Guidelines on the Precautionary Matrix for Synthetic Nanomaterials

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Contents

1 Context

Nanomaterials may only be supplied and used 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 toxicological properties of these materials. The OECD plays a significant role in the development and standardisation of the methods for testing these properties. After having reviewed the methods developed for chemicals the OECD concluded that they were also suitable for nanomaterials. However, specific properties of nanomaterials could require adaptations in future. What is currently lacking are standardised methods to determine those physical and chemical 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 existing methods for hazard and risk assessment are in principle also applicable to nanomaterials. However, amendments are needed for the inclusion of the nanospecific properties. As internationally harmonised methods do not yet exist, decisions have to be taken on a case by case basis on whether additional data are needed in order to be able to adequately assess the risks of nanomaterials.

This situation is causing uncertainty in particular for the businesses about how to act and whether to invest. The limited knowledge also makes it difficult to have a public debate on the opportunities and risks presented by nanomaterials.

In 2008 the Federal Council adopted the **Swiss Action Plan on Synthetic Nanomaterials**[3]. The priority actions are:

- creating the scientific and methodological preconditions to recognise and prevent the possible harmful impacts of synthetic nanoparticles on health and the environment,
- creating the regulatory framework for responsible handling of synthetic nanomaterials,
- promoting public dialogue on the opportunities and risks of nanotechnology and nanomaterials, and
- better use of existing promotional instruments for the development and market launch of sustainable applications of nanotechnology

The development of the **precautionary matrix** for products and applications that involve synthetic nanomaterials is the core measure of the action plan for empowering industry, commerce and trade to take greater responsibility in this area and to apply the precautionary principle in a goal oriented and cost-effective manner.

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[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)

[2] OECD, Six Years of OECD Work on the Safety of Manufactured Nanomaterials: Achievements and Future Opportunities; 2012.

[3] See: http://www.bag.admin.ch/nanotechnologie/12167/index.html?lang=en

In 2012 the Federal Council decided to continue the implementation work until 2015[4]. The measures decided in 2008 for handling nanomaterials should be adapted to new findings. This also applies to the precautionary matrix.

[4] See: http://www.bag.admin.ch/nanotechnologie/12161/12162/13155/index.html?lang=en

2 Objective and Area of Application

Nanomaterials, like conventional food additives, chemicals, biocides etc. have to be tested depending on their field of application, and an assessment has to be made on the risks for people and the environment. The assessment methods for the different approval and authorisation procedures are today not tailored to nanomaterials. The precautionary matrix complements the existing non-nanospecific assessment methods with an evaluation of the risk provisions. It should therefore always be employed in parallel to 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 present precautionary matrix helps businesses to assess the need for nanospecific measures (precautionary need) for synthetic nanomaterials and their applications for employees, consumers and the environment, based on selected parameters. In addition it helps to identify potential sources of risk in the development, production, use and disposal of synthetic nanomaterials. However, this pragmatic approach should not in any way be compared with a nanospecific risk assessment process.

Rather, the risk potential should be classified to show what action is appropriate:

"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, if applicable, draw on data from the literature and expert information (see chapter 5.4).

Applications that require clarification can thus be identified independently using the precautionary matrix, and the need for measures for protecting health and the environment can then be reviewed and estimated. As such the precautionary matrix is an instrument that industry, commerce and trade can use for duty-of-care and self-supervision[5] purposes associated with the production and use of synthetic nanomaterials. The precautionary matrix is also intended to assess the precautionary need of 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.

[5] According to the Chemicals Law (SR 813.1), Environmental Protection Law (SR 814.01) and the Chemicals Ordinance (SR 813.11)

The classification of the precautionary need allows a differentiated and objective approach to the opportunities and risks presented by nanomaterials and nanotechnologies.

The precautionary matrix functions simultaneously as a differentiation aid, a detector of gaps in knowledge and an early warning system. The precautionary matrix is freely available and free of charge.

2.2 Area of application

At present internationally there exist various definitions of the term nanomaterial. In most definitions, the size of the primary particle plays a crucial role, wherein external dimensions of less than 100 nm in at least one dimension have become established as the criterion.

However, the use of the 100 nm limit does not represent a scientifically justifiable quantity. Thus, nanospecific effects also occur with particles, whose external dimensions are greater than 100 nm, as particles of up to ca. 300 nm can be taken up by organisms and cells[6] [7].

The precautionary matrix contains two critera for assessing nano-relevance. The first criterion is based on the EU proposed definition 2011/696/EU. The second being the fact that nanospecific effects cannot be excluded even for particles > 100 nm.

The choice of the approach can be made as a function of the field of application and the different legal requirements of the user.

Approach 1 (EU proposed definition)

Manufactured materials are considered as nano-relevant if they comprise particles in the unbound state, as an aggregate[8] or agglomerate[9] and in which at least 50% of the particles in the number size distribution have one or more external dimensions in the range 1 to 100 nm.

In the case that the number size distribution is unknown, specifically manufactured materials are considered nano-relevant if they have a specific surface/volume greater than 60 m^2/cm^3.

Fullerenes, **graphene flakes** and single wall carbon nanotubes are considered to be nanomaterials even when they exhibit dimensions of less than 1 nm.

Approach 2 (precautionary approach)

Specifically manufactured materials are considered as nano-relevant which comprise particles in the unbound state, as an aggregate[10] or agglomerate[11] and in which one or more external dimensions are between 1 and 500 nm. Respirable materials up to 10 µm with

[6] SCENIHR: Risk Assessment of Products of Nanotechnologies, 2009, S. 26
[7] Geiser et al.; Environmental Health Perspectives: VOLUME 113 | NUMBER 11 | November 2005
[8] 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.
[9] 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.
[10] 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.
[11] 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.

nanoscale side branches can likewise trigger nanospecific effects and are likewise considered to be nano-relevant.

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 by 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[12]). These risks must be assessed by conventional standard procedures[13].

Application in various phases of the life cycle

The precautionary matrix can be used to estimate the precautionary need for the health of employees and consumers and for the environment at various points of the entire 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
- Waste management (reuse, recycling, disposal)

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

[13] 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

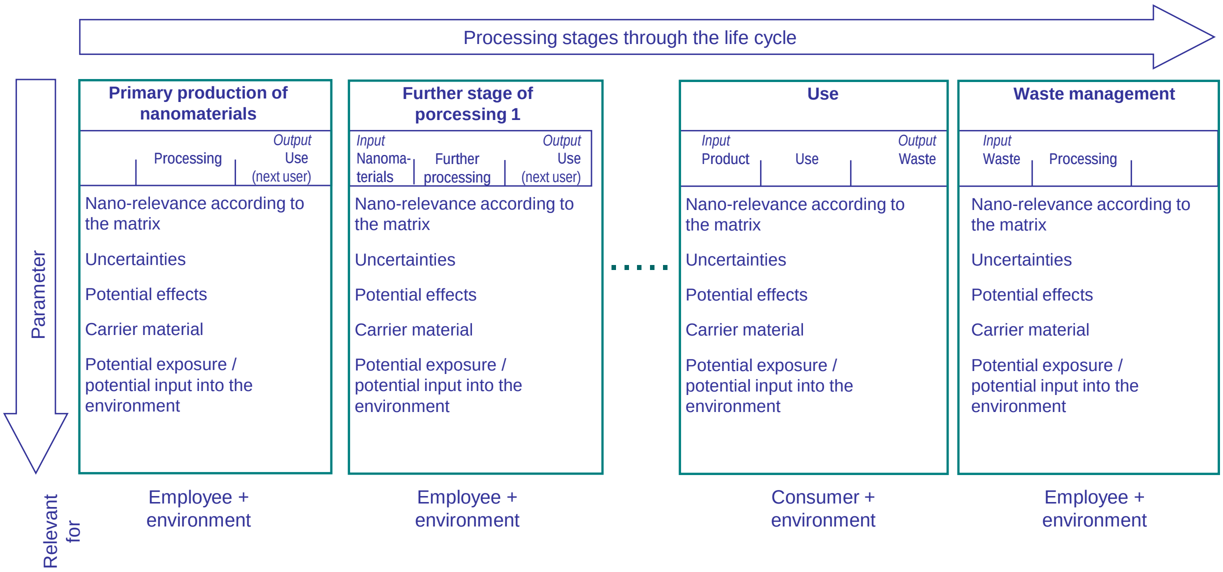

Figure 1: Processing stages as part of the entire life cycle

As a general rule, a precautionary matrix applies to one specific 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 are changed into new nanomaterials during use, for instance through rapid dissolution of a coating.

Evaluation parameters

The precautionary matrix is based on a limited number of evaluation parameters. The **potential effect**[14] is estimated on the basis of the nanomaterials' **reactivity** and **stability**[15]. The probability and degree of exposure (= "**potential exposure**") of humans and the **potential input into the environment** are determined from data on the carrier material of the nanomaterials, on the **amount of the handled nanomaterials**, on the **frequency**, on the **amounts in consumer products,** or on the **amount of specifically disposed nanomaterials**, or on the **amount in exhaust gases, wastewater or solid waste** from development, production or use. In addition, the available information is surveyed.

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.

[14] Capacity of the nanomaterials to act upon their surroundings (humans, environment)

[15] In the context of the precautionary matrix, stability of the nanomaterial is understood to be the persistence of a nanomaterial as such in the surroundings in question (e.g. resistance to dissolving, chemical or physical change, sintering to bulk material, breakdown etc.)

Note:

An online version of the precautionary matrix exists which includes automatic evaluation of entries[16]. 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. These explanations are helpful, but not necessarily essential, for using the online version of the precautionary matrix.

[16] http://www.bag.admin.ch/nanotechnologie/12171/12174/12175/index.html?lang=en

3 Procedure for Completing the Precautionary Matrix

The precautionary matrix should be completed according to the procedure explained below with the help of a template and evaluated in terms of the possible risks to health and the environment. 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 Precautionary Need". The evaluation is always specific for the investigated process and product.

Procedure:

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 precautionary need. 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 in the fields of application of the precautionary matrix. If there is a doubt whether a material is nano-relevant or not, it is recommended to use 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, then 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 workers with different activity profiles in the same (process) step, or for different groups of consumers.
5. **Enter general information in the relevant matrix**. Define the person responsible or contact person in the company for any external contact.
6. **Complete the technical part of the precautionary matrix**, following the parameters described in section 4 as far as possible.
7. **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.).
8. **Obtain information** using the relevant questions from the matrix.

9. **Finish the matrix**, delimit the relevant precautionary need and determine the classification.
10. **Clarify any need for action** and, if appropriate, initiate measures (commence further clarifications, additional measures, protection measures and measures to provide information, communication, etc.).

The precautionary matrices are logically completed and evaluated in two iterative steps:

1. A first rapid evaluation demonstrates knowledge gaps and uncertainties and leads to a preliminary precautionary matrix.
2. Exact clarifications on the fundamentals of the results from step 1 and the specific answers to the knowledge gaps leads to the finished, evaluated, definitive precautionary matrix.

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 (grey background) and the resulting numerical values for the estimation of the precautionary need. 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 precautionary need is represented primarily in relation to the potential effect (W) on the one hand and the potential exposure of humans or inputs into the environment (E) on the other. "Available information" (I) is introduced as an additional parameter. These factor 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)[17] is introduced as a criterion for deciding whether the use of the precautionary matrix is indicated:

Precautionary need = f (N, W, E, I)

where:

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)

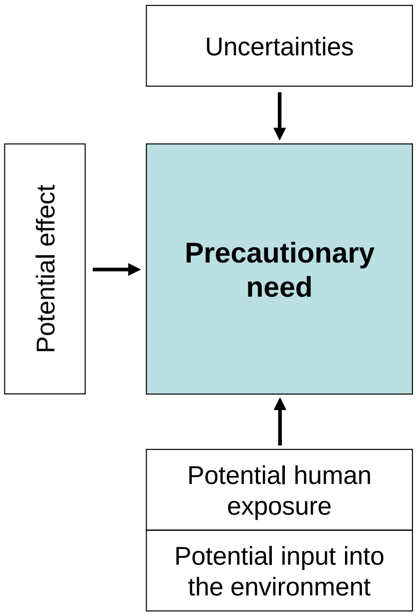

Figure 2: The concept for estimating precautionary need

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

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

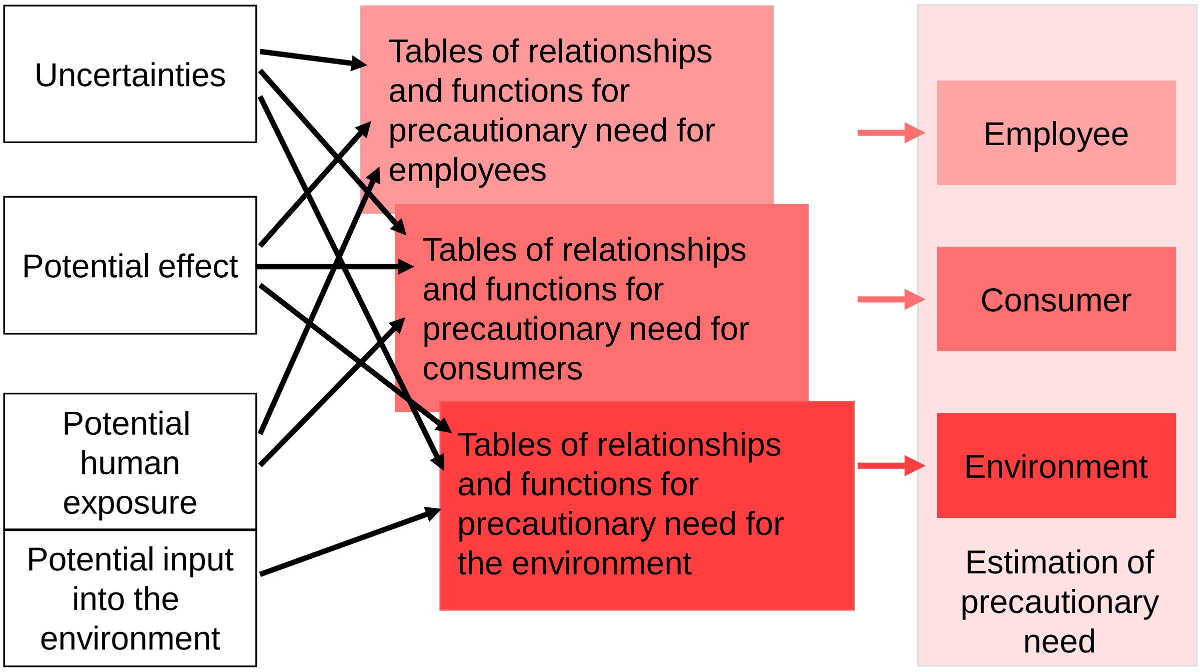

Figure 3: Parameters for estimating the precautionary need

For employees, a "worst case" (WC)[18] is also defined, based on the following consideration: In otherwise identical conditions and the same precautionary need for the normal exposure to the nanomaterials, two employees in different companies can have a significantly different precautionary need in an accident, in the case when a significantly greater amount of nanomaterials is stored in one of the companies.

For the purposes of calculating precautionary need, the input parameters are scored from 1 to 9 (the following ratings are currently used: low = 1, medium 5, high = 9. In all cases in which it is not possible to conduct an assessment according to the guidelines in the matrix (e.g. low, medium, high) because the information is not available, the value that would ultimately give the highest precautionary need must be used.

[18] Worst case scenarios are considered to be relevant for the precautionary matrix only if they involve accidents during production, storage, packaging and transport which lead to an increase in exposure in the workplace. The precautionary matrix cannot take account of natural disasters and attacks. Since incorrect use of materials and products falls within the sphere of responsibility of employees and consumers, it is not considered in the matrix. The effects of major accidents on the population are not considered.

4.2 Parameters

The parameters and their sub-divisions are summarised in Table 1: Classification of the parameters used.

	Parameter	Abbreviation
Nano-relevance	**Nano-relevance according to the precautionary matrix**	N
	• Material containing primary particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the primary particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm or (Ii the number size distribution is unknown) • Material where the specific surface area by volume is greater than 60 m^2/cm^3 or • Material consists of fullerenes, graphene flakes or single wall nanotubes.	N-EU
	Size of the primary particles) in the materials (free, bound, aggregated or agglomerated)	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
Uncertainties	**Information on the life cycle**	I
	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**	W
	Redox activity, catalytic activity, oxygen radical formation potential or induction potential for inflammatory reactions of the nanomaterial	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	**Carrier material**	E1
	Potential for release related to human exposure	$E1_{A,V}$
	Potential for release related to the environment	$E1_U$
	Maximum possible human exposure	E2
	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
	Frequency with which an employee handles nanomaterials	E2.3
	Amount of nanomaterials handled by a consumer per day via the utility product	E2.4
	Frequency with which a consumer uses the utility product	E2.5
	Maximum possible input into the environment	E3
	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 disposed nanomaterials per year	E3.3

Table 1: Classification of the parameters used

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

Parameters N-EU[19], N1 and N2 examine the nano-relevance of the system. The criteria mentioned in chapter 2.2 “Field of application” serve as the benchmark.

Approach 1 (EU-proposed definition): Number size distribution of the primary particles (in the free or bound state, as an aggregate or agglomerate) contained in the materials	At least 50% >1 nm, <100 nm	At least 50% >100 nm	unknown
	or	and	and
If the number size distribution is unknown, manufactured materials are considered nano-relevant if they have a specific surface/volume greater than 60 m2/cm3	yes	no	unknown
	or	and	and
Fullerenes, graphene flakes and single wall carbon nanotubes are considered to be nanomaterials even when they exhibit dimensions of less than 1 nm.	yes	no	unknown
N-EU	1 (go to N1a)	0	1 (go to N1)
Approach 2 (precautionary approach): size of the primary particles (in the free or bound state, as an aggregate or agglomerate) contained in the materials	>1 nm, <500 nm		>500 nm
N1	1		0
Do the primary particles form agglomerates or aggregates >500 nm.	yes	no	unknown
N1a	1 (go to N2)	1	1

Table 2: Nano-relevance

[19] N-EU: This parameter defines the nano-relevance based on the EU proposal for a definition for nanomaterials (cf. chapter 2.2).

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 precautionary need for health (N2A,V), while stability under ambient conditions is important for assessing the precautionary need for the environment (N2U).

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
N2A,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
N2U	1	0
Only if N2A,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 process for establishing nano-relevance is summarised in simplified form in the following diagram. For a more detailed description see appendix 6.1.

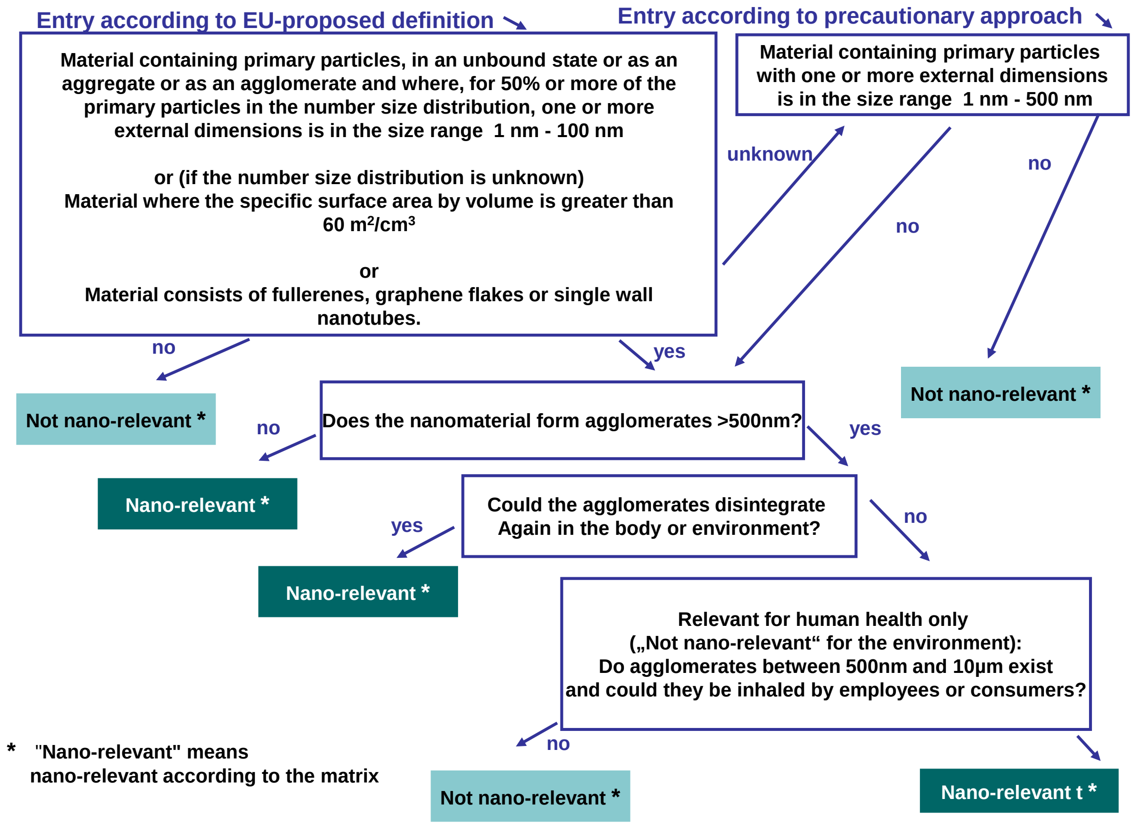

Figure 4: Process for establishing nano-relevance

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	3	5
Is sufficient information available to complete the precautionary matrix for nanoscale starting materials?	yes	partly	no
I2	0	3	5
Are the next users of the considered nanomaterials known?	yes	partly	no
I3	0	3	5
How accurately is the material system known, or can disturbing factors (e.g. impurities) be estimated?	accurately	not accurately	not known
I4	0	3	5

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)

The precautionary matrix assumes that nano-relevant materials can come into contact with cells and tissue or can be taken up by them and can cause effects therein as a function of their potential action. The potential action of nanomaterials on health and the environment is estimated by:

1. the redox activity, the catalytic activity[20], the activity of formation of oxygen radicals (reactive oxygen species ROS) and the consequential induction of an oxidative stress or the induction of inflammatory reactions (e.g. production of interleukines) of the nanomaterials (W1)
2. the stability of the nanomaterials under the relevant conditions in the body ($W2_{A,V}$) or the environment ($W2_U$)

The reactivity, evaluated with the parameters cited in point 1, are based on mechanisms of activity that are highly significant for nanomaterials. If these data are unavailable it is possibly necessary to determine or to calculate them for the nanomaterial being assessed, that otherwise is assumed to have a high reactivity. 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. The more complete the data, the better appropriate measures can be implemented. The assignment of the value of parameters as low-, medium- and highly-reactive can be approximated using the following illustrative listing of comparable nanomaterials (Table 5).

Redox activity: 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 are found in reference books. The redox potential of a chemical reaction can be calculated from the sum of both half reactions (oxidizing 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. Gold, for example, in its oxidised form Au^{3+} has a high oxidation potential with +1.42 V and easily takes up electrons. In many cases the redox potentials established under standard conditions are less meaningful, because many reactions are pH-dependent. These have to be converted for the respective prevailing pH conditions. For semiconductors or metal oxides the redox activity can also be estimated fairly accurately based on the position of the conduction band in comparison to the redox potential of enzymatic reactions[21].

[20] This also includes photochemical and photocatalytic activity
[21] H. Zhang et al.:Use of metal oxide nanoparticle band gap to develop a predictive paradigm for oxidative stress and acute pulmonary inflammation; acsnano, 6(5), 4349-4368, 2012.

Under environmental conditions some metallic nanomaterials are rapidly oxidised, at least on the surface (passivation). The redox potential then corresponds rather to that of their oxides. If a material exists both in bulk form as well as a nanoscale material then in most cases the redox potential of the nanomaterial can be estimated based on that of the bulk material. Quantum effects are expected only at a particle diameter of less than 15 nm.

Catalytic and photocatalytic activity: Catalytically active nanomaterials can perturb cell metabolism, in that they promote and accelerate specific reactions in the cell. Photocatalytically active materials are semiconductors that under the influence of light form reactive radicals that can damage the cells. There are various methods to determine the catalytic activity of nanomaterials. It is mostly determined by means of an easily measurable reaction such as the reduction of a dye[22]. An ISO standard (ISO 22197) exists for the measurement of the activity of photocatalytic materials. Although it was not designed for powdered 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[23].

Data that are relevant for the precautionary matrix are those on the catalytic and photocatalytic activity, measured at physiological temperatures.

As a criterion for reactivity, data on the induction of oxidative stress[24] can be used, in particular on the **formation of oxygen radicals** (ROS) or for the **induction of inflammatory reactions** in cell systems or tissue (e.g. the formation of interleukins). Various *in vitro* methods are now available for both parameters. It should be noted that the nanomaterial-induced ROS formation and the induction of inflammation markers can vary depending on the cell line used[25]. Table 5 contains the results of studies, in which several well-characterised nanomaterials were tested with the same method. This allows a comparable evaluation of their reactivity.

For the **assessment of the reactivity**, it is recommended to use the most sensitive reactivity marker (redox activity, catalytic/photocatalytic activity, formation of oxygen radicals, induction of inflammation markers). In the absence of data on the reactivity of the nanomaterial, a worst case scenario of a high reactivity should be assumed.

[22] Su Peng et al., Modern Applied Science, Vol. 4 No 5, May 2010: Studies on activity of nanostructure Mn2O3 prepared by solvent-thermal method on degrading crystal violet.
[23] NA Lee et al., Photochem Photobiol Sci, 2011, 10(12), 1979-82: Development of multiplexed analysis for the photocatalytic activities of nanoparticles in aqueous suspensions.
[24] 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 texic effects.
[25] A. Kroll et al,; Particle and Fiber Toxicology, 2011, 8:9.

Nanomaterial Reactivity (data refer to uncoated and non-functionalised nanomaterials)	Redox activity (pH7) Estimated, based on the standard redox potential or the position of the conduction band[19]			ROS-formation behaviour or induction of inflammation reactions			(Photo)catalytic activity (at environmental temperatures)		
	low (1)	medium (5)	high (9)	low (1)	medium (5)	high (9)	low (1)	medium (5)	high (9)
Ag[0]		X			X[c]			X	
Ag_2O		X						X	
CeO_2	X				X[a]		X		
CuO		X					X		
Fe[0]		X			X *			X *	
FeO		X			X *			X *	
Fe_3O_4	X				X *			X *	
Fe_2O_3		X			X[b]		X		
SiO_2 (amorph)	X			X[b]			X		
TiO_2 (anatase)		X			X[a,b,c]				X
TiO_2 (rutile)		X			X[c]			X	
ZnO	X					X[c]		X	

Table 5: Examples of evaluations of the potential activity (W1) for some nanomaterials

a: Kroll, A. et al.; Particle and Fibre Toxicology 2011, 8:9
b: Limbach, L.K. et al.; Environ. Sci. & Technol. 2007, 41 (11), pp 4158–4163
c: Kermanizadeh, A. et al.; Particle and Fibre Toxicology 2012, 9:28
* For Fe[II]: average ROS-formation behaviour or catalytic activity inserted, due to correlation of the conduction band with the Fenton reaction with H_2O_2. Also assumed for Fe[0] as such nanoparticles also usually comprise oxidised Fe[II] on their surface

As already discussed in section 2.2, biopersistent fibres of more than 5 micrometers in length that can be regarded as nanomaterials should be further assessed in a separate analysis[9].

In the present context, **stability** takes into account the stability of the employed synthetic nanomaterials towards dissolution, chemical or physical transformation (for example silver nanoparticles to silver sulfide 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 type of exposure, transport, chemical transformation and separation or enrichment, to complete several precautionary matrices for the different conditions (pH, temperature, presence of proteins…).
- 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 relevant scenarios should be worked out first and then each should be evaluated with new precautionary matrices.

Strictly speaking, for the environment a differentiation must be made between the stability in biotic and abiotic systems. Biotic systems in most cases can be estimated using the same stability as applied for humans. For the abiotic systems, in a first approximation, the same stability as for biotic systems can be assumed ($W2_{A,V}$ and $W2_U$). This is applicable as long as there is no evidence to suggest that stabilities differ in abiotic systems from those in biotic systems.

Redox activity, catalytic activity, oxygen radical formation potential or induction potential for inflammation reactions of the nanomaterials[26]	low	medium	high
W1	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 6: Potential effect

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. If another nanomaterial is produced as a result, a separate precautionary matrix must be completed for it.

The presence of a coating or a 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 cases[28]:

[26] Because of their special toxicokinetics synthetic nanomaterials could reach places in the organism which are not normally accessible for the basic chemical substances, in soluble form. If the nanomaterial reaches these places when in solution, then high local concentrations of these chemical substances may occur with new toxic effects. This possible influence on the potential effect is not considered in the present context.

- 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.

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. Usual standard methods for the evaluation of chemicals can be used to determine the effects of the dissolved coating.

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

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

1. the carrier material 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 fundamental idea is the following: the maximum possible extent of the exposure corresponds exactly to the total amount of material handled. This worst-case reasoning underlines the precautionary thinking. This maximum possible exposure in the worst case is limited and simultaneously "scaled" by taking into consideration the respective carrier material of the nanomaterial and consequently by the probability of an exposure according to the different availability of the nanomaterials.

[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)

4.6.1 Carrier material

The potential availability of the carrier material of the nanomaterial differs depending on its type (Table 7). Only one of the given surroundings can be (accurately) selected per matrix. Selecting the physical surroundings assigns predefined values for availability in relation to the potential human exposure ($E1_{A,V}$) and input into the environment ($E1_U$).

Carrier material	$\mathbf{E1_{A,V}}$	$\mathbf{E1_U}$
Air, aerosols <10 µm (intake into lungs; possible input into environment)	1	1
Air, aerosols >10 µm (intake into lungs and GIT; possible input into environment)	0.1	1
Liquid media (intake through GIT; possible input into environment)	0.1	1
Solid matrix, not stable under process conditions or conditions of use (intake through lungs, GIT and skin; possible input into environment)	0.1	1
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, stable under process conditions or conditions of use, nanomaterial not mobile (improbable exposure for people and input into environment)	10^{-4}	10^{-4}

Table 7: Exposure of people and input into the environment as a function of the carrier material of the nanomaterials

In the case of human exposure, a distinction is made between possible exposure of the lungs ($E1_{A,V}$ =1) and other target organs[29] ($E1_{A,V}$ = 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.

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).

When estimating potential exposure, parameters $E1_{A,V}$ and $E1_U$ have a multiplicative effect on the extent of exposure.

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

4.6.2 Maximum possible human exposure

For employees and consumers, the maximum possible exposure is estimated via the amount of nanomaterials and frequency with which those people come in contact.[32] The associated parameters are evaluated as shown in Table 8.

Amount of nanomaterial with which a worker[33] comes into contact per day[34]	<1.2mg	<12mg	>12mg
E2.1	1	5	9
Amount of nanomaterial with which a worker could come into contact in the "worst case"	<12mg	<120mg	>120mg
E2.2	1	5	9
Frequency with which a worker handles the nanomaterial	monthly	weekly	daily
E2.3	1	5	9
Amount of nanomaterial which a consumer handles daily through the utility product	<1.2mg	<12mg	>12mg
E2.4	1	5	9
Frequency with which a consumer uses the utility product	monthly	weekly	daily
E2.5	1	5	9

Table 8: Potential human exposure

The extent of potential exposure is then estimated by factoring in the availability of the nanomaterials as a function of their carrier material and intake (Table 7). This is done separately for employees and consumers.

4.6.3 Maximum possible input into the environment

Environmental inputs during the production phase (including manufacture, processing, packaging, transport and disposal) and consumer phase are considered separately. In the consumer phase, two additional scenarios have to be considered, namely the use **with** and **without** specific waste disposal[35]. Subsequent to the consumer phase with specific disposal, the disposal process has also to be evaluated in a separate precautionary matrix.

[32] Since failure to wear or the wearing of inadequate personal protective equipment falls within the sphere of responsibility of employees and consumers, this is not considered in the precautionary matrix.
[33] If different employees are subject to markedly different exposures, it is recommended that separate precautionary matrices be completed for these employees
[34] For the derivation of the specified values see appendix 6.1. In this context "handle" means the physical presence of the material in the vicinity of the employee or consumer without taking account of specific protective measures
[35] The FOEN working group for "Environmentally compatible and safe disposal of nanomaterial waste products" is preparing a guide that will provide information on the disposal of industrial and commercial waste. Contact: FOEN, Industrial chemicals Section, ernst.furrer@bafu.admin.ch

The following Figure presents the procedure for handling the possible environmental inputs and subsequent matrix-relevant processes:

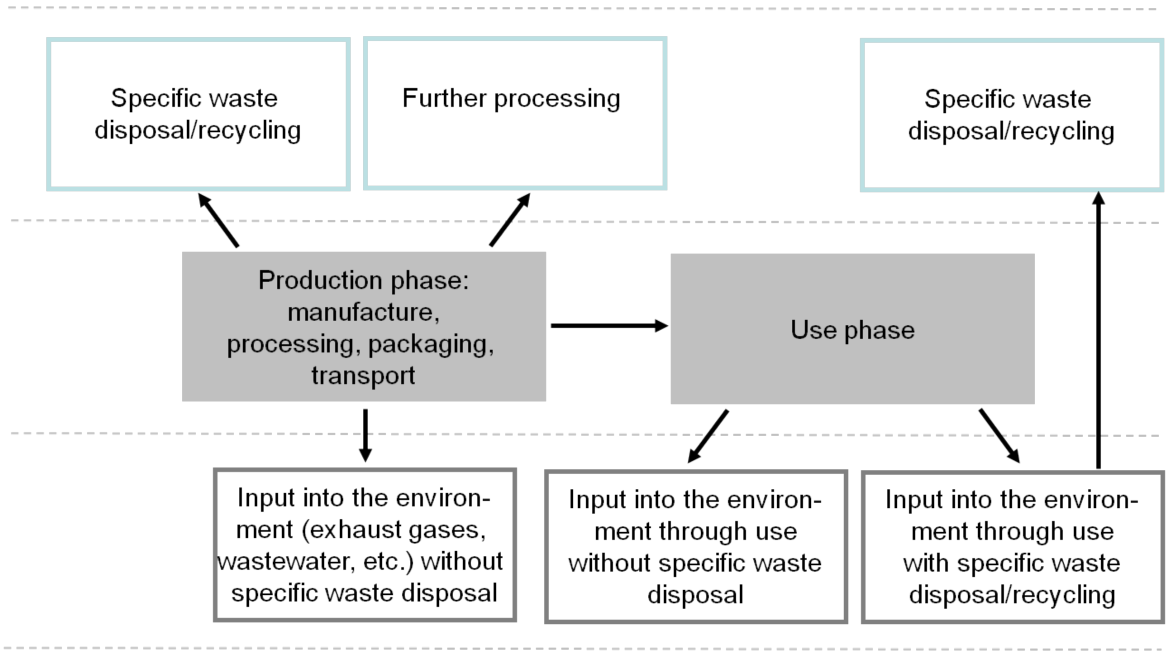

Figure 5: Environmental input scenarios

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

   During the nanomaterial production phase, input of nanomaterials into the environment may occur via exhaust air, wastewater or unspecific waste disposal. This is assessed in the precautionary matrix by the unwanted emission of nanomaterials during the process under consideration (E3.1).

   Any **input during specific waste disposal e.g. as a hazardous waste, recycling or further processing occurs in a separate process step and must be estimated in its own precautionary matrix**. The estimate in this case is made for the quantity 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. In regard to this, see also the activities in the context of disposal of nanowaste[36].

2. **Use phase**

   Here there are two separate scenarios:

   a) In the case of use **without specific waste disposal** (e.g. of utility products) it is often difficult to quantify the 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) For use **followed by specific waste disposal**, only inputs during use are considered. Input is estimated via the total amount of nanomaterials in the marketed utility products (E3.2) taking account the carrier material ($E1_U$).

Since environmental inputs via a specific method of disposal or recycling after use represent individual process steps, these are estimated in their own precautionary matrix. The parameter E3.3 (quantity of specifically disposed/recycled nanomaterial after the use phase) is also applied in this case.

The environmentally relevant parameters are evaluated as follows:

Annual quantity of nanomaterial that during the production phase reaches the environment via wastewater, exhaust gases or solid waste[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 (from the production or use phase)	< 5 kg	< 500 kg	>500 kg
E3.3	1	5	9

Table 9: Input into the environment

[36] The listed values are derived according to Appendix 6.3

5 Linking of Parameters and Estimation and Classification of the Precautionary Need

The linking of the parameters presented and explained in section 4, the estimation of the consequent precautionary need and its classification are presented in the following sections. This section is only intended to provide supplementary information and is not essential for using the computerised version of the precautionary matrix.

5.1 Linking and estimation of parameters

5.1.1 Nano-relevance according to the precautionary matrix

Nano-relevance is determined using the flow diagram in section 4.3, where:

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

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 $W_{A,V}$ on humans and W_U on the environment are estimated using the following equations:

$$\mathbf{W_{A,V} = W1 \cdot W2_{A,V}}$$

$$\mathbf{W_U = W1 \cdot W2_U}$$

5.1.4 Potential Exposure of Humans

Potential Exposure of Workers:

$$\mathbf{E_A = E1_{A,V} \cdot E2.1 \cdot E2.3}$$

additionally in the "worst case": $\mathbf{E_A^{WC} = E1_{A,V} \cdot E2.2}$

where:

$E1_{A,V}$: Carrier material, specific for the "workers/consumers" target groups (section 4.6.1)

E2.1: Amount of nanomaterial with which a worker comes into contact per day

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

E2.3: Frequency with which a worker comes into contact with nanomaterials

[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

Potential exposure of consumers:

$$E_V = E1_{A,V} \cdot E2.4 \cdot E2.5$$

where:

$E1_{A,V}$: Type of carrier material, specific for the "workers/consumers" target groups (section 4.6.1)

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

E2.5: Frequency with which a consumer comes into contact with the nanomaterial

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):

$$E_U^P = E3.1$$

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 ($E1_U$):

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

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 4.6.1)

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:

$$E_U^G = E3.2$$

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 ($E1_U$):

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

where:

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

$E1_U$: Carrier material, specifically for the environment (section 4.6.1)

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:

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

where:

$\mathbf{E_U^{GSE}}$ maximum possible input into the environment during the disposal process of utility products

$\mathbf{E1_U}$ carrier material, specifically for the environment (section 4.6.1)

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

5.2 Estimation of the precautionary need (V)

To estimate the precautionary need, 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:

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

Precautionary need for employees

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

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

Precautionary need for consumers

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

Precautionary need for the environment

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

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

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

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

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

where:

V_U^P: Precautionary need during production

V_U^{PSE}: Precautionary need during a disposal step of production waste

$V_U^{G,spez}$: Precautionary need during use with specific waste disposal

V_U^{GSE}: Precautionary need during a disposal step of a utility product

V_U^{G}: Precautionary need during use without specific waste disposal

5.3 Classification

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

Score	Classification	Importance
0 - 20	A	The nanospecific need for action can be rated as low even without further clarification.
>20	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 10: Nanospecific action requirement

The differentiation limit between classes A and B has been defined as 20 both for the case health as well as for the case environment, independently of the different evaluation algorithm. This is based on considerations that appear acceptable to each of the assumed cases and unacceptable (viz. Tables 11 and 12).

The result of the evaluation does not say anything about actual risks. Establishing the precautionary need should motivate the user to think about whether existing protective measures meet this precautionary need 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 nano-relevant 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 20 or less.

	Potential effect			
Potential e 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 B**	**Class B**	**Class B**

Table 11: Classification of nanomaterial that results in exposure via the air (aerosols <10µm).
A value 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 11 shows in the case of air exposure which combinations of parameters leads to which classification of the precautionary needs 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 11, Table 12 shows an example for the possible classification of an input into the environment via wastewater from a manufacturing process.

	Possible 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 12: Classification of the input of a nanomaterial into the environment in wastewater from a manufacturing process. A value 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) and stability ($W2_{A,V}$ =1), low maximum possible exposure (E2=1): 1 point
- High reactivity (W1=9) and stability ($W2_{A,V}$ =9), high maximum possible exposure (E2=81): 6561 points

For the environment:

- Low reactivity (W1=1) and stability ($W2_{U}$ =1), low input into the environment (E3=1): 1 point
- High reactivity (W1=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 precautionary need 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, rather only that there is 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 precautionary need, then protective measures or additional explanations 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 precautionary need enough, then additional data can be obtained which enable a risk assessment.

Active parameters:

The precautionary matrix considers the reactivity and the stability of a nanomaterial as the active 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]. However, a number of questions arise with the test strategy. For conventional chemicals, acute effects, for example, are examined as of delivery volumes of 1 tonne per year, wherein in the majority of cases, only oral intake being examined[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.

Table 13 lists possible further clarifications as a function of the reactivity and stability. Similar considerations are contained in the final report of the “REACH Implementation

[40] OECD, Six Years of OECD Work on the Safety of Manufactured Nanomaterils: Achievments and Future Opportunities; 2012.
[41] Guidance on registration, ECHA-12-G-07_EN, May 2012.

Project on Nanomaterials (RIP-oN 2) Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH)”[42].

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 13: Further clarifications for nanomaterials as a function of their stability and reactivity

Exposure of Humans:

The exposure of humans is estimated in the precautionary matrix from the daily quantity of nanomaterial which can come into contact with a person and the frequency with which this occurs. 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.

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. Against this background, SUVA has published

[42] Hankin S.M. et al: RNC/RIP-oN2/FPR/1/FINAL, 1st July 2011(page 141 ff).

recommendations for the protection of employees[43]. If the precautionary matrix indicates a precautionary need for employees, then the possible preventive measures listed by SUVA are to be examined and the most suitable measures for the particular case adopted.

[43] Nanoparticles in the workplace**,** Suva: http://www.suva.ch/startseite-suva/praevention-suva/arbeit-suva/branchen-und-themen-filter-suva/nanopartikel-arbeitsplaetzen-suva/filter-detail-suva.htm#/txt75521-73073

6 Appendix

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 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 NPRs 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 E2.1 and E2.3

For the determination of the threshold values for assessing parameters E2.1 and E2.3, the Suva threshold values in the workplace 2007 (MAK value) for diesel soot pollution has been used[44] (Suva, December 2013). This is 100 µg/m^3 for 8 hours' exposure in the workplace, related to the elemental carbon (EC) core of the particle, which is able to penetrate the alveoli. Since the density of these particles is very low, the amount of particles provides a very effective threshold value for daily pollution exposure: the same amount of denser particles (i.e. most of all particles) means fewer particles in the same volume, and so an overestimate of exposure. This is done deliberately to ensure that the risk of exposure to nanomaterials will never be underestimated.

[44] Diesel particles provide a good model system for nanomaterials: these are primary particles measuring a few nanometres across with aggregates of a few dozen nanometres and agglomerates up to 1 micrometre. Diesel soot was classified by IARC in 2012 as a carcinogen (http://www.iarc.fr/en/media-centre/pr/2012/pdfs/pr213_E.pdf) and must be minimised. However, diesel soot has, just as before, a MAC value. Although it cannot be assumed that all nanomaterials are carcinogenic, on precautionary grounds the definition of the limit value for nanomaterials was taken as the SUVA MAC value (2013) for diesel soot.

According to Freijer et al., 1997, the average volume of air breathed by a person during normal physical exertion can be calculated by:

$$Q_{inh} = 2.3 \cdot B_w^{0.65}\ m^3/day$$

where B_w is body weight in kg. To convert this to a value for 8 hours, the volume obtained must be divided by 3, since the equation gives the value for an entire day (24 hours).

Using an assumed average weight of 70 kg, the volume of air breathed during 8 hours is about 12 m^3. Multiplying this by 100 µg/m^3 gives an acceptable maximum quantity of 1200 µg of nanomaterial. In other words: If all nanomaterials enter the air and are then breathed in by an employee or consumer, these are still within the range of the MAK value. Since this is very likely to be a massive overestimate of the possible exposure, the value of 1200 µg can legitimately be termed a "low" material quantity.

This approach represents a rough approximation for estimating E2.1 and E2.3, whose values will have to be further refined and adapted during practical use of the precautionary matrix.

Strictly speaking, the amount of particles given for E2 only applies in air; however, it can be taken as an initial approximation of nanomaterials in all surroundings (air, liquid and solid matrices). E1 can be used to differentiate potential exposure according to these parameters. This may result in overestimations of exposure in liquid and solid surroundings.

6.3 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 (ca. 8 million), the considered annual volume is 580 x 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.

Notes: