Guidelines on the Precautionary Matrix for Synthetic Nanomaterials

Version 4.0
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Schweizerische Eidgenossenschaft
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Contents

1 Context

Nanomaterials make it possible to introduce innovative functions in products and technologies. However, nanomaterials may only be placed on the market if their intended use does not endanger people and the environment. Responsibility for the safe handling of synthetic nanomaterials therefore rests with the manufacturer and importer.[1]

An important basis for the danger and risk assessment is data on the physico-chemical and toxic properties of these materials. The OECD plays a significant role in the development and standardisation of the methods for testing these properties. The OECD has decided that the methods developed for conventional chemicals can in principle be adopted for nanomaterials, but will have to be adapted to their specific properties. Some individual specific methods for nanomaterials have now been standardised. However, it will be some time before these are available in their entirety and capable of determining those properties that could influence the behaviour of nanomaterials in organisms and the environment and their interaction with biological systems, and hence their effects on organisms.[2]

The same applies by analogy to existing hazard and risk assessment methods, which are in principle also applicable to nanomaterials. However, these will need to be amended to take on board nanospecific properties. As an internationally harmonised testing strategy does not yet exist, decisions on data requirements for risk assessment have to be taken on a case-by-case basis.

This situation is causing businesses uncertainty about how to act and whether to invest, as well as making it difficult to have a public debate on the opportunities and risks presented by nanomaterials.

The Swiss Action Plan on the Safe Handling of Synthetic Nanomaterials ran from 2008 to 2019. Results of the action plan:

- Various dialogue events were held with consumer and environmental organisations, the business and scientific communities and the public authorities.
- Infonano.ch was set up – the Swiss federal government's website on nanotechnology.
- A number of guides were published covering the identification of potential risks associated with nanomaterials and passing on important safety information to the production and supply chain (e.g., "Precautionary Matrix for Synthetic Nanomaterials", "Safety Data Sheet (SDS): Guide for Synthetic Nanomaterials").
- Various nano-specific requirements have been defined in Swiss law and aligned to the EU provisions governing nanomaterials.
- New measurement and testing methods have been developed for nanomaterials, especially for their characterisation.

[1] Art. 5 Chemicals Act (ChemA, SR 813.1), Art. 26 Environmental Protection Act (EPA, SR 814.01), Art. 7 Chemicals Ordinance (ChemO, SR 813.11); Art. 82 Accident Insurance Act (AIA, SR 832.20), Chapter 2, Section 1 Accident Prevention Ordinance (APO, SR 832.30).

[2] See: https://www.oecd.org/env/ehs/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

The development of the **precautionary matrix** for products and applications that involve synthetic nanomaterials was a core measure of the action plan and sets out to empower industry, commerce and trade to take greater responsibility in this area and to apply the precautionary principle in a goal-driven, cost-effective manner. The Action Plan ended in 2019 but framework conditions are in place for the precautionary matrix to be aligned to new findings over the years to come.

2 Objective and Area of Application

Depending on their field of application, nanomaterials have to be tested like conventional food additives, chemicals, biocides etc., and an assessment has to be made on the risks to humans and the environment. The assessment methods used in the different approval and authorisation procedures have yet to be tailored to nanomaterials. The precautionary matrix supplements the existing non-nanospecific assessment methods by providing an evaluation of the need for precautions. It should therefore always be employed in parallel with the existing assessment methods and not instead of them.

The precautionary matrix is not legally binding. It can be used on a voluntary basis and serves as an evaluation tool for the safe handling of nanomaterials in the context of existing knowledge.

2.1 Objective

The precautionary matrix helps businesses to assess the need for nanospecific measures (“need for precautions”) in connection with synthetic nanomaterials and applications of these materials for employees, consumers and the environment. In addition, it helps to identify potential sources of risk in the development, production, use and disposal of synthetic nanomaterials. This pragmatic approach of applying a limited number of meaningful parameters should under no circumstances be equated with a nanospecific risk assessment.

Classifications are instead intended to demonstrate the need for precautionary action for the scenario in question. By classifying the need for precautions, it is possible to differentiate and objectivise the opportunities and risks presented by nanomaterials and nanotechnologies.

"Class A": The nanospecific need for action for the considered materials, products and applications can be rated as low and does not need further clarification.

"Class B": Nanospecific action is needed. Existing measures should be reviewed, further clarification undertaken and, if necessary, measures to reduce the risk associated with development, manufacturing, use and disposal implemented in the interests of precaution.

As regards further clarification, users of the precautionary matrix can carry out their own investigations on human exposure, inputs into the environment and the effects of nanomaterials. They may also draw on data from the literature, models and information provided by experts (see section 5.4, 5.5, 5.6).

Applications that require clarification can thus be identified independently using the precautionary matrix, and the need for measures to protect health and the environment can then be reviewed and estimated. The precautionary matrix is therefore an instrument that industry, commerce and trade can use for duty-of-care and self-supervision[3] purposes associated with the production and marketing of synthetic nanomaterials. The precautionary matrix is also intended to assess the need for precautionary measures for existing or new products and processes. The matrix facilitates a structured approach and allows the major potential sources of risk to be identified. Thus, it also provides the basis for early decision-making on whether to proceed with new product developments.

[3] According to the Chemicals Act (SR 813.1), Environmental Protection Act (SR 814.01) and Chemicals Ordinance (SR 813.11).

By functioning simultaneously as an aid to differentiation, a detector of gaps in knowledge and an early warning system, the precautionary matrix promotes safe use of nanomaterials and thus incorporates a safe-by-design approach right from the start. The precautionary matrix is freely available and free of charge.

2.2 Area of application

Internationally there are currently a number of different definitions of the term nanomaterial. In most definitions, the size of the primary particle plays a crucial role, with external dimensions of less than 100 nm in at least one dimension having become the criterion.

However, the use of the 100 nm limit is not scientifically justifiable. Thus, nanospecific effects also occur in cells and organisms with particles whose external dimensions are greater than 100 nm, as cells are capable of absorbing particles of up to approx. 500 nm with particular ease.[4] [5]

The precautionary matrix contains two approaches to assessing nano-relevance. Users can choose their approach in line with the field of application and the different legal requirements.

Approach 1 (Recommendation European Commission on the definition of nanomaterials, 2022/C 229/01)[6]

'Nanomaterial' means a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50 % or more of these particles in the number-based size distribution fulfil at least one of the following conditions:

a) one or more external dimensions of the particle are in the size range 1 nm to 100 nm;

b) the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm and the other dimension is larger than 100 nm;

c) the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm.

In the determination of the particle number-based size distribution, particles with at least two orthogonal external dimensions larger than 100 µm need not be considered.

However, a material with a specific surface area by volume of < 6 m^2/cm^3 shall not be considered a nanomaterial.

Approach 2 (precautionary approach)

Deliberately manufactured materials are considered to be nano-relevant if they contain particles in the unbound state as an aggregate[7] or agglomerate[8] and in which one or more external dimensions are between 1 and 500 nm. Respirable materials up to 10 µm with nanoscale side branches can likewise trigger nanospecific effects and are likewise considered to be nano-relevant. Fullerenes, graphene flakes and single wall carbon nanotubes are considered to be nanomaterials even when they exhibit dimensions of less than 1 nm.

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[4] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) Publication: "Risk Assessment of Products of Nanotechnologies" (2009, S. 26).

[5] Publication: A. Bruinink, J. Wang, P. Wick, "Effect of particle agglomeration in nanotoxicology" in Archives of Toxicology (2015) 89:659–675.

[6] See EUR-Lex: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32022H0614%2801%29.

[7] According to ISO/TS 80004-4 (2011): Particles of solidly bound or molten particles, whose resulting surface may be much smaller than the sum of the calculated surfaces of the individual components.

[8] According to ISO/TS 80004-4 (2011): Arrangement of loosely bound particles or aggregates or mixtures of both in which the resulting surface is similar to the sum of the surfaces of the individual components.

Exemptions from the scope of the application

Regardless of whether a nanomaterial is present, nanometre-size particles can also be produced by abrasion or combustion processes. The resultant possible risks are dealt with in connection with the exposure to fine dust and ultrafine particles and are not considered in the precautionary matrix. The precautionary matrix is not influenced by non-nanospecific risks to health or the environment, e.g., risks resulting from the toxicity of a nanomaterial's chemical composition (classical "chemical toxicity") or its specific structure (e.g., toxicology of biopersistent fibres longer than 5 micrometres).[9] These risks must be assessed by conventional standard procedures.[10]

Note: Since 1 March 2018, manufacturers and importers have been required to notify intentionally produced biopersistent nanofibers and nanotubes of more than 5 micrometres in length (Art. 48, para. 1 ChemO).

Application in various phases of the life cycle

The precautionary matrix can be used to estimate the need for precautionary measures to protect the health of employees and consumers and for the environment at various points across the life cycle of nanomaterials. The following processes in the life cycle are considered (see Figure 1):

- Research and development
- Production (including primary production, further and final processing, storage, packaging processes and transport)
- Use
- Recycling
- Disposal

[9] See e.g., Schinwald A. *et al*.: The Threshold Length for Fiber-Induced Acute Pleural Inflammation: Shedding Light on the Early Events in Asbestos-Induced Mesothelioma; Toxicological Sciences 128(2), 461-470 (2012), http://toxsci.oxfordjournals.org/content/128/2/461.fullhttp://toxsci.oxfordjournals.org/content/128/2/461.full.

[10] See: ECHA Guidance on Information Requirements and Chemical Safety Assessment http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

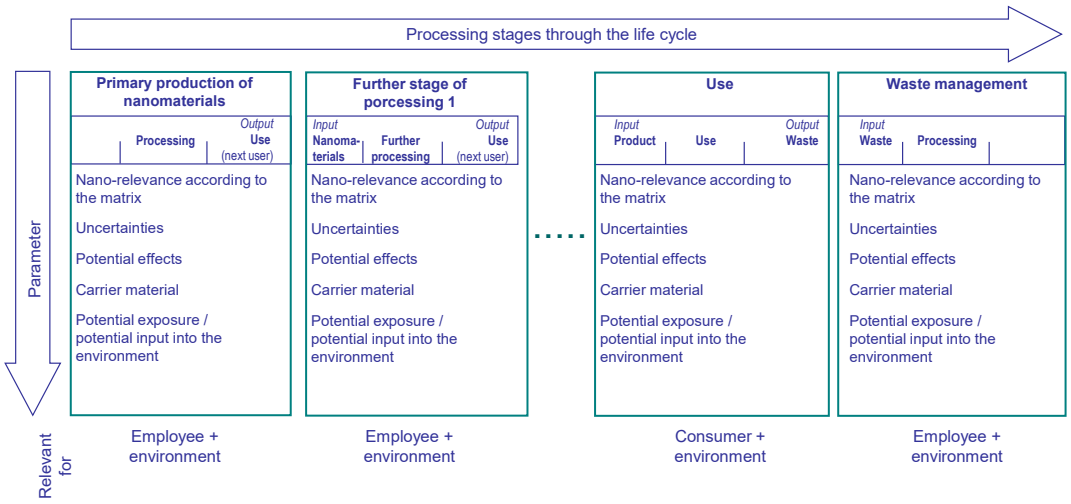

Figure 1: Processing stages as part of the entire life cycle.

As a general rule, a precautionary matrix only applies to the selected type of nanomaterial in a precisely defined environment. If the carrier material (e.g., solvent, matrix/substrate, state of aggregation, etc.) or the conditions of use change, a new precautionary matrix has to be completed for this situation. A new matrix also has to be completed if the original nanomaterials change during use, for instance through rapid dissolution of a coating. If the amount handled per day differs considerably from the amount of nanomaterial or material containing nanomaterial that is kept in storage, it is recommended to complete a separate precautionary matrix for the stored amount in order to depict the worst-case scenario.

Evaluation parameters

The precautionary matrix is based on a limited number of evaluation parameters, which can be divided into three categories.

1. The **information knowledge relating to the life cycle** of the nanomaterial have to be entered.
2. The **potential effect**[11] is estimated on the basis of the nanomaterials' **reactivity** and **stability**[12].
3. The probability and degree of **exposure (= potential exposure) of humans** are determined from data on the carrier material of the nanomaterials (nanomaterial category, emission factor), the amount of nanomaterials handled, the frequency of use, the exposure route, the premises, and the amount in consumer products.

   The extent of the **potential input into the environment** is determined from the amount of specifically disposed nanomaterials or the amount in **exhaust gases, wastewater or solid** waste from development, production or use.

[11] Ability of nanomaterials to affect their surroundings (humans, environment).
[12] For purposes of the precautionary matrix, the stability of a nanomaterial is taken to be the resistance of the nanomaterial as such to change/transformation in the observed surroundings (e.g., resistance to dissolution, chemical or physical transformation, sintering into bulk material or degradation, etc.).

The precautionary matrix is made up of modules for these evaluation parameters. This structure ensures that new scientific information on effects, human exposure or input into the environment can be taken into account at any time.

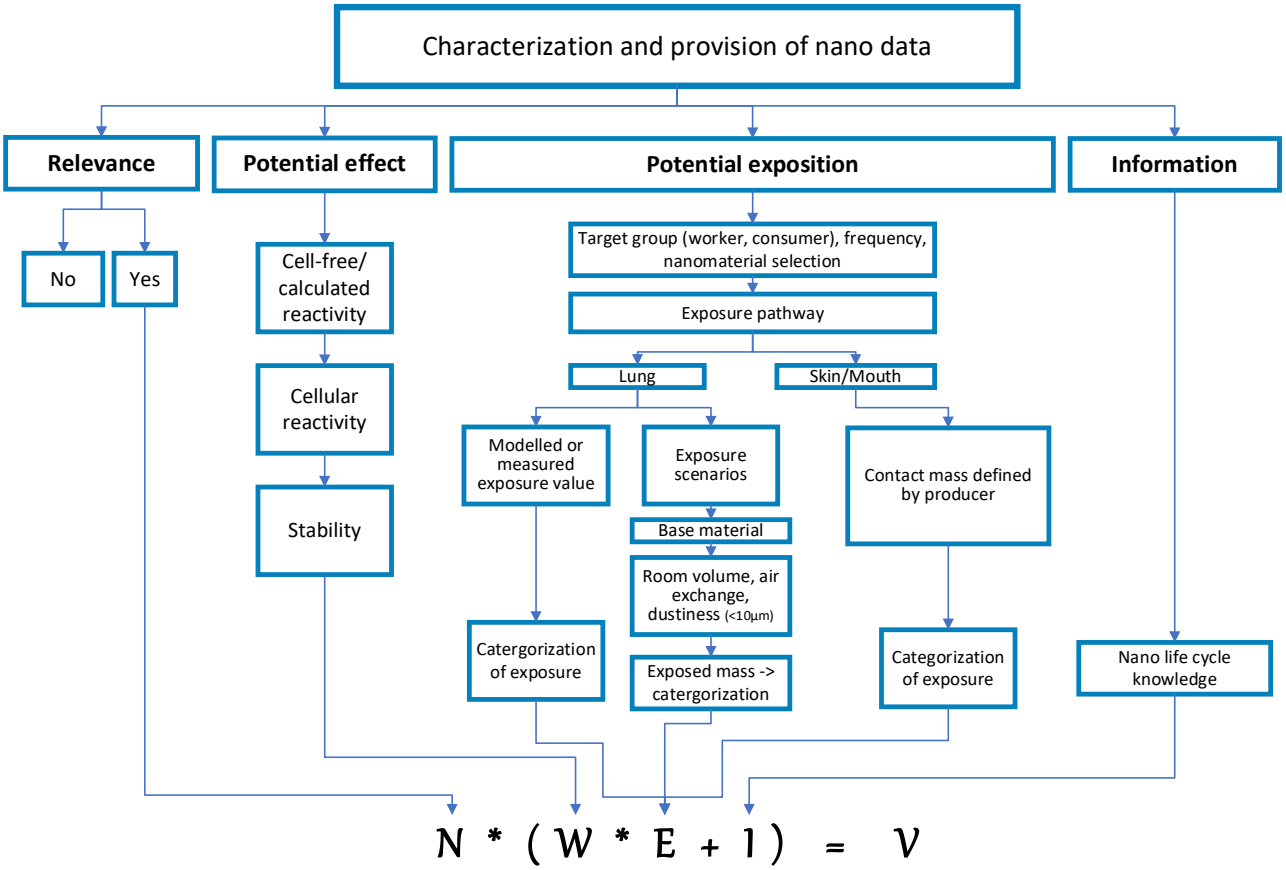

Figure 2: For illustration purposes, the decision paths and parameters in the precautionary matrix that affect human health.

Note:

The precautionary matrix version 4.0 is available as a web application. Both can automatically evaluate data input.[13] This simplifies processing and evaluation and saves a lot of time. These guidelines incorporate basic deliberations about the concept of the precautionary matrix and describe the evaluation algorithms.

[13] Precautionary matrix: https://www.bag.admin.ch/bag/pmx-en.

3 Procedure for Completing the Precautionary Matrix

The precautionary matrix should be completed with the help of a template and evaluated in terms of the possible risks to health and the environment. Evaluation is automatic. Explanations and guidance on completing the precautionary matrix are provided in section 4 "Concept of the Precautionary Matrix", for the evaluation of the precautionary matrix in section 5 "Linking of Parameters and Estimation and Classification of the Need for Precautionary Measures".

Application functions on the user interface:

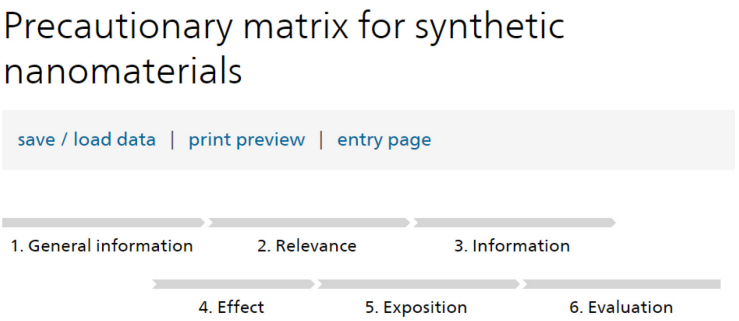

Figure 3 User interface for the precautionary matrix.

- save/load data: allows the data to be exported in an XML file format and imported back into the precautionary matrix at a later date for further work.
- print preview: enables the precautionary matrix to be printed with all the inputs made.
- entry page: takes the user to the entry page of the online precautionary matrix.
- navigation: clicking on one of sections 1-6 takes the user directly to the questions covered in that section.

Procedure for determining the need for precaution

It is reasonable to complete the precautionary matrices in two iterative steps:

1. A first rapid evaluation demonstrates knowledge gaps and uncertainties and leads to a preliminary precautionary matrix.
2. Precise investigations based on the results of step 1 and specifically closing existing knowledge gaps produce a definitive precautionary matrix.

Process:

1. **Draw up an inventory of materials/products/applications**, which are to be tested for nano-relevance in the context of the precautionary matrix and need for precautionary measures. Include any materials / products / applications where there is doubt about whether nanomaterials are involved.
2. **Check the nano-relevance** of each material / product / application listed in the inventory on the basis of the parameters described in section 4.3. Exclude non nano-relevant materials / products / applications which do not fall into the fields of application of the precautionary matrix. If there is a doubt whether a material is nano-relevant or not, it is advisable to complete the precautionary matrix so as to avoid excluding any possible nano-specific risks.

If the same material / product contains several nanomaterials, or if several are used in the same application, a separate matrix must be filled in for each nanomaterial. If the nanomaterials change specifically in the body or in the environment (e.g. dissolution of a coating, oxidation etc.) and could be present at the same time in these new forms, a separate matrix must be completed for each of these nanomaterials.

3. **Find and separate (process) steps** for all nano-relevant materials / products / applications that are covered for assessment by the precautionary matrix (no change in the carrier material of the nanomaterials). A separate matrix must be completed for each step.
4. Using Figure 1, **position each (process) step** found in the value chain: Decide on the groups – employees, consumers and the environment – for which a matrix should be completed.

   If appropriate, separate matrices must be completed for employees with different activity profiles in the same (process) step, or for different groups of consumers.
5. **Complete the technical part of the precautionary matrix** as far as possible, following the parameters described in section 4.
6. **Specify information sources**: Give the name of the person in charge in case any data or information is missing (e.g. suppliers, research departments, universities, experts, etc.).
7. **Obtain information** using the relevant questions from the matrix.
8. **Finish the matrix**, delimit the relevant need for precautionary measures and determine the classification.
9. **Determine any need for action** and, if appropriate, initiate measures (commence further investigations, additional protection measures and measures to provide information, communication, etc.). See sections: Recommendations for further investigations (5.4), possible protective measures at the workplace (5.5), information and advice for more information (5.6).

4 Concept of the Precautionary Matrix

This section describes the structure of the precautionary matrix and the parameters used. The tables illustrate queries and possible responses in the precautionary matrix and the resulting numerical values for the estimation of the need for precautionary measures. The linking of the numerical values is described in section 5, as are the metrics and the evaluation of the precautionary matrix.

4.1 Principles

The need for precautionary measures is represented primarily in relation to the potential effect (W) and the potential exposure of humans or inputs into the environment (E). "Available information" (I) is introduced as an additional parameter. This factors in uncertainties that take account of gaps in knowledge about the background and the future life of the nanomaterials, or of lack of clarity in the system under consideration (impurities or inaccurately determined size distribution of nanomaterials, etc.). "Nano-relevance according to the precautionary matrix" (N)[14] is introduced as a criterion for deciding whether the use of the precautionary matrix is indicated:

Need for precautionary measures = f (N, W, E, I)

where:

N: Nano-relevance according to the precautionary matrix (section 4.3)

I: Available information on the life cycle (section 4.4)

W: Potential effect (section 4.5)

E: Potential human exposure / potential input into the environment (section 4.6)

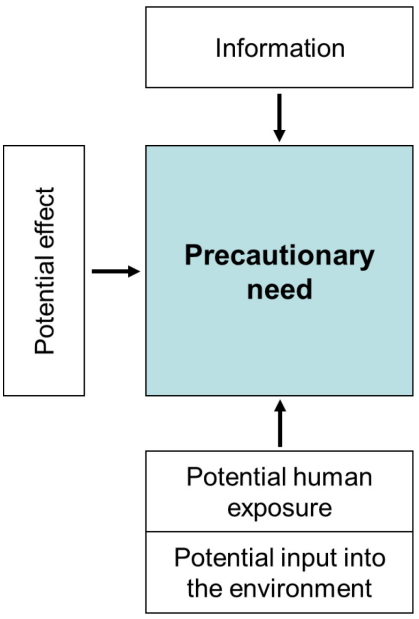

Figure 4: The concept for estimating need for precautionary measures.

Potential human exposure, potential input into the environment, potential effect, and available information are each evaluated using a parameter selected for the class, and related together to

[14] A system is considered to be relevant in the context of the precautionary matrix if it contains nanomaterials according to section 2.2.

determine the need for precautionary measures. To this end, tables of relationships and corresponding parameter-dependent functions are both used. See section 5 for details on evaluation.

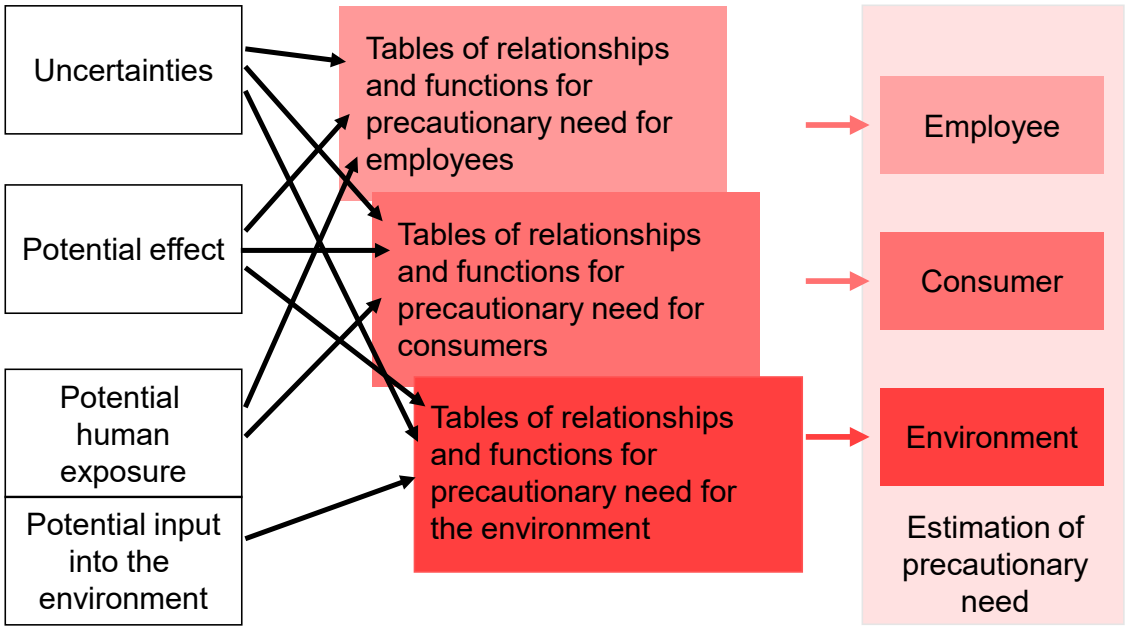

Figure 5: Parameters for estimating the need for precautionary measures.

For the purposes of calculating the need for precautionary measures, the input parameters low need, medium and high are scored. In all cases in which it is not possible to conduct an assessment because the information is not available, the value that would ultimately give the highest need for precautionary measures must be used.

4.2 Parameters

The parameters and their sub-divisions are summarised in Table 1:

	Parameter	Abbreviation
General	**General**	
	Precautionary need for employee or consumer	*(keine)*
	Frequency with which an employee handles nanomaterials	E2.3
	Frequency with which a consumer uses the utility product	E2.5
	Category of nanomaterial (carbon nanotubes and nanofibers, nanosilver, other nanomaterials)	*(keine)*

Nano-relevance	**Nano-relevance according to the precautionary matrix**	

	• 'Nanomaterial' means a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50 % or more of these particles in the number-based size distribution fulfil at least one of the following conditions:
	  • one or more external dimensions of the particle are in the size range 1 nm to 100 nm;
	  • the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm and the other dimension is larger than 100 nm;
	  • the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm.
		N-EU

	• Size of the primary particles in the materials (free, bound, aggregated or agglomerated) in the size range 1 bis 500 nm • Material consists of fullerenes, graphene flakes or single-walled carbon nanotubes	N1
	Do the nanomaterials form agglomerates >500nm?	N1a
	Only if N1a = yes: Does deagglomeration of agglomerates (or aggregates) to primary nanoparticles or agglomerates <500nm occur under physiological conditions?	$N2_{A,V}$
	Only if N1a = yes: Does deagglomeration of agglomerates (or aggregates) to primary nanoparticles or agglomerates <500nm occur under the respective environmental conditions?	$N2_{U}$
	Only if $N2_{A,V}$ = no: If agglomerates between 500nm and 10µm are present, can employees or consumers take these in via the lungs?	N2a
Information	**Information on the life cycle**	
	Is the origin of the (nanoscale) starting materials known?	I1
	Is sufficient information on nanoscale starting materials available to complete the precautionary matrix?	I2
	Are the next users of the considered nanomaterials known?	I3
	How accurately is the material system known, or can disturbing factors (e.g. impurities) be estimated?	I4
Potential effect	**Potential effect**	
	Redox activity, catalytic activity, oxygen radical formation potential, induction potential for inflammatory reactions of the nanomaterial, decrease in glutathione, induction of protein carbonylation	W1
	Stability (half-life) of the nanomaterial in physiological conditions	$W2_{A,V}$
	Stability (half-life) of the nanomaterial under environmental conditions	$W2_{U}$
Potential human exposure / potential input into the environment	**Potential exposition**	
	Exposure value (modelled or measured)	E_0
	Potential for release related to employee and consumer	$E1_{A,V}$
	Potential for release related to the environment	$E1_{U}$
	Carrier material (emission factor)	E1.1
	Dustiness	E1.3
	Room conditions	E1.4
	Room volume	E1.5a
	Air exchange rate	E1.5b
	Dailey exposure in (h)	E1.5c
	Maximum possible human exposure	
	Amount of nanomaterials handled by an employee per day	E2.1
	Amount of nanomaterials with which an employee could come into contact in the worst case	E2.2
	Amount of nanomaterials handled by a consumer per day via the utility product	E2.4
	Maximum possible input into the environment	
	Amount of nanomaterials reaching the environment from wastewater, exhaust gases, solid waste per year	E3.1
	Annual amount of nanomaterials in utility products	E3.2
	Amount of specificallydisposed nanomaterials per year	E3.3

Table 1: Classification of the parameters used. It should be noted that depending on the selected input path, not all input parameters are queried.

4.3 Nano-relevance according to the precautionary matrix (N)

Parameters N-EU[15], N1 and N2 examine the nano-relevance of the system. The criteria mentioned in section 2.2 “Field of application” serve as the benchmark.

Approach 1 (Recommendation European Commission on the definition of nanomaterials, 2022/C 229/01): ’Nanomaterial’ means a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50 % or more of these particles in the number-based size distribution fulfil at least one of the following conditions: • one or more external dimensions of the particle are in the size range 1 nm to 100 nm; • the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm and the other dimension is larger than 100 nm; • the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm. In the determination of the particle number-based size distribution, particles with at least two orthogonal external dimensions larger than 100 µm need not be considered. However, a material with a specific surface area by volume of < 6 m^2/cm^3 shall not be considered a nanomaterial.	yes	no	unknown
N-EU	1 (go to N1a)	0	1 (go to N1)

[15] N-EU: This parameter defines the nano-relevance based on the EU’s proposed definition for nanomaterials (cf. section 2.2). More information: https://ec.europa.eu/environment/chemicals/nanotech/faq/definition_en.htm.

Approach 2 (precautionary approach): size of the primary particles (in the free or bound state, as an aggregate or agglomerate) contained in the materials Fullerenes, graphene flakes and single wall carbon nanotubes are considered to be nanomaterials even when they exhibit dimensions of less than 1 nm.	>1 nm, <500 nm (one or more external dimensions) or yes		>500 nm
N1	1		0
Do the primary particles form agglomerates or aggregates >500 nm.	yes	no	not known
N1a	1 (go to N2)	1	1

Table 2: Nano-relevance

If the primary particles (individual particles between 1 and 500nm) are in an aggregated or agglomerated form >500nm, the key factor for determining their “nano-relevance” is whether these aggregates or agglomerates are capable of disintegrating into primary particles or smaller agglomerates (< 500nm) (N2) under ambient conditions (in the body or the environment). If there are stable agglomerates as well as free primary particles, parameter N2 must always be designated with 1.

A nanoparticle’s stability in the body is important for assessing the need for precautionary measures to protect health ($N_{2A,V}$), while stability under ambient conditions is important for assessing the need for precautionary measures for the environment ($N2_U$).

Even for stable agglomerates >500nm, structural elements (nanoscale side branches) which have nano-specific toxicity when in contact with biological tissues can be produced. The cases should be treated as N2a in the precautionary matrix.

Only if N1a = yes: Does deagglomeration of agglomerates (or aggregates) to primary particles or agglomerates <500nm occur in the body?	yes	no
$N2_{A,V}$	1	1 (proceed to N2a)
Only if N1a = yes: Does a deagglomeration of agglomerates (or aggregates) to primary particles or agglomerates <500nm occur under the respective environmental conditions?	yes	no
$N2_U$	1	0
Only if $N2_{A,V}$ = no: Are agglomerates between 500nm and 10µm present, such that employees or consumers can inhale them?	yes	no
N2a	1	0

Table 3: Nano-relevance of agglomerates. The lowercase letters mean: $_A$ = employee; $_V$ = consumer; $_U$ = environment.

The process for establishing nano-relevance is summarised in simplified form in the following diagram. For a more detailed description see appendix 6.1.

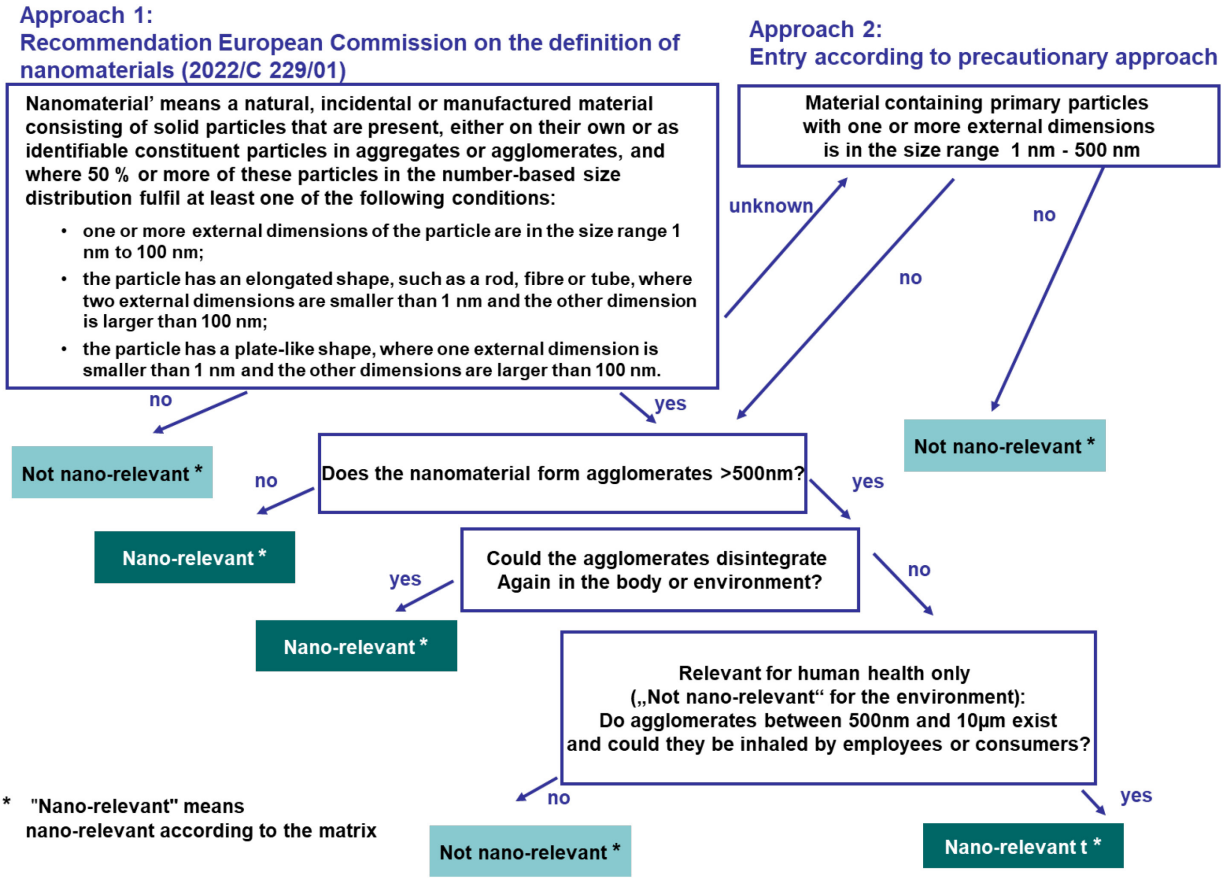

Figure 6: Process for establishing nano-relevance.

4.4 Available information (I)

Parameters I1 to I3 evaluate the uncertainties that result from gaps in knowledge about the background of the nanomaterials (Figure 1) and of their future life cycle. This also includes knowledge of other likely effects on the nanomaterial during its life cycle. I4 takes account of uncertainties about the system under consideration, including impurities, inaccurately determined size distribution of the nanomaterials. The sum of parameters I1 to I4 gives the factor I.

Is the origin of the (nanoscale) starting materials known?	yes	partly	no
I1	0	4	7
Is sufficient information available to complete the precautionary matrix for nanoscale starting materials?	yes	partly	No
I2	0	4	7
Are the next users of the considered nanomaterials known?	yes	partly	No
I3	0	4	7
How accurately is the material system known, or can disruptive factors (e.g. impurities) be estimated?	accurately	not accurately	not known
I4	0	4	7

Table 4: Available information about the life cycle

For primary manufacturers of nanomaterials I1 and I2 should be completed as follows:

- I1: Answer the question for non-nanoscale starting materials
- I2: Answer 'yes' for this parameter if no nanoscale starting materials are present

4.5 Potential effect (W)

This section describes the procedure for estimating the potential effect of a nanomaterial and the data required to do so. The methods needed to determine and evaluate these data are explained in detail.

The precautionary matrix assumes that nano-relevant materials can come into contact with cells and tissue or could be taken up by them. Depending on their hazard potential, they may produce detrimental effects in the cells or organs. The precautionary matrix uses nanomaterials' reactivity and stability to estimate their potential effect. Various studies have compared different effects of nanomaterials measured using cell-free or cellular methods with their *in vivo* effects (Table 5, ref. a, e, f, h). The reactivity parameters listed in point 1 below were mainly selected on the basis of such comparative studies. The parameters listed were also chosen in the light of the currently known mechanisms of action that are relevant for the adverse effects of nanomaterials on organisms.[16]

The precautionary matrix proposes estimating the potential effect of nanomaterials on health and the environment using the following reactivity parameters:

1. calculated parameters or parameters obtained in cell-free test systems: redox activity calculated by means of the energy between the valence and conduction bands (band gap), photocatalytic activity and biological oxidative damage (W1.1);

   Parameters measured in cells: formation of oxygen radicals (reactive oxygen species, ROS), reduction in GSH concentrations (glutathione, a sulphurous tripeptide), protein carbonylation and cellular induction of mediators of inflammation such as cytokines or chemokines (W1.2).

2. stability of the nanomaterials under the relevant conditions in the body ($W2_{A,V}$) or the environment ($W2_{U}$).

If the data needed to estimate potential effect are unavailable it may be necessary to determine or to calculate them for the nanomaterial being assessed, since the reactivity may otherwise be assumed to be too high. Calculations or determinations can be especially necessary when human exposure or release into the environment cannot be avoided by protective measures or by a suitable product design.

For the purposes of classifying the reactivity parameters as low, medium or high, criteria were defined for each of the studies listed in Table 5 (Basis for estimating W1 in chapter 6.2). Table 5 contains only results of studies in which several well-characterised nanomaterials were tested with the same method. Consequently, it is possible to make a comparative evaluation of the reactivity parameters within a particular study.

[16] Publication: A. Nel *et al.*, "Nanomaterial toxicity testing in the 21st century: use of a predictive toxicological approach and high-throughput screening" in Accounts of Chemical Research (2013) 3: 607-621.

Nano-material (uncoated and non-functionalised)	Cell-free or calculated reactivity (W1.1)			Cellular reactivity (W1.2)			
	Redox activity (band gap)	Photocatalytic activity	Biological/oxidative damage (BOD)	Induction of IL-8, IL-1b or TNFa	ROS induction	GSH reduction	Protein carbonylation
Ag (0)			**c** (Ø: 35-60nm)	**d,** NM300 (Ø:8-47nm)	**d,** NM300	**d,** NM300	
CeO_2	**a** (Ø: 18.3nm)		**c** (Ø: 7-25nm)	**f, h** (Ø: 9.7nm)			
Co_3O_4	**a** (Ø: 10.0nm)		**c** (Ø: 20nm)	**f** (Ø: 18.4nm)			
CuO	**a** (Ø: 12.8nm)		**c** (Ø: 18-34nm)	**f** (Ø: 23.1nm)			
Fe_2O_3	**a** (Ø: 12.3nm)		**c** (Ø: 30nm)	**h** (Ø: 15nm)			
Fe_3O_4	**a** (Ø: 12.0nm)		**c** (Ø: 25nm)				
Mn_2O_3	**a** (Ø: 51.5nm)		**c** (Ø: 45nm)				
SiO_2 (amorph)	**a** (Ø: 13.5nm)		**c** (Ø: 15nm)	**h, i** (Ø: 14nm)	**g, i,** NM200, NM203 (Ø: ~15nm)		**g** (Ø: 15nm)
TiO_2 (anatase)	**a** (Ø: 12.4nm)	**b** (Ø: 10-100nm)	**c** (Ø: 10-25nm)	**h, i,** P25 Ø: 20-80nm)	**i,** P25	**d,** NM101 (Ø: 4-100nm)	**g,** NM105 (Ø: 21nm)
TiO_2 (rutil)		**b** (Ø: 100nm)	**c** (Ø: 5000nm)	**f** (Ø: 30nm)	**d** (Ø: 80-400nm)	**d** (Ø: 80-	
ZnO	**a** (Ø: 22.6nm)		**c** (Ø: 25->100nm)	**d, e, f, h** (Ø: <10->100nm)	**d, g,** NM110	**d,** NM110	**g** (Ø: 80nm)
$BaSO_4$				h, NM 220 (Ø: 25nm)			g, NM 220 (Ø: 32nm)
MWCNT			**c** (Ø: 8nm, L: 20µm)	**d,** NM400 (Ø: ~14nm, L: ~850nm)	**d,** NM400	**d,** NM400	**g,** NM400
MWCNT			**c** (Ø: 15nm, L: 1-40µm)	**d,** NM402 (Ø: ~12nm, L: ~1370nm)	**d,** NM402	**d,** NM402	**g,** NM402

Table 5: Evaluation of reactivity (W1) for selected nanomaterials.

The table summarises the results of studies of calculated and measured reactivity parameters. It only takes account of studies in which different nanomaterials were investigated using the same method. The reactivities in studies e and f refer to the surface, the reactivities in the other studies to the weight of the nanomaterials. Uniform criteria were defined for the different studies for the purpose of categorising their reactivity as low, medium or high (see section evaluating reactivity).

Green = low reactivity; yellow = medium reactivity; red = high reactivity. Dia. = diameter of primary material
L = Length of the MWCNT

Sources quoted:
a: Zhang, H. *et al.*; acsnano, 6(5), 4349-4368, 2012
b: van Driel, B.A. *et al.*; Microchemical Journal 126 (2016) 162-171
c: Hsieh S.-F. *et al.*; Small 2013, 9, 9-10
d: Kermanizadeh, A. *et al.*; Particle and Fibre Toxicology 2012, 9:28
e: Cho, W.-S. *et al.*; Nanotoxicology 2012, 6 (1), 22-35
f: Cho,W.-S. *et al.*; Particle and Fibre Toxicology 2013, 10:55
g: Driessen, M.D. *et al.*: Particle and Fibre Toxicology 2013, 10:55
h: Wiemann, M. *et al.*; J Nanobiotechnol (2016), 14:16
i: Winter, M. *et al.*: Nanotoxicology 2011; 5(3), 326-340

Methods for determining the reactivity of nanomaterials

Mathematical and cell-free methods of determination:

Redox activity can be used as a reactivity parameter. Redox active materials can perturb electron transfer reactions in cells. Redox potentials of metals and metal compounds are determined under standard conditions against a hydrogen electrode and can be found in specialist encyclopaedias. The redox potential of a chemical reaction can be calculated from the sum of both half reactions (oxidising and reducing reactions). The more negative the potential, the more reducing is the reduced form. An example for this is lithium; in its metallic form Li^0 is a strong reducing agent with -3.02 V and easily gives up its valence electron. The more positive the potential, the more oxidising is the oxidised form. For example, gold – in its oxidised form Au^{3+} – has a high oxidation potential with +1.42 V and therefore takes up electrons easily. Under environmental conditions some metallic nanomaterials are rapidly oxidised, at least on the surface (passivation). Their redox potential then corresponds rather to that of their oxides. Scale effects resulting from physical and chemical properties should only be expected at a particle diameter of less than 30 nm.[17] The redox potential of a material that is available in bulk or at nanoscale can therefore be estimated on the basis of the redox potential of the bulk material in many cases.

The redox potentials that apply under standard conditions are not sufficiently meaningful in many cases and need to be converted for the actual conditions in living cells. It is difficult to carry out this conversion in practice due to the many influencing factors.

One good way of estimating the redox activity of semiconductors or metal oxides is their band gap. This involves estimating the redox activity in biological systems using the energy in the conduction band compared to cellular redox potentials.[18] Nanomaterials whose conduction band energy overlaps with the redox potentials of cells (-4.12 to -4.84 eV) are regarded as redox active.

An ISO standard (ISO 22197) exists for the measurement of the activity of photocatalytic materials. Although it was not designed for powder-type materials, it can be used in principle for nanomaterials too. In addition, specific methods have been developed for the determination of photocatalytic activity of nanomaterials and have been published.[19] [20]

Furthermore, various cell-free test systems can be used to determine the reactivity of nanomaterials. One of these methods involves determining the biological oxidative damage (BOD), which records the reduction in the antioxidant capacity of human blood serum induced by a nanomaterial.[21]

[17] Publication: M. Auffan *et al.*, "Towards a definition of inorganic nanoparticles from an environmental, health and safety perspective" in Nature Nanotech. (2009) 4: 634-641.
[18] Publication: H. Zhang *et al.*, "Use of Metal Oxide Nanoparticle Band Gap to Develop a Predictive Paradigm for Oxidative Stress and Acute Pulmonary Inflammation"; in ACS Nano (2012) 6, 5: 4349-4368.
[19] Publication: NA Lee *et al.*, "Development of multiplexed analysis for the photocatalytic activities of nanoparticles in aqueous suspensions" in Photochem Photobiol Sci (2011) 10: 1979-1982.
[20] Publication: B.A. van Driel *et al.*, "A quick assessment of the photocatalytic activity of TiO_2 pigments – From lab to conservation studio!" in Microchemical Journal (2016) 126: 162-171.
[21] Publication: S.-F. Hsieh. *et al.*, "Mapping the Biological Oxidative Damage of Engineered Nanomaterials" in Small (2013) 9: 9-10.

Cellular methods of determination:

In addition to cell-free methods of determining the reactivity of a nanomaterial, various *in vitro* cell systems can be employed. In contrast to cell-free test systems, these systems take account of effects that require the presence of an intact cell system.

Data on the induction of oxidative stress[22], particularly on the formation of ROS, reduced glutathione content or protein carbonylation can be used as a reactivity criterion. Induction of mediators of inflammation e.g. cytokines or chemokines (TNFα, IL-8 or IL-1β) provides an indicator of nanomaterial reactivity. The literature describes *in vitro* methods for these various reactivity parameters (see Table 5). It should be noted that the effects induced by nanomaterials may vary depending on the cell line used.[23]

Evaluating reactivity

Table 5 classifies the reactivities of nanomaterials in the bands of low, medium and high. As the basic concept behind this classification, 100% was assigned to the highest measured value in any given study. Values of less than 10% were classified as low, values equal to or greater than 10% but less than 60% were classified as medium, and values of 60% or more were classified as high. Users of the precautionary matrix are therefore recommended to also include a highly reactive nanomaterial in their reactivity experiment so as to permit a relative reactivity comparison. If only isolated reactivity measurements are available for the nanomaterial, it is recommended that the nanomaterials in Table 5 be taken as a guide for classifying reactivity and that the method used be compared with the one in the primary literature. If the experimental conditions are identical, it would be possible to adopt the reactivity estimate for the target nanomaterial.

Table 5 shows that an evaluation based on individual parameters can lead to different assessments. A comparison of the derived reactivities of nanomaterials with acute and subchronic inflammatory responses provoked by inhalation shows that the best correlation is achieved with a combination of calculated, cell-free and cellular reactivities (see Annex 6.2 for details). Basing the evaluation on as many of the above-mentioned reactivity parameters as possible is therefore recommended. If more than one value has been found for a reactivity parameter, the one with the highest reactivity should be used in the precautionary matrix. Photocatalytic reactivity should be used for evaluation, particularly in cases of environmental exposure and in applications that lead to skin exposure.

In the absence of data on the reactivity of the nanomaterial, a worst-case scenario of a high reactivity should be assumed. The results of the precautionary matrix always draw attention to that proportion of the need for precautionary measures that is attributable to “unknowns”. This highlights the additional investigations that might reduce the need for precautionary measures.

[22] Oxidative stress is the imbalance between the formation of free radicals (ROS) and endogenous antioxidants. When the concentration of free radicals is too high, the redox systems of the cell are destroyed; this may lead to toxic effects.

[23] Publication: Cho,W.-S. *et al*.; “Predictive value of in vitro assays depends on the mechanism of toxicity of metal oxide nanoparticles” in Particle and Fibre in Toxicology (2013) 10: 55.

Stability

In the present context, stability considers the resistance of the employed synthetic nanomaterials to dissolution, chemical or physical transformation (for example silver nanoparticles to silver sulphide nanoparticles in wastewater treatment plants), sintering, sorption, agglomeration/aggregation or particle degradation or conversion into metabolic products.

Since conditions (and hence stability) in the body under physiological surroundings and different environmental compartments (water, sediment, biota) can diverge from each other, stability was apportioned to both areas. Care should be taken that the respective conditions are known prior to working with the precautionary matrix:

- Conditions in the body:
  It is sometimes necessary, depending on the route of exposure, chemical transformation and separation or enrichment, to complete several precautionary matrices for the different conditions (pH in lungs or stomach). Specific solvents[24] [25] have been developed for the purpose of determining the solubility of nanomaterials in biological media. The solubility of various nanomaterials in solvents of this kind has been determined (see Table 6).[26]

- Environmental conditions:
  the possible conditions in the environment vary strongly with the considered compartment as well as with the physical and chemical factors that prevail there. Here the most relevant scenarios should be worked out first, after which the other scenarios should be evaluated with new precautionary matrices.

Strictly speaking, when considering the environment, a differentiation ought to be made between the stability in biotic and abiotic systems. If there is no evidence to suggest that stability in abiotic systems differs from stability in biotic systems, these can be assumed to be the same in a first approximation ($W2_{A,V}$ and $W2_{U}$). If this is not the case, both the biotic and abiotic stability should be investigated.

[24] Publication: Utembe W *et al.*,"Dissolution and biodurability: Important parameters needed for risk assessment of nanomaterials" in Particle and Fibre Toxicology (2015) 12: 11.
[25] Publication: Pelfrêne A *et al.*, "In Vitro Investigations of Human Bioaccessibility from Reference Materials Using Simulated Lung Fluids" in Int. J. Environ. Res. Public Health (2017) 14: 112.
[26] Publication: Arts J, Irfan MA *et al.*, "Case studies putting the decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping) into practice" in Regulatory Toxicology and Pharmacology (2016) 76: 234-261.

Nanomaterial	t ½ Lung (STIS)	Solubility in water	Solubility in biolog. fluids
CeO2 (NM211)	> 40d	< 10 mg/l	**< 10 mg/**l (DMEM+FCS: 24h; PBF: 28d)
CuO	-	0.4% (pH 7.5)	**120 mg/l** (PSF: pH 4.3, 28d) **1 mg/l** (Gamble: pH 7.5, 28d)
Fe2O3	< 40d	< 1mg/l	**1 mg/l** (PSF: pH 4.3, 28d; Gamble: pH 7.5, 28d)
SiO2 (NM200, amorph)	-	67-115 mg/l	**Soluble** (Gamble: 24h); **3< 10 mg/**l (DMEM+FCS: 24h)
TiO2 (anatase)	> 40d	Ti < 1mg/l	
ZnO (NM110)	Rapid clear-ance	Insoluble	**< 100 mg/l** (Gamble: pH 7.4; 72h) **> 1800 mg/l** (ALF: pH 4.5; 72h)
BaSO4 (NM220)	< 40d	6 mg/l	**7 mg/l** (PSF: 28d); **12 mg/l** (PBS: 28d)
MWCNT (NM400)	-	Insoluble	-
MWCNT (NM402)	-	Insoluble	-

Table 6: Examples of half-lives (t ½) and solubilities of nanomaterials.

The half-lives of nanomaterials in the lung were extrapolated from data obtained in acute inhalation studies in rats (STIS). Nanomaterials with half-lives > 40 d or solubilities < 100mg/l are deemed to be biopersistent[26]. ALF (Artificial lysosomal fluid), DMEM (Dulbecco's modified Eagle medium) + FCS (foetal calf serum), PSF (phagolysosomal simulant fluid) and PBS, (phosphate buffered saline) were used as a synthetic substitute for lung fluid.

If a nanomaterial becomes unstable during a processing step or during use / application, resulting in the complete disappearance of the nanomaterial and its agglomerates/aggregates, further evaluation for the subsequent steps is not necessary. However, should a different nanomaterial be formed from the original nanomaterial as a result of transformation, then a separate precautionary matrix should be prepared for the new material.

The presence of a coating or functionalisation represents a special case for analysing the stability of the nanomaterials. If a coated or functionalised nanomaterial is present[27], a distinction must be made between the following options[28]:

- If the coating/functionalisation is stable, the precautionary matrix is completed on the basis of W1 and W2 of the coated/functionalised nanomaterial.
- If the coating/functionalisation is conceived in such a way that it dissolves very rapidly in use and thus is not expected to have any impact on the properties of the nanomaterials, the potential effect is to be based on the resultant uncoated/unfunctionalised nanomaterials' W1 and W2 parameters.
- If the coating/functionalisation dissolves during use or application (or in the body / the environment) during a period that leads to the existence of coated/functionalised nanomaterials as well as uncoated/not functionalised nanomaterials, a precautionary matrix must be completed for the coated/functionalised nanomaterials in addition to the matrix for the uncoated/not functionalised particles.

[27] In this precautionary matrix the term "coating" also covers all other types of surface functionalisation.
[28] These considerations apply in a similar way if, during the production or use of the nanomaterial, new defined nanomaterials can be produced by chemical reactions (e.g. oxidation).

In the case of soluble nanomaterials, the underlying chemical substance may exhibit greater or more rapid bioavailability than when present in the non-nanoscale form. This could result in increased acute toxicity, which can be detected by the classical toxicity tests for chemical substances (even if only at fairly high dosages). This possible impact on the potential effect has therefore been omitted from the precautionary matrix. The usual standard methods for the evaluation of chemicals can be used to determine the effects of the dissolved coating.[29]

Evaluating the potential effect

The potential effect parameters are evaluated as follows:

Cell-free/calculated reactivity (W1.1): (biological oxidative damage; redox activity (band gap energy); photocatalysis. Cellular reactivity (W1.2): induction of mediators of inflammation, induction of ROS, reduction in glutathione content; induction of protein carbonylation.	Low	Medium	High
W1.1 – W1.2	1	5	9
Stability (half-life) of the nanomaterial in the human body	hours	days-weeks	months
$W2_{A,V}$	1	5	9
Stability (half-life) of the nanomaterial under environmental conditions	hours	days-weeks	months
$W2_{U}$	1	5	9

Table 7: Potential effect

4.6 Potential exposure of humans / potential input into the environment (E)

Two groups of parameters in particular are important to estimate potential human exposure and potential input into the environment:

1. the emission quantity of the nanomaterials in the relevant process conditions or conditions of use as a measure of the availability of the nanomaterial (E1)
2. the maximum possible extent of human exposure (E2) or the input into the environment (E3) in the worst case

The precautionary matrix offers different input paths for determining the exposure amount:

- modelling values or exposure measurements
- selection of a carrier material (exposure scenarios)

[29] Because of their special toxicokinetics, synthetic nanomaterials may be able to reach sites in the organism that are not normally accessible for the underlying chemical substances in dissolved form. If the nanomaterial goes into solution at these sites, high local concentrations of these chemical substances may arise, with new toxic effects. In the present context, this possible influence on the potential effect is not considered.

4.6.1 Exposure estimation using a model value or exposure measurement

Users of the precautionary matrix can enter modelled or measured exposure values in an input box. Taking into account the reference value and the contact frequency, this value will then be classified as low (1), medium (5) or high (9) potential exposure.

4.6.2 Exposure estimation using contact amount

The potential availability of nanomaterials differs depending on the type of carrier material employed (Table 1). In many cases, the user will only know the overall amount of nanomaterial and not the nano fraction released during production and use. Based on new scientific findings, the precautionary matrix offers a selection of generic (solid matrix, liquid media, air) and specific emission factors (plastic, textiles, surfaces, paints/dyes, pigments, composites) for different product categories. Only one of the specified emission scenarios can be selected for each precautionary matrix scenario. The selected scenario is then used to assign predefined emission values for potential human exposure ($E1_{A,V}$) and for input into the environment ($E1_{U}$).

If the exposure routes of skin (dermal) or mouth (oral) are selected, no exposure scenarios will be displayed, since the contact amount is to be defined by the manufacturer for the application in question.

Carrier material	**$E1_{A,V}$**	**$E1_{U}$**
Solid matrix, stable under process conditions or conditions of use, nanomaterial not mobile (human exposure and input into environment unlikely)	10^{-4}	10^{-4}
Solid matrix, stable under process conditions or conditions of use, nanomaterial mobile (low exposure for people and input into environment)	10^{-2}	10^{-2}
Solid matrix, not stable under process conditions or conditions of use (intake through lungs, GIT and skin; possible input into environment)	0.1	1
Surfaces, paints/dyes, pigments	$2 * 10^{-4}$	1
Textiles	$7 * 10^{-3}$	1
Plastic	$3 * 10^{-5}$	1
Composite	$7 * 10^{-5}$	1
Liquid media (intake through GIT and skin; possible input into environment)	0.1	1
Air, aerosols >10 µm (intake into upper respiratory tract and gastrointestinal tract (GIT); possible input into environment)	1	1
Air, aerosols <10 µm (intake into lungs; possible input into environment)	To be defined by user	1
Emission factor of the carrier material is known	To be defined by user	1

Table 8: Human exposure and input into the environment as a function of the carrier material of the nanomaterials

If the nanomaterials are incorporated in or bound to a solid matrix (plastic, ceramic, metal), they are always evaluated on the basis of the matrix's stability under the particular conditions of use[30] and the strength of the nanomaterial's bond to the matrix[31] regardless of the exposure path (only relevant for stable matrices).

In the case of human exposure, a distinction is made between possible exposure of the lungs ($E1_{A,V}$ =1) and other target organs[32]($E1_{A,V}$ = 0.1) when evaluating nanomaterials in the air and liquid media (including aerosols). No such distinction is relevant for the environment. In the case of aerosols, the change in aerosol sizes over time "aerosol ageing" should be taken into account where appropriate.

In the case of aerosols <10 µm, the user has the option of using measured values of the dustiness.

In case the user knows the emission factor rate of the carrier material, this value can be included in the precautionary calculation via the input field.

4.6.2.1 Dustiness

The characterisation of dustiness constitutes one of the relevant physico-chemical endpoints applied to assess nanomaterials in the field of workplace exposure. Data on the dustiness of a nanomaterial can be used to calculate the proportion of powdered nanomaterial that makes its way into the indoor air.

In the event of exposure to nanomaterials in powdered form (aerosols <10 µm), users can enter dustiness data in an input box and have it included in the calculation for determining the need for precautionary measures.

If the dustiness has been measured and robust results are available, this value can be used directly in the precautionary matrix. If this is not the case, data supplied by one of two measuring methods (rotating drum, venturi) can be used to allocate the nanomaterials to four dustiness categories on the basis of the following table.

Dustiness classification	**Respirable fraction (%) determined by rotating drum method** (European Committee for Standardization (CEN) 2013)	**Respirable fraction (%) determined by venturi method** (Boundy, Leith *et al.*, 2006), three orders of magnitude larger (Evans, Turkevich *et al.*, 2012)	**Emission factor in the precautionary matrix**
None to very low	<0.002	<2	0.02
Low	0.002-0.007	2-7	0.07
Medium	>0.007-0.03	>7-30	0.3
High	>0.03	>30	1

Table 9: Dustiness categories.

[30] An example of an "unstable" matrix would be wax for skis, while a bicycle frame would be a "very stable" matrix.

[31] If the nanomaterials are not in the presence of a substance that promotes dissolution in the matrix, they can be designated as strongly bound. Surface-bound nanomaterials cannot be classified a priori. Clarification is needed in such cases.

[32] It should be noted that evidence exists to indicate that exposure via the skin does not have the same importance as exposure via the gastrointestinal tract (GIT). The precautionary matrix makes no further differentiation on this point at present.

4.6.2.2 Premises and air exchange rate

With the inhalation exposure route and estimation on the basis of exposure scenarios, users are able to enter information on the premises and the number of air exchanges.

The following options are available

- two rooms of defined volume with a defined air exchange rate (household, workplace)
- freely entered values for room volume, air exchange rate and length of stay

The air exchange rate in rooms with window ventilation is 0.2 to 1 h^{-1} and, in rooms with mechanical ventilation, generally 2 to 5 h^{-1} .[33] A threefold exchange of air is frequently recommended or implemented as the minimum at the workplace, while a minimum of 0.2 h^{-1} is applied for calculations in households. To facilitate application of the precautionary matrix, standard dilution rates have been defined for households and industry. These are 0.3 h^{-1} for households and 2 h^{-1} for workplaces.

4.6.2.3 Maximum possible human exposure

To determine potential exposure, users are required to select one of three amount categories. The category selected should correspond to the maximum possible amount of nanomaterial that an employee or consumer handles per day.

The precautionary matrix calculates the three amount categories from information on the target person (consumer/employee) and nanomaterial category (reference value), the exposure frequency and the emission factor selected.

4.6.2.3.1 Worst-case scenario

The basic consideration behind the determination of a worst-case scenario is that, given otherwise identical conditions and the same need for precautionary measures with correctly handled nanomaterials, two employees in different companies may have a significantly different need for precautionary measures in the event of an accident if one of the companies keeps a significantly greater amount of nanomaterials in storage.

- In the case of the inhalation path and determination on the basis of exposure scenarios: Worst case (WC)[34] amount categories for employees are automatically proposed to the user.
- In all other cases:
  A separate precautionary matrix should be completed for the total amount of nanomaterials available in order to depict the worst-case scenario.

[33] «Lüftung» in der Wegleitung zu Art.17 ArGV: https://www.seco.admin.ch/seco/de/home/Arbeit/Arbeitsbedingungen/Arbeitsgesetz-und-Verordnungen/Wegleitungen/wegleitung-zur-argv-3.html.

[34] Only accidents during production, storage, packaging and transport that lead to an increase in exposure at the workplace are considered as relevant worst-case scenarios within the framework of the precautionary matrix. Natural disasters and attacks cannot be taken into account within the framework of the precautionary matrix. The use of materials and products for purposes other than those for which they are intended is the responsibility of workers and consumers and is therefore also not taken into account in the precautionary matrix. The effects of major accidents on the population are also not taken into account.

4.6.2.4 Maximum possible input into the environment

Environmental inputs during the production phase (incl. production, processing, packaging, transport and disposal) and the use phase are treated separately. Two distinct scenarios (with and without specific disposal) must be taken into considered.[35]

The treatment of the possible environmental inputs and downstream grid-relevant processes are shown in Figure 7. The estimates of environmental inputs were defined by quantity thresholds (Table 10).

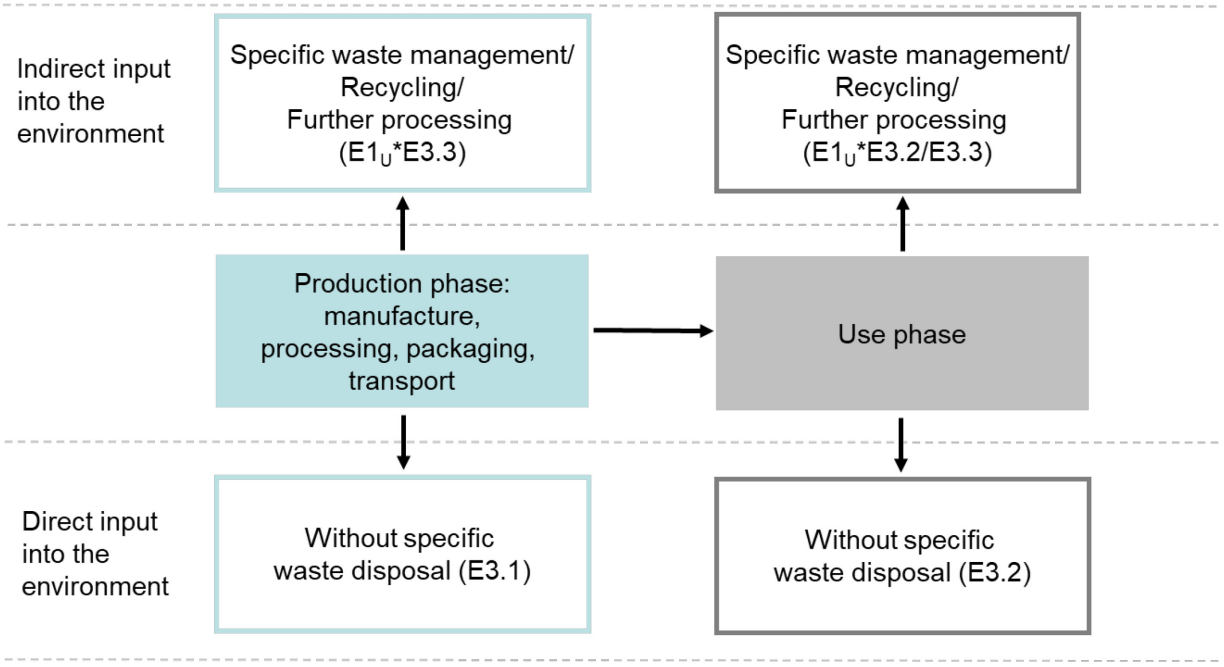

Figure 7: Environmental input scenarios.

1. **Production phase (manufacture, processing, packaging, transport, disposal)**

   During the nanomaterial production phase, an input of nanomaterials into the environment can occur either directly, via waste air or waste water, or indirectly via unspecific waste disposal.

   Two scenarios are taken into consideration for the production phase:

   a) For production **without specific waste disposal** the estimate in the precautionary matrix is based on the loss of nanomaterials during the process under consideration (E3.1). The estimate of the input into the environment does not take into account the carrier material ($E1_U$), since, when looked at in the long term, all nanomaterials are introduced into the environment independently of the carrier material.

   b) For use **followed by specific waste disposal** only the input during the production phase is considered. This input is estimated via the amount of specifically disposed nanomaterials per year (E3.3) including the carrier material ($E1_U$).

[35] See: https://www.bafu.admin.ch/bafu/de/home/themen/abfall/abfallwegweiser-a-z/nanoabfaelle.html.

Any **input during specific waste disposal, e.g. as hazardous waste, or during recycling or further processing, occurs in a separate process step and must be estimated in its own precautionary matrix.** In this case, the estimate is made for the amount of specifically disposed nanomaterial coming from the production phase (E3.3). In order to select a suitable disposal method, it is recommended to fill out the precautionary matrix in collaboration with a suitable waste disposal company. See also the activities in the context of disposal of nanowaste.**Fehler! Textmarke nicht definiert.**

2. Use phase

In the same way, when it comes to input into the environment during the use phase, a distinction is drawn between use with and without specific waste disposal.

a) In the case of use **without specific waste disposal** (e.g. of utility products) it is often difficult to quantify the direct input into the environment. The estimation is based on the total amount of nanomaterials in the marketed utility products (E3.2). Estimated input into the environment does not include the carrier material ($E1_U$) since, when looked at in the long term, all nanomaterials are introduced into the environment independently of the carrier material.

b) In the case of use **followed by specific waste disposal** only the input during use and after use are considered.

Input during use is estimated via the total amount of nanomaterials in the marketed utility products (E3.2) taking into account the carrier material ($E1_U$).

Input after use occurs in separate process steps which should therefore be estimated in their own precautionary matrix using parameter E3.3 (amount of specifically disposed/recycled nanomaterial after the use phase).

The environmentally relevant parameters are evaluated as follows:

Annual quantity of nanomaterial that reaches the environment via wastewater, exhaust gases or solid waste during the production phase[36]	< 5 kg	< 500 kg	>500 kg
E3.1	1	5	9
Annual quantity of nanomaterials in utility products	< 5 kg	< 500 kg	>500 kg
E3.2	1	5	9
Annual quantity of specifically disposed nanomaterial	< 5 kg	< 500 kg	>500 kg
E3.3	1	5	9

Table 10: Input into the environment. These amount thresholds are only of value with diffuse inputs and are not applicable to point-source inputs.

[36] For the derivation of the specified values see chapter 6.4.

4.6.3 Exposure frequency

Taking the toxicity reference value, which is calculated on the basis of chronic exposure, the following factors are used to express the toxicological reference value as a function of exposure frequency:

Daily exposure: factor 1

Weekly exposure: factor 7

Monthly exposure: factor 30

The toxicological reference values are based on chronic exposures (reference value), which is why a factor of 1 is used for daily exposure. According to ECHA (2012), an assessment factor of 2 is used to calculate a Derived No-Effect Level (DNEL) for chronic exposure from subchronic data (exposure period: 90 days). In arithmetic terms, chronic exposure thus corresponds to exposure over 180 d. Weekly exposure is then 26 exposure days within a period of 180 d and hence equivalent to a total exposure that is lower than daily exposure by a factor of ~7 (180/26). ECHA (2012) employed an assessment factor of 6 for extrapolation to chronic exposure from subchronic toxicity data (28 d). Monthly exposure is 6 exposure days within a period of 180 d. This means a total exposure that is 30 times lower (180/6).

4.7 “Uncertainty of input” section

The precautionary matrix supports industry in assessing the need for precautionary measures for synthetic nanomaterials and helps identify potential risk sources at different points in the life cycle of synthetic nanomaterials. To ensure that the need for precautionary measures can be suitably interpreted, the associated uncertainties must be considered and described in an appropriate manner. Uncertainty analyses in scientific assessments aim to identify and describe all sources of uncertainty. Knowledge of scenarios or parameters can be inaccurate, incomplete or distorted.

A qualitative uncertainty analysis can be performed with this version of the precautionary matrix. The uncertainty prompt appears in the "Effect" section (cell-free, cellular reactivity, stability) and "Exposition" section.

Users of the precautionary matrix can estimate the uncertainty of the measurements and inputs made with the aid of the information set out in Table 11. The three aspects (available knowledge, data representativeness and data quality) are assessed for each input and a total score worked out. The corresponding uncertainty classification can then be read off Table 12 and entered into the precautionary matrix.

Table 11: Definition of the orders of magnitude of uncertainty (low, medium, high) for available knowledge, data representativeness and data quality:

Uncertainty	**Low**	**Medium**	**High**
Score	1	3	5
Available knowledge	Manufacturer themselves or data provided by the manufacturer of the NM	Experience in chemical synthesis/NM production OR data that are taken from a technical report	No direct experience in chemical synthesis AND/OR based on external advice
Data representativeness	Experimental data for the examined nanomaterial	Similar chemical composition OR based on a group approach	Bulk material OR other material
Data quality	Experimental data measured by standardised protocols (OECO, ISO, CEN) or in accordance with protocols drawn up by NANoREG or an agency, or provided by the manufacturer of the NM	Data have been published in peer-reviewed articles, the test method was reported but is not an SOP	Grey literature, similar nanomaterial, test method not reported

Table 12**:** Cumulated uncertainty values:

Total score	**Final classification**
≤ 5	Low
6 – 9	Medium
> 10	High

The uncertainty is included at input parameter level. A parameter is thus not given a fixed value. Instead, it is allocated a probability distribution based on the value selected for the parameter and the chosen uncertainty level. If, for example, a medium reactivity (value 5) is selected for the cellular reactivity, together with medium uncertainty, the probability distribution will be as follows: in 60% of cases the value will be 5, in 25% of cases the value will be 9 and in 15% of cases it will be 1.

Taking all the input parameters and their uncertainties, the probability of all possible output values from the precautionary matrix is calculated. The “Evaluations” section sets out the probability (sum of the probability of all combinations) with which the precautionary score will exceed the threshold indicating the need for precautionary measures (5%).

The probability distributions used for the uncertainty categories can be found in Figure 8 in Annex 5.1.4.1.

5 Linking of Parameters, Estimation and Classification of the Need for Precautionary Measures

The linking of the parameters presented and explained in section 4, the estimation of the consequent need for precautionary measures and its classification are presented in the following sections.

5.1 Linking and estimation of parameters

The basic equation of the precautionary matrix:

$$N * (W * E + I) = V$$

Legend:

N: Nano-relevance according to the precautionary matrix (section 4.3)

W: Potential effect (section 4.5)

E: Potential human exposure / potential input into the environment (section 4.6)

I: Available information on the life cycle (section 4.4)

V: Need for precautionary measures

$_A$: Employee

$_V$: Consumer

$_U$: Environment

5.1.1 Nano-relevance according to the precautionary matrix

Nano-relevance is determined using the flow diagram in section 4.3. As a rule,

$$\mathbf{N = N\text{-}EU}^{37} \cdot \mathbf{N1} \cdot \mathbf{N1a}^{38} \cdot \mathbf{N2}^{39} \cdot \mathbf{N2a}$$

N = 1: "nano-relevant" according to the precautionary matrix

N = 0: not "nano-relevant" according to the precautionary matrix

5.1.2 Available information

The sum of parameters I1 to I4 gives the factor I:

$$\mathbf{I = I1 + I2 + I3 + I4}$$

5.1.3 Potential effect

The overall potential effects of $W_{A,V}$ on humans and W_U on the environment are estimated using the following equations:

$$\mathbf{W_{A,V} = (W1.1 \text{ or } W1.2) \cdot W2_{A,V}}$$

$$\mathbf{W_U = W1.1 \text{ or } W1.2) \cdot W2_U}$$

[37] For N-EU = no: N1 and N2 are inapplicable.
[38] For N1a = no: N2 and N2a are inapplicable.
[39] For N2= yes: N2a is inapplicable.

5.1.4 Potential exposure of humans

The precautionary matrix includes three different pathways for assessing potential exposure.

5.1.4.1 Estimation of exposure with modelled or measured value inputs

Users can enter modelled or measured exposure values (section 5 “Exposition”: exposure value (E0)). The precautionary matrix classifies potential exposure by comparing the calculated exposure categories (reference value (target person, exposure pathway, nanomaterial category), frequency) with the entered exposure value (E0). The exposure (E_A or E_V) is assessed and assigned to the categories low (1), medium (5) and high (9).

5.1.4.2 Estimation of exposure using exposure scenarios (inhalation)

Potential exposure of employee

In the “Exposure” section, the user enters data on the carrier material ($E1.1_A$) and the premises (E1.4).

Taking into account other parameters entered (target person: employee, nanomaterial category, frequency), the system calculates three amount categories for nanomaterials which correspond to low, medium and high exposure and offers the user these options under “Maximum possible human exposure (E2.1)”.

Calculation performed by the system:

> (reference value*frequency) * ((number of air exchanges*hours)* room volume) / (emission factor carrier material) = (R* F) * ((λ * t_E) * V_R) / E1.1 = (R* F) * (E1.4) / E1.1 → **E2.1**
>
> Additionally, for the worst case: E1.2 categories * 10 → **E2.2**

Taking the amount category E2.1 selected by the user, the system classifies exposure as low (1), medium (5) or high (9).

where:

E1.1 Carrier material (emission factor)

E1.4 Room conditions (=(λ * t) * V_R))

E2.1: Amount of nanomaterial with which an employee comes into contact per day

E2.2: Amount of nanomaterial with which an employee could come into contact in the "worst case"

F: Frequency with which an employee comes into contact with nanomaterials (1, 7, 30)

R: Reference value

λ: Air exchange rate (1/h)

V_R: Room volume

t_E: Exposure duration (h)

Potential exposure of consumers:

The calculation is performed in the same way as for the potential exposure of employees except that, in this case, the reference value for a consumer is used and no worst-case scenario is calculated.

$$(R^* F) * ((\lambda * t) * V_R) / E1.1 = (R^* F) * (E1.4) / E1.1 \rightarrow \mathbf{E2.4}$$

Taking the amount category E2.4 selected by the user, the system classifies exposure as low (1), medium (5) or high (9).

where:

E1.1 Carrier material (emission factor)

E1.4 Room conditions (=(λ * t) * V_R))

E2.4: Amount of nanomaterial with which a consumer comes into contact per day

F: Frequency with which a consumer comes into contact with nanomaterials (1, 7, 30)

R: Reference value

λ: Air exchange rate (1/h)

V_R: Room conditions

t_E: Exposure duration (h)

5.1.4.3 Estimation of exposure with the contact amount

Calculating oral or dermal exposure requires knowledge of the amount of nanomaterial that comes into contact with the skin or is ingested orally. Since skin contact and oral exposure differ greatly depending on the production conditions and use (e.g. spray applications, nanosilver-treated underwear, lipstick, surface-treated toys, etc.), the contact or ingestion amounts should be requested from the manufacturer or, where possible, determined by the user of the precautionary matrix.

The amount of nanomaterial ingested via the mouth or coming into contact with the skin can be entered in the input box in the “Exposition” section.

The precautionary matrix classifies potential exposure by comparing the calculated exposure categories (reference value (target person, exposure pathway, nanomaterial category), frequency) with the amount of nanomaterials entered in the input box. The exposure is assessed and assigned to the categories of low (1), medium (5) and high (9).

5.1.4.1 Overview of calculation parameters

To ensure the user has an overview of the parameters selected and the calculation, the values are displayed in a green zone under “Potential exposure” in section 5.

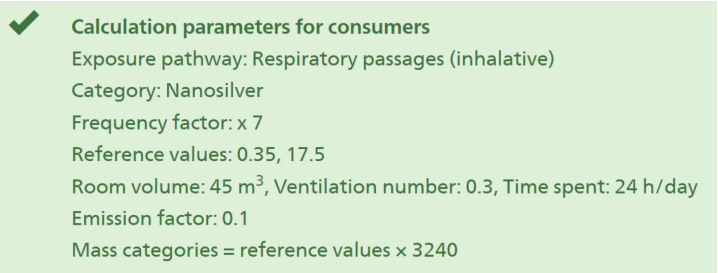

Figure 8: Example of an overview of calculation parameters.

The “Reference value” category shows the amount thresholds for the exposure category low-medium and medium-high. These are used for calculating the proposed amount categories in combination with the other input parameters (frequency factor, room volume, number of air exchanges, emission factor).

5.1.5 Potential input into the environment

Production phase: Input of nanomaterial via exhaust air, wastewater or unspecific waste disposal. This is assessed by the decrease in nanomaterial during the process under consideration (E3.1):

$$\mathbf{E_U^P = E3.1}$$

where:

E_U^P: Maximum possible input into the environment during the production phase

E3.1: Annual amount of nanomaterial reaching the environment via wastewater, exhaust air or solid waste

Specific waste disposal step after the production phase: Input of nanomaterial via exhaust air or wastewater is estimated from the disposed quantity of nanomaterial during the waste disposal throughout the year (E3.3) factoring in the carrier material ($E1_U$):

$$\mathbf{E_U^{PSE} = E1_U \cdot E3.3}$$

where:

E_U^{PSE}: Maximum possible input into the environment from a disposal step subsequent to production

$E1_U$: Type of carrier material specific to the environment (section 4.6.2)

E3.3: Annual quantity of disposed nanomaterial (from the production phase)

Use phase, without specific waste disposal: Input into the environment is estimated without factoring in the type of carrier material ($E1_U$). For the real input of nanomaterial from utility products into the environment, weathering, abrasion and leaching processes are responsible:

$$\mathbf{E_U^G = E3.2}$$

where:

E_U^G: Maximum possible input during use without specific disposal

E3.2: Annual amount of nanomaterial in utility products

Use phase, with specific waste disposal: Input is estimated via the total amount of nanomaterial in the marketed utility products (E3.2) taking account of the carrier material ($E1_U$):

$$E_U^{G,spez} = E1_U \cdot E3.2$$

where:

$E_U^{G,spez}$: Maximum possible input during use with specific waste disposal

$E1_U$: Carrier material, specifically for the environment (section 4.6.2)

E3.2: Annual amount of nanomaterial in utility products

Specific disposal step subsequent to the use phase: Input into the environment is estimated from the quantity of disposed nanomaterial per year (E3.3) by taking into account the carrier material:

$$E_U^{GSE} = E1_U \ E3.3$$

where:

E_U^{PSE}: Maximum possible input into the environment during the disposal process for utility products

$E1_U$: Carrier material, specifically for the environment (section 4.6.2)

E3.3: Annual quantity of disposed nanomaterial (from the use phase)

5.2 Estimation of the need for precautionary measures (V)

To estimate the need for precautionary measures, the values determined for potential effect W and potential human exposure / input into the environment E are multiplied by each other. Then I is added and the result is multiplied by N:

$$V = N \cdot (W \cdot E + I)$$

Need for precautionary measures for employees

$$V_A = N_{A,V} \cdot (W_{A,V} \cdot E_A + I)$$

$$V_A^{WC} = (W_{A,V} \cdot E_A^{WC}) + V_A$$

Need for precautionary measures for consumers

$$V_V = N_{A,V} \cdot (W_{A,V} \cdot E_V + I)$$

Need for precautionary measures for the environment

$$V_U^P = N_U \cdot (W_U \cdot E_U^P + I)$$

$$V_U^{PSE} = N_U \cdot (W_U \cdot E_U^{PSE} + I)$$

$$V_U^{G,spez} = N_U \cdot (W_U \cdot E_U^{G,spez} + I)$$

$$V_U^{GSE} = N_U \cdot (W_U \cdot E_U^{GSE} + I)$$

$$V_U^G = N_U \cdot (W_U \cdot E_U^G + I)$$

where:

V_U^P: Need for precautionary measures during production

V_U^{PSE}: Need for precautionary measures during a disposal step for production waste

$V_U^{G,spez}$: Need for precautionary measures during use with specific waste disposal

V_U^{GSE}: Need for precautionary measures during a disposal step for a utility product

V_U^G: Need for precautionary measures during use without specific waste disposal

5.3 Classification

Evaluating a precautionary matrix with the metrics used here produces a total score. The size of this total score allows a general classification of the nanospecific need for action:

Total score	Classification	Significance
<25	A	The nanospecific need for action can be rated as low even without further clarification.
≥25	B	Nanospecific action is needed. Existing measures should be reviewed, further clarification undertaken and, if necessary, measures to reduce the risk associated with manufacturing, use and disposal implemented in the interests of precaution.

Table 13: Nanospecific action requirement.

The differentiation limit between classes A and B has been defined as 25 both for the “health” case as well as for the “environment” case, independently of the different evaluation algorithms. This definition is based on plausibility considerations for sample cases (cf. Table 14 and Table 15).

The result of the evaluation does not say anything about actual risks. Establishing the need for precautionary measures should motivate the user to think about whether existing protective measures meet this need for precautionary measures or whether further measures are required. In this regard it should be noted that if a nanomaterial is unstable during processing, during use or under the given environmental conditions and these cause the nanomaterial and its agglomerates to totally disappear, then any further evaluation of the subsequent steps becomes unnecessary. However, should another type of nanomaterial be formed, then its own precautionary matrix would need to be filled out.

In the context of precaution, class B represents an evaluation which, in case of doubt, can be applied to all nanorelevant materials according to the precautionary matrix. The need for action can only be rated as low without further clarification in cases where evaluation using the precautionary matrix produces a score of 25 or less.

	Potential effect			
Potential exposure of humans		**Low** **Low** reactivity and **low** stability	**Medium** **Medium** reactivity and **low** stability Or vice versa	**High** **Medium or high** reactivity and **medium or high** stability
	Low **Low** amount of nanomaterial handled by a consumer/employee per day and **low** frequency of consumer product use /exposure of nanomaterial to an employee	**Class A**	**Class A**	**Class B**
	Medium **Medium** amount of nanomaterial handled by a consumer/employee per day and **low** frequency of consumer product use /exposure of nanomaterial to an employee Or vice versa	**Class A**	**Class B**	**Class B**
	High **High** amount of nanomaterial handled by a consumer/employee per day and **high** frequency of consumer product use /exposure of nanomaterial to an employee	**Class A**	**Class B**	**Class B**

Table 14: Classification of nanomaterial that results in exposure of consumers via the air (aerosols <10µm). A value of 0 was used for the available information (I).

Total scores are derived from the estimates that are entered for the specific framework conditions, the potential effect and the potential human exposure / potential input into the environment. An analysis of these chosen estimations of the individual parameters enables a differentiated view of the gaps and uncertainties to be made and results in an additional specification of the handling needs.

For example, Table 14 shows in the case of air exposure which combinations of parameters lead to which classification of the need for precautionary measures for health

In the case of a consumer product, this for example would mean the following: since it can be assumed that consumers exposed to nanomaterials via the air entails a low potential exposure in just a very few cases, only products that contain nanomaterials with a low potential effect would be rated as class A (low reactivity and low stability).

In analogy with Table 14, Table 15 shows an example for the possible classification of an input into the environment via wastewater from a manufacturing process.

	Potential effect			
Potential input into the environment		**Low** **Low** reactivity and **low** stability	**Medium** **Medium** reactivity and **low** stability Or vice versa	**High** **Medium or high** reactivity and **medium or high** stability
	Low **Low** amount of nanomaterial disposed per year in wastewater, exhaust air or solid waste which reaches the environment	**Class A**	**Class A**	**Class B**
	Medium **Medium** amount of nanomaterial disposed per year in wastewater, exhaust air or solid waste which reaches the environment	**Class A**	**Class B**	**Class B**
	High **High** amount of nanomaterial disposed per year in wastewater, exhaust air or solid waste which reaches the environment	**Class A**	**Class B**	**Class B**

Table 15: Classification of the input of a nanomaterial into the environment in wastewater from a manufacturing process. A value of 0 was used for the available information (I).

Minimum and maximum values

For cases where the available information does not make any additional contribution (I=0) and the type of carrier material permits maximum nanomaterial availability (E1=1), the minimum and maximum values are as follows:

For employees and consumers:

- Low reactivity (W1.1 or W1.2=1) and stability ($W2_{A,V}$ =1), low maximum possible exposure (E2=1): 1 point
- High reactivity (W1.1 or W1.2=9) and stability ($W2_{A,V}$ =9), high maximum possible exposure (E2=81): 729 points

For the environment:

- Low reactivity (W1.1 or W1.2=1) and stability ($W2_{U}$ =1), low input into the environment (E3=1): 1 point
- High reactivity (W1.1 or W1.2=9) and stability ($W2_{U}$ =9), high input into the environment (E3=9): 729 points

Conclusion: Significance of a high score

- The precautionary matrix is based on the assumption that no protective measures of any kind are in place for employees, consumers or the environment. Consequently, the score represents a measure of the need to **review existing measures** or **evaluate new measures**. A statement about the specific need for precautionary measures can be made only by analysing the individual parameters.
- High scores can also result from a lack of knowledge and the consequent precautionary high scores for individual parameters. This possibility should also be taken into account when analysing the results.
- High scores do not necessarily mean that the reviewed nanomaterials represent a hazard or involve definite risks, can also indicate a **great need for knowledge procurement, additional explanations and testing** as well as possible specific measures.

5.4 Recommendations for further investigations

If the precautionary matrix indicates a need for precautionary measures, then protective measures and/or additional investigations are appropriate. These can concern the effect as well as the human exposure or the input into the environment.

In a first step it may be expedient to check whether suitable measures can be taken to avoid or at least limit human exposure or the input into the environment. If this is unable to lower the need for precautionary measures enough, then additional data can be obtained which enable a risk assessment.

Reactivity parameters:

The precautionary matrix considers the reactivity and the stability of a nanomaterial as the reactivity parameters. The reactivity parameters are characteristics that indicate for a given exposure that short- or long-term effects may occur with humans and environmental organisms.

Acute and chronic effects of nanomaterials on biota can be identified, with few exceptions, with the conventional test methods developed for chemicals.[40] The test methods for subacute (OECD 412) and subchronic (OECD 413) inhalation toxicity were amended in 2017 to include the investigation of nanomaterials.[41] If the possibility exists of exposure by inhalation during manufacture, use or disposal, then the risk assessment should include inhalation studies. For reactive and stable nanomaterials, depending on the accumulation behaviour in organisms, data should also be obtained on (sub)chronic toxicity. The possibility of regeneration after the test animals have been exposed should be included in the assessment.

Table 16 lists possible further clarifications as a function of the reactivity and stability. Similar considerations are contained in the final report of the "REACH Implementation Project on Nanomaterials (RIP-oN 2) Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH)".[42]

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Reactivity	**High**	If exposure via the lungs probable: information on acute inhalation toxicity required	If exposure via the lungs probable: information on acute inhalation toxicity required If accumulative: data on long term effects required	If exposure via the lungs probable: information on acute inhalation toxicity required If accumulative: data on long term effects required
	Medium	If exposure via the lungs probable: information on acute inhalation toxicity required	If exposure via the lungs probable: information on acute inhalation toxicity required If accumulative: data on long term effects required	If exposure via the lungs probable: information on acute inhalation toxicity required If accumulative: data on long term effects required
	Low	No further nanospecific testing required	No further nanospecific testing required	No further nanospecific testing required
		Low	**Medium**	**High**
	Stability			

Table 16: Further clarifications for nanomaterials as a function of their stability and reactivity.

[40] OECD, Six Years of OECD Work on the Safety of Manufactured Nanomaterials: Achievements and Future Opportunities; 2012.
[41] OECD Testguidelines: http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm.
[42] Project report Hankin S.M. *et al.*, "Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH (RIP-oN 2)" (1st of July 2011) page 141 sqq.

Exposure of humans:

In the precautionary matrix, the exposure of humans is determined either from the amount of nanomaterial the person can be in contact with per day, or on the basis of data from models or measured exposure values, with consideration to frequency in each case. If the exposure of the person was only roughly estimated, then additional literature data or one's own measurement results have to be used for a more accurate assessment.[43]

Medium or high reactivity parameters combined with a low exposure will result in a need for precautionary measures (score ≥25). In this case, it is recommended to conduct a specific assessment or exposure measurement in order to evaluate the risk.

Input into the environment:

If no mention is made of a specific disposal path, then it is assumed in the precautionary matrix that the total amount is input into the environment. Depending on the input path, additional data can be used here for a better estimation of the input amount. Clarifications on the behaviour of the nanomaterial in sewage or waste incineration plants or for mineral building materials in landfills for inert materials can provide valuable information for the assessment.

5.5 Possible protective measures at the workplace

Employees can come into contact with nanomaterials in research and development laboratories, in production and further processing as well as during waste disposal and recycling. Recommended or threshold values in the workplace have been derived for exceedingly few nanomaterials. Nevertheless, employees must be adequately protected against exposure to nanomaterials Workplace hygiene provides a wide range of protective measures against respirable dust pollution with proven efficacy against certain nanomaterials. If the precautionary matrix indicates a need for precautionary measures to protect employees, the possible preventive measures are to be examined and the most suitable measures for the particular case adopted, possibly in consultation with an occupational hygienist and/or the SUVA, which is responsible for the prevention of occupational diseases.

5.6 Information and advice

The contact point www.contactpointnano.ch can, if necessary, provide information on experts who can be consulted on protective measures, risk investigation and legal issues associated with nanomaterials. E-mail: contactpointnano@empa.ch.

In addition to publications, databases in the field of nanomaterials can serve as a helpful source of information, such as the eNanoMapper database (https://search.data.enanomapper.net/).

[43] A possibility to assess the work place concentration: EN17199:2019 Workplace exposure - Measurement of dustiness of bulk materials that contain or release respirable NOAA and other respirable particles.

6 Annex

6.1 Assessment of agglomerates in the precautionary matrix

When assessing the nano-relevance of a system in the context of the precautionary matrix, the size of the primary particles, the ability of the system to create agglomerates and the stability of those agglomerates are all important. It is important to note that, even for stable respirable agglomerates >500nm with nanoscale side branches, nano-specific toxicity can occur in the lung when in contact with pulmonary tissue. Employees and consumers must take this aspect into account.

Accordingly, there are three possible scenarios:

1. The primary particles create agglomerates that are not stable in the body or the environment and which disintegrate into primary particles <500nm. This scenario is treated as nano-relevant in the precautionary matrix and it applies generally to humans and the environment.
2. The primary particles create agglomerates which are stable in the body and which do not disintegrate into primary particles <500nm. The nanomaterials are not produced or integrated into a utility product in a manner that could entail exposure via the lungs. This case applies only to employees and consumers and is not treated as nano-relevant in the precautionary matrix.
3. As in 2, the nanomaterials are, however, produced or integrated into a utility product in a manner that could entail exposure via the lungs (agglomerates in the range between 500 nm and 10µm). In this case the nano-scaled side branches are assessed as nano-relevant, as they can lead to effects in the lungs. A precautionary matrix should be completed (with E1 = air). This case applies only to employees and consumers and is not relevant for the assessment of the environment.

6.2 Basis for estimating W1

Table 5 classifies the reactivities of nanomaterials into three bands – low, medium and high. For the purposes of this classification, criteria were defined for each of the studies used. In most cases the following basic approach was applied:

100% was assigned to the highest measured value in a particular study. Values of less than 10% were classified as low, values equal to or greater than 10% but less than 60% were classified as medium, and values of 60% or more were classified as high. By adjusting the classification bands, it would be possible to influence a correlation between *in vitro* and *in vivo*. However, fitting was not carried out.

Table 17 compares the reactivities obtained for the various nanomaterials in Table 5 with published data on acute and subchronic inflammatory responses provoked by inhaling nanomaterials and indicates the consistency of the reactivities for predicting pulmonary toxicity.

Nano-material	Cell-free or calculated reactivity (W1.1)	Cellular reactivity (W1.2)	Acute inhalation toxicity Trigger value for classification as "highly reactive": Rat STIS NOAEC ≤10 mg/m3; mouse oropharyngeal inhalation NOAEC ≤20 µg/animal	Subchronic inhalation toxicity Trigger value for classification as "highly reactive": 90d rat study: NOAEC ≤1 mg/m3; 28d rat study: NOAEC ≤2 mg/m3
Ag (0)	**M**	**H**	**Rat acute inhalation:** no adverse effects at 0.076-0.75 mg/m3 (a)	**Rat inhalation 90-day:** Chronic alveolar inflamation and small granulomatous pulmonary lesions (49-515 ug/m3; regress in males but not in females after exposure cessation. NOAEC: 0.1 mg/m3 (b, c)
CeO_2	**L**	**H**	**Rat STIS:** NOAEC <0.5 mg/m3; partialy reversible during post-exposure period at 0.5 mg/m3 but not at 5 mg/m3 (overload) (d)	**Rat inhalation 90-day:** NOAEC <1 mg/m3; Permanent effects during 90d post-exposure period (e)
Co_3O_4	**H**	**L**	**Mice oropharyngeal aspiration:** Increase of IL-6, MCP-1 and Neutrophils in BAL fluid after 40h (f)	
CuO	**H**	**H**	**Mice oropharyngeal aspiration:** Increase of IL-6, MCP-1 and Neutrophils in BAL fluid after 40h (f) **Rat STIS:** NOAEC 0.6 mg/m3. dose-dependent toxicity , which almost completely resolved during a 3-week post-exposure period (g)	
Fe_2O_3	**L**	**L**	**Rat STIS:** NOAEC ≥ 30 mg/m3 (h)	
Fe_3O_4	**L**		**Mice oropharyngeal aspiration:** No Increase of IL-6, MCP-1 and Neutrophils in BAL fluid after 40h (f)	**Rat inhalation 90-day**: NOAEL 4.7 mg/m3; MMAD aprox. 1.3 µm (i)
Mn_2O_3	**H**		**Mice oropharyngeal aspiration:** Increase of IL-6, MCP-1 and neutrophils in BAL fluid after 40h (f)	
SiO_2 (amorph)	**L**	**H**	**Rat STIS (NM 200, NM 203):** NOAEC 1 mg/m3; partialy reversible during post-exposure period (h, j)	**Rat inhalation 90-day (NM 200, NM 203)** NOAEC 1 mg/m3 (h)
TiO_2 (anatase)	**H**	**H**	**Rat STIS (NM 105):** NOAEC: <2 mg/m3; partialy reversible during post-exposure period (k)	**Rat inhalation 90-day (NM105)**: NOAEC: 0.5 mg/m3 (h)
TiO_2 (rutil)	**L**	**H**	**Rat Instillation:** No increase of granulocytes in BAL at 24h after instillation (150cm2/rat) (l)	

Nano-material	Cell-free or calculated reactivity (W1.1)	Cellular reactivity (W1.2)	Acute inhalation toxicity Trigger value for classification as "highly reactive": Rat STIS NOAEC ≤10 mg/m3; mouse oropharyngeal inhalation NOAEC ≤20 µg/animal	Subchronic inhalation toxicity Trigger value for classification as "highly reactive": 90d rat study: NOAEC ≤1 mg/m3; 28d rat study: NOAEC ≤2 mg/m3
ZnO	**L**	**H**	**Rat STIS NOAEC** (NM110): <8 mg/m3; reversible during post-exposure period (h)	**Rat inhalation 28-day**: NOAEC: <2 mg/m3. Inflammation was not persistent during recovery phase (n)
$BaSO_4$		**L**	**Rat STIS NOAEC** (NM220): >50 mg/m3; Effects transient effects (m)	**Rat Inhalation 90-day NOAEC** (NM220): NOAEL:50 mg/m3 (h)
MWCNT	**H**	**H**	**Rat STIS NOAEC** (NM400): <2 mg/m3; Effects persisting during post-exposure period (m)	**Rat inhalation 90-day NOAEC** (NM400): <0.1 mg/m3. At 0.1 mg/m3 minimal granulomatous inflammation in the lung and in lung-associated lymph nodes (o)
MWCNT	**M**	**H**	**Rat STIS NOAEC** (NM402): <2 mg/m3; Effects persisting during post-exposure period (m)	**Rat Inhalation 90-day NOAEC** (NM402): 0.25 mg/m3. The slight changes in BALF parameters at 0.25 mg/m3 recovered and signs of lung clearance were observed. No pathological changes were observed on the pleura (p)

Table 17: Overview of calculated reactivities determined by cell-free and cellular methods (cf. Table 5) and inflammatory responses measured in animal tests following exposure of the lung to certain nanomaterials.
Green = low reactivity/toxicity; yellow = medium reactivity; red = high reactivity/toxicity.

Sources quoted:

a Sung JH, Ji JH, Song KS *et al.*, Toxicol. Ind. Health 27(2), 149-154 (2011)
b Sung JH, Ji JH, Park JD *et al.*, Toxicol. Sci. 108(2), 452-461 (2009)
c Song KS, Sung JH, Ji JH *et al.*, Nanotoxicology 7(2), 169-180 (2013)
d Keller J, Wohlleben W *et al.*, Arch. Toxicol. 2014, 88: 2033-59
e Schwotzer D, Ernst H *et al.*, Particle and Fibre Tox. 2017, 14:23
f Zhang H, Ji Z *et al.*, ACSnano 6, no. 5, 4349-4368 (2012)
g Gonsens I, Cassee FR *et al.*, Nanotoxicology 10(8), 1095 (2016)
h Arts J, Irfan MA *et al.*, Regulatory Toxicology and Pharmacology 76 (2016) 234-261
i Pauluhn J., J. Appl. Toxicol. 2012; 32: 488-504
j Arts J, Muijser H *et al.*, Food Chem Toxicol 2007, 45:1856-67
k Ma-Hock L, Burkhardt S *et al.*, Inhalation toxicology 2009 21(2): 102-118
l Cho W-S *et al.*, Particle and Fibre Tox. 2013, 10:55
m Klein CL, Wiench K. *et al.*, Arch Toxicol (2012) 86: 1137-1151
n Morimoto Y, Int. J. Mol. Sci. 2016, 17, 1241
o Ma-Hock L, Treumann S *et al.*, Toxicol. Sci. 2009 112(2): 468-481
p Pothmann D, Simar S *et al.*, Particle and Fibre Tox. 2015, 12:21

The calculated and cell-free reactivities reveal a low accuracy for predicting *in vivo* acute and subchronic pulmonary toxicity. The cellular test systems show a better correlation here. The best correlation with no false negative results is obtained with a combination of calculated, cell-free and cellular reactivities (Table 18). Reactivity assessments do not consider the possibility of recovery after exposure due to the nanomaterial having a low stability or half-life (e.g. nanomaterials made of ZnO or CuO). However, assessments of potential effect take nanomaterial stability on board.

The impact potential of biopersistent fibres and tubes longer than 5 micrometres, which can be described as nanomaterials, is based on special mechanisms. They should therefore be specifically assessed (cf. Chapter 2.2).

	Prediction			
	correct	False-positive	False-negative	Evaluable datasets
Calculated and cell-free reactivities → Acute lung toxicity (in vivo)	9	1	3	13
Calculated and cell-free reactivities → Subchronic inhalation toxicity (in vivo)	4	0	3	7
Cellular reactivities (in vitro) → Acute lung toxicity (in vivo)	9	2	1	12
Cellular reactivities (in vitro) → Subchronic inhalation toxicity (in vivo)	8	0	0	8
Calculated/cell-free or cellular reactivities (in vitro) → Acute lung toxicity (in vivo)	10	2	0	12
Calculated/cell-free or cellular reactivities (in vitro) → Subchronic inhalation toxicity (in vivo)	8	0	0	8

Table 18: Accuracy of calculated reactivities or cell-free and cellular reactivities for predicting *in vivo* data for pulmonary toxicity (inflammatory response). Calculated, cell-free and cellular reactivities: Nanomaterials with a medium or high reactivity were evaluated equally for the purposes of comparison.

6.3 Basis for the assessment of exposure

In order to assess the potential exposure for the consumers and workers, a classification by means of a reference value is required. The toxicological reference value evaluates the exposure and shows whether a toxicologically relevant exposure is to be expected by classifying the potential exposure into the classes "low", "medium" and "high". The reference value and thus the classification is specific to the exposure pathway (inhalation, oral, dermal) and the target person (worker, consumer). The reference values are the result of a literature search and interpretation of existing exposure limits for nanomaterials.

6.3.1 Inhalation reference values

6.3.1.1 Reference values for employees

Reference value general

- Reference value for the calculation „high exposure“: >500 µg/m^3
- Reference value for the calculation „medium exposure“: 100-500 µg/m^3
- Reference value for the calculation „low exposure“: <100 µg/m^3

Reference values for CNTs and nanofibers

- Reference value for the calculation „high exposure“: >50 µg/m^3
- Reference value for the calculation „medium exposure“:1-50 µg/m^3
- Reference value for the calculation „low exposure“: <1 µg/m^3

Reference value for nanosilver

- Reference value for the calculation „high exposure“: >10 µg/m^3
- Reference value for the calculation „medium exposure“: 0.19-10 µg/m^3
- Reference value for the calculation „low exposure“: <0.19 µg/m^3

6.3.1.2 Reference values consumers

Reference value general

- Reference value for the calculation „high exposure“: >125 µg/m^3
- Reference value for the calculation „medium exposure“: 25-125 µg/m^3
- Reference value for the calculation „low exposure“: <25 µg/m^3

Reference values for CNTs and nanofibers

- Reference value for the calculation „high exposure“: >13 µg/m^3
- Reference value for the calculation „medium exposure“: 0.25-12.5 µg/m^3
- Reference value for the calculation „low exposure“: <0.25 µg/m^3

Reference value for nanosilver

- Reference value for the calculation „high exposure“: >2.5 µg/m^3
- Reference value for the calculation „medium exposure“: 0.05-2.5 µg/m^3
- Reference value for the calculation „low exposure“: <0.05 µg/m^3

6.3.2 Oral reference values

6.3.2.1 Reference values for employees

Reference value general

- Reference value for the calculation „high exposure“: >63’000 µg/kg bw/d
- Reference value for the calculation „medium exposure“: 53-63’000 µg/kg bw/d
- Reference value for the calculation „low exposure“: <53 µg/kg bw/d

Reference value for nanosilver

- Reference value for the calculation „high exposure“: >230 µg/kg bw/d
- Reference value for the calculation „medium exposure“: 0.02-230-µg/kg bw/d
- Reference value for the calculation „low exposure“: <0.02 µg/kg bw/d

6.3.2.2 Reference values for consumers

Reference value general

- Reference value for the calculation „high exposure“: >22’500 µg/kg bw/d
- Reference value for the calculation „medium exposure“: 19-22’500 µg/kg bw/d
- Reference value for the calculation „low exposure“: <19 µg/kg bw/d

Reference value for nanosilver

- Reference value for the calculation „high exposure“: >80 µg/kg bw/d
- Reference value for the calculation „medium exposure“: 0.006-80 µg/kg bw/d
- Reference value for the calculation „low exposure“: <0.006 µg/kg bw/d

6.3.3 Dermale reference values

Due to the lack of reliable data on dermal toxicity, no subdivision was made.

6.3.3.1 Reference values for employees

Reference value general

- Reference value for the calculation „high exposure“: >7’500 µg/kg bw/d
- Reference value for the calculation „medium exposure“: 13-7’500 µg/kg bw/d
- Reference value for the calculation „low exposure“: <13 µg/kg bw/d

6.3.3.2 Reference values for consumers

Reference value general

- Reference value for the calculation „high exposure“: >1‘339 µg/kg bw/d
- Reference value for the calculation „medium exposure“: 2.2-1‘339 µg/kg bw/d
- Reference value for the calculation „low exposure“: <2.2 µg/kg bw/d

6.4 Basis for estimating E3.1, E3.2 and E3.3

The derivation of the estimation limit of 500 kg for the amount of nanomaterial disposed per year which reaches the environment in wastewater, exhaust air or solid waste, the amount of nanomaterial in utility products and the amount of disposed nanomaterial per year (E3.1 and E3.2) is based on the following model: based on ecotoxicity data of nano TiO_2, a PNEC of 1 µg/l is assumed. For an estimated use of 200 l per day for each inhabitant of Switzerland (approx. 8 million), the considered annual volume is $580 \cdot 10^9$ l. Together with the assumed PNEC, this results in 550 kg per year as the limit, below which no effect occurs. Taking into account a precautionary approach 500 kg per year was taken as the relevant limit.

This projection is very general and set at a high level for Switzerland as a whole. It should be pointed out that locally strongly different quantitative scenarios are possible. This is not however considered in the scope of the precautionary matrix.

6.5 Probability distributions of the uncertainty categories

The combination of “parameter value - uncertainty value” is translated into a probability distribution for the parameter value.

The probability distribution employed is based on the following principles:

1. Probabilities ought to be on the safe side, which means that, in most cases, a higher uncertainty for one and the same value ought to lead to a higher probability of poorer values. For example, a parameter value of 5 (medium value) and a high uncertainty lead to a higher probability of value 9 (poorest value) compared with the probability of value 1 occurring.

2. A logical consequence of principle 1 is that, in the case of the poorest value (i.e. 9), this poorest value will always have a probability of 1.0, irrespective of the degree of uncertainty. This approach has been selected so as to maintain the precautionary nature of the model.

3. The probabilities ought to increase in identical increments when moving from one uncertainty value to the next so as to give the same weight to the different degrees of uncertainty in all the parameters. In other words, each degree of uncertainty has the same impact.

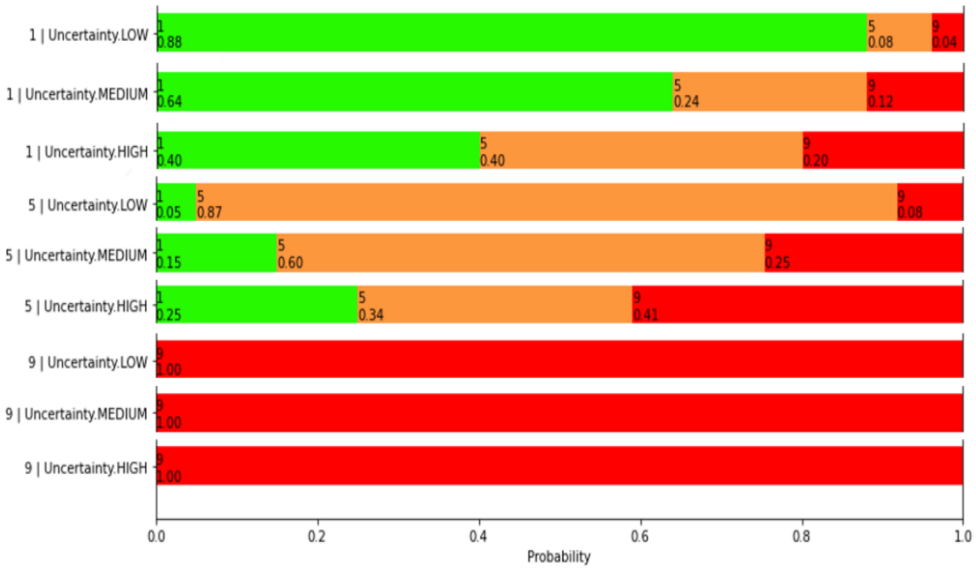

Figure 9: Value distribution of the parameters in relation to the selected uncertainty.

Notes: