

NANoREG

Safe-by-Design (SbD)

Concept

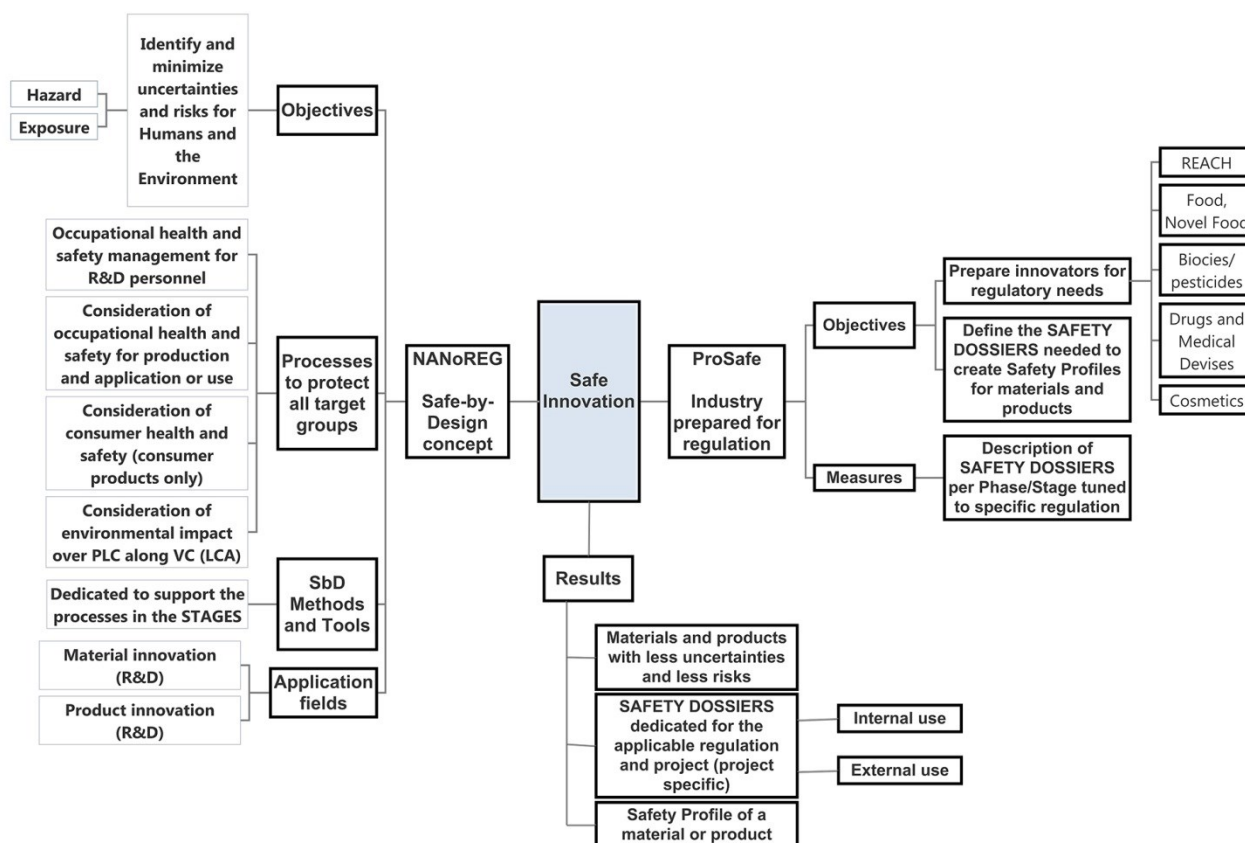
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Summary

Within NANoREG, a Safe-by-Design (SbD) concept is worked out. Within ProSafe, the SbD concept has been complemented with preparation of industry for regulation. Within Nanoreg2, the Safe-by-Design (SbD) concept will be combined with Regulatory Preparedness (regulators being prepared for innovation) into the Nanoreg2 Safe Innovation Approach (SIA).



Safe Innovation

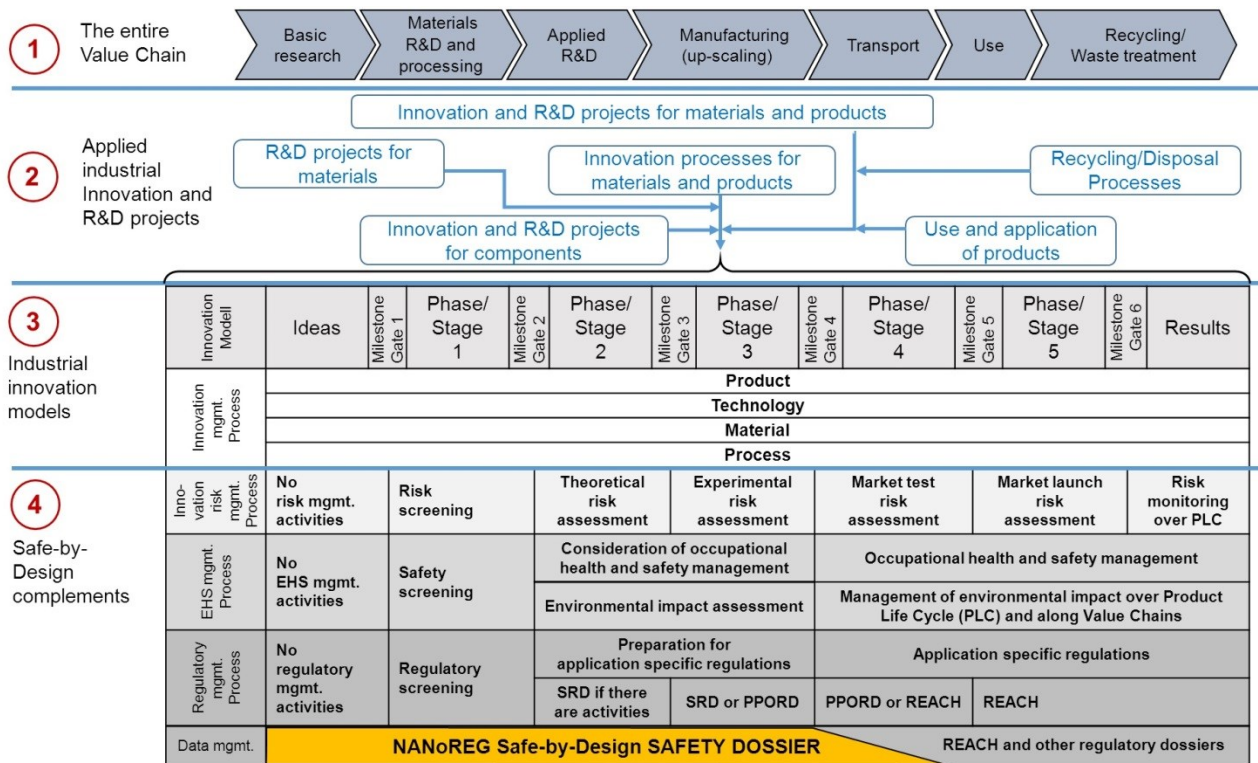
Safe Innovation aims at:

1. Safe-by-Design: Identified, reduced and managed uncertainty and risks of innovative materials, products and processes at the time of market introduction.
2. Industry prepared for regulation: Description of Safety Dossiers (SD) tuned to specific regulations as a basis for the Safety Profiles (SP) to improve communication along the value chain and with regulatory authorities.

Safe innovation will focus on the nanospecific characteristics and peculiarities of manufactured nanomaterials (MNMs) or products containing MNMs and related processes. MNMs are an example of highly innovative new materials fraught with a lot of uncertainties and thereby perceived risks for both the innovators and the regulatory authorities.

It should be noted, that uncertainties and risks cannot be reduced by a process alone. To reduce uncertainties and risks more and/or "better" data/information is needed. In addition, commonly accepted validated and qualified tools and procedures to obtain the data/information are necessary. Any process is merely a way of handling data and the SbD concept should improve the handling of safety data.

The conceptual basis for the SbD concept consists of the already industrially used innovation and risk management processes which are integrated into a coherent framework:



The NANoREG SbD concept

- ① Exemplary illustration of a value chain as a basis for the arrangement of the various innovation and R&D projects along this chain.
- ② Illustration of the arrangement of different types of Innovation- and R&D projects along the entire value chains of a material or product.
- ③ Exemplary illustration of an industrial innovation model with the different phases / stages and the corresponding milestones/gates in between.
- ④ Representation of the various sub-processes within the Safe-by-Design concept such as: Innovation risk management process, EHS management process, pre-regulatory and regulatory management process.

For the essential task of information handling and sharing, a safety dossier template was developed.

Within the SbD concept, the focus is on risk assessment in the early stages. For this purpose control banding tools (such as the Swiss Precautionary Matrix), decision trees and screening tools (such as the RIVM safety screening strategy {NANoREG D6.4}), exposure scenarios, life cycle maps and the safety dossiers could be used, amongst others.

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I. Introduction

1. Preface

Emerging technologies such as nanotechnology and new materials such as graphene can rely on huge public and private funding to stimulate their development into commercial utilization.

However, if and when innovative technologies, materials and products approach commercialisation, discussions about human and environmental safety between industry and regulatory authorities seem to threaten the investments.

Overall, the discussions are more about uncertainties rather than not knowing how to deal with identified risks. This leads to endless circular discussions frustrating all stakeholders. Even worse, these discussions prevent industry from achieving safe innovations in an efficient and feasible way.

Industry and regulatory authorities first have to rely on the precautionary principle to achieve the common objective of safe innovation.

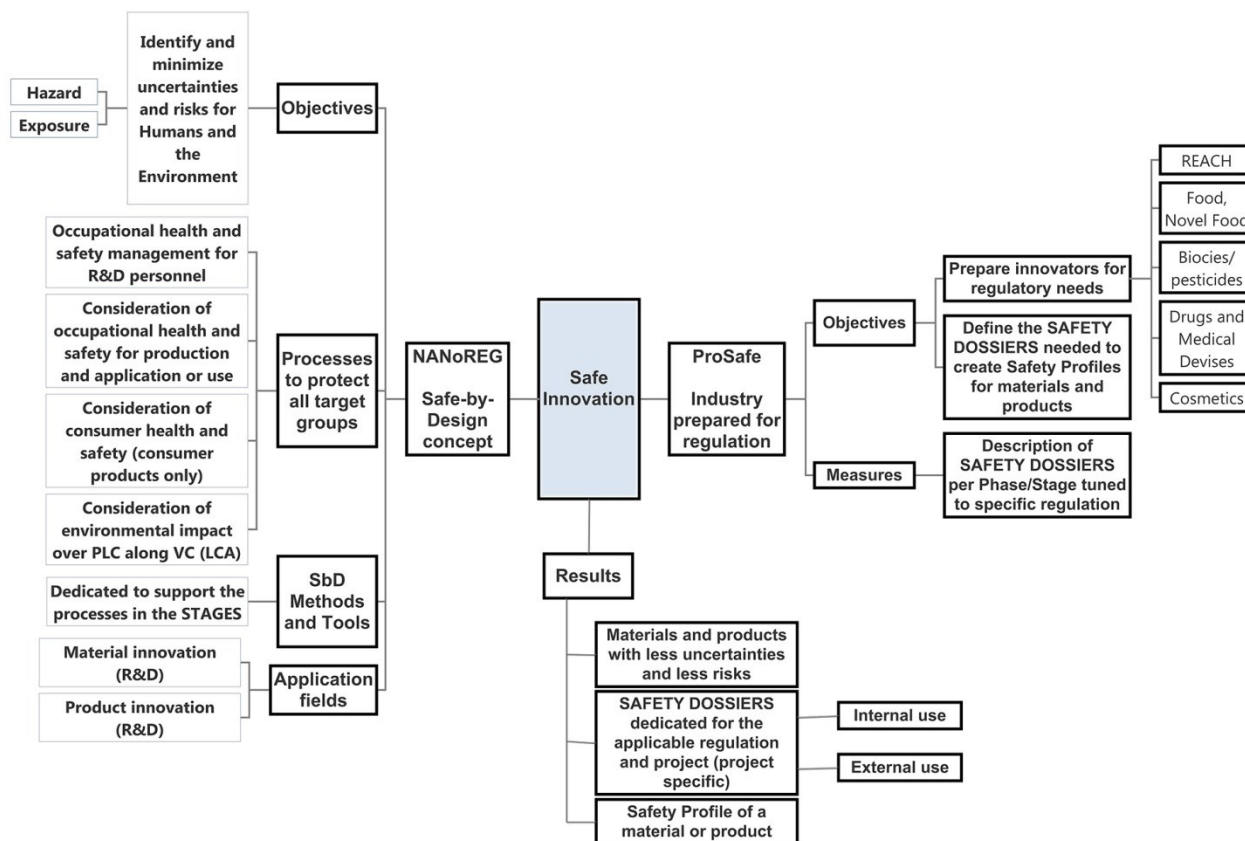


Figure 1: Safe Innovation

Within NANoREG and ProSafe, the Safe-by-Design (SbD) concept (described in this paper) leading to Regulatory Preparedness of industry is worked out (**Figure 1**):

1. SbD: Identified, reduced and managed uncertainty and risks of innovative materials, products and processes at the time of market introduction.
2. RP: Elaboration of regulation specific Safety Dossiers (SD) as a basis for the Safety Profiles (SP) to improve communication along the value chain and with regulatory authorities.

The design of an innovation and risk management process alone - as envisioned in the SbD concept - cannot completely eliminate uncertainties or risks; it can only help to reduce them.

In addition, to improve the present situation, it is inevitable that there must be a closer collaboration between industry and regulatory authorities within a generally accepted overall framework containing common standards.

Such a framework would be the Safe Innovation Approach (SIA). Within NanoReg2, the SbD concept will be expanded with the regulation oriented Regulatory Preparedness (RP) into the overall Safe Innovation approach (SIA). Within this framework, industry and regulatory authorities should join their expertise to support safe innovations.

2. Important remarks and definitions

It should be noted that it is difficult if not impossible in most cases to prove safety. Also, a common misconception is that absolute safety (or freedom of risks) can be achieved: risks can only be reduced and weighed against each other (because avoiding one risk often leads to exposure to another risk) as well as costs associated with risk reduction can be compared to the costs of the risk itself / the risk effect.

The SIA will especially consider the characteristics and peculiarities of Manufactured Nano Materials (MNMs¹) and products containing MNMs because they are often fraught with a lot of uncertainties and perceived risks for both the innovators and the regulatory authorities. But, as already mentioned above, the problems arising from the information used (with respect to amount, quality etc.) cannot be solved by process design, but only with more and better data.

Unfortunately, there is no generally accepted definition and no common understanding about safety, uncertainty, what constitutes a nanomaterial etc. For general nano-related definitions the Consolidated Framework for EHS of Manufactured Nanomaterials is used.²³

One final remark: it must be understood that even if no MNM-related risks are present and/or if all nano-specific regulations are fulfilled, then health risks related to the dissolved materials need to be assessed and substantiated with relevant studies. Other risks may be present and other regulations may still have to be fulfilled. Thus, other risks and uncertainties must also be considered and possibly reduced as well as other regulations fulfilled!

¹ Throughout the document, only MNM or MNMs will be used as an abbreviation.

² http://www.siinn.eu/bin/D2.6_Consolidated_Framework_for_EHS_FinalVersion.pdf

³ JRC „NANoREG harmonised terminology for EHS assessment of nanomaterials”, 2016

3. Industrial processes, enterprise value chains and product life cycles

3.1. Value chains and product life cycles

The different processes and activities of a given business unit, company, industry etc. constitute their respective value chains containing the different value chain steps:

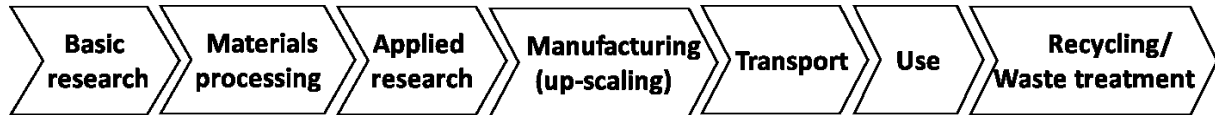


Figure 2: An exemplary value chain with standard value chain step types

Although there is a myriad of different activities and processes, they belong to only a small number of standard value chain step types corresponding to the typical product life cycle stages through which a product goes during its life cycle. Thus, value chains focus on the activities of an enterprise whereas products are the focus of a product life cycle.

The position of a value chain step in a value chain is given relative to one specific step associated with one specific company:

Upstream refers to any activity in a value chain step supplying the precursors of a company's products, i.e. the activities of its suppliers and their suppliers up to and including the extraction of natural resources as the first step of any material value chain: e.g. raw material extraction, precursor production.

Downstream refers to any activity in a value chain step using a company's products, i.e. the activities of its customers and their customers down to and including the consumers: e.g. product application, use, fate of a product/material.

Recycling closes the loop by converting used goods back into raw materials; i.e. the recycling value chains run antiparallel to the normal value chains.

3.2. Industrial processes relevant for SbD

There are two types of MNM-related and thus relevant industrial activities and processes.

1. **Industrial innovation activities and processes** create the knowledge and knowhow of/for the large scale industrial activities and processes with the standard value chain step types/ life cycle stages: applied R&D, product and process development etc. Any risks for the R&D personnel have to be managed by the existing occupational hazard management systems as well as any prudent GLP (Good Laboratory Practice). Hence, current industrial innovation processes are used as the basis for the development and implementation of the SbD concept. Also, in this phase, waste handling needs to be in line with the regulations.

2. **Large scale industrial** activities and processes convert precursors to products or vice versa (recycling) with the standard value chain step types/life cycle stages: extraction of natural resources, in-bound logistics, production incl. formulation⁴, packaging, out-bound logistics, transportation, trade, professional and consumer application or end use, and waste-handling (collection, storage, processing). But, the large scale processes have to be considered during an industrial innovation concept, with or without SbD.

In the past, the industrial innovation and large scale activities and processes were closely linked within one company; nowadays, with the ever more collaborative value chains (e.g. CRO or CMO, i.e. Contract Research Organisations or Contract Manufacturing Organisations), knowledge sharing becomes ever more important to avoid unnecessary risks.

Even though the large scale industrial activities and processes pose the real risks – large amount of MNMs produced by large scale production – they must be considered during the innovation activities and processes: Once the development is completed, only limited design freedom and thus risk management options remain.

4. R&D in non-profit organisations

Research and development in non-profit organizations (NPO) (such as universities, research institutions etc.) is usually conducted in small scale by professionals. Nevertheless, occupational hazard management systems and waste management have to be in place.

⁴ Formulation is the process of “mixing” ingredients together to obtain a new product (e.g. drug or paint or plastic). Often, the formulation is separated from the production of the ingredients and formulators may form an own (sub-) branch (e.g. pharmaceutical industry formulates drugs, plastic processing industry, adhesives, paints and coatings etc.) separate from the chemical industry proper producing “only pure ingredients”.

II. The Safe-by-Design (SbD) concept

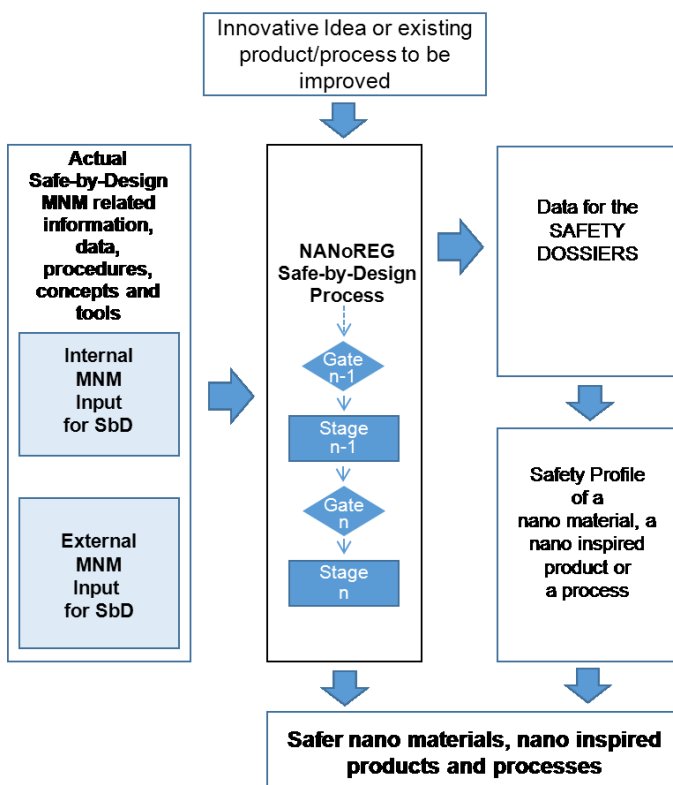
1. Objective and scope of the SbD concept

The SbD concept for R&D projects in industrial innovation processes should help with the transfer of the precautionary principle into practical use. This includes precautionary measures and tools for the timely identification of uncertainties and potential risks as well as timely actions to reduce or eliminate these uncertainties and if possible the respective risks at the earliest possible and/or feasible stage of development.

Thus, the aim of an implemented SbD concept can neither be proven nor be absolute safety! Instead, an implemented SbD concept should help to reduce uncertainties and risks (this includes total reduction via risk exclusion and/or avoidance). In addition, the concept should help to discuss/draft/show risk management options together with their associated costs, help to determine the costs of a risk and its effect, and help to detect knowledge gaps / to determine missing information.

2. SbD, industrial management processes and safety dossiers

There must be a strict differentiation between the Safe-by-Design concept and its industrial management processes on the one hand and the MNM-related data the processes are using on the other hand:



The SbD process integrates different industrial management processes; these and thus the concept remain relatively unchanged over time and always use the best currently available data no matter the source.

Whereas the concept can be applied for many different products, companies and industries – albeit with slightly differing industrial management processes – the data is case specific, i.e. for every product a new data set is needed and will be collected in safety dossiers.

MNM-related data is continuously generated in industrial R&D and academia to be used for many different purposes one of which would be the Safe-by-Design concept and its industrial management processes; in addition, a lot of MNM-related data has yet to be generated. Data is used by industry, academia and regulatory authorities alike.

Figure 3: The SbD concept incl. industrial management processes, data, procedures, and safety dossiers of the material/ product under development.

3. The Safe-by-Design (SbD) concept

To facilitate the industrial implementation of the SbD concept, it is not intended as a substitute for currently used industrial innovation processes. Instead, it integrates currently used management processes for innovations, risks, EHS, regulatory affairs and data handling:

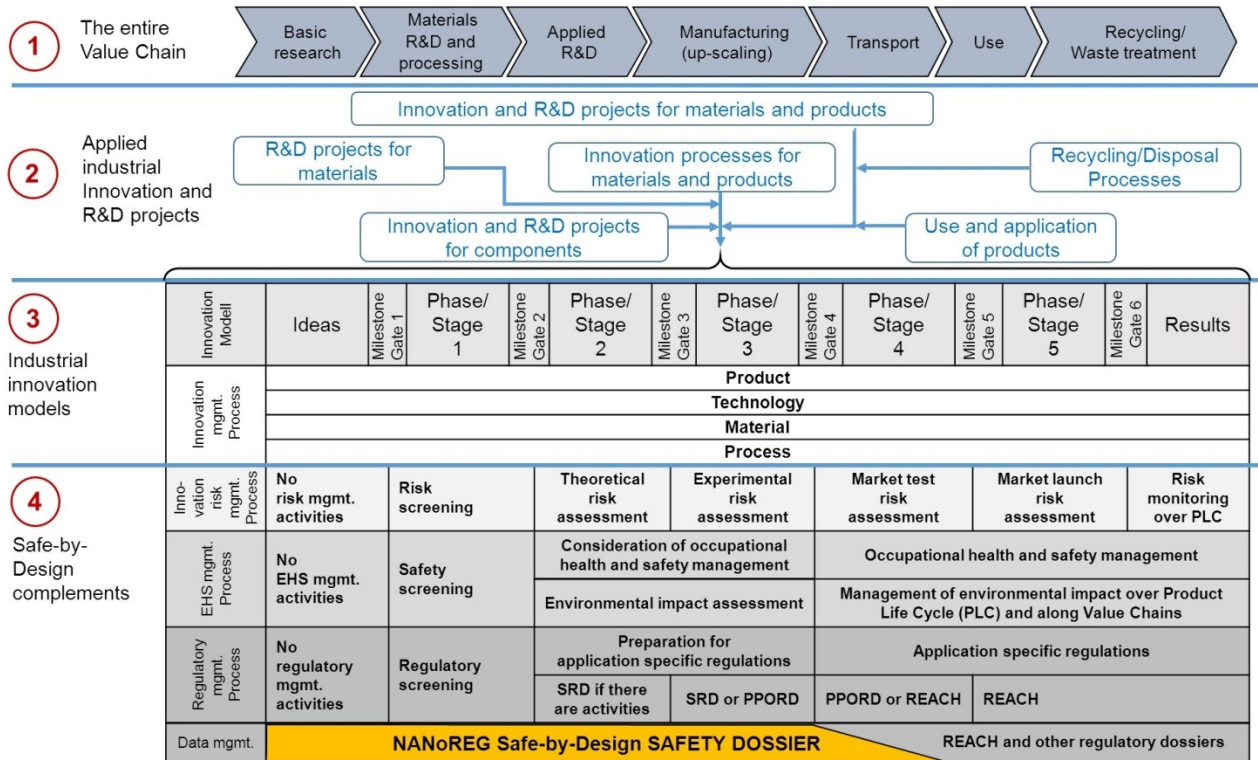


Figure 4: The SbD concept

- 1 Exemplary illustration of a value chain as a basis for the arrangement of the various innovation and R&D projects along this chain.
- 2 Illustration of the arrangement of different types of Innovation- and R&D projects along the entire value chains of a material or product.
- 3 Exemplary illustration of an industrial innovation model with the different phases / stages and the corresponding milestones/gates in between.
- 4 Representation of the various sub-processes within the NANoREG Safe-by-Design concept such as: Innovation risk management process, EHS management process, pre-regulatory and regulatory management process.

4. SbD and value chain/life cycle

Within the SbD concept, an innovation project has to consider the whole life cycle of a product along an entire value chain or a part of it with respect to a specific project or a company. In addition, not only a MNM or a product containing a MNM has to be analysed but their production processes and uses/applications; see **Figure 5** (on the next page). To receive the "picture" on an entire value chain, information from the different projects along a value chain is needed. For that purpose, sharing of information amongst stakeholders is a prerequisite.

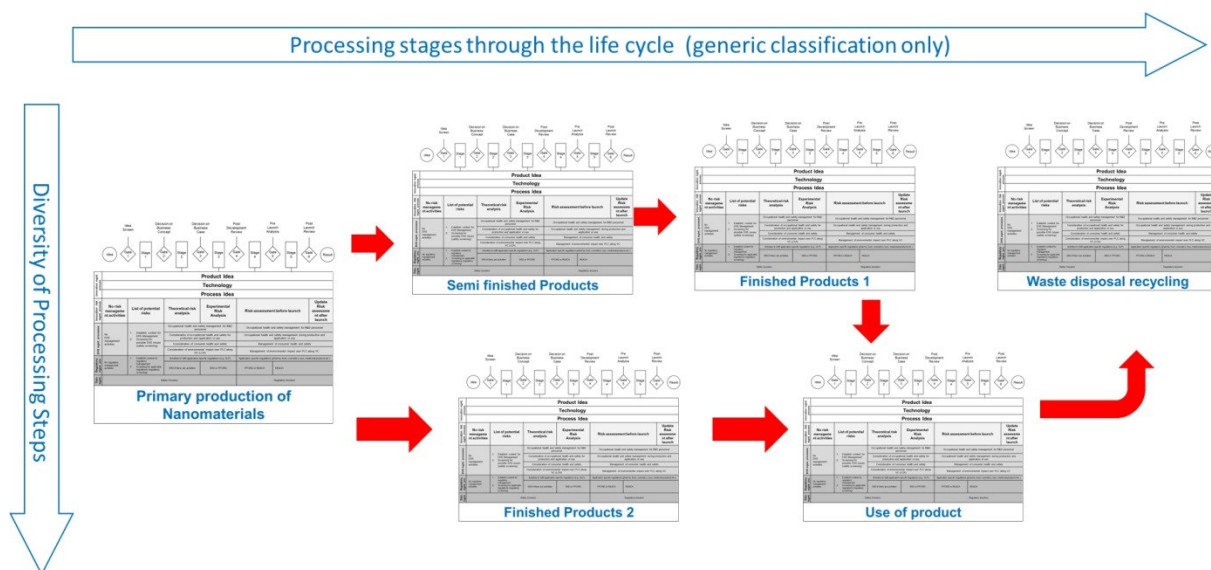


Figure 5: The SbD concept for different life cycle stages

5. Uncertainties and uncertainty reduction

Because ambiguous or missing or faulty information/data causes uncertainties, they also cause risks. Often, uncertainties hinder the identification and proper assessment of potential risks:

- Repeatedly, the problem is not the risk analysis, but the exhaustive, systematic and methodical identification of potential risks or risk areas. Evidently, before any risk can be theoretically or experimentally assessed, it has to be identified!
- With the current knowledge about MNMs, there is also a problem with the theoretical and the experimental assessment of risks due/leading to a lack of information/data. If a risk cannot be properly assessed, then the worst case is assumed, which in turn may terminate a complete project.

Hence, there are certain problems with the currently used industrial risk analyses which cannot be solved by the design of the SbD concept (process design), but only with:

- more and/or more reliable/objective information/data,
- the right tools for the problem at hand,
- altering the way the processes are run for an individual innovation project (i.e. flexible adaption and fit size of processes to extent of risks),
- being aware of case specific uncertainties and risks (e.g. the similarities and differences between macro- and nano-scalar materials).

For these reasons, the SI approach and the SbD concept:

- will be supplemented by a toolbox containing standard, adapted and specific tools,
- will be supported by nano-related data being collected from various sources (National and EU projects, academia etc.),
- will be run in case studies' demonstrators and dedicated projects providing process and implementation knowhow.

III. Industrial management processes in the SbD concept

1. Structured innovation management processes

In industry, some sort of structured innovation management process for R&D projects (to develop products, processes, technologies etc.; for different TRLs e.g. basic and applied research etc.) is the de facto standard today. Consequently, one of the most common structured innovation processes, the stage gate model⁵, is the backbone for the SbD concept.

1.1. The stage gate innovation model: Stages and Gates

During the **stages** the proper work is carried out: ideation, development, tests, up-scaling etc.

In each **gate** so-called gatekeepers decide on the fate of an innovation project: proceed, alter (proceed through gate but with minor alterations in the next phase), recycle (repeat the stage with major alterations), on-hold (wait for other projects, technologies, licenses, regulations etc.), and terminate. The decision is always based on balancing costs and benefits.

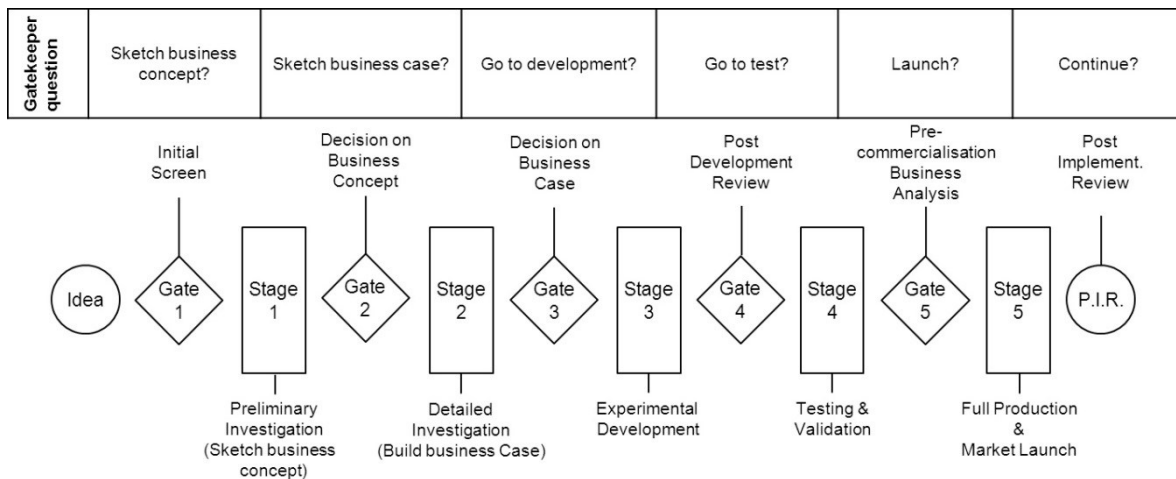


Figure 6: The stage gate innovation model

1.2. IT-tools used for structured innovation processes

Today it is state of the art to support structured innovation processes with (adapted) proprietary (such as Gensight®) or completely homemade IT-tools, esp. in bigger companies. Nonetheless, also the smaller companies use some IT support e.g. Gantt charts or Excel® lists.

Thus, the adaption of the currently used IT-tools to the Safe-by-Design concept is underway; also with respect to data formats, such as ISA TAB, etc.

⁵ Dr. Robert G. Cooper: <http://www.bobcooper.ca/about-dr-cooper>

1.3. *Stages and Gates in real life*

Whether, how and to which extent a stage gate process is run depends on the scope of an R&D or innovation project:

- For smaller projects stages 1 and 2 and/or stages 3 and 4 can be merged; with only 1 idea for a smaller project gate 1 may be merged with gates 2 and 3.
- The stage gate process can be run in two or more sequences and these also in parallel: E.g. During the first stage gate process /innovation project a technology is developed, during a second a product platform using this technology (there might be other platforms and products developed in yet other stage gate processes) and in the third every geographical business unit develops a product for its market's requirements (i.e. several daughter projects run parallel) (**Figure 5**).
- The stage gate process can even contain built in loops within a stage e.g. if certain criteria are failed.

Basically, there are different generalised types of stages which can be combined ad libitum:

- Idea phases (generate ideas)
- First conceptual phases (find technical solutions for 1 idea, screening phases)
- Second conceptual phases (development planning for 1 technical solution)
- Different development stages (Basic research, Technology development, System development)
- Market testing phases
- Initial market phases (up until the Post Implementation Review PIR)

In addition, a couple of parallel processes could be drawn: laboratory work (functionality, IP value chain), marketing, sales, production (physical value chain), safety (also lab work)/risk etc. etc. i.e. like a puzzle, not necessarily symmetric.

2. Risk management processes

Within NANoREG the ISO standard specification family ISO 31000:2009⁶ for risk management is used. Risk management is split into risk assessment (incl. risk identification and formulation, analysis, evaluation) and risk treatment.

ISO also designed its ISO 21500 Guidance on Project Management standard to align with ISO 31000:2009. This is an important remark, because proper project management is a prerequisite and necessity for a successful innovation project.

In FP7 EU-projects like MARINA, GUIDEnano and SUN specific risk assessments are developed.

⁶ 2009 refers to the publication date November 13th 2009 and is the newest version of ISO 31000: ISO 31000:2009 contains risk management implementation principles and guidelines. ISO/IEC 31010:2009 contains risk management and assessment techniques. ISO Guide 73:2009 contains the vocabulary of risk management.

2.1. Risk of an innovation project versus risk of an innovation project's outcome

There are two objects within an innovation project which can have a risk:

- An innovation project is subjected to project management risks (missing due dates, failure to achieve the goals of a project etc.)
- The outcome of an innovation project, i.e. a material, product or process, can have risks relating to its properties (e.g. toxicity) or use (e.g. financial return, exposure, etc.).

One problem here is that the risk of an outcome could be the risk of the innovation project itself: e.g. a too high toxicity of a potential product can kill the complete project.

2.2. Uncertainty and risk: risk definition and quantification

According to the ISO standards, a risk is the “negative or positive or deviation from the expected effect of uncertainty on objectives”. Hence, risks are the consequences of uncertainties and uncertainties are the cause of risks. Risk is also often described by an event, a change in circumstances or a consequence.

In addition, a risk can be split into the probability of risk occurrence (e.g. exposure) and the risk effect (e.g. costs, toxicity, hazard) once it occurs. Thus, there can be:

- Uncertainty about the risk occurrence expressed as a range of risk probabilities (if a single probability was stated without a safety/error margin and without a caveat or assumption, then the uncertainty must be 0%!).
- Uncertainty about the risk effect once it occurs.

Because ambiguous or missing or faulty information/data causes uncertainties, they also cause risks. Hence, to reduce uncertainties and risks, more or more reliable/objective information/data is needed.

For the purpose of a risk assessment, values for probability for a negative effect and impact of the effect – e.g. on a scale from 1-9 – are derived in a risk analysis and the risk (R) itself then is mathematically expressed as the product of probability of risk event (P) and effect of risk event (E): $R=P \cdot E$. The toxicological approach considers a risk as a combination of expected exposure and hazard of the compound.

Uncertainty (U) can be included in this formula as additional weighing factor either overall ($U \cdot P \cdot E$) or for both probability (P) and effect (E) ($U \cdot P \cdot U \cdot E$) or summand ($P \cdot E + U$).

2.3. Types of risks and their general risk treatment options

In a risk assessment, once risks have been identified, analysed and evaluated, all techniques for the risk treatment fall into one or more of four major categories from best to worst option (or biggest to smallest risks):

Typical risk type	High impact and High probability	Low impact and High probability	High impact and Low probability	Low impact and Low probability
Risk treatment option	Risk Avoidance	Risk Reduction	Risk Sharing	Risk Retention
What to do with the risk?	eliminate withdraw from avoid involvement	optimise mitigate (impact) reduce probability	transfer outsource insure and budget	accept and budget

Table 1: Risk types and their treatment options

SbD allows a selection of the best options. The followings aspects need to be looked at in any case in the course of a SbD approach:

Risks with low occurrence but high impact are often overestimated because of their high impact (and the public discussion tends to focus on these risks with nuclear energy being the prime example for this). These risks tend to be perceived as catastrophes. With respect to hazard, these types of risks should be thoroughly examined for both acute and chronic toxicity (even though it's probably more long-term effects of acute toxicity than true chronic toxicity).

In contrast risks with low impact but high exposure are underestimated because of inurement. I.e. people tend to neglect the effect of exposure and tend to focus on the impact of a risk, be it consciously or unconsciously. With respect to hazard, these types of risks should be thoroughly examined for chronic toxicity (with acute toxicity usually being low).

A high exposure or a high hazard in itself does not exclude a MNM a priori; instead, they should be thoroughly examined and proper risk treatment options should be developed (e.g. constrict applications of high hazard MNMs to those with controlled and/or very low exposure; prescribe the usage of personnel protection equipment to reduce the exposure to a only slightly hazardous MNM).

In the context of chemicals, it should be noted that a high reactivity/functionality is often correlated with high hazardousness and thus it is impossible to substitute all hazardous chemicals; this is often completely ignored in the public discussion by the laymen.

2.4. *Costs in the risk analysis*

Costs of measures to reduce a risk have a direct impact on the remaining risk: the higher the costs, the lower the remaining risk. However, the costs of risk reduction have to be balanced with the costs of the remaining risk to find the most efficient solutions (e.g. a reduction of a risk to zero is usually inefficient because of exponentially increasing costs).

As can be seen from **Table 2**, the earlier a potential risk is addressed, the smaller the necessary costs for a given risk-reduction or for a given remaining risk potential.

	Risk reduction investment	Benefit of investment	Remaining risk	Remark
Early	small	large	Small	Small investments have large benefits
in time	medium	medium	Medium	
Late	large	small	Large	Large investments have small benefits

Table 2: *Cost of uncertainty and risk reduction*

Also, if somebody further down the value chain obtains windfall benefits of upstream risk reduction, the price setting or market power (i.e. the power of accessing the windfall benefits) has to be taken into consideration. A similar situation arises if somebody downstream demands a higher than necessary risk reduction with which higher benefits are possible.

Figure 7 shows that:

- The costs of uncertainty reduction and the risk potential of each stage need to be treated individually.
- There are costs attached to achieving some pre-defined safety level.
- Every risk management option has some investment cost attached to it and that there always will be a residual risk remaining which itself can be monetised.

In addition, every assessment is based on current knowledge which later on can be superseded by newer knowledge.

Moreover, risk-benefit is weighed differently in different risk assessments: e.g. In the case of drugs with MNMs side effects are accepted to a certain extent, whereas this is not the case for most consumer applications of MNMs.

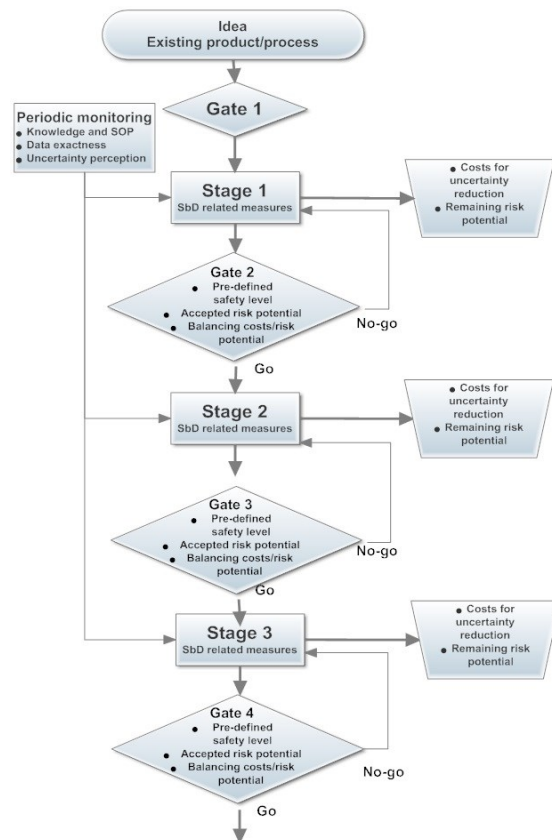


Figure 7: Cost and the SbD processes

The funnel graph (**Figure 8**) visualises in a nutshell for each scenario and risk the associated

- uncertainty (opening width of funnel),
 - risks levels and costs for risk reduction (both on y-axis)
- along the innovation process/development project or against time/amount of knowledge (x-axis).

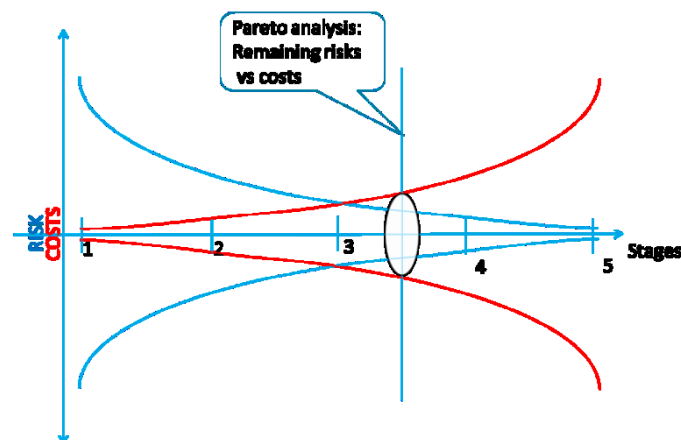


Figure 8: funnel like development of costs and risks per stage

3. Risk management in the stage gate model

In some companies, a risk management process (environmental, health and safety {EHS}, economic, technical and other risks) is already implemented in the stage gate processes.

Obviously, a full-fledged risk management process like a full-fledged stage gate process is only carried out for major projects, not for minor alterations. Hence, the process design must make sure that small but risky alterations (such as label changes) are subjected to an appropriate risk management process. On the other hand, there must not be too much red tape esp. for smaller and riskless projects.

Innovation Modell	Ideas	Milestone Gate 1	Phase/ Stage 1	Milestone Gate 2	Phase/ Stage 2	Milestone Gate 3	Phase/ Stage 3	Milestone Gate 4	Phase/ Stage 4	Milestone Gate 5	Phase/ Stage 5	Milestone Gate 6	Results
Innovation mgmt. Process	Product												
	Technology												
	Material												
	Process												
Inno- vation risk mgmt. Process	No risk mgmt. activities	Risk screening	Theoretical risk assessment	Experimental risk assessment	Market test risk assessment	Market launch risk assessment	Risk monitoring over PLC						

Figure 9: Current industrial innovation and risk management processes

As mentioned in chapter 2, innovation risk management is split into risk assessment and risk treatment. No risk identification must be carried out prior to stage 1: in gate 1, mainly external (e.g. economic potential) and internal (e.g. capabilities, strategic fit) factors of an idea should be considered. The risk assessment then starts after gate 1 in stage 1. It is a living, iterative process incorporating ever more specific data from stage to stage.

Risk assessment in the stages:

During stage 1 potential risk situations and scenarios are formulated as well as risks identified and listed for gate 2.

During stage 2 a theoretical (i.e. only using subjective and existing objective data) risk assessment is carried out and risk treatment options are prepared for gate 3.

During stage 3 the risk assessment and risk treatment options are updated with the development results for gate 4.

During stage 4 the risk assessment and risk treatment options are updated with the results of market testing and upscaling for gate 5.

During stage 5 the risk assessment and risk treatment options are updated with the feedback from the market introduction for gate 6, the post launch review (PLR).

Risk treatment in the gates, decision on risk treatment options:

For gate 2, the gate keepers only have a list of potential risks and formulated risk situations. Their main task is to check the formulated situations and scenarios and esp. the assumptions made therein. Certain risks such as regulatory risks may warrant special attention in the form of additional approval or additional processes.

In each gate from gate 3 on, in addition to checking the assumptions of the risk assessment, the gate keepers have to decide on the risk treatment options (balancing of risk reduction costs with costs of remaining risk) for each risk and weigh the costs of the risk against the (monetary or monetised) benefits resulting from the innovation project. In a gate, one or several specific risks or the whole risk assessment can be the reason why a project is terminated, put on hold, altered or recycled.

4. Innovation risk management in the development process/project

The innovation risk management can be split into a late and an early part of the development process/project:

- The early - i.e. premarket and thus preregulatory – stages in which data/information quality is typically poor (i.e. more subjective and qualitative) esp. with respect to exposure, but the design freedom is bigger. This early part is the focus of SbD.
- The later stages – when a product is (at least partially) on the market and thus is regulated – in which there should be sufficient (quantitative) data (also for exposure), but there is less design freedom if at all, and thus nearly no SbD. This late part may be non-existent if there is consecutive second development process
- There is a certain overlap starting with the first development phase and ending with the post implementation review (PIR) after there is (almost) no development work left (of course for tailor made products, a certain amount of development will always be carried out during the time the products are on the market). Focus is on controlling the risks and acting accordingly (which again can lead to some development work).

4.1. The early development part: non or partially quantitative risk assessment

Obviously, in the early stages the challenge is to perform a sufficient risk assessment with a low amount of data to shift from an ex post to an ex ante analysis. Once some hazard information is available (database, grouping, experiments, MNM supplier etc.), exposure scenarios (with exposure modelling and “rules of thumb”) and rudimentary risk assessments can be carried out. Real life exposure data can only be collected once test under real life conditions have started. Still, experiments can be carried out earlier, see **Table 3**.

		stage 1	stage 2	stage 3	stage 4	stage 5
R&D personnel	Hazard	control banding	Existing human toxicology	experimental human toxicology	market human toxicology	market human toxicology
	Exposure	control banding	exposure scenarios with existing data	exposure scenarios with exposure data	exposure scenarios with exposure data	exposure scenarios with exposure data
Production workers	Hazard	control banding	control banding	Existing human toxicology	experimental human toxicology	market human toxicology
	Exposure	control banding	control banding	exposure scenarios with existing data	exposure scenarios with exposure data	
Downstream workers	Hazard	control banding	control banding	Existing human toxicology	experimental human toxicology	market human toxicology
	Exposure	control banding	control banding	exposure scenarios with existing data	exposure scenarios with exposure data	
Consumers	Hazard	control banding	control banding	Existing human toxicology	experimental human toxicology	market human toxicology
	Exposure	control banding	control banding	(exposure scenarios with existing data)	(exposure scenarios with exposure data)	
Environment	Hazard	control banding	Existing ecotoxicology data	Experimental ecotoxicology data	Market ecotoxicology data	Market ecotoxicology data
	Exposure	control banding	exposure scenarios with existing data	exposure scenarios with exposure and existing data	exposure scenarios with exposure data	

Table 3: Possible approaches to risk assessment under data constraints.

This challenge is esp. pronounced for developers of de novo nanomaterials because they don't even have hazard data and, making matters worse, may only have a limited amount of application knowhow without which exposure is difficult to assess.

By contrast, the companies formulating and incorporating nanomaterials into products are not only closer to (specific) applications and thus exposure data, but also should have sufficient hazard data of the pure nanomaterials from the beginning; however, their hazard challenge is to assess the formulated or incorporated nanomaterial.

Even further down the value chain, the hazard data of both the pure and formulated nanomaterial should be known. To ensure this flow of information, collaboration and data sharing along the value chain is necessary; this should be achieved with the safety dossier.

Early phase risk assessment activities (precautionary measures) before the first quantitative risk assessment include:

- Risk identification and formulation
- Qualitative or semi-quantitative risk assessments with control banding tools (e.g. Swiss Precautionary Matrix)
- Exposure scenarios
- Screening for risk potentials

4.1.1. Risk identification and formulation

Before any risk can be subjected to a risk assessment, it has to be identified. A life cycle map may help in detecting potential risks esp. for environmental exposures; see **Figure 10** and **Figure 11** (on the next page).

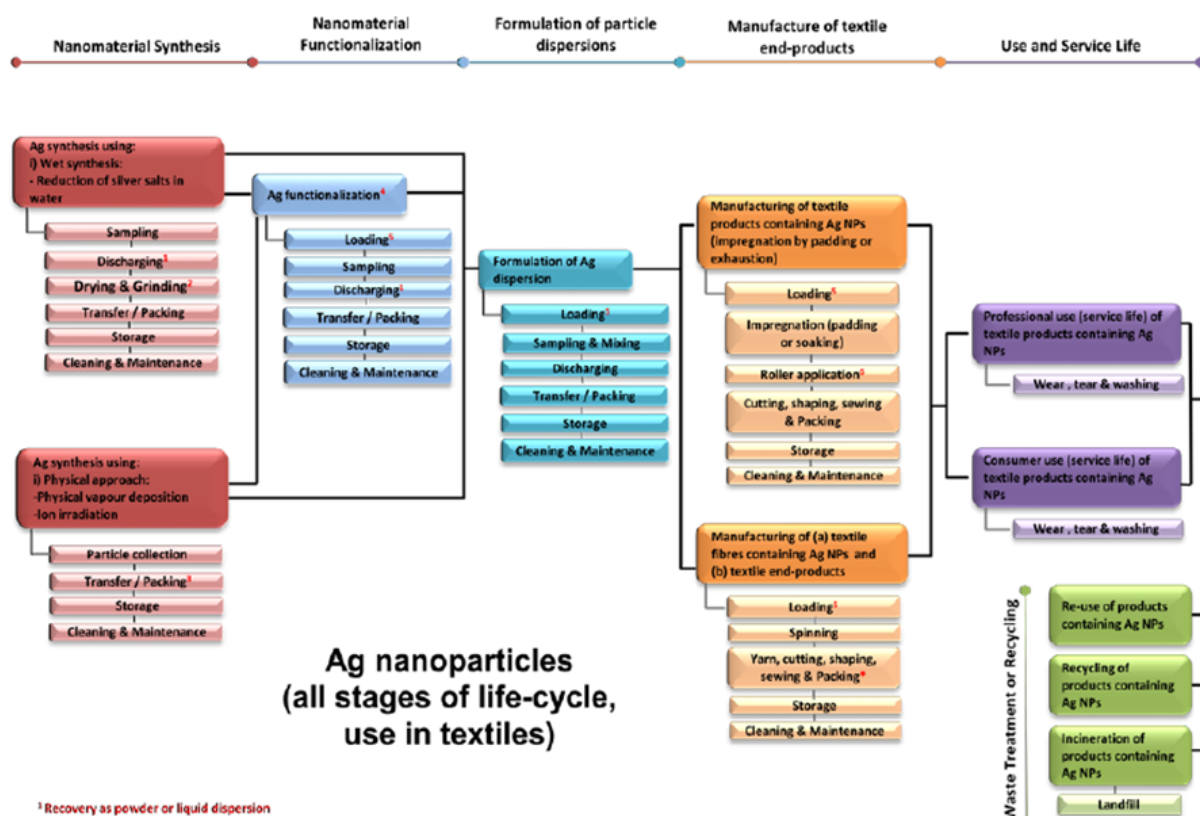


Figure 10: Life cycle map for Ag nanoparticles used in textile⁷

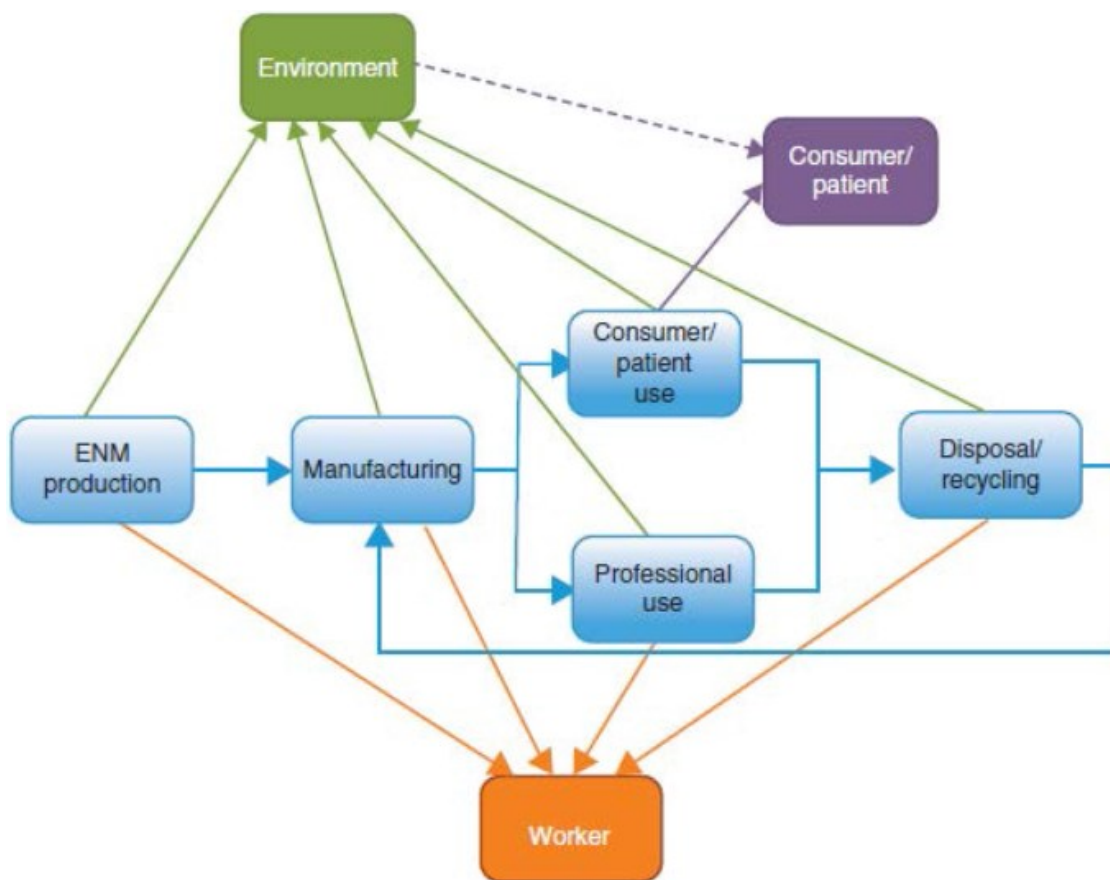


Figure 11: Life cycle stages and potential exposures of workers, consumers, and the environment⁷

To identify risks, typical situations and scenarios in the life cycle of a product have to be created. These scenarios should contain the most relevant (“bad”) situations of the product whilst it is produced, formulated, applied, used and recycled. Often, the problem lies in the risk identification.

Risk assessment is further complicated as MNMs can undergo intended or unintended changes during formulation, incorporation into products and release: In case nanomaterials dissolve into ions or molecules, a risk assessment for these substances has to be carried out as well.

4.1.2. Qualitative or semi-quantitative risk assessment with control banding

In the early stages of an innovation process, the amount and quality of data is insufficient to conduct a quantitative risk assessment. Thus, Qualitative or semi-quantitative risk assessments have to be carried out.

For a qualitative or semi-quantitative risk assessment the control banding concept has been developed. Several MNM specific control banding tools have been generated. These tools are based on a series of exposure determinants and hazard factors/ potentials that are relevant in environmental, occupational and consumer settings, respectively. Not all settings can be investigated with every tool.

⁷ NANoREG, D 3.1 :Gap analysis report, identifying the critical exposure scenarios within the key value chains

4.1.3. Exposure, exposure scenarios and exposure targets

Exposure for a specific risk analysis is usually investigated with the help of relevant exposure scenarios with potentially high exposures. They are the same or very similar scenarios like the ones formulated for risk identification. Realistic user scenarios are key tools in this context.⁸

There are no really specific nano-related exposure scenarios because the situations leading to exposure are not nano-specific. The amount of exposure, however, may vary in the same circumstances due to the specific properties of MNMs: spilling of a material may lead to a higher exposure for nanomaterials because of their smaller particle mass and thus their higher flowability/dispersibility.

Each exposure scenario contains human (occupational, i.e. industrial use by workers' and professional⁹ users, and consumer) and environmental exposure targets. From a liability and thus from a prevention (or SbD) perspective, the responsibility for the exposure of the different exposure targets depends on the exposure target and the type of use.

Moreover, the potential control of exposure varies between the uses: E.g. professional exposure to VOCs (Volatile Organic Compounds) is usually regulated (with the obedience to the regulation being the responsibility of the employing legal entity), whereas consumer exposure to VOCs is not regulated (directly) (or only indirectly by regulating the maximally allowed VOC content of a product).

The reason may be that intended professional use and application is narrowly defined and assumed to be carried out by professionals (assumed to have background knowledge about risks and dangers of what they are using) in a controlled environment/under controlled circumstances, whereas consumer use by laymen is more unpredictable and thus more difficult to (directly) regulate.

In case a substance is metabolised or transformed, the metabolisation or transformation must be taken into account in the risk assessment of a substance. This implies that the presence of a metabolising/transformation capacity in a test system is pivotal for the assessment of a substance's hazard.

4.1.4. Safety screening strategy: specific risk potentials for MNMs

Different approaches and strategies for the risk assessment of nanomaterials are being developed in projects such as MARINA, GUIDEnano, ITS NANO and NANoREG. Although the approaches have different aims and expected users, there is overlap between the different approaches.

Using the overlapping elements, six risk potentials (solubility/dissolution rate, stability of the particle coating, accumulation, genotoxicity, immunotoxicity, ecotoxicity)¹⁰ have been identified for a safety screening strategy within the risk assessment of nanomaterials by RIVM. Each risk potential can be characterised by different parameters and each parameter can be used to characterise more than one risk potential. For each parameter one or more measurement methods could be used.

⁸ Assessing health and environmental risks of nanoparticles current state of affairs in policy, science and areas of application. RIVM Report 123456789/2015

⁹ Industrial use is the industrial processing of goods; professional use is the small scale application of final goods (e.g. painter applying coatings).

¹⁰ NANoREG I Project: Deliverable D 6.4: Inventory of existing regulatory accepted toxicity tests applicable for safety screening of MNMs

The aim of this RIVM safety screening strategy is to give direction to further steps within the risk assessment process. Hence, not all of the risk potentials are necessarily considered at the beginning of an innovation project (or at all) and not all parameters may have precise values initially. Thus, the potentials are open to a stepwise approach for assessing these risk potentials of MNMs:

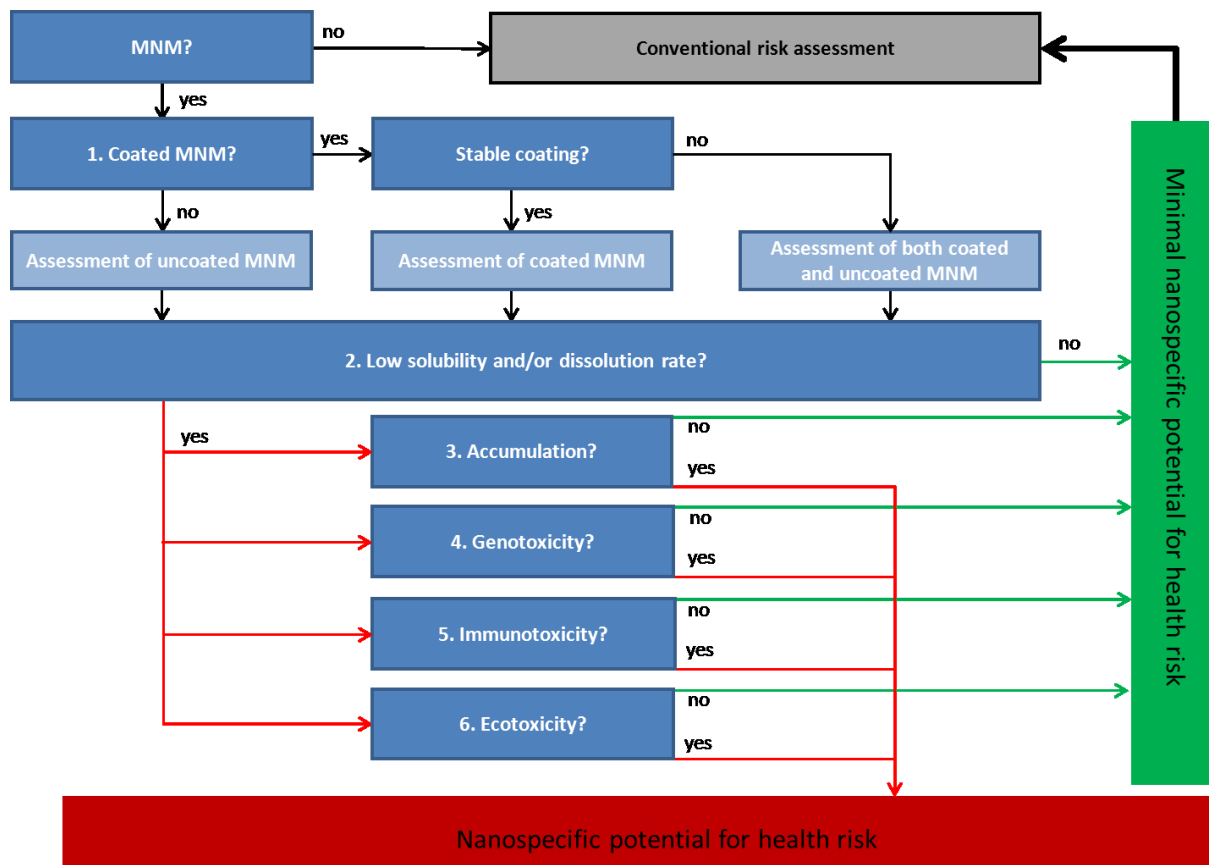


Figure 12: RIVM safety screening strategy

4.2. *The late development part: quantitative risk assessment*

As mentioned above, in the later part of the development there should be sufficient data (even for exposure: Real life exposure data can only be collected once tests under real life conditions have started. Still, experiments can be carried out earlier) for a fully quantitative risk assessment. Because design options are limited, risk management is also limited.

5. EHS Management processes

The EHS management processes for innovation projects typically include:

1. An initial screening for possible EHS issues
2. Occupational hazard management for workers. For R&D personnel, this has to be considered in stage 2, for production in stage 3. Relevant safety information for downstream activities has to be prepared and transferred in time (safety dossiers).
3. The environmental impact of the innovation has to be examined. This is typically done with a Life Cycle Analysis (LCA), if feasible.
4. The LCA can be coupled with a risk assessment. This can even be applied to MNMS.¹¹ However, this requires a lot of data, which may not be available at the beginning of an innovation process.

6. Industrial regulatory management processes

The regulatory management processes for innovation projects typically include:

1. Screening for applicable regulations (stage 1).
2. Definition of data needs per regulation: selection of appropriate information requirements in safety dossier(s).
3. Ensure that data for regulations is there once application is filed: filling of safety dossiers.
4. Manage contact to/with regulatory authorities /act as “internal regulatory authority”.
5. Once regulations are required, ensure conformity (e.g. SRD in stage 3, PPORD in 4, full REACH in 5, application specific regulation such as cosmetics, drugs etc.).
6. Contact along the value chain with other companies esp. for application specific regulations.

¹¹ OECD Guidance Manual on the Integration of Risk Assessment Data into Life Cycle Assessment Studies of Nano-Enabled Applications (draft, November 19th, 2014)

7. Data management and handling in the SbD concept

7.1. Data quality

No data will ever be exact i.e. 100% objective: there is a continuous evolution process from more subjective to less subjective or from less to more objective data, see **Table 4**.

More subjective data sources	More objective data sources
Personal assumptions	References from databases (usually material specific)
	Laboratory work; esp. under standardised conditions (SOPs) in validated processes, with validated methods and with qualified instruments
Simulations (source of subjectivity are not the calculations but the underlying personal assumptions and the quality of the data input)	
Comparisons or similarities (e.g. grouping)	
Inter- and Extrapolations: Interpolations are usually more objective than Extrapolations and using reference data is more objective than using (own) laboratory work	

Table 4: List of data sources according to subjectivity or objectivity of data.

7.2. Databases and Data formats

A prerequisite for comparing data within a database are harmonized data formats (such as ISA-TAB-nano) or computer infrastructure (such as developed by the project eNanoMapper).

7.3. Safety Dossier

Now the big question remains, which data is necessary for a sufficient risk assessment and how can this information be generated or obtained?

Safety dossier contains information requirements which may be necessary according to regulations, stakeholders etc. vs. stages.

The safety dossier will be set up in stage 1 after the screening for applicable regulations, safety issues, risk uncertainties etc.

From gate 2 on, in each following gate, within the safety dossier, the data to be generated in each following stage have to be defined. The generated data together with its interpretation then forms the Safety Profile.

7.4. Safety Profile

The Safety Profile is the structured collection of the information elaborated during the execution of the project. As conclusion in the Safety Profile, the safety relevant information for the different stakeholders will be summarized.

The layout of the Safety Profile will be generated from the required project specific information of the Safety Dossier.