulation concerning the Registration, Evaluation, Authorisation, and Restriction of Chemicals (“REACH”) (EC 1907/2006) establishes a number of supply chain communications requirements for manufacturers, processors and users of chemicals.

26) Most chemical regulatory regimes, including REACH in the EU and TSCA in the US, include provisions for protecting CBI.

9 Review and adapt

9.1 General

In this “review and adapt” step, the organization should implement a process of periodic and “as needed” reviews to ensure that the information, evaluations, decisions, and actions regarding manufactured nanomaterials are kept up-to-date. These reviews could be integrated into an organization's existing processes, such as the “management review” step in ISO 9001 or 14001.

The essence of these reviews is that the organization identify and evaluate new information, determine whether such new information should cause adjustments to the risk assessment, and re-evaluate the adequacy of the risk management measures for the nanomaterial or application. In other words, does the current risk evaluation or risk management practices need to be revised in light of new information?

As with the other steps in this process, it is expected that the level of detail will vary, depending on the phase of development for the given nanomaterial or application.

9.2 As needed reviews

The organization should conduct a risk management review whenever there has been a significant change in hazard or exposure information, production volume, or use profile. In general, “significant” means serious enough to potentially require a revision in the risk-evaluation or risk management procedures for the nanomaterial or application. Examples include:

— A change in production, processing, or use patterns for the manufactured nanomaterial or application that would alter the lifecycle exposure profile.

— The acquisition of new data relevant to the risk evaluation for the nanomaterial or application, such as results from testing initiated by the review team, or new hazard or exposure information learned from the literature.

— Changes in legal requirements that would affect the regulatory status of the product or material.

9.3 Regular reviews

In addition to as-needed reviews that respond to unanticipated new information or situations, organizations should also establish a regular schedule for periodically reviewing recent data and the adequacy of the current risk management process. The schedule should be based on the degree of risk and uncertainty associated with the particular nanomaterial or application, and it should align with any data-development activities so that the new data can be promptly reviewed and acted on.

In these regular reviews, the review team should:

— Analyze any new data on properties, hazards, exposure, or risk management, as well as any relevant changes (or anticipated changes) in legal requirements.

— Decide on any additional data needs and how they are to be met.

— Determine whether previous decisions on development or deployment of the nanomaterial application remain valid.

— Determine any needed changes in the risk evaluation or the associated risk management practices.

These reviews should also include any information that will help assess how well the selected risk management practices are performing. In particular, the review team should consider any monitoring data that have been collected so that it can determine whether the risk management practices are keeping exposure levels below the maximum allowable exposure goals. In addition, the review team should consider any data from health screening or monitoring programs in order to ascertain whether the nanomaterial application might be causing any unexpected effects in employees or other monitored populations. Finally, the team should consider whether any new monitoring programs need to be initiated or existing monitoring programs require modification.

The team should also consider the broader issues addressed in the initial decision making phase, including any new information on emerging regulations, public and worker perspectives, liability concerns, potential for design changes to reduce risk, and related influences.

Based on its review of any relevant new information or situations, the team should update the risk evaluation as necessary and then choose (or recommend to senior management for its decision) the most appropriate risk management options to address the altered conditions.

9.4 Adapting risk management and collecting additional information, as appropriate

The team should decide or make recommendations on what actions should be taken as a result of the review. These can include:

— Confirm and continue ongoing actions, including the production, use, and marketing of the nanomaterial or application, as well as the current risk management practices.

— Provisionally continue ongoing actions, with additional information required (and a plan to obtain such information).

— Put a provisional hold on current actions, pending generation and review of new information

— Revise current actions in any part of product development, including the design, production, use, and marketing of the nanomaterial or application, or revise current risk management practices.

— Terminate current actions (e.g. stop the development, production, or use of a nanomaterial or application, initiate a communications strategy or recall, or pursue other remediation activities)[27)].

Once the decision is made on how to proceed, the review team should determine and assign responsibilities for implementing it. In the case of a provisional hold or continuation that requires additional information, the team should designate how the required information is to be generated and set a follow-up date to review it and determine its consequences

9.5 Documenting and communicating any new decisions and actions

Each review should be documented (which could be an update or expansion of the existing documentation). The documentation should include:

— Information reviewed by the team.

— Significance of new information or situational changes.

— Changes to the lifecycle profiles and risk evaluations (and reasons for the changes).

— Changes to assessments of risk management options (and reasons for the changes).

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27) A decision to stop producing or distributing a product for risk-based reasons may trigger legal requirements, including notifications to regulators and product recalls. Organizations must be familiar with these requirements in the markets in which they do business, and be aware that such requirements frequently require quick action.

— Changes to risk management practices (and reasons for the changes).

— Updated decision to move ahead on, redirect, or terminate the development, manufacture, use, or sale of the product or application.

— If there are any changes, specific actions that will be taken.

— Additional data to be collected, and how and when it will be collected.

— Endorsement of any assumptions used in place of data, or recommendations for review and revision of assumptions

— Updated implementation timeline for the risk management, monitoring, and compliance process

— Updated product-review cycle, including timing and conditions for the next review

— Updated plan to communicate this information across the participating organizations and to other stakeholders, consistent with the organization's existing communication plan.

It is especially important for the review team to communicate any changes in the risk evaluation or risk management practices to those who will be affected. These audiences can include:

— Workers who handle the nanomaterial or product.

— Customers who purchase and use the nanomaterial or product.

— Other companies within the supply chain, including those involved in managing waste from the manufacture, use, recycling, or disposal of the nanomaterial or product.

— Members of the public who might be exposed to the nanomaterial or product.

— Regulatory agencies that have oversight over the risks presented by the nanomaterial or product.

— Public-interest groups (NGOs, governmental organizations) with a legitimate concern about the nanomaterial or product.

In some instances, updating the information might be required by law (e.g. updating safety data sheets). The team should document any feedback it receives from the above groups, the company's responses to the feedback, and any actions or changes that result from them.

Finally, before completing any given review process, the team should set a date for the next scheduled review and specify the conditions that would trigger the next as-needed review. The team should also establish clear responsibility for monitoring those conditions.

Annex A
(informative)

Data set of physical and chemical properties[28)]

A.1 List of physical and chemical properties

- Technical Name
- Commercial name
- Common form
- Chemical composition (including surface coating)
- Molecular structure
- Crystal structure
- Physical form and shape (at room temperature and pressure)
- Particle size, size distribution and surface area
- Particle density
- Solubility (in water and biologically relevant fluids)
- Dispersability
- Bulk density
- Agglomeration state
- Porosity
- Surface charge
- Surface reactivity

A.2 Detailed information for physical and chemical properties

A.2.1 *Technical and Commercial Names.* A descriptive name (e.g. AB-123 or surface-treated nano rutile TiO_2) should be used to distinguish the nanomaterial from similar nanomaterials or those in bulk form. Similarly, if a series of samples of different compositions has been generated, a unique designation should be used for each so that their corresponding physical properties can be tracked.

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28) See “Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy,” Oberdorster et. al., Particle and Fibre Toxicology, October 2005.

A.2.2 *Common Form.* Is the nanomaterial a loose powder, contained in a liquid dispersion, agglomerated into larger-size particles, or aerosolized? The form of the nanomaterial will have implications for the potential route of human or environmental exposure.

A.2.3 *Chemical Composition.* What are the concentrations of elemental chemicals or chemical compounds, particularly those known to be harmful, in the nanomaterial? Moreover, accompanying substances should not be overlooked; surface treatments and lattice doping are often used in nanomaterials and should be reported, as they can affect toxicity and exposure. Note too that chemical composition can change as nanomaterials are incorporated into products or break down, either during use or after disposal or recycling. Impurities in the nanomaterial, and the extent of contamination, should be identified as well.

A.2.4 *Crystal Phase/Molecular Structure.* How elements or molecules are arranged physically in a nanomaterial can influence its potential toxicity. Early understanding of phase and molecular structure can lead to better understanding of potential structure-property relationships.

A.2.5 *Physical Form/Shape.* Is the nanomaterial crystalline or amorphous? Are the edges round or angular? What are the dimensions of the nanomaterials, e.g. are they plates, fibres, or particles? Physical form and shape influence how the nanomaterials flow, interact with other particles (to agglomerate), how easily they disperse when entering various media or the environment, and how they interact with plants and animals.

A.2.6 *Size and Surface-Area Distribution.* What are the mean particle size, the mean surface area, and the distributions around the means? What are the mass and number-count distributions? These measures are important because an increased surface-area-to-mass ratio of nanomaterials appears to be a critical feature in understanding some aspects of their toxicity[29)], particle surface energy[30)], and reactivity[31)].

A.2.7 *Particle Density*. What is the mass of particle per unit volume? This physical property, used in the determination of how easily the nanomaterial is dispersed in air and water and how easily it settles from air and water, has implications for the behaviour of the nanomaterial in gases and liquids.

A.2.8 *Solubility.* Does the nanomaterial dissolve in water or other substances? Whether the nanomaterial is soluble in acids, bases, organic solvents, or biological media might be important at various stages in its lifecycle as it interacts with other product components, materials, organisms, or the environment. Solubility plays a role not only in determining how the nanomaterial behaves during its useful life but also in affecting its potential persistence in the environment thereafter.

A.2.9 *Dispersibility.* This property is “the ease with which an insoluble solid or liquid nanomaterial may be dispersed uniformly in a liquid”[32)]. The dispersibility of a nanomaterial, particularly in water, has implications for exposure and fate throughout the product lifecycle. It will influence the partitioning of the nanomaterial should it enter an aquatic environment.

A.2.10 *Bulk Density.* Bulk density provides a quick indication of how much dust the nanomaterial might generate when being handled in its powder form. Low bulk density materials often have a higher degree of dusting than high bulk-density materials of the same chemical composition.

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29) Günter Oberdörster et al., “Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles,” 113, Environmental Health Perspectives, 823-839 (2005).

30) Günter Oberdörster 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.

31) M. C. Daniel & D. Astruc, “Gold Nanoparticles: Assembly, Supramolecular Chemistry, Quantum-size-related Properties, and Applications toward Biology, Catalysis, and Nanotechnology,” 104 Chemicals Review, 293-346 (2004).

32) FAO Plant Production and Protection Paper 173, Pesticide Specifications, Manual on Development and Use of FAO and WHO Specifications for Pesticides, First Edition, Prepared by the FAO/WHO Joint Meeting on Pesticide Specifications, World Health Organization and Food and Agriculture Organization of the United Nations, Rome, 2002; see http://www.fao.org/docrep/007/y4353e/y4353e0g.htm.

A.2.11 *Agglomeration State.* This measure gives another indication of how much dust the nanomaterial might generate when handled in its powder form. Moreover, the agglomeration state provides information on the likely size distribution of inhalable particles as well as on their relative ease of dispersion.

A.2.12 *Porosity.* This measure is an indication of the fraction of the particle that is devoid of material. The porosity and pore-size distribution of the nanomaterial has implications for its interaction with substances in its surroundings.

A.2.13 *Surface Charge.* The electric potential of a nanomaterial also suggests its likelihood of interacting with other materials. In solution, the surface charge, often determined by measuring the zeta potential[33)] , has implications for the stability and aggregation of particles.

A.2.14 *Surface Reactivity.* This measure provides an indication of the likelihood and nature of a nanomaterial's interaction with other materials. Specific assays might need to be tailored to specific nanomaterials; examples include a Vitamin C test, a haemolysis test, and a reactive oxygen species (ROS) assay.

A.3 Other considerations

In addition to the physical and chemical characteristics of the specific manufactured anomaterial, information should be gathered regarding whether or how those characteristics will change through the product system's life cycle, including:

— Will the nanomaterial be coated? If so, with what? What impact does the coating have on the nanomaterial's characteristics?

— Will additives be used to minimize or encourage the tendency to aggregate? If so, what additives?

— In what form will the nanomaterial be present at different stages of the product system's life cycle?

— What impact will manufacturing or processing have on the nanomaterial's characteristics? For example, if the nanomaterial is heated, milled, dispersed into liquids, or surface-treated with other chemicals, how do its properties change?

— How does the nanomaterial change as it is produced in larger volumes and moves toward commercialization? For example, will nanomaterials even be present in the final product?

— How does variability in how the nanomaterial is produced or handled change its physical and chemical properties?

— What impurities might be present and what are the impacts of impurities?

33) See http://www.colloidal-dynamics.com/CDElTut1.pdf.

Annex B
(informative)

Tiered testing approach to health hazard data

B.1 Introduction to tiered hazard testing

The accumulation of hazard data could be accomplished through a step-wise process beginning with a general assessment of cytotoxic potential using *in vitro* and *in silico* methods. Once satisfied that the general potential for toxicity of a given nanomaterial is sufficiently low to be further developed, additional *in vitro* assays with greater specificity should then be applied to assess mechanisms of action and the effects on specific toxicity pathways. Animal tests should follow the initial tiers to assess endpoints not yet adequately assessed by non-animal methods.

Tiers I and II are currently available screening assays using biology-based, *in vitro* methods amenable to high-throughput analysis. These tests provide insight into potential mechanisms of toxicity but do not provide reliable quantitative information on doses likely to result in toxicity in humans and other animals. Cell-line choice is crucial; it is important to note that immortalized cell lines might not respond in ways that are indicative of a typical human response.

B.2 Testing tiers

B.2.1 Tier I: General determination of toxicity

The aim of Tier I of this testing strategy is to provide the user with accessible, reliable, cost-effective methods to assess the potential for general toxicity related to the nanomaterial of interest. Tier I test results will allow the user to gauge toxicity and decide whether or how to move forward with the development of the nanomaterial or to rework the nanomaterial so that its potential for toxicity decreases.

B.2.2 Tier II: Specialized assays including portal of entry endpoints

Tier II aims to assess more specific mechanisms of action and toxicity pathways. These tests begin to answer portal of entry questions and serve as methods of screening during the early phases of nanomaterial development. A nanomaterial-specific Tier II testing strategy would be designed following consideration of physical/chemical properties and expected exposure scenarios.

Following the guidelines provided by *EPA's Draft Nanomaterial Research Strategy*, additional (relevant) “virtual body” assays should be employed to assess the *in vitro* pulmonary, cancer, neurological, reproductive, cardiovascular, and developmental toxicities that nanomaterials might induce. EPA also recommends that researchers conduct ADME (absorption, distribution, metabolism, and excretion studies at the cellular and intracellular levels and characterization of the interactions between nanomaterials and cells. ToxCast (http://epa.gov/comptox/toxcast/news.html) offers potential high-throughput and/or computational assessments that might be applicable to nanomaterials.

Several assays have been modified or specifically designed to address toxicity of nanomaterials specific to portals of entry. Once the route of exposure and dose has been determined, cytotoxicity of cell types relevant to portal-of-entry can be assessed using a variety of *in vitro* methods adapted for use with nanomaterials, including those that can measure pulmonary toxicity, neurotoxicity, developmental toxicity and embryotoxicity.

B.2.3 Tier III: Validated OECD test methods that might apply to nanomaterials

This tier is recommended for those nanomaterials that have been proven to have commercial potential. Some of these additional tests might be needed for classification and labelling of the nanomaterials and/or products in which they are used. Depending on the intended use of the product, these tests might be appropriate for an earlier stage of screening.

B.2.4 Tier IV: Testing triggered by results from previous testing tiers

Validated test guidelines can be used to further identify risk related to the nanomaterial being developed for commercial applications. Because nanomaterials vary greatly and can be applied to diverse fields with equally diverse applications in computing, sporting goods, industrial chemicals, and the medical field, it is impossible to prescribe a testing matrix that would be relevant to all sectors. When approaching long-term it is important to have identified specific routes of exposure and the most efficient Test Guidelines to satisfy those testing requirements. Some nanomaterials will not be developed to the stage of Tier III testing as only those nanomaterials proven to be the safest candidates for commercial/industrial uses and for which Tier II results do not indicate potential toxicity will proceed to more in-depth Tier III and Tier IV testing. Tier III and Tier IV testing would include further characterization of specific toxicity (i.e. determination of dose-response) or endpoints not included in Tier II testing (i.e. developmental toxicity).

B.3 Additional data to be developed as needed

If it is determined following consideration of Tier II to IV results, along with physical chemical properties and exposure estimates, that a specific nanomaterial must undergo testing for developmental toxicity, neurotoxicity, or immunotoxicity, the testing using Extended One Generation testing strategy now being developed at the OECD might be considered. This newer guideline combines the aforementioned endpoints and reduces the number of animals used as well as the expense of the older, separate test guidelines.

Annex C
(informative)

Health hazard data set (alternative approach)

C.1 Testing

C.1.1 Introduction

This Annex describes the basic types of testing that might be available to assist in creating the hazard profile. As noted elsewhere, though many of these test methods have long been used on bulk materials, their efficacy and accuracy with respect to the testing of nanomaterials has in many cases not yet been verified[34]. Determining which of the testing methods used should be based, among other things, on the data gaps identified by the literature review and exposure profile. In each case, predictive, reproducible and transferable non-animal testing alternatives including *in vitro* tests and *in silico* solutions should be considered first to address health hazard questions.

C.1.2 Dermal tests

Dermal exposure is typically an important route of exposure to consider for nanomaterials. The following are examples of dermal tests that should be considered:

- Corrositex for SkinCorrosivity (OECD Guide 435)
- In Vitro Skin Corrosion: Human Skin Model Test (OECD Guide 431)
- EpiSkin skin corrosion assay: (OECD Guide 431)
- EpiDerm skin corrosion assay: (OECD Guide 431)
- Rat TER skin corrosivity assay: (OECD Guide 430)
- EPISKIN with MTT Reduction and IL-1a release (For skin irritation. Validated and recommended for regulatory use by ECVAM as a replacement, and by ICCVAM as a screen in a tiered-testing strategy; OECD Guide 431)
- EpiDerm with MTT Reduction and IL-1a release (For skin irritation. Validated and recommended for regulatory use by ECVAM as a replacement -- a negative result might require further testing. Validated and recommended for regulatory use by ICCVAM as a screen in a tiered-testing strategy
- LLNA in mice for skin sensitization (OECD Guide 429)
- In Vitro Skin absorption (OECD Guide 428).

34) The following pages contain many references to test methods developed by the OECD. The OECD Guidelines for the Testing of Chemicals are tools for governments and industry worldwide to assess the safety of chemical products, and are available free of charge on the OECD public website at http://www.oecd.org/env/testguidelines.

C.1.3 Oral tests

If the evaluation of the manufacture or use of the material indicates a potential for ingestion, the following are examples of oral tests that might be considered:

— Acute Toxic Class (ATC) Method (OECD Guide 423)

— Fixed Dose Procedure (FDP) (OECD Guide 420)

— Up-and-Down Procedure (OECD Guide 425)

— 28-day repeated-dose oral toxicity test with full histopathology, over a 90-day observation period. (This modification is designed to help distinguish latent effects from the short-term exposures, particularly if ingestion is virtually exclusive as the known or expected route of exposure.)

C.1.4 Inhalation tests

Inhalation exposure is frequently one of the most important routes of exposure in the occupational setting. The following is an example of an inhalation test that might be considered:

28-day inhalation study with full histopathology, over a 90-day observation period, OR Single-dose instillation study with full histopathology, over a 90-day observation period.

NOTE Acute inhalation studies would not likely provide sufficient meaningful information to warrant the use of animals for such a study.

C.1.5 Ocular tests

Where there is a possibility that nanomaterials could get into the eyes, the following is an example of an ocular test that might be considered for:

OcularBovine Corneal Opacity (BCOP) and Isolated Chicken Eye (ICE)

NOTE 1 ECVAM and ICCVAM support the use of these tests in appropriate circumstances and with certain limitations as screening tests to identify substances as ocular corrosives and severe irritants in a tiered-testing strategy, and as part of a weight-of-evidence approach. ICCVAM does not consider these test methods to be complete replacements for the in vivo rabbit eye test.

NOTE 2 Dust and/or powders by themselves might be irritating when administered into the eye in the in vivo test.

C.1.6 Genotoxicity testing

C.1.6.1 General

Genotoxicity should be evaluated if there is potential exposure, regardless of the route. The following are examples of genotoxicity tests that might be considered.

C.1.6.2 Tier I

— Ames-Bacterial Reverse Mutation Test (OECD Guide 471)

— In Vitro Mammalian Chromosome Aberration Test (OECD Guide 473)

C.1.6.3 Tier II (if necessary)

— In Vitro Mammalian Cell Gene Mutation Test (OECD Guide 476)

— In Vitro Micronucleus Assay (OECD Guide 487 is being drafted)

— UDS (unscheduled DNA synthesis) test in mammalian cell in vitro (OECD Guide 482)

— In Vitro SHE (Syrian hamster embryo) cell transformation assay (OECD Guide 495).

C.1.6.4 Tier III (if necessary)

Chromosomal-aberration assay using in vivo methods such as the micronucleus test or metaphase analysis of bone-marrow cells.

C.2 Additional data to be developed as needed

C.2.1 Introduction

Depending on the outcome of the above testing and other considerations, additional data might need to be developed.

C.2.2 Biological fate and behaviour

The development of test methods for gaining an understanding of the fate and transport of nanomaterials in the body is a widely recognized critical-information need and a priority for near-term research[35]. This information is particularly important for nanomaterials that exhibit significant potential for chronic or repeated exposure to workers, consumers, or the general population. Hence, where nanomaterials are to be used in ways that can result in significant exposure, undertaking these types of studies might be warranted even in advance of the development of standardized methods.

A broad spectrum of study designs and methods has been routinely used to assess biological fate and behaviour of non-nanomaterials, and a number of studies have more recently been conducted to assess the biological disposition of certain nanomaterials. Technical challenges in applying such approaches specifically to nanomaterials are significant, and development of suitable bioassays is at an early stage of development.

C.2.3 Chronic (> 1-year dosing) studies for oral, dermal or inhalation exposure

Chronic dosing or exposure studies might be necessary to identify health risks if there is evidence of toxicity following the acute exposure studies included in the base set or if chronic exposures of the worker, consumer, general public are expected to occur. OECD test guidelines for chronic testing are available online[36].

C.2.4 Reproductive and developmental toxicity

OECD has guidelines both for one and two-generation reproductive-toxicity assays[37]. The U.S. National Toxicology Program utilizes a study design, termed Reproductive Assessment by Continuous Breeding, which is a two-generation study to identify effects on male or female reproduction, characterize toxicity, and define the dose-response relationships for each compound[38]. By contrast, developmental toxicity study designs are more variable. Chemicals are tested in pregnant animals such as mice, rats, or rabbits; and offspring are

35) US National Nanotechnology Initiative (NNI), 2006, “Environmental Health and Safety Research Needs for Engineered Nanoscale Materials” (September 2006). This was followed by NNI's “Strategy for Nanotechnology-Related Environmental, Health and Safety Research,” (February 2008). See also United States Environmental Protection Agency, 2007, Nanotechnology White Paper, February 15, 2007, http://www.epa.gov/osa/nanotech.htm.

36) The OECD Guidelines for the Testing of Chemicals are tools for governments and industry worldwide to assess the safety of chemical products, and are available free of charge on the OECD public website at http://www.oecd.org/env/testguidelines.

37) See note 39 and 40.

38) Chapin and Sloan, Reproductive Assessment by Continuous Breeding: Evolving Study Design and Summaries of Ninety Studies, Environmental Health Perspectives 105 (Supp. 1): 199 – 395 (1997).

assessed for indications of toxicity during fetal development. Exposure duration could be from implantation to the day before delivery, or it could continue to a specific postnatal period. In addition, OECD has methods for a reproductive and developmental toxicity testing[39)].

C.2.5 Neurotoxicity studies

Neurotoxicity is the study of effects of chemicals on the nervous system, including the brain. Significant damage to nervous-system tissue might be detected through an extended histopathology following a repeated-dose toxicity test. More subtle damage might not be detected through histopathology, however.

If neurotoxicity emerges as a concern, available neurotoxicity tests, such as the OECD Neurotoxicity Test Guideline[40)], should be evaluated for applicability and adapted as needed. This guideline is designed to detect major neurobehavioural and neuropathological endpoints, some of which would not be apparent on histopathological examination, in adult rodents.

C.2.6 More extensive genotoxicity studies

Positive results in the initial genotoxicity studies can trigger additional genotoxicity studies or possibly a carcinogenicity bioassay.

C.2.7 Focused toxicity studies

The results of the initial base sets, in combination with known or expected patterns of exposure, could trigger more focused toxicity studies. If, for example, evidence of allergenicity or immunotoxicity is seen in the initial toxicity studies, then an endpoint-specific bioassay might be warranted. If ingestion is considered to be a significant route of exposure, then additional testing on the interaction with or effects on the gut could be pursued. If organ-specific toxicity is identified in the short-term testing, then it could be prudent to conduct additional studies to further characterize such adverse effects. Studies could include organ-specific functional assays or the use of animal models to investigate susceptibility. In addition, prolonged observation periods could be considered in short term (28 days) studies in order to evaluate possible reversibility of the observed adverse effects

C.2.8 Endocrine-disruption studies

Such studies should be triggered by either of the following: 1) the bulk compound is a known or suspected endocrine disruptor; or 2) results of base-set tests, additional reproduction or developmental toxicity testing, or any other available information indicate a potential for endocrine disruption. Several OECD guidelines are available for detection of oestrogenic effects (OECD 440 2007, OECD 455 2009) and androgenic effects (OECD 441 2009). Professional judgment would determine which endocrine-disruption tests should be applied, pending guidance from regulatory authorities.

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39) See, e.g. OECD Series on Testing and Assessment Number 43: Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment, ENV/JM/MONO(2008)(16); OECD Series on Testing and Assessment Number 89: Retrospective Performance Assessment Of The Test Guideline 426 On Developmental Neurotoxicity, ENV/JM/MONO(2008)(15).

40) OECD Series on Testing and Assessment Number 20: Guidance Document For Neurotoxicity Testing, ENV/JM/MONO(2004)(25).

Annex D
(informative)

Environmental hazard data set

D.1 Consideration of aquatic and terrestrial testing

D.1.1 Introduction

Test methods related to bioaccumulation should consider organisms at base trophic levels such as foundation species as well as annelids, nematodes, flatworms, relevant insects and Cladocerans (*Daphnia* spp). On exposure to nanomaterials, if these test organisms show decreased viability and signs of stress, a precautionary approach should be followed. Bioaccumulation is expected to increase with trophic level. Testing the abiotic aspects of ecosystems, followed by relevant foundation species allow researchers to generate important indicators of environmental impact.

The aquatic and terrestrial testing elements and conditions are taken directly from the Screening Information Data Set (SIDS) developed by the OECD. SIDS is utilized in OECD's High Production Volume ("HPV") Program and in the U.S. EPA's HPV Challenge Program. SIDS was developed through international consensus and is considered the minimum data set needed to conduct a screening-level hazard assessment on a substance. Avian toxicity and population/ecosystem-level studies are considered data elements that are above and beyond the SIDS. See

— OECD, Manual for Investigation of HPV Chemicals, Chapter 2: SIDS, the SIDS Plan, and the SIDS Dossier, available at www.oecd.org/dataoecd/13/18/36045056.pdf.

— U.S. EPA SIDS guidance is available at www.epa.gov/chemrtk/pubs/general/sidsappb.htm.

D.1.2 Aquatic toxicity elements

Inclusion of these elements in the data set (they also are present in data sets used in virtually every voluntary and regulatory program used throughout the world) is intended to provide an approach to determine whether nanomaterials are toxic to aquatic organisms. The data set includes acute toxicity tests to fundamentally different classes of aquatic organisms, which might exhibit independent mechanisms and extents of toxicity. The specific organisms identified are those for which standardized, widely employed test protocols are available; thus these organisms should be used, barring a justification for a different test organism. These toxicity tests should be performed as standard procedure, unless release to aquatic environments at any point in a nanomaterial's lifecycle can be ruled out.

Acute toxicity tests are limited in that they typically measure only lethality as an adverse effect; they are not capable of detecting sublethal effects, which could arise through entirely different mechanisms of action. For many nanomaterial applications, sublethal effects resulting from lower levels of exposure over a long period of time are more likely than lethality or other acute effects. Hence the data set provides that chronic toxicity to aquatic invertebrates *(Daphnia)* be assessed, in addition to or instead of acute toxicity, where evidence of possible persistence or bioaccumulation potential is available.

The three classes of test organisms are all residents of the water column in aquatic environments, whereas many materials with low water solubility (a typical feature of nanomaterials) are likely to accumulate in sediments, where exposure to sediment-dwelling or benthic organisms could occur. For this reason, toxicity testing using such organisms, e.g. *Hyalella azteca* (a shrimp-like crustacean), might also be needed.

D.1.3 Toxicity to terrestrial organisms

Where there is evidence (monitoring data, for example) of the presence of nanomaterials in soil or other land environments, or there is reason to anticipate that nanomaterials might be released to or otherwise reach and accumulate in soil or other terrestrial environments, toxicity testing using terrestrial animals and plants might be warranted. Nanomaterials used directly on land, whether by themselves (for example, through fertilizers or pesticides) or in products that might lead to releases to land environments (e.g. from agricultural films or farm structures) are candidates for such testing. Similarly, waste products containing nanomaterials or associated products (such as wastewater sludge) that are intentionally applied to land, or could reach it, should be considered for such testing. Finally, the potential for transfer of nanomaterials from air or water to land (via deposition of airborne particles, for example, or use of untreated water for irrigation) should be considered.

D.2 Additional data to be developed as needed

Where evidence emerges of toxicity to aquatic organisms, or of persistence or accumulation in these organisms or in aquatic environments, additional studies to better understand the longer-term toxicity, biological fate, and behaviour of nanomaterials in aquatic organisms should be considered. For example, chronic toxicity and ADME (absorption, distribution, metabolism, and excretion) studies in Daphnia might be triggered by such findings. Tracing methods, such as radiolabelling, or the use of new or experimental procedures may be needed to conduct these studies.

Annex E
(informative)

Environmental fate data set

E.1 Environmental fate data set

There are several factors that should be taken into account when creating the nanomaterial's profile related to the material's potential transport into the natural environment. These factors include:

- Environmental fate based on physical-chemical properties
  - Complete physical and chemical properties
  - Adsorption-desorption coefficients in release medium (soil or sludge)
  - Nanomaterial agglomeration or de-agglomeration, aggregation or disaggregation in applicable exposure media (e.g. air, water, soil, sludge, sediment)
- Persistence-potential screen
  - Organic-based nanomaterials only - Biodegradability test
  - Both organic-based and inorganic-based nanomaterials
    - Photodegradability/phototransformation
    - Stability in water (hydrolysis)
  - Bioaccumulation-potential screen of bacteria, algae, fish and Daphnia.

E.2 Additional data to be developed as needed

The following information is not part of the recommended data set, but it might be useful for clarifying the fate of nanomaterials in the environment:

Activated sludge respiration inhibition. The degree to which a nanomaterial will inhibit microbial respiration in activated sludge is an indicator of the material's potential for upsetting processes at wastewater-treatment plants.

Inhibitory effects (toxicity) to microorganisms in other relevant media. If a nanomaterial is released/deposited/transported to soils or sediments, then information about its potential inhibition of microorganisms is important for determining adverse ecosystem effects, on carbon or nitrogen cycles, for example.

Persistence potential in relevant media (i.e. along expected exposure pathways). For organic-based nanomaterials, an “inherent-biodegradability test,” “simulation test,” or other relevant biodegradability test is recommended if suitable analytical methods are available. But, as discussed above, there are no current standard methods for the biodegradability assessment of nanomaterials. Therefore adaptation of existing biodegradability guidelines [e.g. U.S. EPA OPPTS (Office of Prevention, Pollution and Toxic Substances), OECD] or development of customized biodegradability studies might be needed. If a nanomaterial is applied or deposited to soil, then an aerobic-soil or anaerobic-soil biodegradability study would be recommended. If a

nanomaterial is expected to pass through a wastewater-treatment plant as part of effluent entering a water body, or it is directly emitted, applied, or deposited (via air) to water, and if the nano-object density indicates a potential for settling to sediments, then the following testing is recommended:

— Adsorption/desorption coefficients in sediment,

— Aerobic/anaerobic sediment biodegradability study.

Transformations in inorganic-based materials. As with inorganic bulk materials, inorganic nanomaterials would not be degraded via biodegradability, though there could be a potential for transformations via oxidation-reduction reactions in the environment. Because there are no existing standards for such tests at present, a customized design might be needed. Its form would depend on the physical-chemical properties of the nanomaterial, expected uses, and exposure media pathways.

E.3 Other considerations when developing environmental fate information

Standard methods not currently available. At this time, there are no standard methods, or even widely accepted methods, for assessing nanomaterials' environmental fate (i.e. where nanomaterials can be found in the environment, and their transformation/persistence potential). There is also uncertainty about whether established methods for bulk materials can be applied to nanomaterials. As suitable analytical methods become available, it might be possible to modify existing environmental-fate assessment methods for bulk materials so that they meet the needs of nanomaterials. In the interim, it will be necessary to conduct environmental-fate assessments using best available scientific approaches.

Physical-chemical properties. For nanomaterials, there is still significant uncertainty about which physical-chemical properties affect partitioning and transport between environmental media (such as air, water, soil, sediments, and biota). For bulk materials, water solubility and vapour pressure are key parameters. But considering that low water solubility and low vapour pressure are common characteristics of nanomaterials, other physical-chemical properties, such as agglomeration state, surface charge, dispersibility, particle density, particle size, size distribution, or surface area (see Box 2), could be the key indicators for determining how a nanomaterial partitions in the environment. Sublimation might also be relevant in some cases. Further, the presence of natural organic matter (NOM) might play a role in the dispersal of carbon-based nanomaterials in the natural aqueous environment[41)].

There are still many unknowns on how physical-chemical properties can influence behaviour of nanomaterials in the environment. In time, when scientists can make accurate correlations between these properties of nanomaterials and their environmental behaviour, it might be possible to develop reliable models for determining partitioning and transport of nanomaterials after their release. For now, an interim understanding of how nanomaterials behave in the environment might be established by determining the following:

— Adsorption/desorption coefficients in soil (if land-applied or deposited to soil) or sludge (if discharged from wastewater treatment),

— Degree of nanomaterial agglomeration/aggregation or dispersibility in applicable exposure media.

Persistence-potential screen. Factors such as a nanomaterial's organic or inorganic basis, its physical-chemical properties, and the analytical methodology available for determining presence in the environment of parent or transformation products will be the main determinants for choosing appropriate tests to determine persistence potential. Biodegradability assessments, for example, should only be conducted on organic-based nanomaterials. A U.S. EPA OPPTS or OECD “Ready Biodegradability” or “Inherent Biodegradability” test is typically recommended, though it might be necessary to customize it. If radiolabelled nanomaterials are available for the biodegradation studies, this can be very helpful to the analysis.

41) H. Hyung, J.D. Fortner, J.B. Hughes, and J-H Kim, 2007, “Natural Organic Matter Stabilizes Carbon Nanotubes in the Aqueous Phase,” Environ. Sci. Technol. 41, 179-184.

For organic and inorganic-based nanomaterials alike, photodegradability/phototransformation studies might be applicable if it is expected that the nanomaterial would be found in air, surfaces of water or soil, or anyplace else where exposure to sunlight is likely. Discrete nanomaterials would likely be stable in water, so hydrolysis might not be a factor. However, if the nanomaterial is tested with a carrier or is incorporated in a bulk material, then hydrolysis might be a consideration for potentially liberating the nanomaterial.

Bioaccumulation-potential screen. No standard methods have been developed for assessing the bioaccumulation potential of nanomaterials. The octanol-water partition coefficient is used as a surrogate for bioaccumulation of bulk materials, but whether or not it is applicable for nanomaterials remains unclear. If the appropriate analytical methodology can be developed, then a Bioconcentration Factor (BCF) test or Bioaccumulation Factor (BAF) test might be appropriate.

Annex F
(informative)

Output worksheet

F.1 Describe nanomaterial and its applications

Develop basic descriptions (general overviews) of the nanomaterial and its intended uses.

- General Overview[42)]
- Nanomaterial description
  - material source or producer
  - manufacturing process
  - appearance
  - chemical composition
  - physical form/shape
  - concentration
  - size distribution
  - solubility
  - state of aggregation or agglomeration
  - material CAS number (if applicable)
- Main applications (current or expected)
- Stage of development
- General physical and mechanical properties of this material
- Past experience with this material or a similar material
- Potential benefits/positives of the material
- Potential risks/negatives of the material
  - health
  - environmental
- Sources of additional information.

42) The general overview should contain descriptions sufficient to guide development of more detailed profiles of the material's properties related to hazard and exposure potential at various lifecycle stages (such as manufacture, use, and end-of-life). This overview should be developed from information in the possession of the user or available in the literature.

F.2 Lifecycle considerations

F.2.1 Profile lifecycles

Define and catalogue the known and anticipated activities in a nanomaterial's lifecycle in the following table, detailing both the product form and the operations and activities that occur at that stage of the product lifecycle. Include activities within the organization's control as well as those upstream or downstream activities about which the organization has information.

Table F.1 — Lifecycle profile

Material lifecycle stage	Material form(s)	Operations and activities
Material sourcing (e.g. producer, supplier)		
Manufacturing level I (e.g. processor)		
Manufacturing level II (e.g. product fabrication)		
Manufacturing level III (e.g. filling/packaging)		
Distribution (e.g. retailer)		
Use/Reuse/Maintenance (e.g. consumer)		
End of life (e.g. recycling, disposal)		

F.2.2 Develop lifecycle properties profile

Identify and characterize the nanomaterial's physical and chemical properties, including property changes, throughout the full product lifecycle.

— Summary

— Data needs and actions: (see Table F.2, Lifecycles properties)

— Additional notes.

Table F.2 — Lifecycles properties: Summary table

Lifecycle stage[a]			
Technical or commercial name			
Common form			
	Result	Method	Remarks[b]
Chemical composition (including surface coatings)			
Component 1:			
Component 2:			
Component n:			
Crystal phase/molecular structure			
Physical form/shape			
Nano-object size and size distribution			
Surface area			
Nano-object density			
Solubility			
Bulk density			
Agglomeration/aggregation state			
Porosity			
Surface charge			

[a] Repeat table entries for each lifecycle stage if properties change

[b] E.g. reference, source of data, degree of certainty

F.2.3 Develop lifecycle hazard profile

Gather information and characterize the nanomaterial's potential health, environmental, and safety hazards over the entire lifecycle.

— Summary

— Data needs and actions (see Table F.3, Nanomaterial Lifecycle Hazard Profile; Table F.4, Base Set of Hazard Data; and Table F.5, Additional tests).

Table F.3 — Nanomaterial lifecycle hazard profile: Base set

Route	Hazard (characterization [e.g. low, moderate, high] and quantification if available [e.g. LOAEL=x mg/kg])	Source of information (e.g. report number)
Health Hazard Data		
1. Short term toxicity		
a. Pulmonary toxicity		
b. Oral toxicity		
2. Skin sensitization/irritation		
3. Skin penetration*		
4. Genotoxicity		
a. Gene mutation in prokaryotic cells		
b. Chromosomal aberration		
Environmental hazard data		
Aquatic toxicity		
1. Fish (fathead minnow or trout)		
2. Invertebrate (Daphnia)		
3. Aquatic plant (algae)		
Terrestrial toxicity (if significant release to terrestrial environments)		
1. Earthworms		
2. Plants		
Environmental fate data		
Water solubility		
Vapour pressure		
Adsorption/desorption coefficients in release medium (soil/sludge)		
Persistence potential screen		
Bioaccumulation potential screen		

Table F.4 — Base set of safety hazard data

Safety Hazard	
Flammability	
Explosivity	
Incompatibility	
Reactivity	
Corrosivity	

Table F.5 — Nanomaterial lifecycle hazard profile: Additional tests

Route	**Hazard** (e.g. low, moderate, high)	**Source of information** (e.g. report number)
Health hazard data — Additional tests as needed		
Biological fate and behaviour		
Chronic inhalation studies		
Chronic oral studies		
Chronic dermal irritation/sensitization studies		
Reproductive and developmental toxicity		
Neurotoxicity studies		
More extensive genotoxicity studies		
Focused toxicity studies		
Environmental hazard data – Additional tests as needed		
ADME studies on aquatic organisms		
Chronic toxicity to soil microorganisms and sediment- and soil dwelling organisms		
Further testing for terrestrial toxicity		
Avian toxicity		
Population/ecosystem-level studies		
Environmental fate data – Additional tests as needed		
Activated sludge respiration inhibition		
Microorganism toxicity		
Persistence potential in relevant media		
Potential for transformations via oxidation-reduction reactions **		

F.2.4 Develop lifecycle exposure profile

Assess potential for exposure from direct human contact or release to the environment at each stage of the lifecycle. The key deliverable from this section is the ***Exposure Characterization,*** a summary and synthesis of the gathered exposure information.

— Summary

— Data needs and actions (see Table F.6, Potential for direct human contact, and Table F.7, Potential for environmental release)

— Elaboration for human contact

  — Lifecycle stage

  — Step name

  — Nanomaterial form

  — Number of people potentially exposed

  — Potential routes for exposure (e.g. inhalation, ingestion, eye, dermal)

  — Personal protection equipment

  — Engineering controls

  — Procedures

  — Exposure potential

  — Estimated exposure and dose

  — Unknowns and uncertainties.

Table F.6 — Potential for direct human contact

Summary table			
Lifecycle stage[a]			
Nanomaterial form			
Nanomaterial			
Step (e.g. process step, transfer step, cleanup/disposal procedures)	**Engineering controls**	**Personal Protection Equipment (PPE)**	**Exposure potential**

[a] Repeat table entries for each lifecycle stage

— Elaboration for environmental release

  — Lifecycle stage

  — Step name

  — Potential release medium (i.e. routes of entry)

  — Engineering controls

  — Procedures

  — Release potential

  — Map fates of the material (e.g. degradation, transformations, or transfers to other media)

  — Estimated exposure and dose

  — Unknowns and uncertainties

    — What is the ultimate environmental fate of the material?

    — Does it accumulate in a particular environmental sink?

    — What are the populations that could be exposed?

    — What is the bioaccumulation potential?

Table F.7 — Potential for environmental release

Summary table			
Lifecycle stage[a]			
Material			
Step (e.g. process step, transfer step)	**Potential release medium (e.g. air, water, soil)**	**Engineering controls**	**Release potential**

[a] Repeat table entries for each lifecycle stage

Table F.8 — Exposure data: Summary table

Summary table					
Nanomaterial manufacture					
	Information				
Stage of development					
Number and location of manufacturing sites					
Annual production volumes (current and expected)					
Manufacturing method					
Number of workers handling nanomaterials at the manufacturing site					
Industrial functions (e.g. adhesive, coloring agent)	**Percent of production**	**Physical form and concentration**			
Function 1:					
Function 2:					
Function 3:					
Function n:					
Material processing					
Type of downstream industrial processing or use					
Number of processing or commercial use sites					
Industrial functions	**Percent of production**	**Number of sites**	**Number of workers at site**	**Number of workers exposed**	
Function 1:					
Function 2:					
Function 3:					
Function n:					
Material use					
Commercial or consumer product types	**Percent of production**	**Setting for use (homes, outdoors)**	**Concentration in product**	**Released during use?**	**Est. number of exposed workers**
Product Type 1:					
Product Type 2:					
Product Type 3:					
Product Type n:					
Distribution/storage					
Methods of delivery and storage					
Manufacturer					
Processors					
Distributors					
Retailers					
Consumers					
Post-use management					
	Expected disposal methods		**Expected recovery reuse/recycle methods**		
Manufacturers					
Processors					
End-users					

Elaborate on the types of employees, handling practices, and environmental containment and control equipment used to mitigate exposure potential at the manufacturing site(s) and the downstream processing site(s).

Elaborate on the use of the material in commercial and consumer products. Is there potential for exposure to the nanomaterial? If so, describe the circumstances. Describe any recommended controls for use. Describe recovery or recall techniques. Are the products intended for use by children or other sensitive populations?

Elaborate on the post-use management of the material across the lifecycle.

F.3 Evaluate risks

Using a synthesis of information collected in Step 2, produce a *Risk Evaluation (*estimates of the nature, likelihood, and magnitude of adverse effects on human health and the environment):

— Summary

— Data needs and actions (see Table F.9, Risk Evaluation).

Table F.9 — Risk evaluation: Summary table

Risk type	Nature, magnitude and probability	Source(s) of risk assessment
Human		
Respiratory	Nature: Magnitude: Probability:	
Dermal	Nature: Magnitude: Probability:	
Ingestion	Nature: Magnitude: Probability:	
Ocular		
Other health (e.g. reproductive, developmental, neural)		
Physical risks (e.g. explosion, fire)		
Environmental		
Aquatic		
Avian		
Mammalian		
Terrestrial		
Other (e.g. sludge)		

F.4 Assess risk management

Determine how to address any potential adverse impacts throughout the product's lifecycle. The key deliverable from Step 4 is the Plan for Risk Management, Monitoring, Compliance, and Reporting, based on the gathered exposure information:

— Summary

— Data needs and actions (see Table F.10, Material safety and handling manufacturer of nanomaterial; Table F.11, Material safety and handling nanomaterial user; Table F.12, Material safety and handling end-product user; Table F.13, Material safety and handling)

— Review cycle and conditions

— Plan and timeline for risk management, monitoring, compliance and reporting.

Table F.10 — Material safety and handling (manufacturer of nanomaterial)

Material event	**Recommended precaution/action**	**Expected effectiveness of recommended action** (e.g. what level of exposure might occur)
Receipt		
Processing		
Storage		
Handling		
Spills		
Transport		
Packaging		
Use		
Recycling		
Disposal (including packaging materials)		
Other		

Table F.11 — Material safety and handling (nanomaterial user)

Material event	Recommended precaution/action	Expected effectiveness of recommended action (e.g. what level of exposure might occur)
Receipt		
Processing		
Storage		
Handling		
Spills		
Transport		
Packaging		
Use		
Recycling		
Disposal (including packaging materials)		
Other:		

Table F.12 — Material safety and handling (end-product user)

Material event	Recommended precaution/action	Expected effectiveness of recommended action (e.g. what level of exposure might occur)
Receipt		
Storage		
Handling		
Spills		
Transport		
Packaging		
Use		
Recycling		
Disposal (including packaging materials)		
Other:		

Table F.13 — Material safety and handling (end of life)

Material hazard event	Recommended precaution/action	Expected effectiveness of recommended action (e.g. what level of exposure will be achieved)
Receipt		
Processing		
Storage		
Handling		
Spills		
Transport		
Packaging		
Use		
Recycling		
Disposal (including packaging materials)		
Other		

Annex G
(informative)

Sources and references for data sets

For each of the data sets of Step 2, existing and proposed test batteries and information sets were reviewed and adapted for nanotechnology applications. Step 2A's data set for product characterization was derived from the efforts of the International Life Sciences Institute (ILSI)[43] and the ongoing characterization work of the U.S. National Cancer Institute's Nanotechnology Characterization Laboratory (NCI-NCL)[44]. Sources for Step 2B's data set for hazard characterization included the OECD's Screening Information Data Set (SIDS) program[45] the ILSI Health and Environmental Sciences Institute review of available toxicology tests for nanomaterials[46]. Lastly, sources for Step 2C's exposure data set included reporting requirements for industrial chemicals regulated under the U.S. Toxic Substances Control Act[47] and guidance on nanomaterials provided by the U.S. National Institute for Occupational Safety and Health[48].

A variety of methods and protocols for conducting the kinds of tests included in the data sets, plus additional elements developed for the testing of conventional chemicals, are available (most notably through the OECD)[49].

An initiative sponsored by the European Commission, the AcuteTox program, is developing an entirely *in vitro/in silico* approach to human acute toxicity testing. Toxicity testing for nanomaterials should consider the objectives and advances in knowledge obtained through this program and use the most advanced suite of tests available as the guide for developing an organization's nanomaterial-specific test methods.

The European Center for the Validation of Alternative Methods has developed a tiered strategy that uses quantitative structure-activity relationship ("(Q)SAR") information → cytotoxicity testing → computational model for metabolism → biotransformation assays → cell-specific to toxicity tests[50]. Although (Q)SAR information is not yet available for nanomaterials (at the time of publication), the remaining test methods recommended by ECVAM are available and should be used where appropriate. ECVAM allows for a "very toxic" label if any of the aforementioned tests result in a "very toxic" result. No further testing would be recommended.

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43) http://ilsi.org.

44) See Assay Cascade of the Nanomaterial Characterization Laboratory of the National Cancer Institute (http://ncl.cancer.gov/working_assay-cascade.asp).

45) See OECD, "Manual for the Investigation of HPV Chemicals," chapter 2, available at http://www.oecd.org/document/7/0,2340,en_2649_34379_1947463_1_1_1_1,00.html.

46) 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.

47) See EPA's guidance document "Instructions for Reporting for the 2006 Partial Updating of the TSCA Chemical Inventory Database," available online at http://www.epa.gov/oppt/iur/pubs/tsca_cheminv_database.pdf (especially Section 1 and Table 1-1).

48) See NIOSH's "Approaches to Safe Nanotechnology," available online at http://www.cdc.gov/niosh/topics/nanotech/safenano/.

49) The OECD Guidelines for the Testing of Chemicals are tools for governments and industry worldwide to assess the safety of chemical products, and are available free of charge on the OECD public website at http://www.oecd.org/env/testguidelines.

50) The OECD issued additional guidance on QSAR in 2010: "Report of the Expert consultation on Scientific and Regulatory Evaluation of Organic Chemistry Mechanism-Based Structural Alerts for the identification of DNA-binding Chemicals" (OECD 2010).

Bibliography

[1] ISO 9001, *Quality management systems — Requirements*

[2] ISO 14001, *Environmental management systems — Requirements with guidance for use*

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