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1. CHARACTERIZATION OF CONTENTS AND STRUCTURE OF AN IUCLID DATASET

This task will identify the data requirements of the IUCLID datasets and Chesar boxes, including both non endpoint and endpoint sections. At this stage, each data entry fields included in the reporting tools will be characterized in terms of mandatory contents and structure.

For the various information requirements we have been taken into account the assessment done in the B.2. A need for nano-specific data requirements is identified for the following thematic areas:
1. Substance identity and characterization
2. Fate and kinetics
3. Toxicological information
4. Ecotoxicological information
5. Exposure, risk characterization and risk management measures.

Where appropriate in this heading only a short summary of that analysis is given.

Substance identity and characterization
Currently, to determine the substance identity in REACH (EU, 2006) at least the parameters listed in Annex IV, Item 2 should be used (Table 1). A substance is usually identified by its chemical composition, the chemical identity and the content of each constituent in the substance. However, to identify and distinguish different forms of a substance (e.g. nanoform and non-nanoform, or different nanoforms) other parameters are necessary as well.

In principle, two approaches can be chosen to relate nanomaterials to the substance in its non-nanoform and to other related nanoforms.

One approach is that each nanomaterial with specific size, shape and surface characteristics is a substance on its own that should be seen as distinct from another material with the same molecular structure and chemical composition. The other is that each nanomaterial or non-nanomaterial is a specific form of one substance that is defined by molecular structure and chemical composition. This second approach is within the meaning of the current REACH provision that registration is based on the 'one substance, one registration' principle.

The two approaches have different consequences for the registration of nanomaterials under REACH. The first approach – where size, shape and surface characteristics are seen as 'identifiers' of different substances – implies separate REACH registrations for each nanomaterial, and would thus contribute to increased visibility of nanomaterials. However as the REACH registration obligation applies only above a specific threshold (1 tonne/year per registrant in current REACH legislation), nanomaterials below this threshold will become 'invisible' to REACH. Therefore, several proposals have been put forward to lower this threshold.

The second approach, where nanomaterials are considered as different manifestations of the same substance, and are consequently registered together with non-nanoform materials, yields a

higher chance of nanomaterials being registered under REACH, although they may be somewhat hidden (which may result in invalid use of information, e.g. when information for the non-nanomaterial is being used for the nanomaterial as well). So, while separate REACH registrations for nanoforms may improve the visibility of nanomaterials, a registration together with non-nanomaterial– where size, shape and surface characteristics are considered as so-called 'characterisers' – is likely to generate more data specific to nanomaterials as the different forms should still be properly characterised. In the case of the latter option, further information is still required for the nanoform(s) of the substances, as information for the non-nanomaterial (or another nanomaterial) may not be suitable for all forms.

Table 1. Substance identification parameters in REACH Annex VI Section 2

2 IDENTIFICATION OF THE SUBSTANCE
For each substance the information given shall be sufficient to enable each substance to be identified. If it is not technically possible or if it does not appear scientifically necessary to give information on one or more items below, the reason shall be clearly stated.
2.1 NAME OR OTHER IDENTIFIER OF EACH SUBSTANCE
2.1.1 Name(s) in the IUPAC nomenclature or other international chemical name(s)*
2.1.2 Other names (usual name, trade name, abbreviation)*
2.1.3 EINECS or ELINCS number (if available and appropriate)
2.1.4 CAS name and CAS number (if available)
2.1.5 Other identity code (if available)*
2.2 INFORMATION RELATED TO MOLECULAR AND STRUCTURAL FORMULA OF EACH SUBSTANCE
2.2.1 Molecular and structural formula (including SMILES notation, if available)
2.2.2 Information on optical activity and typical ratio of (stereo) isomer (if applicable and appropriate)
2.2.3 Molecular weight or molecular weight range
2.3 COMPOSITION OF EACH SUBSTANCE
2.3.1 Degree of purity (%)
2.3.2 Nature of impurities, including isomers and by-products
2.3.3 Percentage of (significant) main impurities
2.3.4. Nature and order of magnitude (... ppm, ... %) of any additives (e.g. stabilising agents or inhibitors)*
2.3.5. Spectral data (ultra-violet, infra-red, nuclear magnetic resonance or mass spectrum)
2.3.6 High-performance liquid chromatogram, gas chromatogram

It is a subject of discussion which size, shape and surface characteristics are relevant in deciding on the sameness of the nanoform and the non-nanoform and among different nanoforms. As the physicochemical variations for nanomaterials are so large and diverse (clearly exceeding variations in molecular and structural formulae), setting a minimal set of morphological and physicochemical properties to distinguish between the different forms presents a huge challenge, at least in the near future. Nevertheless, as nanomaterials are generally defined by their particle size distribution and/or specific surface area by volume (EU, 2011), these parameters are obvious candidates for inclusion in such a minimal set of properties. In particular, however, where behaviour and

reactivity are concerned, for the time being distinguishing different nanoforms remains a case-by-case decision, as currently data are too scarce to enable generalisations.

A further challenging issue in the sameness discussion is a decision on the most appropriate test program for safety assessment of the different forms, which – apart from additional physicochemical properties – may require additional data on kinetics and toxicity/ecotoxicity to be considered (Pronk et al., 2009). A sameness analysis that includes such data as well is essential to conclude on whether or not the different forms are sufficiently identical to justify read-across in the safety assessment.

To conclude on the sameness issue, one should first build on insights gained by treating morphological differences a priori as toxicologically or ecotoxicologically relevant to improve the understanding of the specific issues pertaining to the sameness of nanomaterials. After such improvement of knowledge, a new approach to sameness can be designed based on morphological and physicochemical properties, potentially in combination with limited data on toxicity/ecotoxicity and kinetics.

Characterisation of nanomaterials

It is generally acknowledged that nanomaterials may change during their life cycle, i.e. their particle size distribution (and thereby other properties) may change, resulting in other nanomaterials or materials that are no longer considered to be nanomaterials (e.g. Environmental Defense – Du Pont Nano Partnership, 2007; Antunović et al., 2011; JRC, 2012). Similarly, non-nanomaterials may change into or release nanomaterials during their life cycle.

Characterisation may, therefore, differ between the material as produced, as delivered, as used, as tested, as occurring in the environment or the human body, etc. This suggests that a material needs to be characterised both during the performance of toxicity/ecotoxicity tests and during several critical phases in the life cycle.

Currently, information on several morphological and physicochemical properties is required under REACH (Table 2). For nanomaterials, many of these properties will be just as relevant as for non-nanomaterials. Specifically for nanomaterials, however, the following properties are currently identified as relevant parameters for identification and understanding of their reactivity and may need adaptation or addition in the current REACH requirements: particle size distribution, specific surface area by volume, aggregation and agglomeration behavior, appearance / morphology (shape, aspect ratio, surface charge / zeta potential / isoelectric point, other surface properties (surface structure, surface acidity, surface energy, surface reactivity – incl. surface chemistry) and catalytic properties / photocatalytic properties / radical formation potential.

Table 2: Physicochemical properties currently required in REACH

7 PHYSICOCHEMICAL PROPERTIES TONNAGE LEVEL	TONNAGE LEVEL
7.1 State of substance at 20 °C and 101.3 kPa	≥ 1 tonne/year
7.2 Melting / freezing point	≥ 1 tonne/year
7.3 Boiling point	≥ 1 tonne/year
7.4 Relative density	≥ 1 tonne/year
7.5 Vapour pressure	≥ 1 tonne/year
7.6 Surface tension*	≥ 1 tonne/year
Specific surface area by volume*	
Surface charge / zeta potential / isoelectric point*	
Other surface properties (surface structure, surface acidity, surface energy, surface reactivity – incl. surface chemistry)*	
7.7 Water solubility*	≥ 1 tonne/year
Dissolution kinetics*	
Dispersibility / dispersion stability*	
7.8 Partition coefficient n-octanol / water*	≥ 1 tonne/year
Fat solubility / oleophilicity*	
7.9 Flash-point	≥ 1 tonne/year
7.10 Flammability	≥ 1 tonne/year
7.11 Explosive properties	≥ 1 tonne/year
7.12 Self-ignition temperature	≥ 1 tonne/year
7.13 Oxidising properties	≥ 1 tonne/year
Catalytic properties / photocatalytic properties / radical formation potential*	
7.14 Granulometry*	≥ 1 tonne/year
Particle size distribution*	
Aggregation and agglomeration behaviour*	
Appearance / morphology (shape, aspect ratio)*	
Dustiness*	
7.15 Stability in organic solvents and identity of relevant degradation products	≥ 100 tonnes/year
7.16 Dissociation constant	≥ 100 tonnes/year
7.17 Viscosity	≥ 100 tonnes/year

* These parameters (may) need to be added or adapted for nanomaterials. Those without a number are currently not (explicitly) mentioned in the REACH requirements.

Fate and toxicokinetics

To understand environmental behavior and toxicokinetics, the following additional properties are proposed: Dissolution kinetics, Dispersibility / dispersion stability, Dustiness, Fat solubility / oleophilicity.

Toxicological information

To assess the intrinsic toxicity of nanomaterials the existing REACH requirements on toxicity (Table 3) need amendments. Such adjustments may include:

- The monitoring of changes in the physical form and characteristics of nanomaterials during toxicological testing. Understanding how nanomaterials change during testing will – in the long run – allow the use of read-across to fill data gaps and is therefore instrumental in reducing the need for extra testing.

- Two extra tests for genotoxicity (using human or mammalian cells) additional to the gene mutation study in bacteria because such a bacterial test is considered to be not discriminative enough in the case of nanomaterials, i.e. it gives a large number of false negative results (Antunović et al., 2011)

- Use of the inhalation route as the preferred route of exposure for testing, instead of the oral route often chosen in conventional testing schemes, because inhalation is the most likely route for (nano)particle exposure. This is also included in the nanomaterial specific appendix of the REACH Guidance on Information Requirements and Chemical Safety Assessment.

- Chronic/repeated dose toxicity studies are preferred above acute toxicity tests. Due to the relatively slow uptake processes of nanomaterials, acute studies are expected to be of limited value for the risk profile of nanomaterials (Antunović et al., 2011). If acute toxicity testing is performed, extended pathology/histology is recommended (Hankin et al., 2011), but it may also be considered to withdraw acute toxicity testing altogether for nanomaterials and replace this by the requirement for chronic/repeated dose toxicity studies.

- The inclusion of additional parameters to the standard repeated dose toxicity study, such as cardiovascular and/or inflammatory parameters, and the use of sensitive species/strains for these effects. The rationale for these inclusions is the scientific evidence suggesting 'nano-specific' cardiovascular and/or inflammatory effects (SCENIHR, 2007, 2009).

- Adaptation of standard repeated dose studies to include a prolonged exposure-free follow-up phase (i.e. 'recovery phase'), as well as the inclusion of kinetic parameters in order to identify the distribution of nanomaterials in organs and potential particle persistence and associated delayed effects. As these distribution processes are generally slower for nanomaterials than for non-nanomaterials (i.e. molecules), additional time is needed to observe the effects. Furthermore, the inclusion of kinetic parameters will provide anchor points for toxicokinetic modelling.

- This information is especially relevant in the event that the toxicological information from one nanomaterial is to be used for the assessment of several other related ('same') nanomaterials (or non-nanomaterials).

- Lowering the existing tonnage band for information requirements for nanomaterials, resulting in extra and more (nano-specific) information at tonnage levels below 10 tonnes/year.

Table 3: Current toxicological information requirements in REACH

8 TOXICOLOGICAL INFORMATION*	TONNAGE LEVEL
8.1 Skin irritation / corrosion – in vitro	≥ 1 tonne/year
8.1.1 Skin irritation – in vivo	≥ 10 tonnes/year
8.2 Eye irritation – in vitro	≥ 1 tonne/year
8.2.1 Eye irritation – in vivo	≥ 10 tonnes/year
8.3 Skin sensitization	≥ 1 tonne/year
8.3.1 In vitro gene mutation study in bacteria**	≥ 1 tonne/year
8.3.2 In vitro cytogenicity study in mammalian cells or in vitro micronucleus study**	≥ 10 tonnes/year
8.4.3 In vitro gene mutation study in mammalian cells**	≥ 10 tonnes/year
8.4 In vivo mutagenicity studies**	≥ 100 tonnes/year
8.5.1 Acute oral toxicity**	≥ 1 tonne/year
8.5.2 Acute inhalation toxicity**	≥ 10 tonnes/year
8.5.3 Acute dermal toxicity	≥ 10 tonnes/year
8.6.1 Short-term repeated dose toxicity study (28 days)**	≥ 10 tonnes/year
8.6.2 Sub-chronic toxicity study (90 days)**	≥ 100 tonnes/year
8.6.3 Long term toxicity study (≥ 12 months)**	≥ 1000 tonnes/year
8.6.4 Further studies**	≥ 1000 tonnes/year
8.7.1 Screening for reproductive / developmental toxicity (OECD 421 or 422)**	≥ 10 tonnes/year
8.7.2 Pre-natal developmental toxicity study**	≥ 100 tonnes/year
8.7.3 Two-generation reproductive toxicity study**	≥ 100 tonnes/year
8.8.1 Assessment of the toxicokinetic behaviour of the substance to the extent that can be derived from the relevant available information**	≥ 10 tonnes/year
8.9.1 Carcinogenicity**	≥ 1000 tonnes/year

*In general, monitoring of changes in the physical form and characteristics of nanomaterials during toxicological testing is recommended, as this is instrumental for read-across approaches in the future.
** These parameters (may) need adaptation for nano materials.

Ecotoxicological information

The following adaptations/additions of the current REACH requirements on ecotoxicological information for nanomaterials (Table 4) are identified:

- Application of the extensive testing requirements to lower tonnage bands in the case of nanomaterials, resulting in extra and more (nano-specific) information, also at tonnage levels below 10 tonnes/year. This is essential in filling current knowledge gaps.

- Especially data on the stability (i.e. fate and kinetics) of nanomaterials in different environmental media is necessary in order to understand the environmental exposure and subsequent effects. For example, exposure during testing may be different from nominal exposure due to aggregation, agglomeration, dissolution, adsorption and sedimentation.

Furthermore, exposure may change during the testing period as a consequence of such processes.

- Adaptations of standard tests to reflect that sediment/soil is a particularly relevant exposure route in the case of nanomaterials, due to the water solubility/dissolution and dispersibility issues with most nanomaterials.

Table 4: Current ecotoxicological information requirements in REACH

9 ECOTOXICOLOGICAL INFORMATION*	TONNAGE LEVEL
9.1.1 Short-term toxicity testing on invertebrates (preferred species Daphnia)**	≥ 1 tonne/year
9.1.2 Growth inhibition study aquatic plants (algae preferred)**	≥ 1 tonne/year
9.1.3 Short-term toxicity testing on fish**	≥ 10 tonnes/year
9.1.4 Activated sludge respiration inhibition testing	≥ 10 tonnes/year
9.1.5 Long-term toxicity testing on invertebrates (preferred species Daphnia)**	≥ 100 tonnes/year
9.1.6 Long-term toxicity testing on fish**	≥ 100 tonnes/year
9.2.1.1 Biotic degradation – ready biodegradability	≥ 1 tonne/year
9.2.1.2 Simulation testing on ultimate degradation in surface water	≥ 100 tonnes/year
9.2.1.3 Soil simulation testing	≥ 100 tonnes/year
9.2.1.4 Sediment simulation testing	≥ 100 tonnes/year
9.2.2.1 Abiotic degradation – hydrolysis as function of pH	≥ 10 tonnes/year
9.2.3 Identification of degradation products	≥ 100 tonnes/year
9.2 Further biotic degradation	≥ 1000 tonnes/year
9.3.1 Adsorption / desorption screening study	≥ 10 tonnes/year
9.3.2 Bioaccumulation in aquatic species, preferably fish**	≥ 100 tonnes/year
9.3.3 Further information on absorption / desorption**	≥ 100 tonnes/year
9.3.4 Further information on the environmental fate and behaviour and/or degradation products**	≥ 1000 tonnes/year
9.4.1 Short-term toxicity to invertebrates**	≥ 100 tonnes/year
9.4.2 Effects on soil micro-organisms	≥ 100 tonnes/year
9.4.3 Short-term toxicity to plants**	≥ 100 tonnes/year
9.4.4 Long-term toxicity testing on invertebrates	≥ 1000 tonnes/year
9.4.6 Long-term toxicity testing on plants	≥ 1000 tonnes/year
9.5.1 Long-term toxicity to sediment organisms	≥ 1000 tonnes/year
9.6.1 Long-term or reproductive toxicity to birds	≥ 1000 tonnes/year

* In general, monitoring of changes in the physical form and characteristics of nanomaterials during ecotoxicological testing is recommended, as this is instrumental for read-across approaches in the future.
** These parameters (may) need adaptation for nano materials.

2. CHARACTERIZATION OF CONTENTS AND STRUCTURE OF CHESAR.

CHESAR is the chemical safety assessment and reporting tool developed by the European Chemicals Agency (ECHA) with the aim to support companies in carrying out their Chemical Safety Assessments (CSA) and in preparing their Chemical Safety Reports (CSR).

To use Chesar it is essential to have sufficient information available on the properties of the nanoparticle, the uses of the nanoparticle, the related quantities and the conditions under which the uses take place. Based on these inputs the tool calculates exposure estimates that are compared to the predicted no-effect levels. The purpose of this comparison is to determine whether safe use of a substance can be established. Workers' exposure estimations provided by CHESAR are calculated using the 'ECETOC TRA worker' tool while environmental exposure estimates are based on the EUSES 2.1 fate model. Where hazards are identified but predicted no-effect-levels are not available, Chesar supports exposure scenario building with qualitative risk characterization.

There are no provisions in CHESAR referring specifically to nanomaterials; ECETORC TRA and EUSES are not developed for nanomaterials, so, it could appeared several problems because of the difficulty, in the case of nanomaterials, in obtaining some endpoints which are necessary to run both programs.

Chesar is divided in seven major groups of functionalities called Boxes (figure 1). All Boxes are connected and contribute to the generation of the Chemical Safety Report and/or the Exposure Scenario for the extended Safety Data Sheet (extended SDS). The content of each one is described below, with the exception of boxes 6 and 7 which are related to the internal operation of the tool.

	Box 1	Manage substance
	Box 2	Use management
	Box 3	Assessment management
	Box 4	CSR management
	Box 5	SDS ES management
	Box 6	Library management
	Box 7	User management

Figure 1. CHESAR Structure

BOX 1. Manage substance and CSAs

When starting the assessment process for a certain substance with Chesar, it is assumed that the hazard assessment according to Annex I of REACH has been finalized. Thus, all the information related to the substance intrinsic properties needed for exposure assessment and risk characterisation should be available in the single endpoint summaries and the overall toxicological and ecotoxicological summaries in IUCLID. All this information is imported into Chesar with the Box 1 functionalities. This includes the conclusions from the hazard assessment, directly determining the required scope of exposure assessment and the type of required risk characterisation (qualitative or quantitative).

This mainly concerns:

- Physico-chemical properties
- Environmental fate properties
- Environmental hazard conclusion, including PBTstatus
- Human health hazard conclusion

Physical-Chemical Properties/Fate

For most of the physico-chemical and fate properties that can be reported in IUCLID 5, the Key value for chemical safety assessment identified in the related endpoint summary is imported in Chesar. Some of those properties are directly used by exposure estimation tools (see table 2 and 3) and some are only displayed for information.

Table 2. Detailed information for physico-chemical properties.

Property name	Input parameter for
Physical Form	TRA Worker v3
Molecular Weight	TRA Worker v3 TRA Consumer v3 EUSES 2.1.2
Melting Point	[EUSES 2.1.2]
Boiling Point	
Relative Density	
Vapour Pressure	TRA Consumer v3 EUSES 2.1.2 [TRA Worker v3]
Partition Coefficient(Log Kow)	EUSES 2.1.2
Water solubility	EUSES 2.1.2
Solubility in standard fat	
Solubility in organic solvents	
Surface tension	
Oxidation Reduction Potential	

Property name	Input parameter for
Dissociation Constant	
Viscosity	[EUSES 2.1.2]
Henry's Law Constant	

As is possible to see in the previous table, there are some nanoform-specific physicochemical properties which are not taken into account for the assessment in CHESAR. However, those nano specific endpoints may be essential, due to their direct relationship to the toxicity of nanomaterials; that is the case of "granulometry" which is expected to have a direct impact on toxicology.

These nano-specific endpoints adopted from results of RiP-on project are:

- Crystallite and grain size
- Aspect/ratio shape
- Specific surface area
- Zeta potential
- Surface chemistry
- Dustiness
- Porosity
- Pour density
- Photocatalytic activity
- Radical formation potential
- Catalytic activity

Table 3. Detailed information for fate.

Biodegradation	
Property name	**Input parameter for**
Biodegradation in Water: screening tests	[EUSES 2.1.2]
Half-life In Water	[EUSES 2.1.2]
Half-life In Sediment	[EUSES 2.1.2]
Half-life In Soil	[EUSES 2.1.2]
Bioaccumulation	
Property name	**Input parameter for**
Bioaccumulation: BCF (aquatic species)	[EUSES 2.1.2]
Bioaccumulation: BCF (terrestrial species):	[EUSES 2.1.2]

Abiotic Degradation	
Property name	**Input parameter for**
Biodegradation in Water: screening tests	[EUSES 2.1.2]
Degradation Rate Constant with OH radicals	[EUSES 2.1.2]
Half-life in Air (phototransformation)	[EUSES 2.1.2]
Half-life for Hydrolysis	[EUSES 2.1.2]
Half-life in Water (photolysis)	[EUSES 2.1.2]
Half-life in Soil (photo transformation)	
Adsorption Coefficients	
Property name	**Input parameter for**
Biodegradation in Water: screening tests	[EUSES 2.1.2]
Adsorption/Desorption: Koc	[EUSES 2.1.2]
Log Kp (soil-water)	[EUSES 2.1.2]
Log Kp (solids-water in soil)	[EUSES 2.1.2]
Log Kp (solids water in sediment)	[EUSES 2.1.2]
Log Kp (solids-water in suspended matter)	[EUSES 2.1.2]
Log Kp (solids-water in raw sewage sludge)	[EUSES 2.1.2]
Log Kp (solids-water in settled sewage sludge)	[EUSES 2.1.2]
Log Kp (solids-water in activated sewage sludge)	[EUSES 2.1.2]
Log Kp (solids-water in effluent sewage sludge)	[EUSES 2.1.2]
Log Kp (suspended matter-water)	
Log Kp (sediment-water)	

As explained in the previous section, to understand environmental behavior and toxicokinetics of nanomaterials, could be necessary other properties which are not included in CHESAR, such as disolution kinetics, dispersibility / dispersion stability, dustiness, fat solubility / oleophilicity.

Physical-Chemical Hazard

The physico-chemical hazard of the substance is imported from the relevant endpoint summaries in IUCLID (IUCLID sections 4.11, 4.12, 4.13, 4.14, 4.15):

- Flash Point at 101 325 Pa
- Auto flammability/Self-ignition temperature:
- Flammability
- Explosiveness
- Oxidising Properties

Environmental and Human health hazard conclusion

Based on the information on hazard conclusions uploaded from IUCLID (also described in the previous section), Chesar describes the type of risk characterisation required. The environmental protection targets to be taken into account are: water and sediment organisms (freshwater and marine), predators in the aquatic food chain (freshwater and marine), sewage treatment plant organism, agricultural soil organisms, predators in the terrestrial food chain, and air. For the human hazards it should be taken into account the different routes (dermal, inhalation, eyes) and type of effect (local/systemic effect after short/long-term exposure)

In the table below, it is shown the correspondence between hazard assessment conclusions indicated in the endpoint summary 6 and 7 of IUCLID 5 (substance properties) and the scope of assessment type triggered in Chesar:

Table 4. Scope of assessment – Environment

Environmental Hazard conclusion (IUCLID)	Protection target to which this conclusion apply	Scope of assessment triggered in Chesar
PNEC (Predicted no effect level)	All	Quantitative
No data: aquatic toxicity unlikely	Freshwater, Marine water and STP	Not needed
No data: testing technically not feasible	All except Air	Qualitative
No emission to STP expected	STP	Qualitative
No exposure of sediment expected	Freshwater sediments and Marine sediments	Not needed
No exposure of soil expected	Soil	Qualitative
No or insufficient data available at present	Freshwater sediments and Marine sediments, Soil	Qualitative - testing proposal
Hazards related to composition of atmosphere identified	Air	Qualitative

Environmental Hazard conclusion (IUCLID)	Protection target to which this conclusion apply	Scope of assessment triggered in Chesar
No potential for bioaccumulation	Predators	Not needed
No potential to cause toxic effects if accumulated (in higher organisms) via the food chain	Predators	Not needed
No hazard identified	All	Not needed

Table 5. Scope of assessment – Human health

Human health hazard conclusion (IUCLID)	Route/ type of effect to which this conclusion apply	Scope of assessment triggered in Chesar
DNEL (Derived No Effect Level)	All except Eyes	Quantitative
DMEL (Derived Minimum Effect Level)	Only long term	Semi-quantitative
Other toxicological threshold	All except Eyes	Semi-quantitative
Low hazard (no threshold derived)	All	Qualitative
Medium hazard (no threshold derived)	All	Qualitative
High hazard (no threshold derived)	All	Qualitative
Hazard unknown (no further information necessary)	All	Qualitative
No hazard identified	All	Not needed
No DNEL required; short term exposure controlled by conditions for long-term	Only Dermal acute	Not needed
Insufficient data available (information necessary) Insufficient data available: testing proposed (from IUCLID 5.3 migrated file only)	All except Eyes	Qualitative - testing proposal
Exposure based waiving (from IUCLID 5.3 migrated file only)	All (except Eyes as did not exist in IUCLID 5.3)	Qualitative

No-threshold effect and/or no dose-response information available (IUCLID 5.3 migrated file only)	All (except Eyes as did not exist in IUCLID 5.3)	Qualitative
No data available: testing technically not feasible (IUCLID 5.3 migrated file only)	All (except Eyes as did not exist in IUCLID 5.3)	Qualitative

BOX 2. Reporting uses

Within this box, it is possible to describe the uses of the substance in a structured way to ensure consistency between the use description, the exposure assessments and the exposure scenario building.

For this description, Chesar uses a life cycle tree structure in which is possible to report the relevant uses of the substance, considering human health and environmental aspects as well as the tonnage breakdown to the different uses. A life cycle tree can have 8 life cycle stages (= use types) as maximum. At each life cycle stage, one of more uses can be created, depending on differences in the conditions of use and potentially resulting in differences in the emission factors. For each use created in Box 2, an exposure scenario is created in Box 4.

For each use, one environmental contributing scenario is automatically created and other contributing scenarios for human health and for the environment can be created in addition. Contributing scenarios describe the conditions of use for those processes and activities that contribute to the use.

The identification of uses in this section of CHESAR is based on the predefined use descriptors, but, the use descriptor system was developed without considering specific uses of nanomaterials. However, Both, CHESAR and IUCLID allows with some free text to indicate for the uses selected what they refer to, e.g. to which form.

Based on names, use descriptors assigned and further specifications, it will be created a default conservative exposure assessment (with quantitative risk characterisation ratios) in Box 3.

BOX 3. Exposure Assessment

In Box 3, it is carried out one or more quantitative exposure assessment for each contributing scenario depending on the exposure assessment method selected. The route/types of effects (for humans) and environmental compartments to be covered have been determined when importing the hazard conclusions from IUCLID (Box 1). The purpose of exposure assessment under REACH is the description of use conditions ensuring control of risk (and hence safe use) and to make a

quantitative or qualitative estimate of the dose/concentration of the substance to which humans and the environment are or may be exposed, so, in this box it would be necessary to introduce all conditions of use and risk management measures involved in nanomaterials manufacture and use.

Depending on the substance properties and the uses, it may be sufficient to apply only the plugged in exposure estimation tools to demonstrate that the expected exposure is lower than the DNELs and PNECs. However, additional assessment methods may be needed in the following situations:

- The processes or activities relevant for a use cannot be assessed with the plugged-in tools (e.g. use of solid substances in liquid mixtures which is not covered by the ECETOC TRA for workers)

- The substance properties and/or the conditions of use are outside the boundaries of applicability of the tool (e.g uses of solids at elevated temperatures)

In such situations, other exposure assessment methods need to be applied (including measured data).

BOX 4. Exposure scenario building and CSR generation

The final exposure scenarios are built in Box 4 by consolidating the assessments carried out in Box 3 per contributing scenario. At this stage, also, hazards without DNELs or PNECs are taken into account, and appropriate conditions of use are added, if needed to reach a sufficient level of exposure minimization for these hazards. Finally, it should be completed the risk characterisation, quantitatively and/or qualitatively as appropriate.

From Box 4 it is possible to enter explanations (for the CSR) on the overall assessment approach applied or specific explanations at the level of single exposure scenarios. It is also possible to report on general information on risk management related to toxicological hazard or to physicochemical hazard that may be applicable to all uses (in the first case) or to packages of exposure scenarios (in the second case) and do not result from the exposure assessment carried out.

BOX 5. Generating exposure scenarios for communication

Box 5 supports the generation of the exposure scenarios for communication along the supply chain to be annexed to the extended Safety Data Sheet (SDS). The exposure scenarios for communication are based on the exposure scenarios built in Box 4. All standard phrases assigned to the condition of use as defined in the assessments (box 3 and box 4) are reported, and each assessor may decide to add/remove standard phrases to each single condition of use in the SDS ES.

3. DATA LACKING IDENTIFICATION

Once established the specific contents that must be completed in the reporting tools to prepare the chemical safety report, in this task we aim at identifying the availability of such information to nanoscale materials in general, and to the project nanoparticle panel specifically. To achieve this goal, it will be carried out a complete review of the data collected in the previous actions, manly B.1., as well as other existing published sources of data such us reference books, scientific papers or validated databases. The data obtained will be assessed carefully in order to identify their suitability to fulfilling the fields required under the basis of IUCLID 5 and Chesar statements, identifying later the specific lack of data to complete the dossier.

In fact, although the risk assessment (RA) framework is considered valuable for the RA of conventional chemicals, the analysis of its feasibility to apply to engineered nanomaterials (ENMs) has identified substantial limitations in regard to each of its phases (Hansen et al. 2007).

Several studies relevant for hazard identification have been carried out with different ENMs, but most of them use non standardized tests, generating non-reproducible results, useless for univocal hazard identification (Hansen et al. 2007).

In addition, the severe lack of characterization data makes it difficult to identify which physicochemical characteristics determine the effects documented in the toxicity studies with ENMs and to select appropriate dose metrics (Hansen et al. 2007). The environmental exposure assessment of nanomaterials is hampered by difficulties in monitoring the occurrence and concentrations of nanoparticles in the environment, and by the fact that the environmental behaviour and fate of ENMs are still largely unexplored (Council of Canadian Academies 2008). The occupational exposure assessment of nanomaterials is hindered by the lack of knowledge about: the number of workers exposed to them, the relevant pathways of exposure and the concentrations of nanoparticles in the working settings (Bergamaschi 2009). Many of the information gaps in this respect are due to the lack of adequate methods and tools, which can effectively measure the concentrations of ENMs in the occupational settings and distinguish them from the background particles. The consumer exposure assessment of ENMs is hindered by deficient knowledge about the: ENM production volumes; numbers of products containing ENMs; market penetrations of these products; and ENM releases from the products throughout their life-cycle (Hansen et al. 2008). The published data in the above aspects is scarce partly due to the lack of research studies and due to obscured industry-derived information (Hansen et al. 2008). Each element of RA is restrained by serious limitations and risk characterisation, being at the end of the line, sums all of them. In order to facilitate the sound RA of ENMs, more knowledge in the fields outlined above needs to be generated. This process, however, will take decades (Grieger et al. 2010), while RA results are urgently needed to trigger adequate regulatory response (Hristozov & Malsch 2009).

3.1. DATA NEEDS AND AVAILABILITY

The general data requirements for the Chemical Safety Assessment (CSA) of the manufactured or imported and marketed industrial chemicals in the EU are based on the Minimum Premarketing Set of Data (MPD) and they are specified in Annex VI of REACH (1907/2006). A CSA should include all available data and information on the identity, physicochemical and (eco) toxicological properties, uses, emissions, exposures, environmental fate and behaviour of a substance (ECHA 2007a, b, c). Relevant information can be obtained from the literature and databases, as well as directly from (Q)SAR models, in vivo and in vitro tests, and epidemiological studies.

Data relevant for RA of substances can be obtained from specialised libraries and documentation centres (Leeuwen & Vermeire 2007). However, nowadays with the development of the information technologies a variety of internet based databases containing chemical Environment Health and Safety (EHS) records have been introduced. Most searches for primary or secondary data would now start by interrogating online sources, such as the US Environmental Protection Agency ECOTOX and IRIS, the TOXNET HSDB or the Danish (Q)SAR Database.

In order to find information relevant for the RA of ENMs, a number of online databases could be surveyed. Three kinds of such databanks can be distinguished, based on the type and form of their content: (1) chemical databases; (2) bibliographic databases/digital libraries and (3) project databases.

The “chemical databases” store refined EHS data about substances (e.g., single values, excel sheets, text excerpts). For a risk assessor they are the most valuable source of information because it can be obtained from them directly, in a concise form. The “bibliographic databases” are organized as digital collections of abstracts and references to published literature, while the “digital libraries” go one step further, providing the full-text of the open contents. In case that the data necessary for a RA process are not available in the chemical databanks and they need to be obtained from the literature, the online libraries become appropriate platforms to search for and download relevant publications. The “project databases” store information about on-going, planned or completed projects in the nano-EHS area (e.g., leader, objectives, duration, funding). The latter databanks were included in this report since we consider that they are representative of the state of research in the field and provide a basis for assumptions about the future nano-EHS data availability.

3.1.1. Data in online databases

Some of the existing online databases for useful toxicity, exposure and/or risk data about ENMs are specified below:

(1) NAPIRAhub (Open Science): http://www.napira.eu/;
(2) Hazardous Substances Data Bank (HSDB): http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB;
(3) Chemical Safety Database Searcher (CSDS): http://msds.chem.ox.ac.uk/msds-searcher.html;
(4) Stanford Chemical Safety Database (SCSD): https://chemtracker.stanford.edu/gdnchemsafety/;

(5) Chemical Carcinogenesis Research Information System (CCRIS): http://toxnet.nlm.nih.gov/cgibin/sis/htmlgen?CCRIS;
(6) Woodrow Wilson International Centre for Scholars (WWICS) Inventory of Consumer Products: *http://www.nanotechproject.org/inventories/consumer/*; and
(7) WWICS Silver Nanotechnology Inventory: http://www.nanotechproject.org/inventories/silver/.

NAPIRAhub (Open Science) is the only database especially dedicated to nanomaterials. It contains data about TiO_2, ZnO, Ag and Fe_2O_3 nanoparticles stored in records containing parameters/values and organised into several categories in accordance with the REACH requirements (e.g., physicochemical properties, environmental fate and pathways, (eco)toxicological information, guidance to safe use). Despite that its present dataset is quite scarce (it is filled by scientists on a volunteer basis), the design of the platform implies that it will be continuously updated. Data retrieval, however, is not easy as NAPIRAhub does not allow extracting stored data in an electronic format such as Excel tables. Similar to NAPIRAhub, the HSDB contains relevant (eco)toxicological, environmental fate and exposure information about TiO_2, ZnO, Ag and Fe_2O_3 nanoparticles as well as CNTs and C60 fullerene. The records are organised as refined text excerpts where the contained information is properly cited.

The CSDS and the SCSD store some data about the toxicity and the physicochemical properties of CNTs and C60 fullerene, respectively, but they are both very scarce and unreliable (i.e., not quoted). In the CCRIS some toxicological information was found about C60 fullerene and TiO_2 nanoparticles, including the type of toxicity study (e.g., mutagenicity), the test system (e.g., Chinese hamster lung cells), as well as the corresponding endpoints, doses and test results. The data are stored in the form of quantitative parameters/values and qualitative statements.

The WWICS Inventory of Consumer Products (ICP) and the Silver Nanotechnology Inventory (SNI) deliver limited information from a risk assessor's point of view. However, since they report numbers of nano products on the market, these databanks are valuable sources of data for the formulation of consumer ESs. While still not comprehensive, the inventories include more than 1000 goods, containing nanocomponents. The SNI alone stores information about 244 nano-Ag products, while the ICP reports articles, containing C60 fullerene (7), CNTs (24), TiO_2 (31), ZnO (24), Ag (256) and Fe_2O_3 (24) nanoparticles. In the SNI, the data are organised in several classes (e.g., particle/substrate structure, synthesis method, use of nanotechnology, product testing, antimicrobial claims) and they are downloadable in PDF format, while in the ICP the information can be browsed by name, company or country and is grouped into eight categories (i.e., Appliances, Automotive, Cross Cutting, Electronics and Computers, Food and Beverage, Home and Garden, Goods for Children and Health and Fitness).

3.1.2. Data in the literature

The easiest way to gain access to scientific papers is to search for them in relevant bibliographic databanks/digital libraries.
Some important sources of published literature on nano-EHS issues, including journal articles, books, conference proceedings and reports, are the following:

(1) Toxicology Literature Online (TOXLINE): http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE;
(2) Developmental and Reproductive Toxicology (DART): http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC;
(3) International Council on Nanotechnology (ICON): http://icon.rice.edu/;
(4) National Institute for Occupational Safety and Health (NIOSH) Nanoparticle Information Library: http://nanoparticlelibrary.net/index.asp;
(5) NIOSH NIOSHTIC-2: http://www2.cdc.gov/nioshtic-2/;
(6) SAFENANO: http://www.safenano.org/Newsletter.aspx;
(7) NCBI PubMed: http://www.ncbi.nlm.nih.gov/pubmed;
(8) NCBI Bookshelf: http://www.ncbi.nlm.nih.gov/sites/entrez?db=books;
(9) NCBI PubMed Central: http://www.ncbi.nlm.nih.gov/pmc/; and
(10) ISI Web of Knowledge: http://apps.isiknowledge.com.

Using the above tools, it is possible to gain access to multiple documents, extract the relevant data from them and quantify their availability.

Grieger et al. (2010) searched the ISI Web of Knowledge and the ICON bibliographic databanks for peer-reviewed journal articles within several nano-EHS categories (e.g., exposure, toxicity, ecotoxicity, RA). The majority of the search results (»1300) fell in the “toxicity” and “ecotoxicity” categories, while less publications on “exposure” and “risk assessment” topics were found (»700 and »500 results, respectively). Based on the outcome of the survey, it can be assumed that currently the majority of published nano-EHS data and information exists in the (eco)toxicity domain and less data on exposure and risk estimations are available.

3.1.3. Future data availability

The majority of data found in the literature have been generated within national and/or European research projects.
There are some databases listing projects, concerned with nano-Environmental, Health and Safety (EHS) issues:
(1) The OECD Database on Research into Safety of Manufactured Nanomaterials: http://webnet.oecd.org/NanoMaterials/Pagelet/Front/Default.aspx? and
(2) The WWICS Inventory of Nanotechnology EHS Research: *http://www.nanotechproject.org/inventories/ehs/*.
(3) The EU NanoSafety Cluster (http://www.nanosafetycluster.eu/) is a initiative to maximise the synergies between the existing FP6 and FP7 projects addressing all aspects of nanosafety.

These databanks can provide information about ongoing and planned projects, and therefore they can serve as infrastructure to make informed assumptions about the future research trends and data availability in the field. The OECD database was surveyed for on-going and planned nano-EHS projects using the search criteria defined by Grieger et al. (2010). Plotting the distribution of the on-going/planned nano-EHS projects in the above categories (i.e., exposure, toxicity, ecotoxicity, RA) against the distribution of publications (i.e., results from past projects), an apparent shift in the research efforts from the (eco)toxicity domain to the exposure area is observed. Based on this,

it can be assumed that in future more data and information relevant for the exposure assessment of ENMs will be generated.

3.1.4. Data lacking identification: IUCLID dataset

3.1.4.1. Sameness, read-across, grouping, QSAR

For 'conventional chemicals', it is often a question whether data from one chemical substance can be used to fulfill information requirements for another chemical substance.

For nanomaterials, properties may differ not only because of differences in chemistry, but also due to differences in size (distribution), surface area, shape, surface modification, agglomeration state, etc. These differences are often specifically intended in order to obtain the preferred nano-specific properties of a given material. A key challenge here is to evaluate to which extent specific parameters may differ (e.g. from batch to batch) without significantly affecting the properties of the nanomaterial and, therefore, still be considered as the same substance/material. As pointed out above, a given nanomaterial may change characterization (and thereby properties) throughout its lifecycle.

A key question related to information requirements for nanomaterials is therefore to discern whether information requirements have to be fulfilled via testing, or whether possible alternative approaches such as read-across, grouping and QSAR models could be used. This question currently presents one of the most delicate dilemmas in relation to regulatory information requirements for nanomaterials. On the one hand there is a general consensus regarding the current lack of scientific basis for grouping/read-across or use of QSAR (and similar empirical) models, as these are not yet established/validated for nanomaterials (e.g. RIVM, 2009; RIP-oN2, 2011). On the other hand, it is also widely accepted that it is not possible to test all forms and lifecycle characterization states of nanomaterials.

It could be suggested to test the 'worst case' form of a nanomaterial; however, one does not necessarily know which is the worst case form and secondly, this could ultimately lead to unnecessarily strict risk management for some forms. Assuming that the nanoform of a chemical is at least as toxic as the bulk form could justify refraining from testing the nanoform if the bulk form is already classified in the worst-case category of a toxicological end-point. Testing might however be needed if a no-effect level is required for conducting a risk/safety assessment of the nanomaterial.
Overall, there is a need for further R&D and consensus building on this very important topic as also suggested by e.g. NANO SUPPORT (2012). This further development should consider whether and when read-across within certain groups/types of nanomaterials could be performed, e.g. when the toxicity of a released leading ion(s) would overrule particle properties and thus could be used for read-across.

One of the key conclusions from NANO SUPPORT (2012) is that a prerequisite for addressing different forms, including different nanoforms in a regulatory dossier, is that the forms addressed by the dossier are explicitly described upfront as part of the substance identification (which may

possibly lead to different dossiers for different nanoforms) or as part of a characterization within a given dossier. In addition to providing clarity about nanoforms within the scope of the dossier, it is also the basis for discussing which test data could or should be used in relation to those forms.

3.1.4.2. Adaptation (waiving/triggering)

Currently, as discussed in the previous section, there does not seem to be consensus for wide use of read-across and grouping.
Guidance proposed in RIP-oN2 (2011) and implemented by ECHA in recent guidance updates stresses that read-across, e.g. from bulk to nano and/or between nanomaterials, should only be done if scientifically justified. This may lead to either triggering or waiving depending whether the read-across leads to additional concern or whether the read-across justifies waiving a test. NANO SUPPORT (2012) suggests that REACH Annex XI (with general rules for adaptation), currently referring to possible application from one substance to another substance, should be revised to mention 'form to form' extrapolation when relevant.

3.1.4.3. RA approaches: Tools

EHS data are gradually generated to fill the gaps, but this process advances slowly, while RA results are urgently needed to adequately inform the regulators (Grieger et al. 2010; Hansen 2009; Hristozov & Malsch 2009). This need pushed several regulatory agencies, research institutes and companies (e.g., Environmental Defense and DuPont, SCENIHR) to propose complementary/alternative approaches for near term estimation of nano risks, taking into account the inherent novelties of the materials. To this end, the state-of-art of tools that have been developed by other authors until now are described below.

Considering the overwhelming limitations to the RA of ENMs, the timely nano governance would require flexible methodologies, which demonstrate high accuracy in the assessment of risks even if the available input data are scarce and at the same time adequately consider the degree of uncertainty to ensure robust and reliable estimations.

Both the hazard identification and the dose-response assessment of ENMs suffer from the substantial deficit of characterization data (Hansen et al. 2007, 2009), which makes it difficult to determine the properties which account for their inherent toxicity and set appropriate dose metrics. The enormous structural diversity within each group of ENMs (e.g., CNTs) adds complexity to the situation and further deepens the problem. To address these issues, a number of tools have been suggested in the literature which aim to facilitate the process. For example, Hansen et al. (2007) proposed a novel classification approach to aid the hazard identification of ENMs which categorizes the materials, based on the location of the nanoscale structures in their system/matrix, prior to the assessment, while SCHENIR (2005) suggested a very simple nano hazard screening algorithm, based on a decision tree. Both approaches emphasize that the comprehensive characterization of the test materials is crucial since it enables the correlation between the ENM properties and the measured biological/toxicological responses and provides an adequate reference point for comparing toxicity results with other relevant hazard-based findings (e.g., QSAR results).

While the conventional RA is based on the notion that the chemical identity governs the biological effects of a substance, the situation with nanomaterials is different. There is a general agreement that the toxicity of ENMs is determined by a set of characteristics (e.g., size, aspect ratio, surface area and reactivity, surface charge).
However, given the substantial diversity within each group of nanomaterials (e.g., there are over 20 different structural types of SWCNTs), a large number of property combinations need to be considered to assess the overall hazard of a single material type (i.e., the SWCNTs in this case) (Hansen 2009). Therefore, it seems that, presently, the most feasible solution is to address the hazard/risk estimation of nanomaterials on a case-by-case basis (Environmental Defense and DuPont 2007; SCENIHR 2005). This effort, however, would be very time and resource intensive (Hansen 2009). In this context, the Integrated Testing Strategies (ITSs) have become particularly relevant, since they are intended to speed up the RA process, while at the same time reducing testing costs and animal use (Ahlers et al. 2008; Jaworska et al. 2010).

A key purpose of the ITSs is to efficiently exploit and integrate the existing information with new data, which can be generated by multiple testing and non testing methods (Bassan & Worth 2008). The latter feature makes them potentially valuable in regard to the near term hazard assessment of nanomaterials. In this context, Meng et al. (2009) proposed a paradigm for the estimation of nano hazards for the human health, which uses in vivo outputs to validate in vitro assays as being "predictive" and therefore valid for screening large batches of materials to obtain QSARs. QSAR is an in silico modelling tool, which can be used to predict toxicity effects and/or correlate them with the physicochemical properties of the materials (Puzyn et al. 2010). The development of QSARs is an emerging trend in the nano-EHS field, which holds promise of resolving which characteristics determine the inherent hazards of many ENMs. Despite this, no completed nano-QSAR models have been reported in the literature, and the development of such is planned as part of major research initiatives, such as the EU 7th Framework Programme (FP7) ENPRA project.

To enable computational modelling of the post-exposure absorption, distribution, metabolism and excretion (ADME) dynamics of chemicals or particles throughout the organism physiologically-based pharmacokinetic (PBPK) models are applied. By incorporation of chemical-specific physicochemical and biochemical characteristics along with species specific physiological properties, PBPK models can be used for both dose and species extrapolation in dose response modelling (Lee et al. 2008; Riviere 2009) and therefore they play a key role in the RA of chemicals and nanomaterials. Although no standard PBPK model for ENMs has been reported so far (SCENHIR 2007), a specific, blood flow- limited PBPK model for quantum dots (QDs) was introduced by Lee et al. (2008). Despite this, its authors note that it might be inadequate to entirely explain the complex pharmacokinetics exhibited by the QDs (e.g., the flux of ENPs into specific regions of tissues); this model clearly marks the outset of an emerging tendency in the area of nano hazard assessment. The first general PBPK model for ENMs is currently under development by the UK Institute of Occupational Medicine (IOM) and the US NIOSH in the context of the EU FP7 ENPRA (Tran 2011). It is an adaptation and extension of an earlier IOM PBPK model for larger particles to the ENMs case, which is currently being optimized and modified to ensure high physiological relevance using data generated within the FP7 projects ENPRA, NANOMMUNE and NANOTEST. Such a generalised, predictive model for ENMs can be very useful not only in

characterising the ADME profiles of the materials, but also their biological interactions across a diverse range of species based on particle type and physicochemical properties (Lee et al. 2008). However, a nano-PBPK model, capable of extrapolating responses across doses and animal species, would require an explicit understanding of the flux of ENMs into specific regions of organs and tissues, including good knowledge of any tissue-specific vascular and lymphatic effects and mechanisms of cellular uptake (Lee et al. 2008), which is currently largely lacking. Nevertheless, the production of such knowledge is planned in the context of many current scientific initiatives.
Data on the toxicity of ENMs can be obtained faster, easier and at lower cost from *in vitro* compared to *in vivo* studies. However, a major issue is how to translate the results of *in vitro* experiments into the *in vivo* situation. For a quantitative in vitro–in vivo extrapolation, modelling of continuous, quantal or ordinal dose-response data is needed (Slob 2002), using suitable tools such as the PROAST software (http://www.rivm.nl/en/foodnutritionandwater/foodsafety/proast.jsp), in order to derive and compare *in vitro* and/ or *in vivo* benchmark dose (BMD) and/or effective concentration thresholds (Gosens 2011). Using the model outputs in an empirical approach, one can look for correlations among the in vitro and in vivo data. Assuming that the experimental results have been produced using reliable and standardised protocols, the differences in the in vitro and in vivo dose–response curves would be only due to variations in the physicochemical properties of the ENMs (Gosens 2011). Therefore, using this approach a QSAR-like algorithm (i.e., a quantitative property (in vitro) property (in vivo) relationship (QPPR)) can be obtained. Using this QPPR, in vivo BMD and ECx values can be derived out of in vitro data (Gosens 2011). The disadvantage of this approach is that it requires standardised data for a large number of ENMs, which are generally difficult to acquire. In this context, an alternative mechanistic approach may be more relevant, using information on the complete toxicokinetic profile of the ENMs derived trough PBPK modelling as discussed in the previous paragraph.

A classical quantitative human health RA of ENMs would generally start with a deterministic PBPK model of the exposure-dose-response relationship and its extrapolation to human situation, using data from in vitro to in vivo studies. However, in the case of ENMs such a model would be affected by severe uncertainty and data variability. For this reason, it is recommended that the RA of ENMs is addressed in a probabilistic manner using stochastic approaches such like the Monte Carlo and the Latin Hypercube Simulations.

In this case, a distribution of hazard estimates will be derived instead of a single point estimate as in the traditional deterministic hazard assessment, which can be plotted against a distribution obtained from probabilistic exposure modelling in order to identify central tendencies of expected risk and associated high-end probability of exposure (Tran 2011). Despite that the risk estimates will depend on the extent of uncertainty, by applying sensitivity analysis it is possible to identify the main factors contributing to the overall model uncertainty and reduce it. Although this approach has not been used with ENMs yet, it will be applied in the context of the EU FP7 ENPRA project (Tran 2011).

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