ProSafe
Safe-by-Design (SbD)
Implementation Concept

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1 Introduction

1.1 Overview

ProSafe has developed, based on the NANoREG Safe-by-Design concept (SbD), an implementation concept. This concept has four main elements:

1. The workflows for the implementation of SbD in industrial innovation processes or actor specific needs
2. The Safety Dossier for the SbD
3. The Safety Profile for the material or product under development
4. ProSafe's harmonized inventory of SbD protocols, procedures and data

Within ProSafe, the NANoREG SbD concept has been complemented with the implementation concept and ProSafe's harmonized inventory of SbD protocols, procedures and data: State of the art and requirements for the implementation of the SbD concept.

Beside the implementation concept and the harmonized inventory, ProSafe focuses with the Safety Dossier on the preparation of actors for the existing and future regulations, trends on societal responsibility and expectations on safety, ect.

Within Nanoreg2, the NANoREG SbD concept and the ProSafe implementation concept will be further developed and combined with Regulatory Preparedness (regulators being prepared for innovation). The outcome will be Nanoreg2 Safe Innovation Approach (SIA).

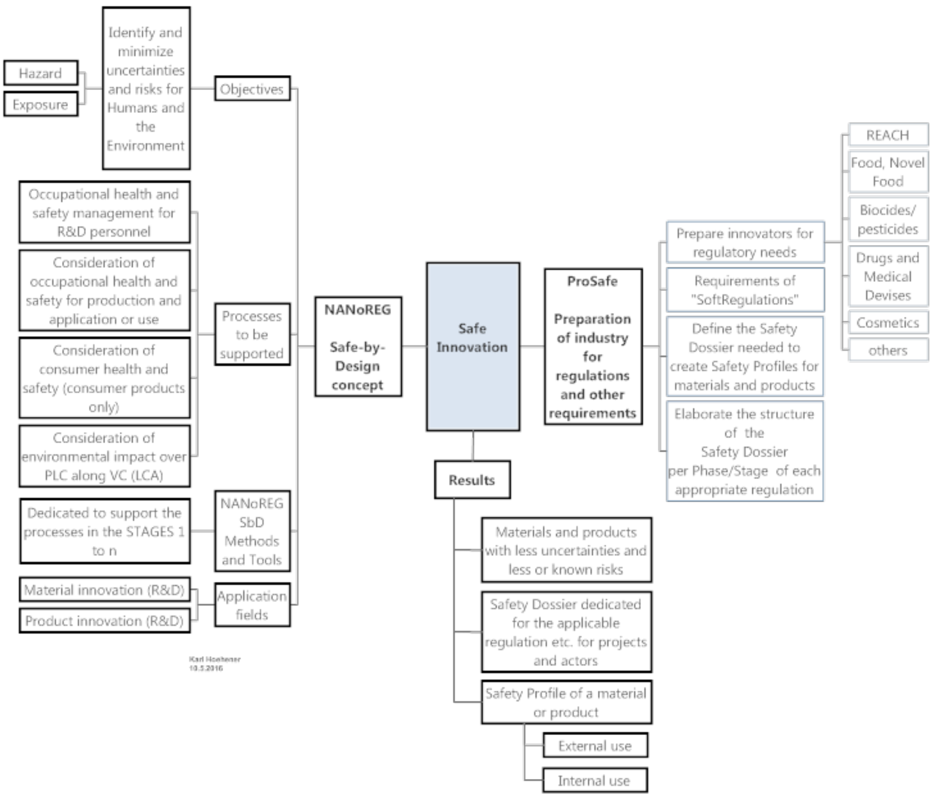

Figure 1: The combination of NANoREG's SbD concept and ProSafe's implementation concept as starting point for NanoReg2's Safe Innovation Approach (SIA)

1.2 Safe Innovation approach (NanoReg2)

Safe Innovation combines:

1. Safe-by-Design (Developed within NANoREG): Identified, reduced and managed uncertainty and risks of innovative materials, products and processes at the time of market introduction.
2. Industry prepared for regulation (Developed under ProSafe): SbD implementation concept, elaboration of regulation specific Safety Dossiers (SD) as a basis for the Safety Profiles (SP) of a material or product. The SbD implementation concept consists of a set of workflows and the harmonized inventory of the state of the art of SbD protocols, procedures, etc.
3. Regulators prepared for innovations (to be developed in NanoReg2): From a policy point of view, the aims is to improve anticipation of regulations for innovation of materials or product and their applications and potential safety issues. In order to do so, regulators should be prepared by being aware of innovations in the early stage of the innovation process in order to timely check on whether current regulations cover all aspects of innovation so that the human health and environmental safety are assessed when the product is ready to go to the market.

1.3 Safe-by-Design concept (NANoREG)

The NANoREG SbD concept integrates currently used management processes for innovations, risks, EHS, regulatory affairs and data handling. It does not substitute, but compliments currently used industrial innovation processes:

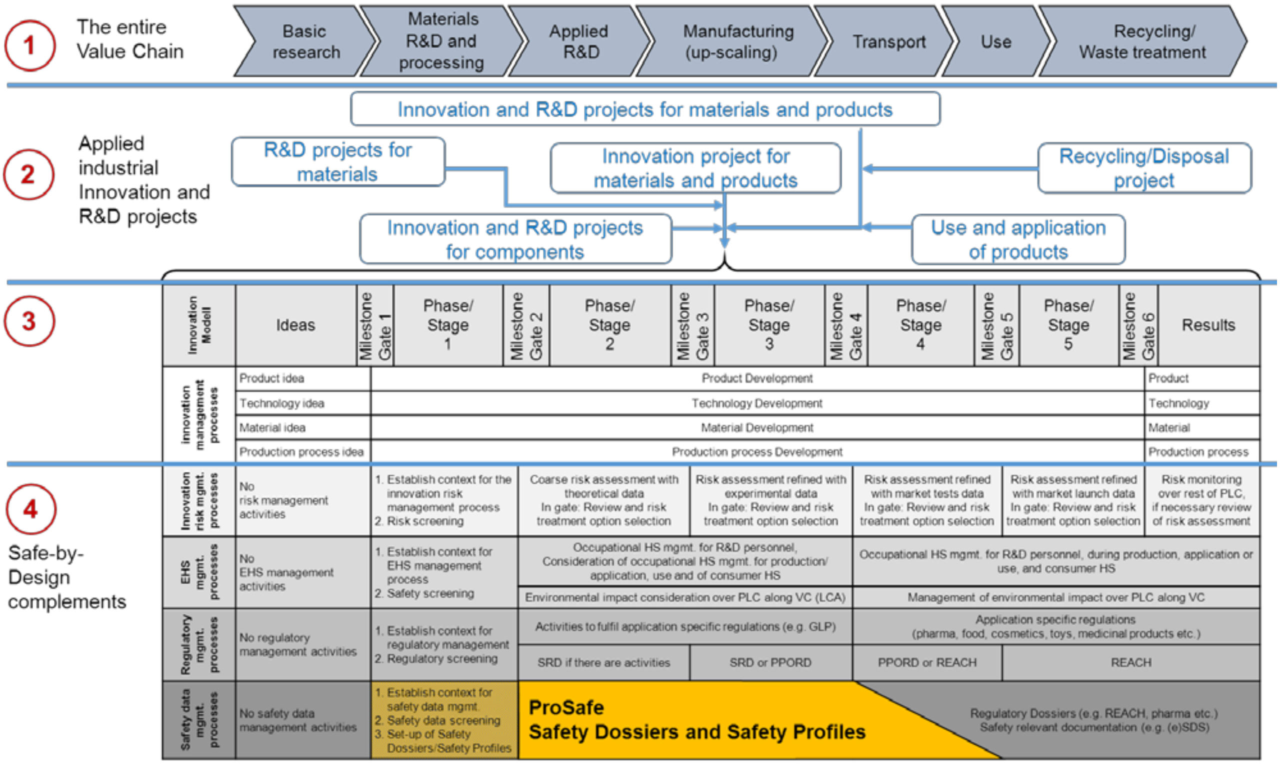

Figure 2: Overview of the NANoREG SbD concept and ProSafe Safety Dossier and Safety Profile

(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.
For each of the R&D projects exemplarily listed under (2), a complete SbD process - as exemplarily listed under (3) and (4) - must be performed.

(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 as well as the safety data management model, the ProSafe's Safety Dossier and the dossier required by the applicable regulation.

For further Information on the NANoREG SbD concept, see CIRCABC.

2 Safe-by-Design implementation

The basis for the ProSafe SbD implementation concept is the NANoREG SbD concept.

The ProSafe SbD implementation process consists of four main elements:

1. The workflows for the implementation
2. The Safety Dossier
3. The Safety Profile
4. The harmonized inventory of the state of the art of SbD protocols and procedures

There must be a strict differentiation between the Safe-by-Design process one hand and the manufactured nanomaterial (MNM) related data management on the other hand.

The SbD process integrates different industrial management processes; these und thus the concept remain relatively unchanged over time and always use the best currently available data from all available sources (Figure 3).

Whereas the concept can be applied for many different products, companies and industries – albeit with slightly differing industrial management processes – the data is project specific, i.e. for every product a set of existing and new data is needed and will be defined in the project specific Safety Dossier and collected in Safety Profile of the material/product under development.

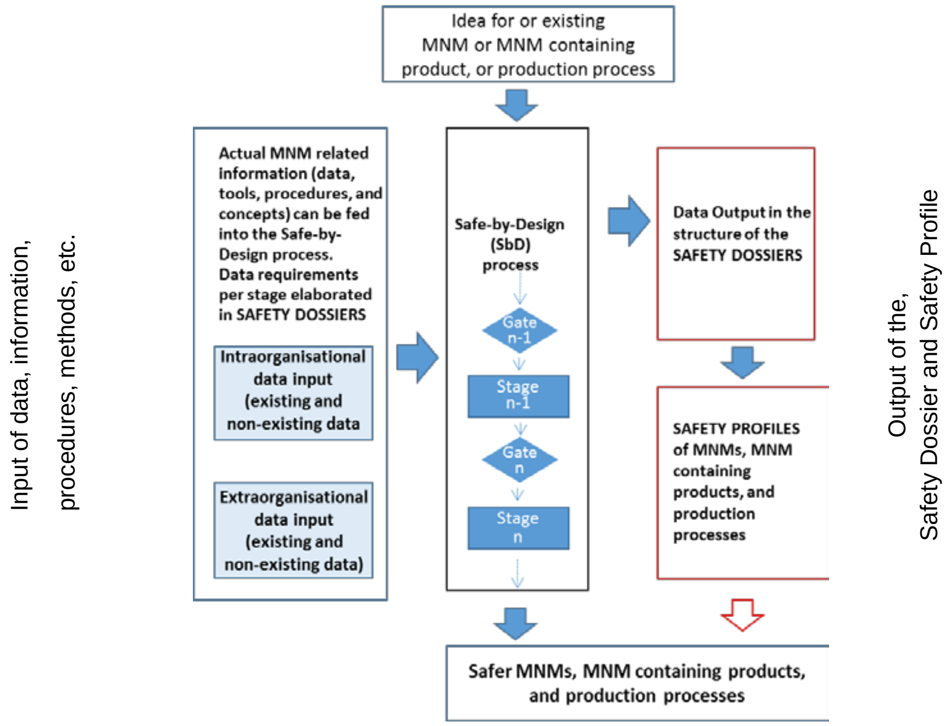

Figure 3: Overview of the SbD implementation process incl. data inputs, procedures, and the output as Safety Dossier and Safety Profile of the material/ product under development.

2.1 Objectives of the SbD implementation

The SbD implementation concept for R&D projects in industrial innovation processes is supporting 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 the ProSafe SbD concept cannot prove safety or absolute safety! Instead, an implemented SbD concept should help to reduce uncertainties and risks. In addition, the result of the application of the concept should focus on risk management options and help to detect knowledge gaps and information as well give support to determine the costs of a risk and its effect.

2.2 Safe-by-Design implementation process

The SbD implementation process for a specific R&D- or innovation project starts with elaboration of the Safety Dossier. For the development of the project specific Safety Dossier see chapter 2.3. The Safety Dossier delivers a set of procedures, concepts etc. to elaborate the necessary information and data for each STAGE of the project. In a first step, the procedures, concepts to be used in the specific project must be selected, defined or checked and then follow the workflow of Figure 4 below.

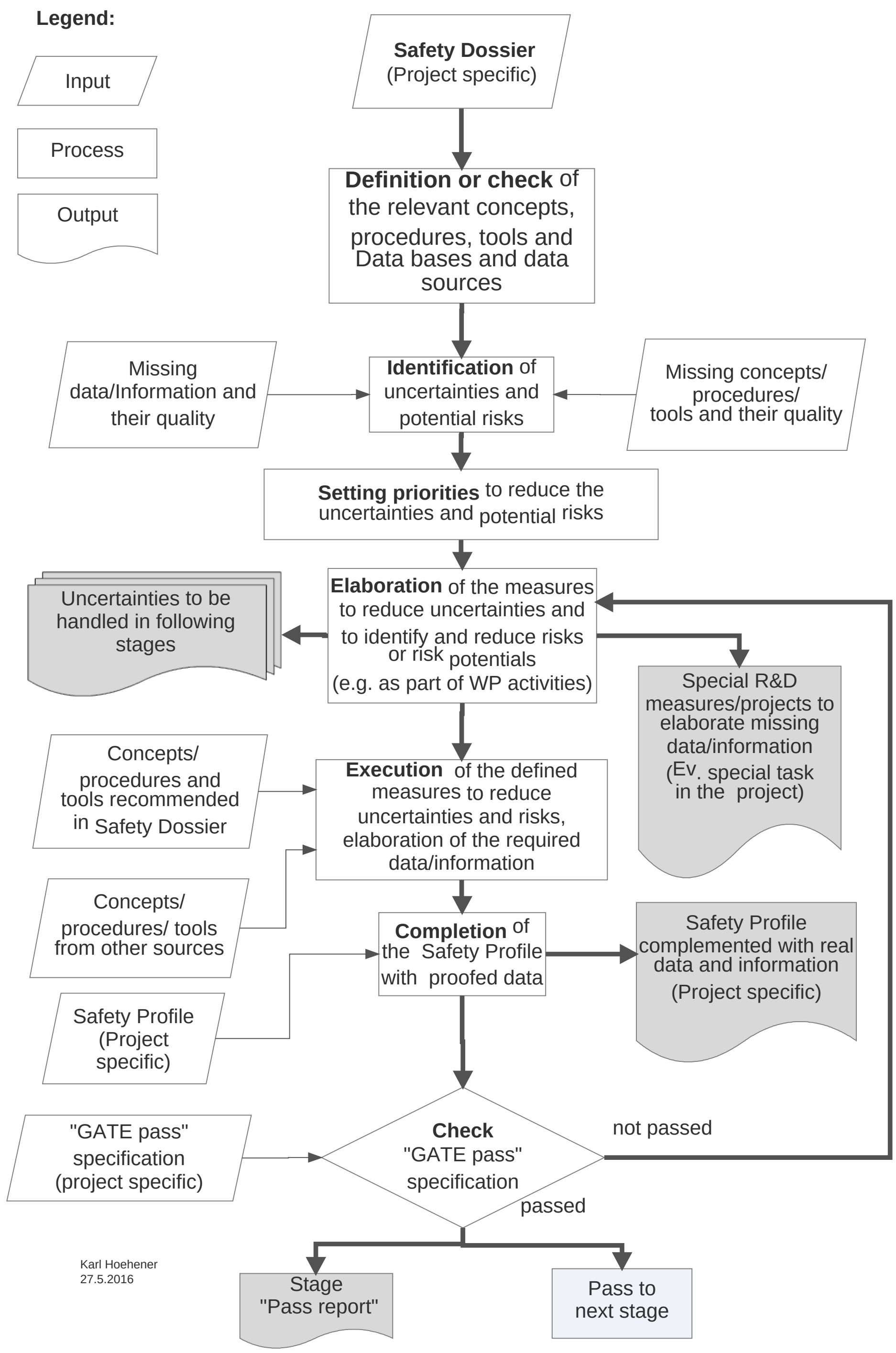

Figure 4: Generic workflow to define the workplan and process for the integration of SbD in an industrial innovation project

The inputs are the selected data requirements (with respect to quantity and quality) needed for a decision about safety at the different STAGES in the innovation process. The limit values of the information and data are defined in the respective GATE specification.

Any qualitative and quantitative uncertainty has to be listed in the Safety Profile.

2.2.1 Definition and check of the project relevant information and data

Figure 5 illustrates an exemplary workflow for the project specific definition and elaboration of the procedures, concepts, tools and data sources (instruments) required for the Safety Profile.

If the available instruments are not available, it may be necessary, that special R&D measures must be initiated in order to elaborate the respective data and or information.

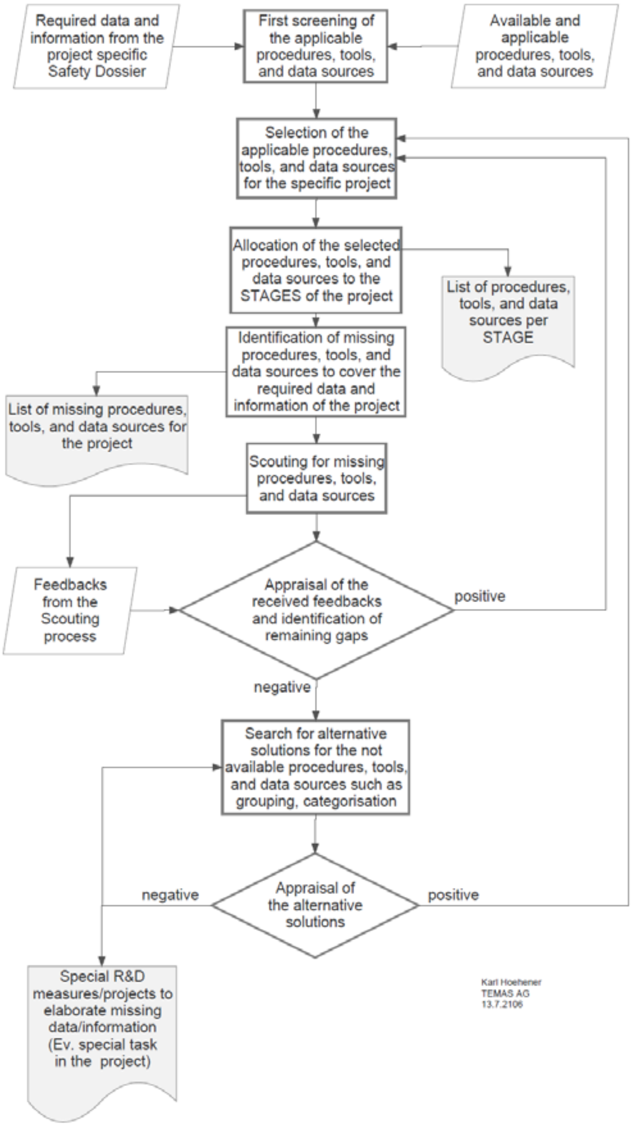

Figure 5: Workflow for the definition and check of the concepts, procedures, tools and data sources to be applied in a specific project

2.2.2 SbD implementation workflow starting with STAGE 1

An important factor of the SbD implementation concept is the fact, that not all finally required information and data must be available for a first safety screening in the early STAGES of a project. The amount and the quality of data can evolve during the development process from STAGE to STAGE. At the beginning, subjective data may be sufficient for a first Safety Profile, when it comes to STAGE 4 and higher, the data and information needs are defined by the applicable regulation.

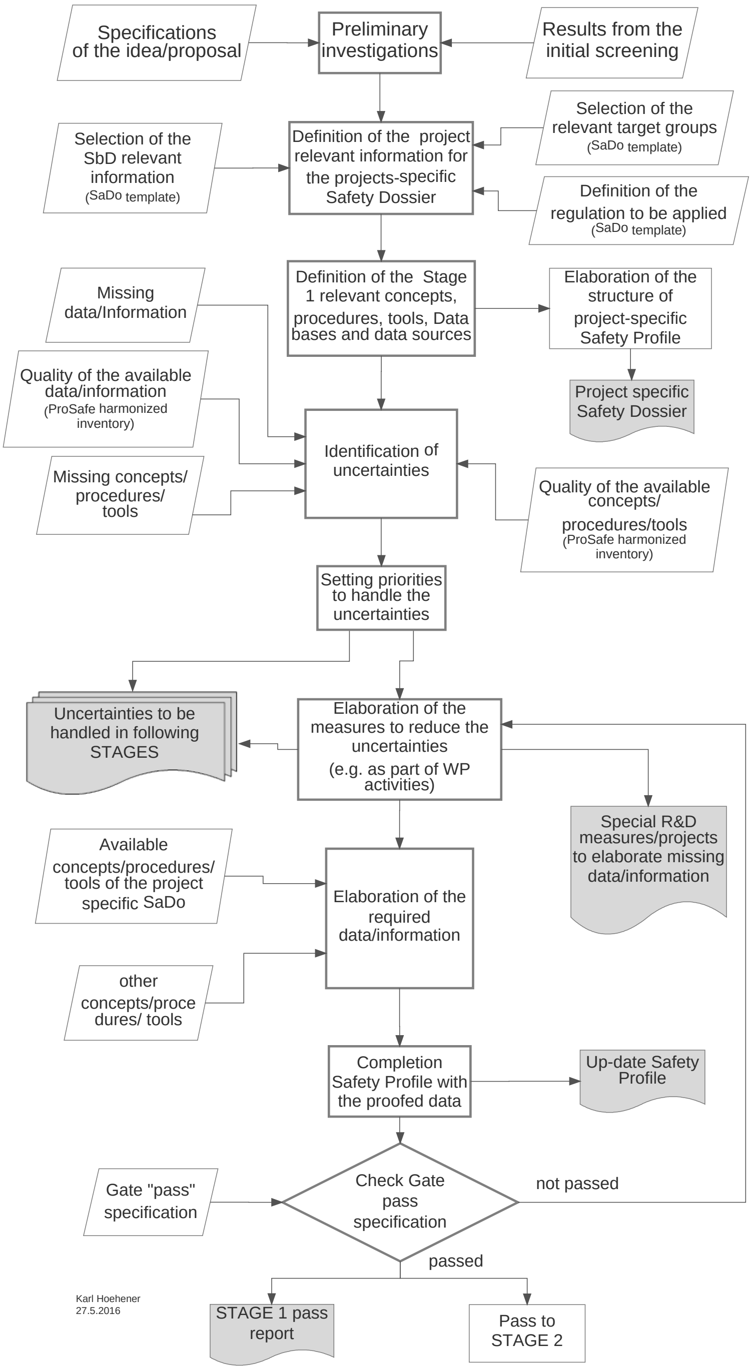

Figure 6: STAGE 1, the starting point for SbD implementation

2.2.3 Dealing with uncertainties

The identification and the reduction of uncertainties is a key topic of the ProSafe SbD implementation concept. Figure 7 shows the generic workflows to deal with uncertainties, especially at the GATES.

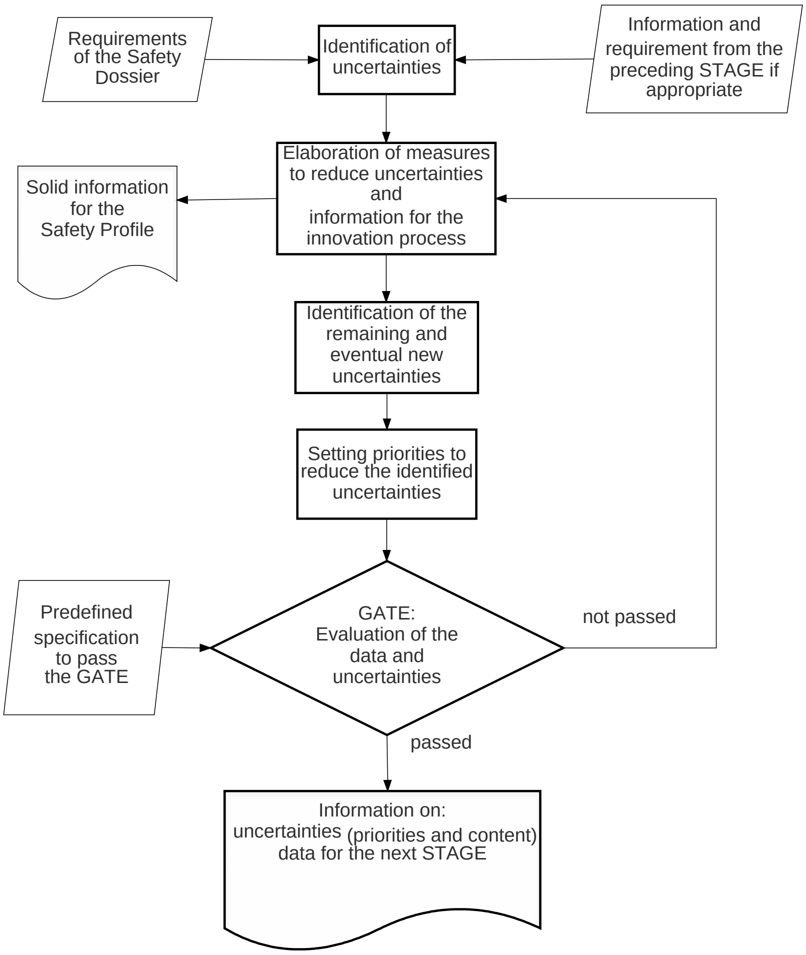

Figure 7: Workflow to handle uncertainties at different STAGES

2.3 The ProSafe Safety Dossier and Safety Profile

2.3.1 The content of the ProSafe Safety Dossier

The idea of an instrument such as a safety dossiers was created as part of the SbD concept development in NANoREG. This idea was then taken up by ProSafe, further developed and split into two separate but interlinked ProSafe tools:

- Safety Dossiers and
- Safety Profiles.

The data needs for the ProSafe Safety Dossier is evolving along the STAGES and will be defined project or actor specific. In STAGE 1, only a few key parameters, mainly subjective will be required.

Along the innovation process, the needs and the accuracy of data will grow from STAGE to STAGE. In the final STAGES, the required data are defined by the applicable regulation.

Besides the regulations, defined by law, complementary information domains, such as SoftRegulation, social and corporate responsibility, etc. must be considered case-by-case.

Figure 8 shows the structure of the ProSafe Safety Dossier. It can be explained as an X-Y matrix.

- The X-axis of the Safety Dossier allows to assign the data and information required for the different STAGES of a project, lists the safety relevant regulations such as REACH, Cosmetics, etc. and the target group to be addressed.
  This process allows to reduce the data requests in early STAGES significantly.
- The Y-axis of the Safety Dossier gives an overview of the data required for the different applicable regulation and target groups.

The Safety Dossier template contains a detailed overview of parameters of data needs for the different regulations and the needs of target groups, etc. For each project, a selection from the predefined parameters will be made and summarized in project specific Safety Dossier. The motivation for this approach is to reduce the required quantity of date to an absolute minimum.

The ProSafe's harmonized inventory provides a selection of protocols, procedures and data sources for the elaboration of the required data and information.

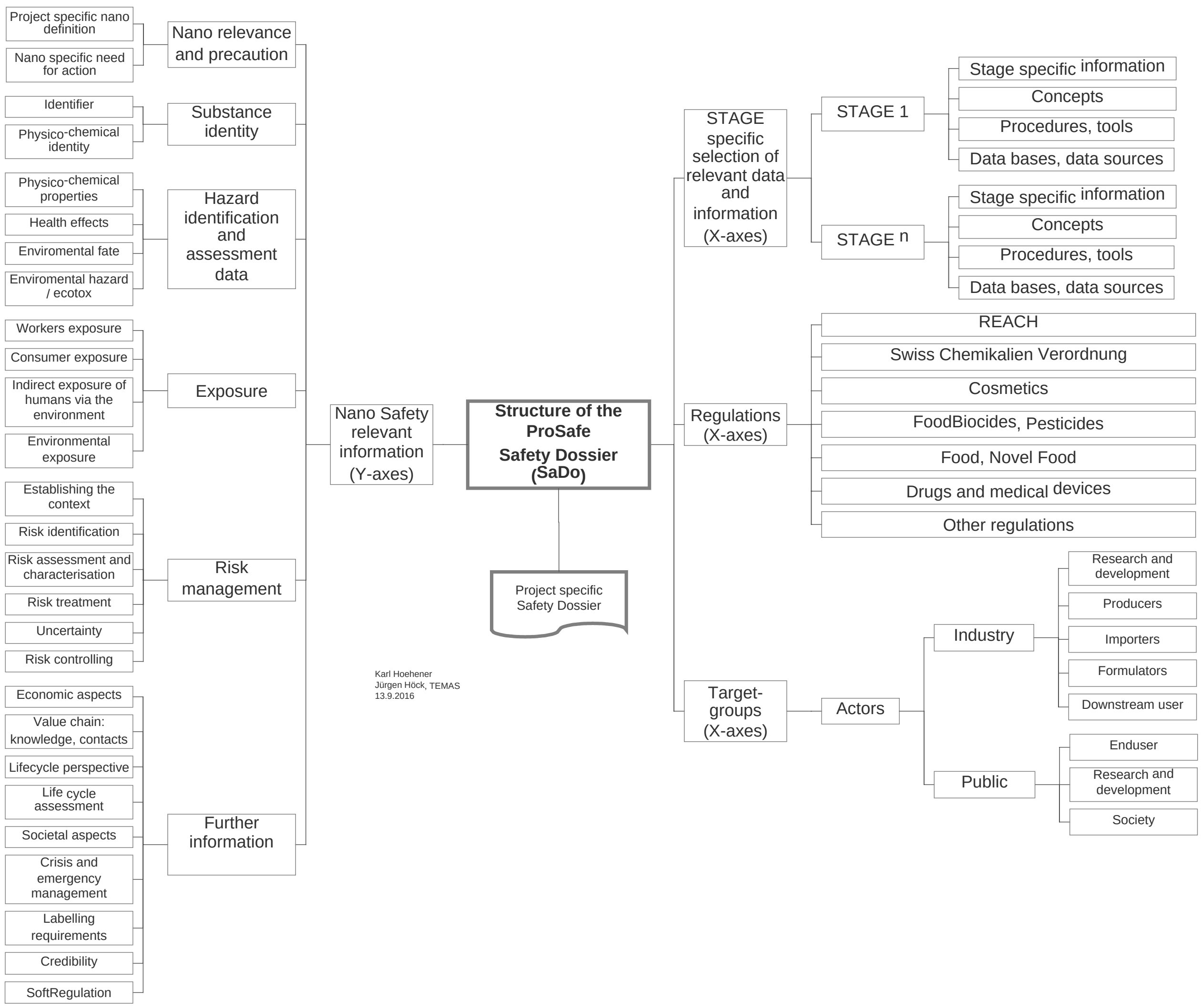

Figure 8: Structure of the ProSafe Safety Dossier

Fore more details on the X- and Y-axis, see Figure 10, Figure 11 and Figure 12.

For the Safety Dossiers and Safety Profiles, the workflows for the elaboration and completion of a SbD implementation are shown on Figure 4 to Figure 7 and Figure 9.

2.3.2 Workflow to elaborate the Safety Dossier and the Safety Profile

Figure 9 shows the specific workflow to elaborate the project specific Safety Dossier and the Safety Profile.

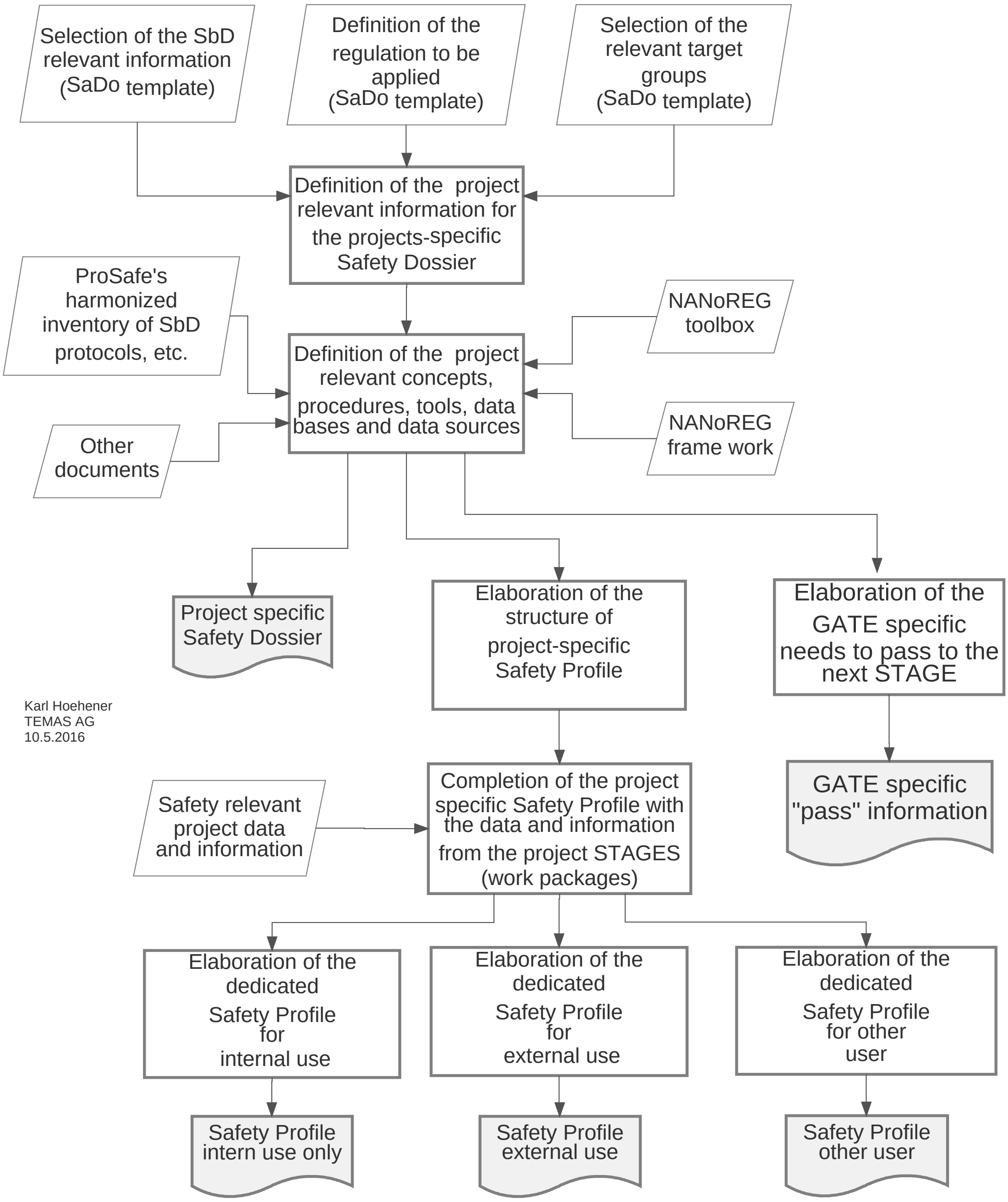

Figure 9: Workflow to elaborate the project specific Safety Dossier and Safety Profile

Selection of the SbD relevant information is specific to the needs of the target groups and/or regulations, e.g. for internal data requirements, data requirements of a customer or a specific application.

The selection of the data requirements as input for the Safety Dossier can be carried out over several STAGES: e.g. selection of the safety relevant information in STAGE 1, relevant target groups in STAGE 2, regulation (s) to be applied in STAGE 3, etc.

The Safety Dossier builds the structure for the content of the Safety Profile. The structured Safety Profile then is filled by all the data/information sourced and obtained according to the Safety Dossier.

2.3.3 Contents of the Safety Dossier

For the general overview of the contents of the template of the Safety Dossier, see Figure 8.

Figure 10 shows exemplarily the content of Y-axis of the Safety Dossier. In this case complemented with additional information from the harmonized inventory of procedures, concepts and data sources for the elaboration of he required data/information.

Information relevant for SbD			Supporting sources for information obtainment		
Category	Sub-Category	Details	Concepts	Tools and procedures	Data bases and data sources
Nanorelevance and precaution	nano definition	precautionary definition		Swiss Precautionary Matrix ---- LICARA NanoScan	
		regulatory definition			
	nanospecific need for action	precautionary measures		Swiss Precautionary Matrix	
Substance identity	identifier	name of substances			
		composition			
		substance, preparation, object of utility			
		new substance			
	physico-chemical identity	particle size distribution (granulometry)			
		shape			
		specific surface/volume relationship			
		coating / other surface functionalisation			
Hazard identification and assessment data	physico-chemical properties	appearance		OHT #1	
		physical state		OHT #1	
		colour		OHT #1	
		melting point		OHT #2	
		freezing point		OHT #2	
		boiling point		OHT #3	
		density		OHT #4	
		particle size distribution (granulometry)		OHT #5	
		fibre length and diameter distribution		OHT #5	
		vapour pressure		OHT #6	
		water solubility		OHT #8	
		solubility in organic solvents		OHT #9	
		surface tension		OHT #10	
		flash point		OHT #11	
		auto ignition temperature		OHT #12	
		flammability		OHT #13	
		explosive properties		OHT #14	
		oxidising properties		OHT #15	
		oxidation reduction potential		OHT #16	
		stability in organic solvents and identity of relevant degradation products		OHT #17	
		storage stability and reactivity towards container material		OHT #18	
		stability: thermal, sunlight, metals		OHT #19	
		pH		OHT #20	
		viscosity		OHT #22	
		additional physico-chemical information		OHT #23-1	
		self-reactive substances		OHT #23-2	
		organic peroxide		OHT #23-3	
		corrosive to metals		OHT #23-4	
		gases under pressure		OHT #23-5	
		nanomaterial agglomeration/aggregation		OHT #101	
		nanomaterial crystalline phase		OHT #102	
		nanomaterial crystallite and grain size		OHT #103	
		nanomaterial aspect ratio/shape		OHT #104	
		nanomaterial specific surface area		OHT #105	
		nanomaterial zeta potential		OHT #106	
		nanomaterial surface chemistry		OHT #107	
		nanomaterial dustiness		OHT #108	

Figure 10: Information of the Y-axis of the Safety Profile, an exemplary extract

Figure 11 shows the template of the needs of data/information for the first 3 STAGES of a project.

Information relevant for SbD			Stage 1				Stage 2				Stage 3			
Category	**Sub-Category**	**Details**	Information needed	Concepts	Tools and procedures	Data bases and data sources	Information needed	Concepts	Tools and procedures	Data bases and data sources	Information needed	Concepts	Tools and procedures	Data bases and data sources
Nanorelevance and precaution	nano definition	precautionary definition			Swiss Precautionary Matrix									
		regulatory definition												
	nanospecific need for action	precautionary measures			Swiss Precautionary Matrix									
Substance identity	identifier	name of substances												
		composition												
		substance, preparation, object of utility												
		new substance												
	physico-chemical identity	particle size distribution (granulometry)												
		shape												
		specific surface/volume relationship												
		coating / other surface functionalisation												
Hazard identification and assessment data	physico-chemical properties	appearance												
		physical state												
		colour												
		melting point												
		freezing point												
		boiling point												
		density												
		particle size distribution (granulometry)												
		fibre length and diameter distribution												
		vapour pressure												
		water solubility												
		solubility in organic solvents												
		surface tension												
		flash point												
		auto ignition temperature												
		flammability												
		explosive properties												
		oxidising properties												
		oxidation reduction potential												
		stability in organic solvents and identity of relevant degradation products												
		storage stability and reactivity towards container material												
		stability: thermal, sunlight, metals												
		pH												
		viscosity												
		additional physico-chemical information												
		self-reactive substances												
		organic peroxide												
		corrosive to metals												
		gases under pressure												
		nanomaterial agglomeration/aggregation												
		nanomaterial crystalline phase												
		nanomaterial crystallite and grain size												

Figure 11: Information of the X-axe of the Safety Profile, an exemplary extract for the first 3 STAGES

Figure 12 gives an overview of the applicable regulations listed in the template, the target group s and actors to be served.

Information relevant for SbD			Regulators								Industry					Consumer
Category	**Sub-Category**	**Details**	**REACH**	**CH: ChemV**	**Cosmetics**	**Food**	**Biocides**	**Pharmaceuticals**	**Plant Protection**	**Any other relevant regulation**	**Producer**	**Importer**	**Distributor**	**Formulator**	**Downstream user**	
Nanorelevance and precaution	nano definition	precautionary definition		x												
		regulatory definition														
	nanospecific need for action	precautionary measures		x												
Substance identity	identifier	name of substances		x												
		composition		x												
		substance, preparation, object of utility		x												
		new substance														
				x												
	physico-chemical identity	particle size distribution (granulometry)		x												
		shape		x												
		specific surface/volume relationship		x												
		coating / other surface functionalisation		x												
Hazard identification and assessment data	physico-chemical properties	appearance		x												
		physical state		x												
		colour		x												
		melting point		x												
		freezing point		x												
		boiling point		x												
		density		x												
		particle size distribution (granulometry)		x												
		fibre length and diameter distribution		x												
		vapour pressure		x												
		water solubility		x												
		solubility in organic solvents		x												
		surface tension		x												
		flash point		x												
		auto ignition temperature		x												
		flammability		x												
		explosive properties		x												
		oxidising properties		x												
		oxidation reduction potential		x												
		stability in organic solvents and identity of relevant degradation products		x												
		storage stability and reactivity towards container material		x												
		stability: thermal, sunlight, metals		x												
		pH		x												
		viscosity		x												
		additional physico-chemical information		x												
		self-reactive substances		x												
		organic peroxide		x												
		corrosive to metals		x												
		gases under pressure		x												
		nanomaterial agglomeration/aggregation		x												
		nanomaterial crystalline phase		x												
		nanomaterial crystallite and grain size		x												
		[illegible]														

Figure 12: Information of the X-axe of the Safety Profile, an exemplary for the applicable regulations and the target groups

3 ProSafe's harmonized inventory

Within ProSafe, a harmonized inventory of SbD protocols, procedures and data: State of the art and requirements for the implementation of the SbD concept, has been elaborated.

This inventory has been elaborated based on the results of a "Search Call" along the partners of the EU NanoSafety Cluster.

The following index gives an overview of the contents (For the complete inventory, see CIRCABC Work packages > WP4 > Task 4.2 - Call topics and harmonisations > 20160831_ProSafe harmonized SbD inventory.pdf):

- 1 DATABASES AND LIBRARIES
  - 1.1 DATABASES
  - 1.2 LIBRARIES
- 2 STANDARDS DEVELOPMENT FOR NANOMATERIALS MEASUREMENTS
  - 2.1 REFERENCE MATERIAL STANDARDS
  - 2.2 NANOMATERIAL STANDARD TEST METHODS
  - 2.3 RELEVANT DOCUMENTARY STANDARDS
- 3 CHARACTERISATION
  - 3.1 DEFINITION OF MINIMUM CHARACTERISATION PRINCIPLES TO DEVELOP STANDARDISED DESCRIPTORS FOR MNMS
  - 3.2 STANDARD REACTIVITY MEASURES AND PROTOCOLS FOR MNMS
- 4 DETECTION AND CHARACTERIZATION OF NANOMATERIALS IN COMPLEX BIOLOGIC AND ENVIRONMENTAL SAMPLES
  - 4.1 MODEL MNMS THAT CAN BE TRACKED WITHOUT INTRODUCTION OF EXPERIMENTAL ARTEFACTS IN EXPOSURE AND TOXICITY STUDIES
  - 4.2 ANALYTICAL TOOLS AND PROCESSES THAT CAN DETECT MNMS AT LOW (RELEVANT) CONCENTRATIONS FOLLOWED BY TOOLS TO TRACK AND CHARACTERIZE MNM PROPERTIES IN SITU OR IN VIVO
  - 4.3 TOOLS AND PROCESSES TO ASSESS THE DEGREE OF TRANSFORMATION OF MNMS IN VIVO OR IN SITU
  - 4.4 NEW PROTOCOLS OR MODIFICATION OF EXISTING PROTOCOLS FOR TOXICITY TESTING
  - 4.5 PRIORITISATION OF IN VIVO ASSAYS AND DEVELOPMENT OF QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR) MODELS
- 5 GROUPING
  - 5.1 GROUPING - REQUIREMENTS
  - 5.2 GROUPING - STATE OF THE ART
    - 5.2.1 The bio-nano-interface in predicting nanoparticle fate and behaviour in living organisms: towards grouping and categorising nanomaterials and ensuring nanosafety by design
    - 5.2.2 The grouping considerations published in the context of the EU-funded projects, NanoSafety Cluster (as well as of the Nanotechnology Industries Association) or put into practice in the context of research activities
    - 5.2.3 Other grouping strategies
    - 5.2.4 Concepts for the grouping of nanomaterials for occupational safety assessment
- 6 EXPOSURE, TRANSFORMATION AND THE LIFE CYCLE
  - 6.1 EXPOSURE, TRANSFORMATION AND THE LIFE CYCLE - REQUIREMENTS
  - 6.2 EXPOSURE, TRANSFORMATION AND THE LIFE CYCLE - STATE OF THE ART
    - 6.2.1 General processes & areas of possible release and exposure (human & environmental)
    - 6.2.2 General Workplace Nanomaterial Guidelines
    - 6.2.3 Laboratory Nanomaterial Guidelines
    - 6.2.4 Priority Research Actions initiatives by integration of Safe-by-Design

4 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 1.

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 1: List of data sources according to subjectivity or objectivity of data

4.1 Databases and Data formats

A prerequisite for comparing data within a database are harmonized data formats, such as ISA-TAB-nano templates of NANoREG and or computer infrastructure as developed by eNanoMapper (http://enanomapper.net/).

4.2 Data needs of the Safety Dossier

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

The 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.

4.3 Data needs for the 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.