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PHYSICAL-CHEMICAL DECISION FRAMEWORK TO INFORM DECISIONS FOR RISK ASSESSMENT OF MANUFACTURED NANOMATERIALS

Series on the Safety of Manufactured Nanomaterials
No. 90

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The Environment, Health and Safety Division publishes free-of-charge documents in 12 different series: **Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides; Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; Safety of Manufactured Nanomaterials,** and **Adverse Outcome Pathways**. More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organisations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

This publication is available electronically, at no charge.

For this and many other Environment, Health and Safety publications, consult the OECD's World Wide Web site (www.oecd.org/chemicalsafety/)

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FOREWORD

The OECD Working Party on Manufactured Nanomaterials (WPMN) is a subsidiary body of the OECD Chemicals Committee. This programme concentrates on human health and environmental safety implications of manufactured nanomaterials (limited mainly to the chemicals sector), and aims to ensure that the approach to hazard, exposure and risk assessment is of a high, science-based, and internationally harmonised standard. It promotes international co-operation on the human health and environmental safety of manufactured nanomaterials, and involves the safety testing and risk assessment of manufactured nanomaterials.

Physico-chemical properties are key starting points for risk assessments of chemicals. They provide a description of the chemical, and prove useful in assessment of environmental behaviour, uptake routes into organisms, toxicokinetics and ultimate effects in organisms. For nanomaterials, relevant physico-chemical properties can differ from those commonly considered for non-nanomaterials (e.g. surface area versus boiling point). With this in mind, The OECD WPMN has striven to develop tools that can assist identifying appropriate physico-chemical parameters to better understand the link between those parameters and potential human health and environmental effects of nanomaterials, and to facilitate prediction of such effects. This document provides guidance on which test methods are (or are not) appropriate to measure a given physico-chemical parameter considered key to characterization and identification, for a given type of nanomaterial. It is supported by the Guiding Principles for Measurements and Reporting for nanomaterials: Physico-Chemical Parameters [ENV/JM/MONO(2019)13], which helps to identify suitable methods, pinpoint method limitations and highlight good reporting practices to address key purposes identified within the present document. The guiding principles are also intended to aid in improving the conduction of the studies, in addition to promoting consistent data reporting (including reporting details on sample preparation and measurement protocols) to maximise utility and comparability of the data. These two project are complementary and are collectively intended to facilitate the identification of the most useful parameters and best available methods while maintaining rigour in data quality and reporting. It is important to note that this document is not intended for risk assessment per se but rather presents an approach to gather fit-for-purpose physico-chemical information to more fully understand the behaviour of nanomaterials in biotic and abiotic systems.

This framework, and its guiding principles, are recognised as a living document, and they will be subject to amendment and refinement as researchers gain greater understanding in using it.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology of the OECD.

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Introduction

1. Physico-chemical properties are key starting points for risk assessments of chemicals. They provide a description of the chemical, and prove useful in assessment of environmental behaviour, uptake routes into organisms, toxicokinetics and ultimate effects in organisms. For nanomaterials, relevant physico-chemical properties can differ from those commonly considered for non-nanomaterials (e.g. surface area versus boiling point). With this in mind, OECD included a number of physico-chemical endpoints in its Testing Programme of Manufactured Nanomaterials[1].

2. For nanomaterials identification, the description methods for "conventional" materials are insufficient to describe nanoscale features such as form, quantum effects, and surface properties that make nanomaterials unique, since different forms of the same manufactured nanomaterial can behave differently. In addition to chemical nomenclature (e.g. IUPAC), it is therefore important to consider additional nomenclature, e.g. ISO nomenclature standards like (ISO, 2014) and (ISO, 2015) and the CODATA-VAMAS document on a Uniform Description System (CODATA-VAMAS, 2016). Risk assessment may further be facilitated by identifying and evaluating the source(s) of a particular nanomaterial (e.g. natural or manufactured, specific industry) as part of the nanomaterial identification.

3. Identifying appropriate physico-chemical parameters has been a priority for the OECD Working Party for Manufactured Nanomaterials (hereafter WPMN) to better understand the link between those parameters and potential human health and environmental effects of nanomaterials, and to facilitate prediction of such effects. Prior efforts within the WPMN have surveyed the applicability of existing physico-chemical characterisation methodologies to the assessment of nanomaterials in the OECD Testing Programme of Manufactured Nanomaterials, and the OECD published a *Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials* (OECD, 2009) which includes a review of the applicability of 22 physico-chemical methods for use with manufactured nanomaterials. Few of the existing test guidelines were considered to provide information relevant to the potential toxicological impact of such nanomaterials, and the document identified the following set of physico-chemical characteristics as a necessary pre-requisite of toxicological assessment: agglomeration/aggregation, catalytic properties, composition, concentration, crystalline phase, dustiness, fat solubility/oleophilicity, grain size, hydrodynamic size/particle size measurement/distribution, length, purity, shape, specific surface area, surface charge, surface chemistry, water solubility/hydrophilicity, and zeta potential. Subsequently, through two expert meetings – one in Mexico, in collaboration with ISO TC 229 (OECD, 2014a) and one in Washington, DC (OECD, 2016a) – and an evaluation of the data developed under the WPMN Testing Programme (OECD, 2016b), the OECD WPMN has worked toward developing guidance on the appropriate characterisation of manufactured nanomaterials and identifying which test guidelines should be either developed or adapted for specific physico-chemical endpoints. A number of physico-chemical parameters have

[1] Details of the Testing Programme are publicly available at the OECD website: www.oecd.org/chemicalsafety/nanosafety/testing-programme-manufactured-nanomaterials.htm.

been identified as relevant to and important in the assessment of nanomaterials, however, guidance on how and when to apply these parameters is not yet available.

4. In the Testing Programme, around fifteen different physico-chemical endpoints were identified. Some of these are intrinsic properties of the pristine nanomaterial, where others are extrinsic properties. In contrast with intrinsic properties, the extrinsic properties of a nanomaterial are not only determined by the material itself, but are also influenced by (components in) its surroundings (e.g. dissolution rate of a certain nanomaterial may differ between biological media). Characteristic properties of the nanomaterial as produced may also change under exposure conditions: physico-chemical properties such as surface area or surface charge could change if dissolution occurs under conditions of environmental or biological exposure. This may be further complicated by the fact that nanomaterials will be increasingly manufactured to be more complex in composition, i.e. nanomaterial assemblies with several materials/chemicals, each of which may follow distinct pathways under conditions of environmental or biological exposure. As a result, the number of measurements dramatically increases if such properties need to be measured for all combinations of nanomaterials and environments. Clearly, this is not feasible and needs to be limited with a systematic approach.

5. The Physico-chemical Decision Framework currently presented is the next step in the development of guidance for physico-chemical characterisation and, where necessary, the development of new test guidelines. It is intended to be consistent with and make use of other related projects, including ProSafe (www.h2020-prosafe.eu), NANoREG (www.nanoreg.eu)[2], and the Nano-GRID framework developed by the US (Collier, et al., 2015; Martin D.P et al., 2016; Kennedy AJ, et al, 2017), while being applicable in regulatory contexts like the US Toxic Substances Control Act (TSCA) new chemicals program (US, 1976) or the European REACH Regulation (EU, 2006; EU 2018). Due to the continuous rapid development of methodologies to determine the necessary parameters, the current document does not indicate specific methodologies. Overviews of available methods are available elsewhere (e.g. ISO/TC 229, 2015; and OECD 2018), or scientific literature (Rasmussen K, et al. 2018).

6. The first step in any chemical evaluation is substance characterisation and identification (i.e. “What They Are”). Accordingly, the Decision Framework begins with guidance to manufacturers of nanomaterials with recommendation on test methods that are (or are not) appropriate to measure a given physico-chemical parameter for the purpose of substance characterisation, for a given type of nanomaterial. This includes information on chemical composition, and particle, surface, and intended use properties (see Phases 1 and 2 of the decision framework, below).

7. After this initial characterisation phase, any identified concerns associated with the nanomaterial (e.g. environmental exposure (“Where They Go”) or specific toxicity or reactivity (“What They Do”) can further inform the set of appropriate physico-chemical parameters and test methods. For these later steps, the framework identifies key ‘purposes’

[2] Literature and outcomes of NANoREG and ProSafe can be consulted through these sites:

NANoREG:
www.rivm.nl/en/About_RIVM/Mission_and_strategy/International_Affairs/International_Projects/Completed/NANoREG

ProSafe:
www.rivm.nl/en/About_RIVM/Mission_and_strategy/International_Affairs/International_Projects/Completed/ProSafe

(e.g. human or environmental exposure, environmental fate, toxicity, etc.) for which physico-chemical parameters and data types are needed to aid in addressing concerns. Here the specification of purpose for a particular physico-chemical parameter can vary with the specific question being asked. It is important to note that the later stages of the framework largely deal with extrinsic properties, in particular where the purpose of certain physico-chemical properties aims at predicting environmental fate or toxicokinetics of the material (e.g. what will be the environmental compartment of most concern, or how likely is it that a nanomaterial reaches the target site and in which specific form?). The combination of a physico-chemical parameter with its purpose guides the selection of the most appropriate measurement (including sample preparation considerations (OECD, 2012). These steps (What They Are, Where They Go, What They Do) may in fact overlap. For example, information on particle size distribution might be needed for identification of the material, but may also be necessary for fate assessment. While the parameter (i.e. particle size) remains the same, each individual purpose (i.e. identification and fate assessment) may require different assessment techniques, sample preparation considerations, and fundamentally different measurands (e.g. number-based size distribution, or volume specific surface area) to meet the information needs. For instance, particle size distribution for the substance as manufactured may be relevant for simple substance identification, while the particle size distribution of the substance in environmental media would be more relevant for aiding in evaluation of fate and transport in the aquatic environment. Through the use of decision trees, a user is guided through specific questions to identify the most relevant purposes and related physico-chemical parameters to fill relevant knowledge gaps for hazards or risks.

8. Once essential information for a specific purpose is identified, available data and/or additional testing to fill data gaps can be identified to address the concern. For instance, for a complex nanomaterial that contains heavy metal elements in its core and is coated by multiple shells, where the main (risk) concern is related to the metal in the core, the specific purpose will be to determine if these metals can become bioavailable (regardless of specific behaviour of the multiple shells), which might require leaching studies under accelerated testing conditions in relevant media to assess the availability of the metal in the core, but not necessarily a detailed assessment of the deterioration of the shells. Once key purposes and the related physico-chemical parameter(s) are identified through the Decision Framework, methods (and reporting, e.g. on sample preparation) that were used in generating available data and/or necessary methods to determine such physico-chemical parameter(s) to fill data gaps can be scrutinised by applying the *Guiding Principles for Nanomaterial Characterisation*, which is the companion project to the Decision Framework for selection of fit for purpose test methods (and their reporting).

9. Physico-chemical characterisation endpoints can be measured through multiple methods, each with their own nuances and insights into the material's behaviour and properties. Varied sample preparation requirements and approaches often accompany these measurement methods, and, frequently, sample preparation and measurement protocols require adjustment (OECD, 2012) in order to provide the most relevant information for different purposes (e.g. for material identification versus informing exposure potential). Although each method and each endpoint has its own nuances, the general process for determining method suitability, limitations, and necessary reporting requirements for comparability with other techniques/equipment is similar.

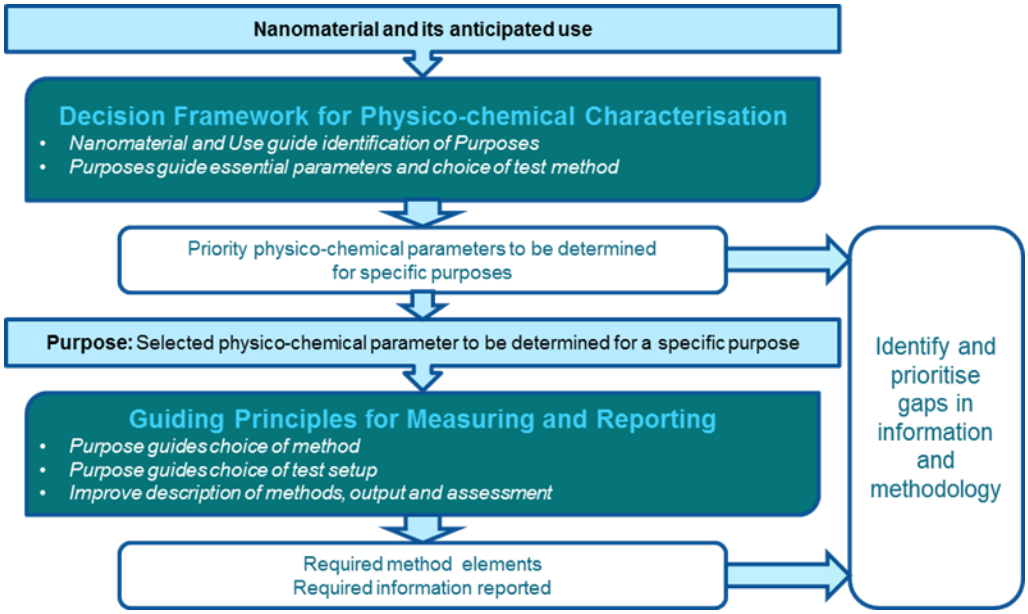
10. The *Guiding Principles* provide guidance that helps identify suitable methods, pinpoint method limitations and highlight good reporting practices to address key purposes identified within the present document. The guiding principles are also intended to aid in

improving the conduction of the studies, in addition to promoting consistent data reporting (including reporting details on sample preparation and measurement protocols) to maximise utility and comparability of the data. These projects are collectively intended to facilitate the identification of the most useful parameters and best available methods while maintaining rigour in data quality and reporting (Figure 1). In addition, the projects intend to support and supplement the work of the WPMN in prioritising the adaptation and development of test methods needed for the physico-chemical analysis of nanomaterials, recognising the growing diversity of nanomaterials and relevant considerations.

11. It is important to note that this document is not intended for risk assessment per se but rather presents an approach to gather fit-for-purpose physico-chemical information to more fully understand the behaviour of nanomaterials in biotic and abiotic systems. The physico-chemical framework can, in part, reduce the need for testing through the facilitation of strategic abiotic testing that, if sufficiently correlated with biotic outcomes, can reduce the need for biological testing (or the range of testing required) for decision making. The hazard levels of constituent chemical components of nanomaterials are utilised to guide and prioritise where additional physico-chemical analysis may be necessary. This process is intended only for narrowing the broad selection of potential physico-chemical parameters based on available hazard classifications and does not go beyond this. Expert judgement is required to determine if the hazard assumptions for the nanomaterials are valid based on the strength and weight of evidence evaluations of each individual chemical constituent and mixtures thereof, and is outside the scope of this document.

12. From a regulatory perspective, this framework helps to identify the appropriate methods for characterising physico-chemical endpoints for different manufactured nanomaterials, or types of nanomaterials, for use in risk assessment and management, starting with basic substance characterisation. This document is intended to provide a generalized process that is capable of identifying the relevant information from relatively simple to more advanced nanomaterial systems. However, for complex mixtures the worksheets and decision trees may need to be completed for the individual particle types. Each decision tree identifies appropriate physico-chemical parameters for a given nanomaterial type and scenario while providing context on the way the information is intended to be used. Additional evaluation of the available methods through the use of Guiding Principles will further identify the methods that are considered appropriate for specific manufactured nanomaterials for a particular purpose (e.g. for use only in screening or needed for use in a more robust risk assessment), but also those that are not considered appropriate. Furthermore, this framework and evaluations through the Guiding Principles could further identify/prioritise which test guidelines on physico-chemical characterisation should be developed or whether existing test guidelines should be modified. The prioritisation will be based, in part, on the evaluation of need and usefulness of the methods in both projects. Some of the identified methods may be considered suitable for all sorts of nanomaterials, others only limited to some or only one nanomaterial type (e.g. Raman spectroscopy may be limited to the determination of the diameter of small carbon nanotubes, and inductively-coupled plasma mass spectroscopy is generally limited to metals and a few non-metals with largely varying limits of detection).

Figure 1. Overview of input and output as well as interlinkages of the Physico-chemical Characterisation Decision Framework and the Guiding Principles for Measuring and Reporting



Framework Overview

13. The presented framework underlines the importance of integrating specific information needs (i.e. purposes) with physico-chemical measurements. As a whole, the framework is intended to clarify requirements and reduce uncertainty in the applicability of testing and measurements for resolving knowledge gaps. Apart from a fundamental base-set of physico-chemical parameters believed to be generally important, the framework does not impose a finite set of parameters and testing regiments. It is intentionally focused on the process of identifying and acquiring the most relevant physico-chemical parameters (and analysis considerations) for resolving perceived data gaps. Recognising the increasing complexity of emerging nanomaterials the use of grouping and read-across approaches are integrated in the process to ensure that the physico-chemical parameters identified remain both current and fit-for-purpose noting continuing advances in knowledge. Considerations and nuances from traditional physico-chemical characterisation of chemicals and particles (including more established nanomaterials) are taken into account throughout this document.

14. The Decision Framework consists of three primary evaluation phases identifying specific purposes and key physico-chemical parameters/endpoints for each purpose Figure 2:

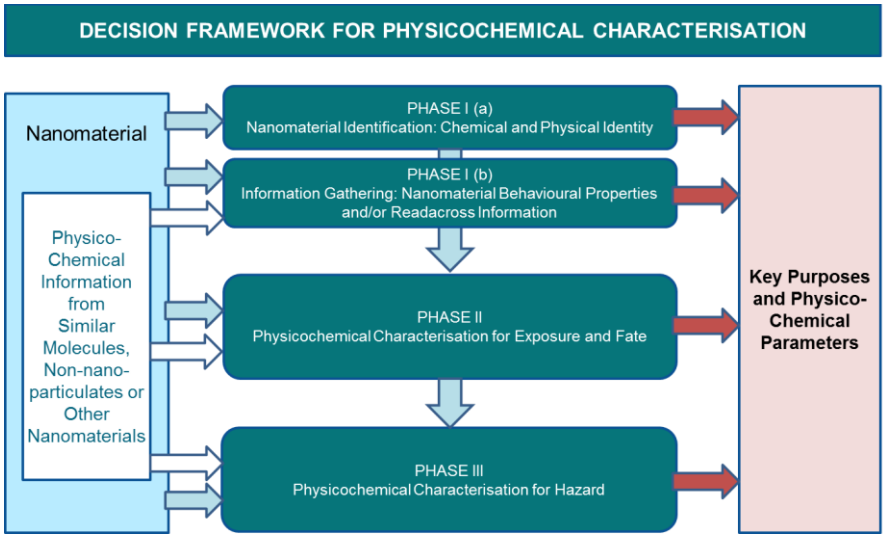
1a) Nanomaterial Identification

1b) Nanomaterial Information Gathering

2) Human and Environmental Exposure and Fate Assessment

3) Human and Environmental Hazard Assessment

Figure 2. Overview of the Decision Framework for Physico-chemical Characterisation



15. ***Nanomaterial Identification*** is a key phase for risk screening programs, such as the US TSCA new chemicals program (US, 1976) or the EU REACH Regulation (EU, 2006) [recently updated with specific requirements for nanomaterials (EU, 2018)], that rely

on molecular identity to drive its assessment. This includes gathering data on relevant physico-chemical parameters that characterise the material, including basic information on the nanomaterial's physical form (shape, size, surface area, etc.) and chemical identity of its components. Based on this identification of the nanomaterial potential issues are identified for further assessment, including the relevance of potential unique and novel properties. Unique and novel properties are material attributes that might result in unanticipated hazard or exposure behaviours when compared to larger substances. Such properties may include unusual resistance to agglomeration or engineered specific reactivity. Additional information on unique properties is provided in Appendix II.

16. ***Information Gathering*** provides context and baseline information useful for judging whether further data is necessary for a given decision. Existing knowledge of the nanomaterial is gathered including its intended uses. To inform the need and extent of phases 2 and 3 of the framework, further information may be gathered in this phase as well. Information from larger particulate chemical substances as well as from other (similar) nanomaterials can be examined to identify if the measurement of additional parameters is warranted based on potential hazard and exposure considerations. Additionally Information Gathering may also identify key analogues or 'source' materials for grouping and read-across approaches that may indicate the need for consideration of additional physico-chemical parameters (see Appendix I). For instance, the identification of fibre-like materials would initiate a need to have information regarding elastic modulus that may be irrelevant for more spherical nanomaterials (Nagai H, et al., 2011). Likewise, conduction band levels might be of interest for semiconductor materials, or surface oxidation states for metal oxides, whereas these parameters are less important for metals, or only useful on a case-by-case basis (Zhang H, et al., 2012). As nanomaterials become more complex (e.g. composite materials, or materials with several layers of coatings and/or functionalisation), the use of source materials may become more important, in particular, when attempting to assess the potential impact of complex materials and those that possess unique properties. 'Source' materials are intended to provide guidance on further characterisation considerations and not replace characterisation in full. For instance, two insoluble solid nanomaterials may be coated with a similar chemical composition. Existing data from one of those substances indicates that the coating is readily dissolved resulting in full exposure of the underlying material in synthetic lung lining fluid. This information would trigger a need to confirm if this scenario manifests itself in the untested material and also would focus consideration on the behaviour of the underlying substance and potential impact of the solubilised constituents of the surface layer in further risk assessment.

17. In the second phase, the key purposes for identifying physico-chemical parameters and measured data relevant to ***Human, Environmental Exposure, and Fate Assessment*** are identified. Based on the form of the substance, likelihood for exposure (e.g. based on intended use) and identified key purposes, the need for additional physico-chemical parameters should become evident from this portion of the framework. Phase III is engaged only when Phase I indicates significant data gaps from existing knowledge (including use, exposure and hazard information) and basic measurements. It is also intended to address scenarios where exposure phenomena might be complex due to transformation, partial dissolution and other complex phenomena taking place. The presence (or the absence) of unique and novel behaviours related to exposure are also intended to be evaluated in Phase II, in addition to relevant physico-chemical considerations that might alter exposure, fate and relevant toxicokinetics. This phase might be entered in material design to bring into consideration safety aspects that would not become apparent through the baseline physico-chemical analysis.

18. In the third phase, key purposes for identifying physico-chemical parameter and measured data relevant to ***Human and Environmental Hazard Assessment*** are identified. Different chemical substances and general classes of materials will affect hypotheses and related purposes for additional physico-chemical characterisation related to hazard characterisation. Specific considerations and their importance will largely depend on the chemical identity and particle structure (i.e. whether a chemical is part of the core or part of the surface) of the nanomaterial. Consequently, information from 'source' materials (chemicals) becomes more important in the overall assessment, as well as the identified links between their physico-chemical properties and the hazard mechanisms that drive the purpose. For instance, conduction band consideration may only be relevant for uncoated semiconductor materials, or certain metal oxides might warrant interpretation of surface oxidation states and reactivity. Likewise, consideration for fibre-like materials would include items like elastic modulus, length, and diameter in addition to biodurability. Complex material designs intended to mitigate the *in vivo* release of hazardous substances (e.g. for biocidal use) would obviously involve relevant testing of the mechanism and any released form or complexes of the hazardous substance. Linking of the physico-chemical testing in this section to relevant bioassays is recommended to fill knowledge gaps and reduce uncertainty.

Phase 1: Nanomaterial Identification and Information Gathering

19. A basic description of the nanomaterial and its potential applications is necessary to begin the process of identifying relevant knowledge gaps and identified purposes for physico-chemical parameter measurements for filling those information gaps. This phase is intended to capture baseline information believed to be generally relevant for characterising (Phase 1a); comparing and assessing nanomaterials (Phase 1b).

20. This basic information involves:

1. Chemical substance information: Chemical composition, known impurities, and crystallinity.
2. Particle properties: Particle size distribution of the substance and contextual particle structure/shape information (e.g. where and how constituent chemical substances are or are believed to be distributed).
3. Surface properties: Specific surface area and information on surface chemistry (general composition and intentional surface functional groups), surface ionisation capacity and residual acid or base content.
4. Intended use properties: Information on intended use and applications.
5. Physical properties: e.g., solubility (although this is media specific)

21. This basic information can then be applied to identify appropriate 'source' materials (e.g. similar[3] nanomaterials or non-nanomaterials) and relevant use scenarios, for identifying concern-based physico-chemical property information and gaps relevant to

[3] How to define or confirm similarity may very well depend on the specific purpose of the use of the data. In case the user intends to use such information for grouping or read-across purposes, more detailed investigation of the similarity is needed (including similarity in fate and toxicokinetic behaviour of both materials, which may extend beyond physico-chemical properties alone).In addition, for a regulatory requirement more rigour is generally needed than for choices in the design phase of materials.

known hazard and exposure considerations. Through this process, additional relevant physico-chemical parameters may be identified and added to the list for consideration. Using this approach, the methodology should remain relevant for next generation nanomaterials that may not be simply classified as, for example, a metal oxide, metal or carbonaceous nanomaterial.

22. This assessment can also screen for other pertinent information such as known material transformations (e.g. dissolution, sulphurisation, and oxidation) and the potential for unique properties (see Appendix II) that may require special consideration through combined nanomaterial attributes and intended use considerations. This could reasonably encompass parameters such as media temperature, pH, conductivity, organic matter content, etc. This phase also provides an overview of the nanomaterial, its potential interactions with humans and the environment, and determines if the baseline physico-chemical parameter information is sufficient or if it needs to be expanded based on the hazard level of chemical constituents or through considerations from 'source' chemical substances. If baseline information is deemed not sufficient, the decision framework proceeds to the subsequent Phases II and III to gather additional information.

23. The decision framework for Nanomaterial Identification is provided in Table 1 and that for further Information Gathering in Table 2.

24. The process begins with compiling basic information on the nanomaterial's chemical composition and particle structure and known impurities. Subsequently, it lists additional physico-chemical parameters related to known hazards and those related to relevant exposure routes. It then identifies how the intended application and use of the nanomaterial (and related design considerations) may add new considerations to the potential for exposure and associated hazards.

25. Next, considering the intended applications, the potential for the nanomaterial to chemically or physically transform is considered. The extent of these transformations and relevant timescales are used to determine if exposure to a nanomaterial is likely, and if so, to which nanomaterial (the pristine or the transformed material). If it is likely that the nanomaterial may no longer exist as a nanomaterial under realistic scenarios (e.g. completely dissolves or irreversibly aggregates to sizes well above the nanoscale under realistic exposure conditions), then additional physico-chemical characterisation of the nanomaterial is not required and the process proceeds with a non-nanomaterial assessment. However, if a significant portion of the substance is likely to remain a nanomaterial (what is considered a significant proportion will need to be further refined with experience and may to some extent depend on the regulatory context), the physico-chemical parameter identification process proceeds with the recognition of the remaining material and the relevant form of the substance. Expert judgement is required to estimate the relevant nanomaterial(s) for evaluation and basic information on that substance is requested as feasible and as needed for further evaluation. Depending on the timescale and degree of transformation, both the original nanomaterial and the transformed nanomaterial may need to be considered throughout the process.

Table 1. Decision framework for nanomaterial identification.

Worksheets are included in a separate document (Annex 1).

Q1-1. General description of the nanomaterial	
Short, general description of product form(s), Synthesis/production route, Typical storage conditions	**Worksheet 1a – Particle Chemical Identification**
Q1-2. What is the chemical composition of the nanomaterial?	
Composition-overall (mass %), Core composition (mass %), Surface composition (mass %), Impurities (mass %), Chemical structure (molecular formula)	**Worksheet 1a – Particle Chemical Identification**
Q1-3. What is the physical identity of the nanomaterial (as manufactured)?	
Surface area, Density, Porosity, Shape (3D dimensions, aspect ratio), Crystallinity, Mean particle size, Particle size distribution (% <100 nm by number, % <100 nm by weight)	**Worksheet 1b – Particle Physical Identification**
Q1-4. What are known physico-chemical properties of the nanomaterial?	
For each component: Physical state, Melting/freezing point, Boiling point, Substance Density, Vapour Pressure, Water solubility	**Worksheet 2a – Baseline Component Physico-chemical Properties**
For the solid particle systems (as manufactured): Peclet number, Photocatalytic activity, Surface reactivity, Other unique/enhanced properties, Isoelectric point, pH of suspension in water, dispersion stability in water, aggregation/agglomeration state	**Worksheet 2b – Baseline Particle Physico-chemical Properties**
Q1-5. Which potential issues of the solid particle system can already be identified?	
Shape, Engineered to promote reactivity, Engineered to prevent agglomeration, unique/enhanced properties	**Worksheet 2c – Potential Issues Of The Solid Particle System**

26. Due to the complexity associated with potentially transformed chemical substances and nuances associated with complex surface compositions, identifying essential physico-chemical parameters to inform hazard and/or exposure assessment may be a challenge. To facilitate this identification, information on important physico-chemical parameters related to hazards or exposure is now sought from source materials that are structurally and compositionally similar. Relevant source materials are chemical substances that may behave similarly to nanoparticle or are nanoparticles, themselves. Larger particles of similar chemical composition and particle structure whose behaviour remains dominated by diffusion and surface properties (e.g. particle Péclet numbers[4] <<1) would be considered a relevant source material along with other nanomaterials. The intended purpose (e.g. informing on environmental fate or on health hazard) and other considerations need to be taken into account when identifying appropriate source materials (see Appendix III). For instance, fibre-like nanoparticles would draw information from structurally similar nanomaterials as well as larger sized materials of similar shape and composition. This evaluation should trigger (the need for) additional physico-chemical information for particle aspect ratio, length evaluation, dissolution kinetics, and information regarding the ability of the substance to be dispersed in air.

4 See Appendix III for further elaborations on this parameter.

Table 2. Decision framework for nanomaterial information gathering.

Worksheets are included in a separate document (Annex 1).

27. In the above process, a range of source materials has been screened for physico-chemical parameters relevant for hazard and exposure considerations. With consideration of this information, the intended use, design (engineered particle structure) of the nanomaterial, and its reported behaviour is considered to identify the potential for any novel properties that would require additional scrutiny. In the context of this framework, a novel property is defined as an atypical material property that has the potential to alter the behaviour of the substance and is typically the reasons for intentionally engineering the nanomaterial. This may involve designed transport properties or engineered reactivity in a manner not consistent with predicted size dependent scaling of larger yet similar materials. Some indicators of novel properties could be unusual resistance to agglomeration in complex aqueous media (e.g. salt water, serum), a step-change in surface catalytic behaviour or significant changes in adsorption of electromagnetic radiation from nanoscale to micron-sized nanomaterials where the hazard implications are not well understood. This topic is discussed in more detail in Appendix II. If novel properties are suspected, targeted experimentation is required to elucidate relevant hazard or exposure defining physico-

chemical parameters. This requires expert judgement and investigative coordination with hazard and exposure assessments.

28. Once the above information has been collected and analysed, a determination is required based on the overall intended purpose, whether or not additional physico-chemical parameters and measurements are required for further exposure, hazard or risk assessment. If additional information is not deemed necessary, (e.g. the nanomaterial is fully soluble in a relevant timeframe, or is likely to simply behave as an inert granular particle in soil), the framework is exited and further exposure, hazard or risk assessment can be based on available information.

Phase 2: Physico-chemical Properties for Exposure and Fate Assessment

29. The relevant physico-chemical properties for exposure and fate assessment define key behaviours that influence the distribution, transport, and fate behaviour of nanomaterials in the environment and exposure to organisms. This portion of the framework identifies physico-chemical parameters for the following purposes (Table 3):

1. Identification of the most relevant material form and exposure routes for human health and the environment.
2. Estimation of environmental compartmental distribution and fate.
3. Estimation of removal during waste water treatment.
4. Estimation of transit from exposure site to systemic circulation in humans and organisms.

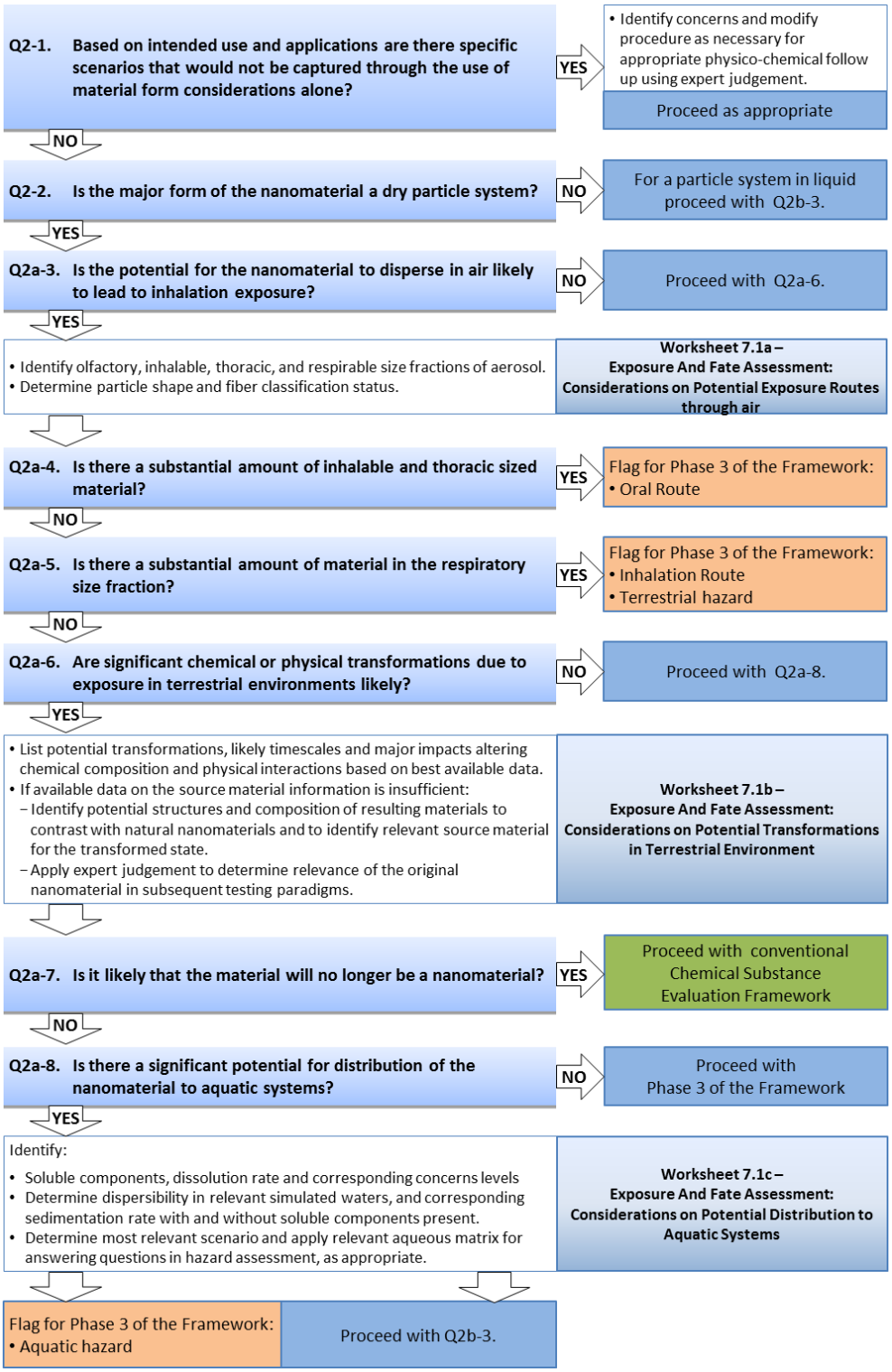
30. Here, the term material form is used to describe how the nanomaterial would likely be presented in a human or environmental exposure situation. Relevant material forms include dry particles systems (e.g. powders, pellets) and particle systems in liquids (e.g. slurries and pastes). Nanoparticles embedded in a solid matrix (e.g. polymer) could fall into either category depending on how the substance is delivered post-manufacturing and the respective continuous phase (e.g. air (gas) or liquid). This initial state is important for prioritising and collecting relevant physico-chemical parameters for exposure assessment and subsequently impacts compartmental distribution and fate.

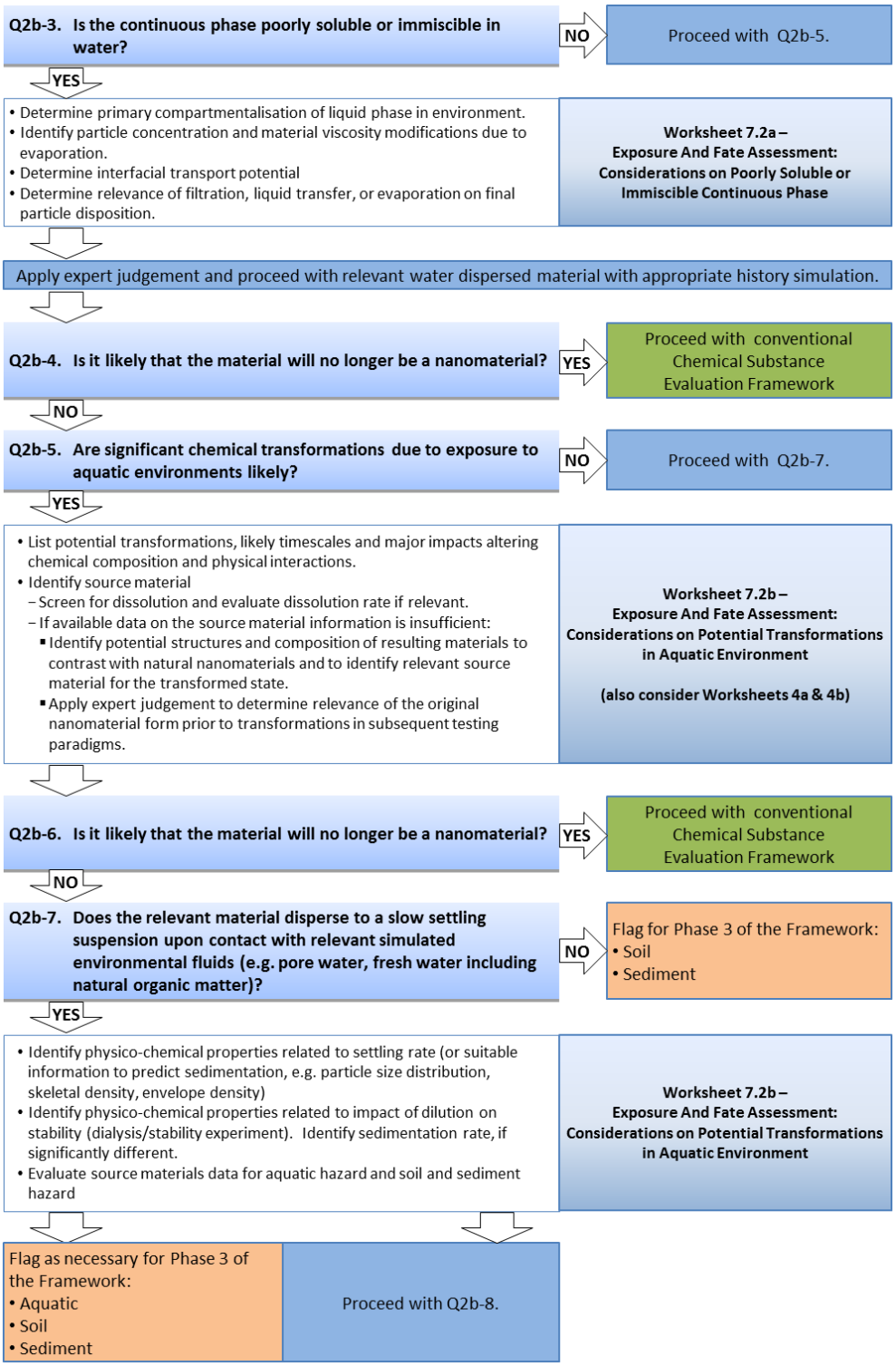
31. A decision framework for physico-chemical parameters for Exposure and Fate Assessment is provided in Table 3.

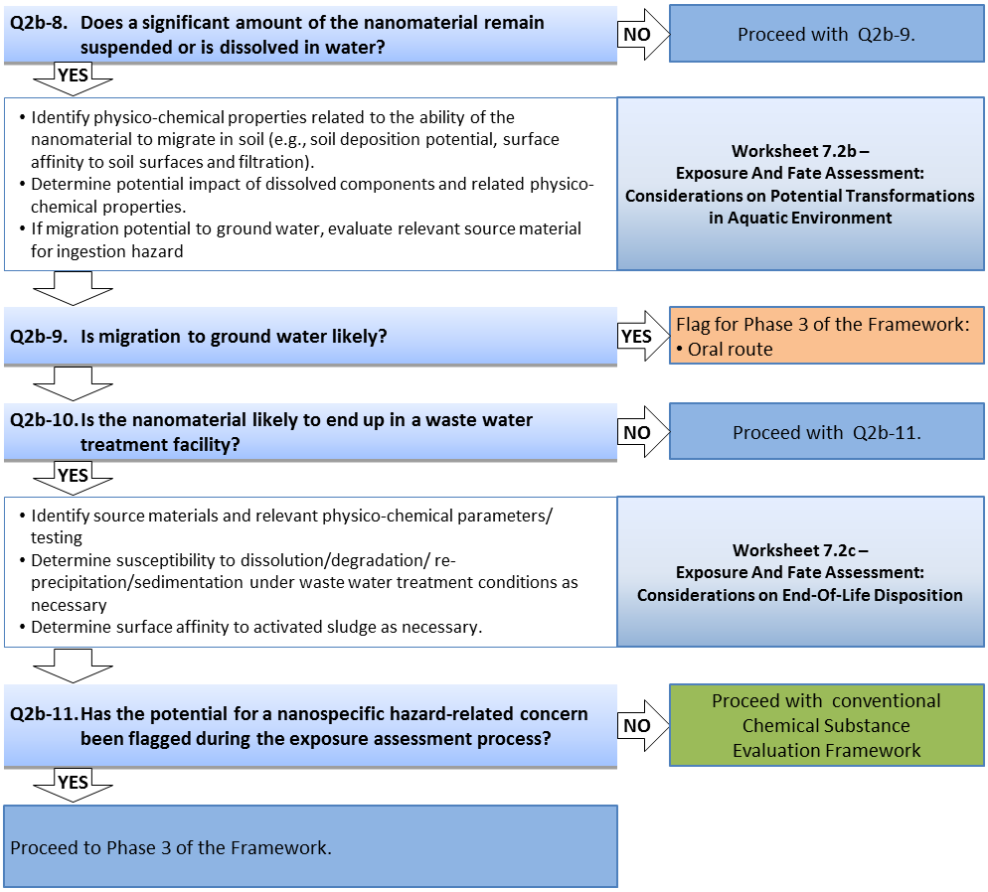
32. The decision framework for Exposure and Fate Assessment begins by determining whether or not there may be intended uses that would result in exposure situations. Example scenarios that may not be appropriately captured would be the use of nanoparticles dispersed in a liquid that is intended to be sprayed as an aerosol or as part of a fluid intended for combustion. Both these scenarios would necessitate that aerosol exposure be considered indicating a need to follow both paths on Q2-1 in Table 3. Expert judgement would be needed to determine the appropriate particles and/or nanomaterials (e.g. composition, transformation) for the most appropriate airborne particle evaluations.

Table 3. Decision framework for physico-chemical parameters for exposure and fate assessment

Worksheets are included in a separate document (Annex 1).




Q2b-3. Is the continuous phase poorly soluble or immiscible in water?
NO
Proceed with Q2b-5.
YES
• Determine primary compartmentalisation of liquid phase in environment.
• Identify particle concentration and material viscosity modifications due to evaporation.
• Determine interfacial transport potential
• Determine relevance of filtration, liquid transfer, or evaporation on final particle disposition.
Worksheet 7.2a – Exposure And Fate Assessment: Considerations on Poorly Soluble or Immiscible Continuous Phase
Apply expert judgement and proceed with relevant water dispersed material with appropriate history simulation.
Q2b-4. Is it likely that the material will no longer be a nanomaterial?
YES
Proceed with conventional Chemical Substance Evaluation Framework
NO
Q2b-5. Are significant chemical transformations due to exposure to aquatic environments likely?
NO
Proceed with Q2b-7.
YES
• List potential transformations, likely timescales and major impacts altering chemical composition and physical interactions.
• Identify source material
– Screen for dissolution and evaluate dissolution rate if relevant.
– If available data on the source material information is insufficient:
▪ Identify potential structures and composition of resulting materials to contrast with natural nanomaterials and to identify relevant source material for the transformed state.
▪ Apply expert judgement to determine relevance of the original nanomaterial form prior to transformations in subsequent testing paradigms.
Worksheet 7.2b – Exposure And Fate Assessment: Considerations on Potential Transformations in Aquatic Environment
(also consider Worksheets 4a & 4b)
Q2b-6. Is it likely that the material will no longer be a nanomaterial?
YES
Proceed with conventional Chemical Substance Evaluation Framework
NO
Q2b-7. Does the relevant material disperse to a slow settling suspension upon contact with relevant simulated environmental fluids (e.g. pore water, fresh water including natural organic matter)?
NO
Flag for Phase 3 of the Framework:
• Soil
• Sediment
YES
• Identify physico-chemical properties related to settling rate (or suitable information to predict sedimentation, e.g. particle size distribution, skeletal density, envelope density)
• Identify physico-chemical properties related to impact of dilution on stability (dialysis/stability experiment). Identify sedimentation rate, if significantly different.
• Evaluate source materials data for aquatic hazard and soil and sediment hazard
Worksheet 7.2b – Exposure And Fate Assessment: Considerations on Potential Transformations in Aquatic Environment
Flag as necessary for Phase 3 of the Framework:
• Aquatic
• Soil
• Sediment
Proceed with Q2b-8.



33. In the absence of such exceptions, the framework continues with the identification of the appropriate material form (i.e. either dry powder system or particle systems in liquid), as different forms may enter the environment differently. For dry powder systems, there is a focus on aerosolisation and inhalation, and terrestrial dissemination. For powder systems in liquid, there is a focus on aquatic exposures, transport in soil and wastewater treatment. However, for both dry powder and powder in liquid, both scenarios can be relevant depending on intended applications and points of release (e.g. if a powder in liquid is meant to be sprayed or aerosolised).

34. For dry particle systems, the potential of the nanomaterial to disperse in air is determined along with relevant particle size fractions in order to identify relevant exposure related hazard pathways. A significant respirable fraction (aerosolised fraction of with at least 1% mass of respirable content below an aerodynamic mass median diameter of 4 µm[5]) triggers further physico-chemical parameter assessments related to pulmonary toxicity. Whereas, significant thoracic and inhalable fractions (with at least 1% mass content of aerodynamic mass median diameters between 10 and 100 micrometre) triggers follow-up on physico-chemical parameters relevant to oral toxicity, since these particles are generally cleared via the mucociliary escalator and ingested. Physico-chemical parameters relevant to terrestrial organism toxicity are implied for aerosolisable dry particles systems in the respirable size range since these are more likely to be more broadly disseminated.

5 The British Standardisation Institute indicated 4 µm as the cut-off value for respirable particles, where 50% can be deposited in the alveoli (BSI, 1993).

35. Consideration is given to potential nanomaterial transformation after terrestrial exposure, wherein the long-term exposure to moisture and precipitation (e.g. rain) and sunlight may result in considerations not captured by transformations screened in Phase 1. This requires expert judgement and has the potential to alter the relevance of the original material entering this decision tree for longer-term terrestrial environmental impact purposes. Dry particles also may be exposed to aquatic systems, if not (e.g. highly hydrophobic nanomaterials that do not transform), this decision tree is exited and the next decision tree begins (Phase 3). If aquatic exposures are relevant, the most appropriate form of the nanomaterial is assessed for dissolution rate and sedimentation rate in the most relevant aquatic media, and flagged for follow up for physico-chemical parameters related to aquatic toxicity. At this point, the decision tree follows considerations for particles systems in liquid where the liquid phase is miscible with water.

36. If the material was not a dry powder system but a particles system in liquid, then the physico-chemical property identification process begins with evaluating the solubility of the dispersion medium in water. If the dispersion medium is poorly soluble or immiscible in water, the nanomaterial fate will largely be tied to the movement of the dispersion medium, however, physico-chemical properties related to surface deposition (e.g. fluid evaporation) and filtration processes are relevant for the dispersion stability of the particles system in liquid. Additionally, physico-chemical properties related to the potential for the nanomaterials to migrate into aquatic media may also need to be considered. These physico-chemical properties may be the outcome of a functional partitioning test or might be guided by the magnitude of interfacial tension between water and dispersion medium, and by viscosity of the dispersion medium. Depending on the outcome of the above characterisation, expert judgement is required to determine if and in what state the nanomaterial may enter aquatic systems as a dispersed form (for example heteroagglomeration processes in waste water treatment plants may influence the state of the nanomaterial in waste water effluents). If it does occur, it requires further follow up, if it does not then the decision tree moves on to Phase 3.

37. Proceeding with the evaluation of particle systems in liquids, nanomaterial transformations are again evaluated, but this time, specific to aquatic environment induced transformations. An understanding of dissolution kinetics, surface passivation and other relevant phenomena is developed for exposure in relevant aquatic media through identified physico-chemical parameters. When possible, learnings from source materials are leveraged, and existing environmental fate models may be applicable. Expert judgement is applied to identify the most relevant nanomaterial form for subsequent evaluation (e.g. through appropriate conditioning in aquatic media). It is critical to also consider the pH of the aqueous media and interactions with other media constituents (e.g. silica with catechol, organic acids) when evaluating these transformations, as solubility is also an extrinsic characteristic, and some nanomaterials can be considered persistent under certain conditions, while transforming or dissolving in others.

38. Whether the nanomaterial transforms or not, the ability of the nanomaterial to remain suspended in water and relevant environmental media is determined. Relevant physico-chemical parameters include settling rate or suitable information to predict settling (e.g. by applying TG 318). Additionally, the impact of dilution on the dispersion state of the nanomaterials is also determined, since in many nanomaterial formulations, dispersants act by maintaining a certain dispersion stability of the nanomaterial within the fluid phase. It is common for dilution to upset this equilibrium resulting in significant changes in the ability for nanomaterials to remain suspended in a fluid.

39. Nanomaterials that are capable of remaining suspended (i.e. Péclet number << 1) are flagged for physico-chemical evaluations related to aquatic toxicity for pelagic species. Physico-chemical parameters related to the ability of these particles to migrate through soil or sediment are also identified to screen if the materials would be capable of migration to underground fresh water sources. All nanomaterials readily transportable by aqueous fluid flag physico-chemical evaluations related to soil and sediment hazards. It is noted that due to current information gaps, these parameters may be limited and may not sufficiently capture all exposure routes (e.g. settling out of material form the water column may not fully remove their availability to aquatic organisms).

40. Next, the potential for the nanomaterial to end up at a wastewater facility is evaluated. Those likely to enter wastewater facilities trigger physico-chemical parameters related to the ability of the wastewater facility to remove the nanomaterial from water.

41. If throughout the decision tree, no hazard flags were raised then the process is exited. No further nanospecific physico-chemical evaluation is needed, and exposure, hazard or risk assessment can be based on information collected information so far, including information for the constituent chemical(s). In case one or more flags have been raised in Phase 2 the process proceeds to Phase 3.

Phase 3: Physico-chemical Properties for Hazard Assessment

42. The relevant physico-chemical properties for hazard assessment define probabilities for initiating events and additional factors that can modulate the intensity of observed effects. The relevance of these phenomena is often substantially dependent on the chemical composition of the nanomaterial (including surface chemistry and related surface reactivity), although particle effects cannot fully be excluded.

43. This portion of the framework (Table 5) identifies physico-chemical parameters for the following purposes:

1. Identify physico-chemical parameters related to mechanisms of concern.
2. To support knowledge generation from hazard assessments.

44. There remains much uncertainty around many of these parameters due to the evolving nature of the science, as well as the interrelationship between intrinsic hazard and various physico-chemical parameters. Specific considerations are anticipated to be being dependent on chemical identity and particle structure (i.e. whether a chemical is part of the core or part of the surface) and shape of the nanomaterial. Hence, information that may allow read-across from source materials (e.g. larger, similar sized, and/or smaller substances) that may share certain key physico-chemical properties – and links hazard effects or concern mechanisms (e.g. fibrous particles) – becomes important. Such information may also be helpful in supporting that a manufactured nanomaterial is "Safe by Design" (e.g. safe design, safe production, safe use).

45. In order to prioritise the requirements for physico-chemical characterisation, it is useful to identify potential mechanisms of concern based on the available knowledge and via which site/exposure scenario the mechanism has relevance. Subsequently perspectives can be framed and assessment prioritised by identifying physico-chemical parameters that are necessary for initiating a mechanism and those that appear to modulate the intensity subsequent to initiation.

46. Table 4 below attempts to do this for a handful of mechanisms identified in literature. The table is not intended to be exhaustive but rather to provide an overview of the concept.

Table 4. Decision Framework for PC parameters for Exposure and Fate Assessment

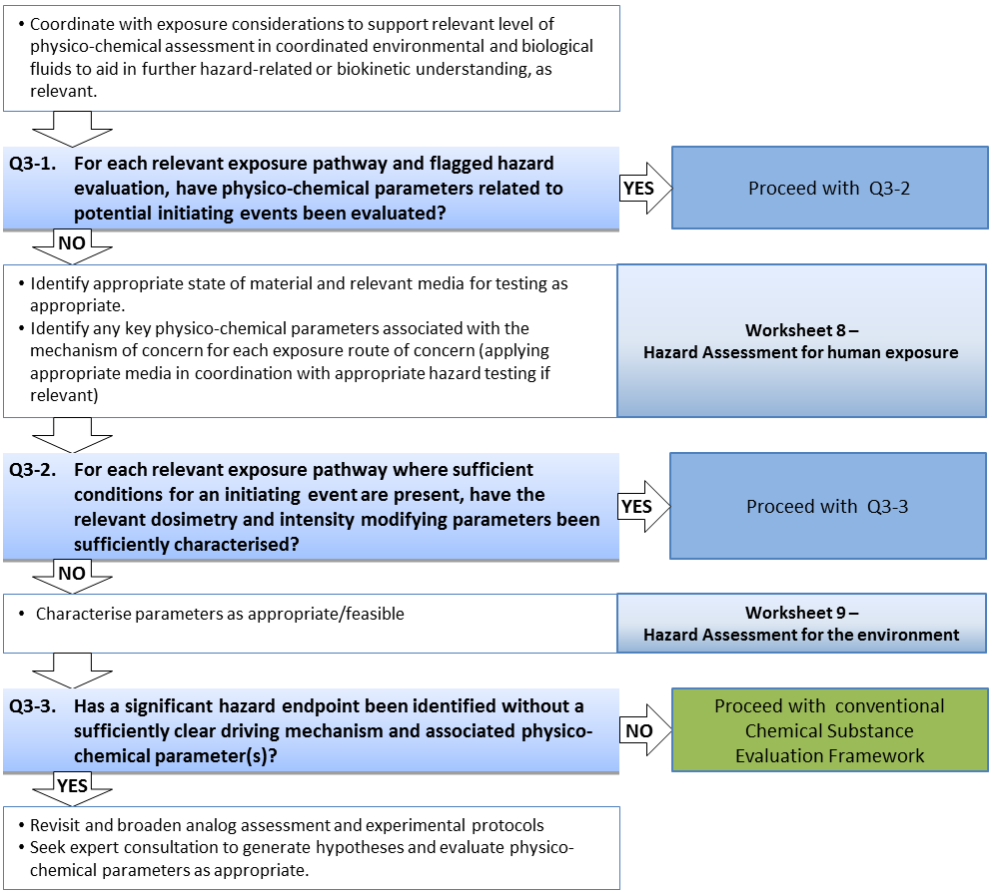
Mechanism of Concern	Relevant exposure route	Potential Initiating Physico-Chemical Properties	Modifying Physico-Chemical Properties
Fiber-like Toxicity	Inhalation	Aspect Ratio Length	Flexural rigidity Dissolution rate in lung fluid Surface Area
Surface Reactivity	All	Surface Chemistry Surface Layer thickness	Surface Area Surface Wettability Surface Charge
Reactive Oxygen Species Generation	All	Surface & Chemical Composition Surface defect sites	Surface Area Adsorption from solution Passivation propensity Surface defect density
Interference with Intracellular Redox processes	All but dermal	Conduction Band Energy level	Particle Surface Structure and Composition Fermi Levels Homo-Lumo Levels of interacting biomolecules Adsorbed molecules (e.g., protein corona)
Photocatalytic Activity	Environmental	UV-Visible Light Adsorption	Band Gap Crystallinity Recombination Rate Surface Area Adsorbed Molecules Adhesion to Impacted Organisms
Trojan Horse Phenomena	All	Surface Chemistry / Affinity	Surface Area Surface Ionisation/Charge Adsorbed molecules Hydrophobicity
Affinity to Aquatic and Terrestrial Organisms	Environmental	Surface Affinity	Hamaker Constant Surface Charge Hydrophobicity Adsorbed Molecules Shape Size Porosity
Soluble Compound Release	All	Chemical/Structural Composition	Surface Area Dissolution Rate Agglomeration State Stability of coating

47. It is recognised that coordinated and thorough physico-chemical characterisation are needed to advance knowledge on hazard mechanisms understanding. To facilitate this, it is occasionally necessary to characterise substances by means that are typically outside of the scope of established protocols. These experiments are necessary to test and challenge current hypotheses and should be conducted whenever possible. Such tests may lead to adaptation of existing protocols or development of new ones.

48. Once Phase 3 is finalised, in general no further nanospecific physico-chemical evaluation is needed, and exposure, hazard or risk assessment can be based on information collected so far, including information for the constituent chemical(s) and for identified similar materials.

Table 5. Decision Framework for Human and Environmental Hazard

Worksheets are included in a separate document (Annex 1).



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Appendix I. Definitions of key terms

Analogue – A chemical whose intrinsic physico-chemical, environmental or toxicological properties are likely to be similar to another chemical based upon a number of potential properties, including structural, physical-chemical and toxicological (OECD, 2014b).

Analogue Approach – A method for filling data gaps for one specific chemical, where empirical data from one or more similar chemical(s) ("the analogue(s)") or "source" chemical can be used to predict the same endpoint for the "target" chemical, which is considered to be "similar" (OECD, 2014b).

Category – A group of chemicals or particle types whose physico-chemical, toxicological, and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity (OECD, 2014b).

Category Approach – A method for filling data gaps for a group of chemicals whose physico-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity (OECD, 2014b).

Chemical Transformation – Changes in the chemistry of a particle due to reaction with its surroundings. These changes may be holistic (i.e. modifies the entire particle) or confined to regions of the particle (e.g. surface).

Continuous Phase – When dealing with a particle system the continuous phase is the connected phase or matrix in which the particles reside. For example, in an aerosol, the continuous phase is air or gas, in a dispersion the continuous phase is the liquid, in a composite the continuous phase is the major solid material (e.g. polymer).

Intrinsic property – A material's property that will not change when the material enters a different environment.

Nanomaterial – Material with any external dimension in the nanoscale (length range approximately from 1 nm to 100 nm) or having internal structure or surface structure in the nanoscale (ISO, 2015).

Novel property – A novel property is defined as a specific behaviour of a nanomaterial that alters for example (but not limited to) its transport properties, its interaction with electromagnetic radiation or its surface reactivity in a manner not predictable from the current knowledge of similar materials (see also Appendix II)

Physical Transformation – Changes in the physical structure of a particle, in whole (e.g. size becomes smaller), or in part (e.g. branches are released) as a result of interactions with its surroundings.

Relevant Particle Substance – The specific particulate chemical substance to which considerations apply. A relevant particle substance is defined as broadly or narrowly as the related scope (e.g. all silica particles versus x-aptamer-coated silica of 50-55 nm in nominal size).

Source Material – A chemical substance/particle type used to predict the properties of another chemical substance/particle type (OECD, 2014b).

Target Material – A target chemical is one with data gap(s), for which a property or hazard is being estimated from the source chemical(s) (OECD, 2014b).

Appendix II. Differences between enhanced properties, nano-enabled and unique and novel properties

49. One of the major issues concerning nanomaterials is their potential to exhibit **unique properties** that differ from non-nanomaterials with the same chemical identity. Due to the high surface area to volume ratio, nanomaterials may be relatively more reactive per unit mass than non-nanomaterials. **Enhanced properties** are generally described as increased reactivity or surface area for the same mass of material when particle size decreases.

50. It is recognised that this framework may not capture all relevant properties that should be assessed, as knowledge is still growing in this area of science. In the context of this framework, a **novel property** is defined as a specific behaviour of a nanomaterial that alters for example (but not limited to) its transport properties, its interaction with electromagnetic radiation or its surface reactivity in a manner not predictable from the current knowledge of similar materials.

51. The behaviours that result from these novel properties may need to be accounted for through additional measurements, or the inclusion of alternative measurands. The idea of what is considered "novel" should also change as more information becomes available. Once a novel property and associated behaviour of concern, can be predicted with reasonable assurance, then the property is no longer considered novel with respect to this framework. Rather the property and association becomes documented and integrated in the assessment by being flagged using chemical composition and/or structural indicators. This approach facilitates the inclusion of new physico-chemical requirements as well as elimination of unnecessary measurements as science develops and matures (the range of materials impacted should narrow as mechanistic confidence increases). Hence, the concept of novel properties is applied to ensure that unusual behaviours are not overlooked and to provide a mechanism to ensure that the framework remains relevant.

52. It is anticipated that many novel properties may result from changes in the intrinsic properties of a substance as the size of the material is reduced into the nanoscale. However, due to the high surface to volume ratio of nanomaterials, many of the properties that are considered intrinsic for non-nanomaterials can become extrinsic for nanomaterials, which complicates prediction. For instance, some nanosensors operate through changes in impedance or conductivity through surface adsorption. Others operate through shifts in the absorbance of electromagnetic radiation upon adsorption. Changes in the interaction with electromagnetic radiation suggest changes in the electronic structure of the material, which consequently may or may not impact hazard. These environment induced changes in properties that are normally considered intrinsic for non-nanomaterials, thus far, have unknown health and safety consequences.

53. Furthermore, it is understood that many catalytic surfaces are readily poisoned or de-activated when exposed to environmental conditions. A catalytic nanomaterial that avoids environmental poisoning mechanisms would be considered novel until the ramifications of the persistent activity is understood and outcomes can be reasonably predicted. Likewise, a nanomaterial that is designed to self-disperse in aquatic media would be considered novel until the consequence of the dispersion mechanism and chemistry is understood and is reasonably predictable in terms of fate and hazard.

Appendix III. Considerations for identifying relevant source materials

54. Throughout the text source, materials have been used to identify relevant physico-chemical properties that might be predictive of behaviours and related to behaviours of concern. The use of analogues is one such approach of identifying relevant source materials and some information on how an analogue might be identified is found below.

Analogue Substances

55. For the purpose of this framework, an analogue is a chemical substance that shares behaviours of concern with the nanomaterial due to similarities in particle structure and/or chemical composition. As with chemicals, information from analogue nanomaterials can aid in identifying relevant physico-chemical parameters leading to an understanding of how a nanomaterial will interact within abiotic and biotic environments [see also OECD, 2014b].

56. Many associations between physico-chemical parameters and concerns exist today in different forms and at different levels of resolution (e.g. insoluble fibre-like particles in relationship to inhalation hazards, and highly lipophilic organic compounds with regard to environmental transport and bioaccumulation potential). The purpose of the decision framework is to provide guidance for additional parameters, outside traditional chemical frameworks, that would be useful to measure when reasonable concerns are present. Analogues could be an essential part of the process, since they provide grounding reference points, especially when data gaps exist (see also OECD, 2014b).

57. The process of choosing appropriate analogue substances for nanomaterials may rely on broader considerations than those for general chemicals [as described in OECD, 2014b], since nanomaterials share behaviours with molecules as well as having particle behaviour. It is often useful to pragmatically assess when nanomaterials are more molecule-like and when they are more particle-like in terms of overall behaviour, while questioning when and under what circumstances their behaviour becomes distinct. Hence, comparisons to larger scale materials of similar (or same) chemical composition and particle structure, as well as to other nanomaterials, become important in order to evaluate hypotheses and, subsequently, gain confidence in predicting behaviour through the appropriate selection of physico-chemical parameters. For some purposes, the relative contributions are understood, while for others, however, clarity is still being sought. The following sections provide context and offer guidance on the selection of analogue materials and their application. A first section provides guidance for exposure, fate related physico-chemical characterisation, and a second section provides guidance for hazard related physico-chemical characterisation.

Exposure and Fate-Related Analogues

58. Physico-chemical characterisation variables related to exposure and transports are better understood than those related to hazard. The movement of particles in the environment is largely a generic process based on non-specific interactions, which can be influenced by chemical and physical transformations induced by environmental exposure. As an example, both agglomeration and fast dissolution processes in the media may make nanospecific considerations irrelevant, although for different reasons. Nanomaterial fate

may be presumed to be largely related to its chemical composition and (molecular) structure, as well as dissolution (see e.g. GD 29 (22) or TG 105 (23), although both require adaptation for nanomaterials) or degradation/reactivity processes. Nevertheless, for some nanomaterials transformations due to surface interactions with environmental media may affect these transformations.

59. Difficulties in estimating fate and transport in the environment are largely due to the complexity of the environment itself and identifying when and which mechanism is dominant under which scenario. Here information from analogue materials would ideally lead to a better understanding of the overall distribution and fate of nanomaterials in the environment, while limiting testing requirements by using a broader set of materials to inform knowledge gaps. In addition, recent developments in modelling environmental fate of nanomaterials can provide directions and guidance towards minimising the information requirements for estimating fate and transport in the environment (e.g Meesters J.A.J., et al., 2016)

60. At the most basic level, the transport of nanomaterials in the environment will depend on how well the material can be dispersed and how far the material can travel before agglomerating or sticking to surfaces. For some materials, dissolution, transformation, and degradation properties will be important. For exposure, fate and transport, physico-chemical properties are applied in this framework to identify suitable analogue materials for filling data gaps and reducing uncertainty.

61. For particle transport, related processes determining the dispersion stability will be informative (see TG 318 (OECD, 2017). Where such data do not exist for analogue particles, potential analogue particles may be initially identified by a proxy. The relevance of analogue materials for predicting particulate behaviour can be roughly gauged through the use of the particle Péclet number and surface affinity considerations. Rather than identifying relevant physico-chemical parameters, key physico-chemical parameters and Péclet numbers are dimensionless numbers commonly applied to identify the relative importance between inertia and diffusion driven transport processes. If the Péclet number is in the appropriate regime (i.e. above or below '1' within two orders of magnitude), then analogue particles may serve as appropriate proxies for environmental transport.

62. The particle Péclet number (Pe) is defined as the balance between Stoke's sedimentation versus the Stokes-Einstein diffusion for individual particles and is given as (Benes K., et al., 2007):

$$\mathrm{Pe} = \frac{4\pi \cdot \Delta\rho \cdot \mathrm{g} \cdot a \cdot r^4}{3 \cdot \mathrm{kB} \cdot \mathrm{T}}$$

63. Where, **Δρ** is the difference in density between the particle and medium, ***a*** is the radius of the equivalent settling solid sphere, **g** = gravitational acceleration constant, **kB** is the Boltzman constant, and **T** is the temperature of the system.

64. A Pe value of '1' represents the equivalence point between surface interaction behaviour dominance and inertial motion dominance. A Pe << 1 (at least two orders of magnitude difference) indicates that the behaviour is diffusion and surface interaction dominated, whereas Pe >> 1 (at least two orders of magnitude difference) indicates that the system is in the inertial-force dominated regime where surface and intermolecular force play a negligible role. In colloidal science, Péclet numbers are used to normalise agglomeration and sedimentation phenomena and also to aid in identifying when agglomerates begin to become dominated by gravitational forces (Benes K., et al., 2007; and Moncho-Jordá A., et al., 2012). By comparing Péclet numbers, it can be shown that the

transport behaviour of nanoparticles is somewhat between the transport behaviour of molecules and granular particles. In addition, it is noted that the explicit change in interaction behaviour depends not only on size but also on the relative density difference between the particles and the medium. Hence, particles in air would need to be compared separately to particles in water or other liquids. Through the use of Péclet numbers it can be illustrated that a clear shift in transport behaviour does not exist at a particle size of 100 nm in diameter — rather for many common systems the transport behaviour between a 50 nm, 100 nm and 300 nm particle are frequently similar. Hence, transport information in some cases can be similar over a range of particle sizes. It is noted that the concept of a Péclet Number is fundamentally similar to the concept of an aerodynamic diameter used in aerosol science. In the case of an aerodynamic diameter the particle density is by definition assumed to be "1" g/cm^3 regardless of the material, such that a phenomenological size is derived where the influence of gravity and inertial is already normalised. Therefore, particles of the same aerodynamic diameter (but not true diameter) deposit similarly. Particles or particle clusters of the same aerodynamic diameter have the same Péclet number. An alternative to the use of the Péclet number would be the application of an equivalent sedimentation diameter, much like an aerodynamic diameter with a set density differential. However, issues would arrive with buoyant particles that are frequently encountered due to entrained air.

65. Ensuring that the surface interactions are similar is a more complicated subject matter. Ideally, comparable surface affinity data would exist; however, this data is typically absent for both nanomaterials and traditional substances. The assumption that similar surface and bulk composition results in similar interaction behaviour is frequently valid; however, dissimilar chemistries can also exhibit similar behaviour if the dominant interaction mechanism and defining characteristics are similar. The media applied also makes a difference, and dominant mechanisms and interaction levels are different in air versus in water. Common surface interactions and defining interactions, along with how these interactions tend to scale, are presented in Table 6. However, it is important to note that at high particle Péclet numbers (Pe >> 1) surface interactions will have little relevance.

Table 6. Common surface interactions, relevant media, key particle properties and scaling with particle size

Interaction Mechanism	Relevant compartment	Defining Particle Characteristics	Size Scaling Dependence
van der Waals forces	aquatic, air, soil	Hamaker Constant Particle Structure (Order of magnitude of surface roughness, porosity, shape, compositional variability) Proxy: Apparent Refractive Index	Proportional to radius
Capillarity	humid air, soil	Hydrophilicity Shape Surface Roughness/Porosity	Proportional to radius
Ion electrostatics	aquatic/wet soil/sediment	Isoelectric Point Surface Charge Profile Shape Proxy: Surface pKa	Proportional to radius squared
Steric interactions from physically adsorbed molecules	aquatic/wet soil/sediment	Solubility of outermost steric layer MW and structure of Steric adsorbate Adsorbed state and quantity	Dominated by adsorption/ desorption level and mechanism
Steric interactions from chemically bound molecules	aquatic/wet soil/sediment	Solubility of steric layer MW and structure of steric layer Steric layer density/composition	None or proportional to radius

66. The selection of analogue substances for the transport of soluble components should follow the chemical substances paradigm, as appropriate. Here, it is important to consider potential differences in the kinetics of dissolution and release which may be altered depending on the particle structure and design of the nanomaterial and depending on the medium.

Hazard-related Analogues

67. Hazard-related phenomena often involve mechanisms with composition/molecular-level specificity. Identifying appropriate analogue materials for prioritising hazard related physico-chemical analysis requires assessment of the probability of encountering known mechanisms through the evaluation of relevant hazard profiles from compositionally and structurally similar materials (i.e. established mechanisms, or as enumerated through the novel property process). Likewise, larger scale analogues of the same substance, or reasonably similar substances, can be assessed with mindful consideration of potential differences due to size and surface area, in addition depending on other relevant dosimetric nuances. A similar process can be undertaken for the particle structure of the nanomaterial, wherein compositionally different structural analogues are assessed for known physico-chemical drivers.

68. It is recognised that the way nanomaterial physico-chemical properties converge to modulate a potential hazard mechanism can be complex and can vary by exposure route and by substance. Here the specific properties that define the potential for the hazard mechanism, as well as those that are likely to modify dose, are important in the context of the overall magnitude of the effect. It is apparent that if the hazard is low, then changes in

properties that might affect dose will be less significant. Conversely, when the hazard is significant, detailed physico-chemical property analysis of dose-modifying characteristics will be substantially more important. Hence, detailing separately the instigating physico-chemical parameter(s) and those that alter the intensity of the behaviour is useful.

Appendix IV. Listings of purposes and related physico-chemical parameters

69. The following tables provide context and examples of purposes and potential physico-chemical parameters derived from the decision framework.

SUBSTANCE IDENTITY & INFORMATION GATHERING	
KEY PURPOSES	**KEY PARAMETERS**
• To provide information on the molecular identity of the substance to facilitate identification of potential hazards, if any, related to component chemical substances.	– Chemical Composition (including that of the surface), – Molecular Structure – Impurities – Crystallinity
• To provide information on and to identify the potential for chemical and physical transformations to occur upon exposure to water and aquatic media.	– Water Solubility – Hydrophobicity/Hydrophilicity – Surface Reactivity (oxidation, sulphidisation)
• To provide information on the characteristic structure of the nanomaterial to identify potential hazards or hazard modifications associated to similar structures.	– Characteristic Particle Structure – Specific Surface Area (BET method) – External Particle Shape (nanoparticle, nanofibre, or nanoplate) – Electron Microscope (Micrograph) – Characteristic Particle Size Distribution (mass and number percent)
• To identify any novel properties that may impact physico-chemical characterisation.	– Comparison of reactivity, fate, and transport behaviour to anticipated behaviour of relevant analogues from current state of the science.
• To identify important physico-chemical parameters from analogue materials	– Molecular Identity and Structure – Established Mechanistic Groups – Surface Affinity – Dissolution/Degradation process – Particle Péclet Number – Common Behaviours of Concern

HUMAN AND ENVIRONMENTAL EXPOSURE AND FATE	
KEY PURPOSES	**KEY PARAMETERS**
TO IDENTIFY THE MOST RELEVANT EXPOSURE ROUTES OF THE SUBSTANCE UPON ENVIRONMENTAL RELEASE.	– Material Form (e.g. product form, particle or aerosol size distribution) – Solubility Information – Transformation Potential (medium dependent)
TO IDENTIFY RELEVANT ANALOGUE PARTICULATE MATERIALS FOR ESTIMATING ENVIRONMENTAL BEHAVIOUR.	– Particle Size Information – Density – Surface Affinity – Transformation potential – Chemical composition and/or functionality
TO ESTIMATE ENVIRONMENTAL COMPARTMENT DISTRIBUTION.	– Dustiness (dispersibility in air) – Density – Particle Size Distribution* – Dissolution Rate* – Dispersibility in aquatic media* – Soil Deposition Potential* – (additional parameters captured by the Substance Identity and Information Gathering Decision Framework) * in appropriate environmental media
Estimation of concentration in air	– Dustiness – Dust settling rate (Aerodynamic size distribution) – Shape – Critical aerosol agglomeration concentration

HUMAN AND ENVIRONMENTAL EXPOSURE AND FATE	
KEY PURPOSES	**KEY PARAMETERS**
Estimate dissolved concentration in relevant environmental media.	– Dissolution rate of component substances – Equilibrium solubility
Estimate dispersion in water column	– Sedimentation rate – heterocoagulation rates – Surface charge – Hydrophobicity – Transformations
Estimate Bioaccumulation and Persistence	– Chemical Degradation rate / Dissolution Rate – Particle size at point of entry (mechanism/site/organism dependent) – Hydrophobicity – Surface Charge – Surface/bulk transformations – Dispersibility – Affinity to predominant environmental surfaces (biota / abiota; e.g. Soil deposition potential as proxy)
TO ESTIMATE EXPOSURE TO HUMANS AND OTHER ORGANISMS THROUGH MAJOR ROUTES	– Dustiness and Aerosol Particle Size Distribution – Aquatic Sedimentation Rate – Soil Deposition Potential (Surface Affinity to relevant simulated soil)
Estimate Inhalation Exposure	– Dustiness – Aerosol Particle Size Fractions (thoracic, inhalable, respirable fractions) – Shape – Static charge potential – Critical aerosol agglomeration concentration – Aerosol Size Distribution
Estimate Transport through skin	– Octanol-water partitioning of media soluble compounds (not intended for particles) – pKa of soluble compounds – Particle size/ Size distribution – Surface Charge
Estimate Transport through the lungs	– Dissolution rate of Respirable fraction in lung fluid – Degradation rate in simulated lung fluid – Shape – Flexural rigidity – Surface properties to evaluate Clearance Rate (i.e. Phagocytosis/endocytosis – Charge, Hydrophobicity
Estimate Transport through the Intestinal tract	– Dispersibility/dissolution in Intestinal Fluid (size) – Affinity to Intestinal Mucosal layer – Properties influencing transcytosis (gap)
Estimate accumulation site or clearance from circulation	– Dispersibility in plasma (size) – Affinity to Cell Surfaces (complex modified by charge, hydrophobicity, dispersion mechanism, protein adsorption, i.e. protein corona formation) – Flexural rigidity
TO ESTIMATE NANOMATERIAL FATE IN THE ENVIRONMENT	– Dissolution Rate (compartment/media specific) – Degradation Rate (compartment/media specific) – Soil Deposition Potential – (evaluation of concerns raised in Substance Identity and Information Gathering Framework)
Estimate Migration through Soil into Groundwater	– Soil Deposition Potential of particles – Soil/Sorption Coefficient of dissolved components
Estimate Removal in Wastewater Treatment	– Dispersibility in Wastewater media – Susceptibility of particles to common Flocculants – Surface Affinity to Activated Sludge

HUMAN AND ENVIRONMENTAL EXPOSURE AND FATE	
KEY PURPOSES	**KEY PARAMETERS**
Estimate precipitation of dissolved components in water.	– Dissolved component chemistry – Environmental media chemistry

HUMAN AND ENVIRONMENTAL HAZARD	
KEY PURPOSES	**KEY PARAMETERS**
TO IDENTIFY PHYSICO-CHEMICAL PROPERTIES RELATED TO THE MODIFICATION OF EXPOSURE SITE SPECIFIC HAZARDS.	– Chemical Composition and Impurities – Specific Surface Area – Particle Size Distribution – Shape – Surface chemistry, coating, functionalisation etc.) – Charge/zeta potential – Free radical generation capacity – Dissolution rate in relevant media – Agglomeration/Aggregation in relevant media – Crystallinity – Conduction band energy level? – Corrosivity
a) Parameters that may modify dermal contact hazards	– Specific Surface Area – Chemical Composition – Size – Shape – (coating, functionalisation etc.) – Charge/zeta potential – Active agent release rate / Dissolution rate – Degradation Rate – Surface chemistry
b) Parameters that may modify pulmonary exposure hazards	– Specific Surface Area – Excluded Volume – Dispersibility – Dissolution Rate of components – Degradation Rate of components – Shape, aspect ratio, length – Flexural rigidity – Free Radical Generation Capacity – Surface Reactivity – Conduction Band Energy – Cell Surface Affinity – Properties that impact Phagocytic Clearance Rate – Surface chemistry – Surface Charge
c) Estimate Transport through skin	– Size – Surface charge – Surface chemistry
d) Estimate Transport though the lungs	– Dissolution rate of Respirable fraction in lung fluid – Degradation rate in simulated lung fluid – Properties that Modify Phagocytosis Clearance Rate (e.g. size, surface properties, flexural rigidity)
e) Estimate Transport through the Intestinal tract	– Dispersibility in Intestinal Fluid – Affinity to Intestinal Mucosal layer and/or predictive surface properties – Properties influencing transcytosis (gap)
f) Estimate accumulation site or clearance from circulation	– Dispersibility in plasma (particle size distribution and stability) – Affinity to Cell Surfaces (complex modified by charge, hydrophobicity, dispersion mechanism, protein adsorption) – Flexural rigidity