

2 Risk assessment of technological innovations

This chapter will introduce relevant terms laying the foundation for the subsequent chapters of this thesis. At first, technological innovation will be defined and described and the relation to the precautionary principle and TA will be shown. Second, technology characterization is shown in the context of TA to systematically analyze technologies in early innovation stages. Third, the components of risk will be introduced together with the risk governance framework. Fourth, the subsequent sections will focus on exposure assessment and its significance in the European chemicals regulation framework. Fifth, the selected materials AgNP and IONP will be characterized with respect to their bulk and nano-specific material properties, which will be used for the bibliometric analysis in chapter 5. Finally, the state-of-the-art and the existing challenges for prospective release and exposure assessment of NOAAs will be summarized.

2.1 Technological innovations

Innovations constitute a key requirement for companies and society to sustain in turbulent contexts. These contexts are characterized by several factors as for example global competition, the need of shorter product life cycles, and the related demand to develop and to innovate (Spur 2006). Innovations promise to ensure the competitiveness and growth¹ of companies and national economies (Hahn 2013). The term “innovation” has several differentiations that were discussed since the 1960s. Even though, this thesis cannot focus on all aspects of the historical scientific discussion, it is important to differentiate between invention and innovation. While the term invention considers new or improved artifacts, innovation also implies its successful introduction to the market that is demanded by society. Thus, not every invention is an innovation as emphasized by Schumpeter (Hahn 2013). The artifacts of innovations comprise products, processes, and services that are related to technical, economical, or societal changes and improvements (Hacklin et al. 2004). Innovations are also differentiated by the degree of improvement and novelty by having an incremental or disruptive character, respectively, which is still controversially discussed (Yu and Hang 2010; Hahn 2013). Disruptive innovations are revolutionary and lead to significant changes, whereas incremental innovations have an evolutionary character with small and continuous improvements (Yu and Hang 2010). However, Hacklin et al. (2004) pointed out that incremental innovations can have a delayed disruptive character. Particularly for converging technologies, incremental innovations can be revealed as disruptive in a cumulatively long-term perspective. Accordingly, criticisms on the rather vague definitions of disruptive and incremental innovations are formulated due to their unclear differentiation.

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It has to be noted that since the early 1970th (Club of Rome) the economical concept of growth and its limitations are in critical discussion (cf. Meadows et al. 1972; Meadows et al. 2004).

Nevertheless, this differentiation enables a first useful categorization of innovations and related impacts.

In the past, the innovation research focused not only on the type of artifacts (e.g., technical, social, etc.), but also on innovation drivers, processes, and contexts (Ruttan 1959; Freeman 1991; Arora et al. 2014). Therefore, innovations can be differentiated by their initial drivers: technology-push and demand-pull (Nemet 2009). On the one hand, innovations that are enabled by a technology-push require the corresponding knowledge about the provided opportunities of a technology. This knowledge is normally gained by research and development, which acts as an impulse and leads to a market potential. However, by following Schumpeter (1964) (cited by Hahn 2013), new combinations of existing knowledge can lead to innovative artifacts as well. On the other hand, demand-pull innovations emerge from social needs and demands that have to be complemented by technological, social, and environmental measures (Nemet 2009). Consequently, both technology-push and demand-pull innovations have bilateral relations, which will only recursively solve problems (Freeman 1991; Arthur 2007). In addition, actors should be able to innovate in terms of economic and technical capabilities for dealing with linked uncertainties and risks (Hahn 2013).

In a procedural understanding innovation passes through the stages: basic research, applied research, prototype, and market introduction as it was proposed by V. Bush in the 1940s (Hahn 2013). Ideally, the basic research gains basic scientific knowledge for innovations. This knowledge and ideas are the basis for the subsequently applied research stage. The research is “applied” to a real world problem and thus it is linked with the needs of society. In the third stage physical prototypes are developed and constructed, which are then further investigated for up-scaling purposes in manufacturing as well as for improving the performance of the product. Finally, the product is introduced to the market. The linear perspective neglects iterations and recursions that are normally prevalent in an innovation process due to the relations between actors (Hahn 2013).

In the following chapters, nano-based innovations are understood as incremental or disruptive technology push innovations, where improved or new functionalities (accessible at the nanoscale) lead to innovations. The innovation process is approached as a linear process to reduce complexity accordingly.

2.2 Precautionary principle and technology assessment

Between the 1960s and 1980s the commonly accepted mindset of technology-optimism (i.e., progress based on science and technology) changed towards a more reflected opinion about the impact of innovations and the limits to growth (Meadows et al. 1972; Grunwald 2010). Technological innovations were no longer considered as the source for endless progress, growth, and prosperity, but also they are always accompanied by immanent risks, which have to be taken to take advantage of potential innovations and desired effects. However, certain technological innovations, especially in the field of nuclear technology and synthetic chemistry, have shown negative side effects not known so far. Such impacts were related to social and environmental effects, which became more important due to the changed mindset (Grunwald 2010).

In 1970s the precautionary principle began to emerge in environmental sciences and legislations as for example in the German Clean Air Act in 1974 to regard environmental hazards and related uncertainties in a preventive manner (Harremoës et al. 2001). The precautionary principle is also known in medicine and public health as the phrase “better safe than sorry” (Harremoës et al. 2001). However, the precautionary principle minimizes potential risks, but does not include the intrinsic safety. Consequently, the main component of the precautionary principle comprises actions or decisions to reduce potential hazards before adverse effects have been finally proven (Harremoës et al. 2001). In particular, such measures apply for irreversible and severe consequences, where first reasons for concern are apparent (Calliess 2008). However, a reason for precaution has to be evident to apply the precautionary principle in legislation (Calliess 2008). In this context, regulators and decision-makers have often to consider a risk-risk trade off, in which positive consequences and negative side effects have to be evaluated (Hansen and Tickner 2013).

In 1972, consequently, the “Office of Technology Assessment” was established to consult policy and decision-makers in the United States. These years are also regarded as the beginning of TA, whereby the German office of TA was established later in 1989 (Jischa 2012). TA has to deal with the often mutually excluding goals of enabling desired effects and preventing detrimental consequences. The institution for such early detections and warnings should be preferably applied in early stages of innovation to avoid or minimize potentially negative side effects (Grunwald 2010). TA has to consider not only the technological development and potential consequences, but also the social, economic, and regulatory aspects in order to frame recommendations and thereby create a reliable basis for political/regulatory actors and decision-makers.

By doing so, TA pursues the classical objective to prepare a comprehensive basis of decision-making for which a disciplinary approach would be not sufficient due to the various involved dimensions (e.g., technical, EHS as well as ethical, legal, and social implications). In fact, TA applies inter- and transdisciplinary approaches and methods to consult policy and decision-makers by formulating unbiased recommendations based on a systemic and scientific view (Dusseldorp and Beecroft 2012). Moreover, the establishment of TA since the 1970s was accompanied with a high prognostic optimism and an attitude, which can be described as technology determinism (Grunwald 2010). The prognostic optimism basically assumes the ability of predicting negative consequences in order to avoid them. Sociological technology research (German: Technikgeneseforschung) questioned the wide spread technology determinism. Finally, it has been shown that technologies result from several decisions of the actors in an innovation system, and thus, they are part of an eminent social process (Weingart 1989; Grunwald 2010).

In an attempt to react adequately to changing types of innovations and to this progress of understanding, several concepts of TA were developed: participatory TA, constructive TA (Rip and Schot 1997), real-time TA (Guston and Sarewitz 2001) as well as “Leitbild”/ guiding principle assessment, and vision assessment (Grunwald 2010). The following brief overview is mainly based on (Grunwald 2010).

The participatory TA focuses on the implementation of stakeholders in a dialogue. This aspect was demanded in the early beginnings of TA, because expert knowledge was not able to cover and represent all interest groups in the development of innovations. The aspect of participation is implemented in almost all TA concepts to support important social debates and to assist in shaping the public opinion (Grunwald 2010).

Real-time and constructive TA simultaneously accompany technological developments and accordingly formulate recommendations for further developments by implementing social sciences and policy research (Rip and Schot 1997; Guston and Sarewitz 2001). However, real-time TA differs from constructive TA by engaging in the knowledge creation process itself and not focusing on experimentation with new technologies. This aspect becomes apparent by the use of different methodologies such as public opinion polling, focus groups, and scenario development (cf. Guston and Sarewitz 2001). Furthermore, the guiding principle assessment attempts to analyze the strategies and communication of stakeholders. It is assumed that guiding principles can be used for shaping technologies, which are linked to a kind of metaphor at an abstract level having a great influence on the development of systemic innovations (Dierkes et al. 1992; Grunwald 2010). In contrast, the vision assessment focuses on mental images of the future such as visions, hopes, wishes (utopia), and fears (dystopia), which can significantly differ between stakeholders. The vision assessment

systematically analyzes these aspects and confronts stakeholders with other stakeholders' visions (Grunwald 2010).

2.3 Technology characterization as a methodology of TA

Following the previous sections, TA has to consult policy and decision-makers in an inter- and transdisciplinary approach, if possible in early innovation stages. In order to prepare recommendations for decision-makers, TA has to collect information about the respective technology, contexts, and consequences. Due to the early stage of the innovation process, TA has to struggle with uncertainties and unknowns. The unknowns can be roughly differentiated into still-unknowns and the unknowable (Steinfeldt et al. 2007). The main difference is that the still-unknowns can be principally uncovered with corresponding time and efforts, whereas the unknowable is impossible to predict, which lies in the nature of the epistemological object (Steinfeldt et al. 2007). Normally, (partial) consequences can be found after the investigation of cause-and-effects chains as well as exposed targets such as biotic or abiotic systems. However, in early innovation stages, this knowledge is often not at hand and a systematic approach is required for assessing such consequences.

Technology characterization offers the opportunity to assess and to provide strategically the still-unknowns by shifting the focus from the effect to the cause – the technology itself (Steinfeldt et al. 2007). Thereby, it is assumed that the applied technology has specific functionalities, which can be linked to potential (technological) chances, but also to potential harms (Pade et al. 2015). The technology characterization is similar to the hazard characterization, which is already established as a crucial step in risk assessments and regulations (cf. chapter 2.4.2). In hazard characterizations substances are analyzed for specific toxicological properties such as carcinogenic, mutagenic, or reprotoxic (CMR), which are used for risk management measures before more specific impact models are known (Steinfeldt et al. 2007). Likewise, also exposure-related characteristics are used for precautionary measures as for example very persistent and very bioaccumulative properties of a substance that would significantly increase the exposure likelihood towards this substance (cf. chapter 2.4.5).

This thesis will apply the technology characterization methodology to nano-enhanced product applications and will extend this approach by release and exposure related aspects. In doing so, it can be expected that specific functionalities will be identified, which are related to certain contexts as well as release and exposure characteristics enabling a prospective TA.

2.4 Conventional risk assessment in the risk governance process

This subchapter describes the terms and definitions related to risk assessment and will create a link to the risk governance process. Subsequently, the terms “hazard” and “exposure” and their assessments will be introduced. It has to be noted that due to the focus of the dissertation, chapter 2.4.3 will discuss terms related to exposure in more detail than other risk assessment elements. In addition, the risk governance process has received a change regarding the significance of hazard and exposure assessment, which will be described in chapter 2.4.5. Finally, a brief review of the state-of-the-art about environmental release and exposure assessment of NOAAs will be given.

Also, this chapter will give insight into the environmental release categories (ERCs) from the European Chemicals Agency (ECHA), which are used for the definition of exposure scenarios in the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) process of new substances.

2.4.1 Definition of risk

The term “risk” is used in various contexts and is consequently interpreted in different ways (Renn and Graham 2005). Therefore, two interpretations of the term “risk” will be introduced depending on different contexts. First, in a decision-oriented context risk *“is related to an uncertain consequence of an event or activity with respects of humans value”* (Kates et al. 1985; Renn and Graham 2005). The uncertain consequence can include positive or negative effects (Renn and Graham 2005). Thereby, the positive or negative connotation of consequences differs depending on discipline and context, where one of both side may prevail. “Risk” is constituted of the *likelihood of an event or action* and the *related severity of positive or negative consequences*. Generally, both risk components have to be present to constitute a risk, which can be further differentiated into linear and non-linear risks (Renn and Graham 2005). While linear risks have clearly determinable cause-effect relations, non-linear risk poses complex relations of causes and effects. Especially, non-linear risks challenge current risk assessment methodologies due to the fact that causes and effects are not directly correlated and are additionally dependent on several parameters as well as time and spatial aspects. For example, climate change is an example for a non-linear risk, which is affected by many parameters, stretches over a long period of time as well as great a spatial area leading to complex behavior. Due to this complexity, another risk assessment approach is required to handle such kind of systemic risks (Renn and Graham 2005).

Second, in a(n) (eco)toxicological understanding, which is often applied in the debate on environmental, health, and safety aspects (EHS), risk is constituted of “hazards” and “exposures”. Hazards are potentially adverse effects emanating from a substance — the so-called agent. Exposure is the quantity of an agent to which an individual or system can come into contact. In the ecotoxicological meaning of risk, both hazard and exposure are

mathematically related, which is why the ecotoxicological risk potential "R" is depicted as a function of hazard "h" and exposure "e" (cf. Equation 1).

$$R = f(h, e) \quad \text{Equation 1}$$

This work will apply the ecotoxicological interpretation due to the focus on environmental releases and exposures of NOAAs. Before the assessment of hazards and exposures is introduced in the next sections, these terms will be firstly linked to the risk assessment and governance process.

2.4.2 Risk and hazard assessment in the risk governance process

In 2003 the German government established an ad-hoc commission on the restructuring of the risk governance process in Germany. The resulting report distinguishes risk governance into: pre-assessment, risk assessment, risk evaluation, and risk management (Renn et al. 2003). These terms will be described in the following paragraphs, which are mainly based on Renn et al. (2003).

The *pre-assessment* is the step of preparation for the risk assessment. In this early stage the pre-assessment aims at the problem definition and the prioritization of the investigated agents. Thereby, the "presorting" limits the scope to a reasonable and practical level and apparent risks can be identified early in the risk assessment. On this basis corresponding risk management measures can be initiated in a precautionary manner, which is valuable for cases in which actions are urgently required (Renn et al. 2003).

The second step comprises the *risk assessment*, which is realized on a scientific basis. As mentioned above, risk is constituted of combined potential hazards and exposures, which are being identified in the risk assessment. The *hazard assessment* aims at the hazard identification, which attempts to identify potential adverse effects together with a dose-response relation of the analyzed agent. The resulting dose-response curve describes the quantitative relation between the effect and amount of the agent.

In *exposure assessments* the environmental concentration of an agent is estimated and the exposed populations are identified. Also, if possible, the exposure likelihood is determined. Besides these two assessments, not only potential adverse effects, as for example CMR properties, have to be characterized (i.e., hazard characterization), but also physico-chemical properties of the agent should be determined. This knowledge can help to facilitate predictions on the agent's behavior in human and environmental media. Then, the results of both hazard and exposure assessment are used for characterizing potential risks. Therefore, both assessments should be applied as early as possible to support precautionary risk managements, for instance by considering reasons for concern (e.g., very bioaccumulative and very persistent substances in REACH). Finally, all potential uncertainties that are related to the gained results have to be transparently communicated to the risk evaluation step.

In a third step, the results of the risk assessment are subsequently evaluated. The potential risks are discussed in a participative process including stakeholders from science, industries, civil society, governmental institutions, and political actors. The objective is to find the “acceptable risk” for all stakeholders and to agree for adequate risk minimizing measures. Thus, it should be ensured that all stakeholders, who can be affected by the subsequent risk management, participate. In addition, the results of the risk assessment can be improved by the critical discussion with experts and third parties (Rehbinder et al. 1999).

Finally, the fourth step concerns the *risk management*. The results of the risk evaluation contain proposed risk management measures, which are used as a basis for developing, evaluating, and choosing appropriate risk minimizing measures. Besides, it is recommended to apply a methodological and transparent approach (e.g., cost-benefit analysis or other methods) for evaluating the identified risk minimizing (or avoiding) measures. The focus of the evaluation should be laid on the overall chances and risks without jeopardizing any stakeholders. On this basis, regulatory institutions can initiate the respective regulatory steps. The effectiveness of the implemented measures has to be continuously controlled (Renn et al. 2003).

Hazard assessment as part of risk assessment

The hazard assessment, in turn, can be differentiated in *hazard identification* and *hazard characterization* in the course of the dose-response assessment (ECB 2003; IPCS 2004; Van Leeuwen et al. 2007). Hazard identification aims at tracing and determining adverse effects (i.e., type and nature of effects) that are caused by a substance in organisms, systems, or (sub)populations (IPCS 2004). Hence, hazard identification is a relevant first step in the hazard assessment. Secondly, the hazard characterization will be conducted, which is strongly related to the dose-response (i.e., effect) assessment. The major objective is to determine the dose-effect relationship of an agent and its mode of action. The dose-response relationship is the minimal amount of a substance, which is administered to, taken up by, or absorbed by an organism, population, or system that can cause an adverse effect (Rehbinder et al. 1999; IPCS 2004). This quantity is also named as the “margin of exposure” or “margin of safety” (IPCS 2004). The margin of exposure is an important concentration level, since it determines the minimal dose for ruling out potential harmful effects. In addition, this limit acts as an orientation for establishing exposure limits. However, it has to be noted that not all substances have such dose-response relationships that are dependent on bioavailable doses. Particularly, CMR substances can cause adverse effects only with single molecules due to their properties such as carcinogenicity, mutagenicity, or reprotoxicity. Therefore, setting exposure limits would not pertain and an additional classification of such substances has to be considered as it is practiced in REACH (ECHA 2014).

In general, experimental tests constitute the basis for hazard assessments in order to analyze the toxicity of agents. Thus far, the experimental data or theoretically derived data from models are considered as the most reliable data (Renn et al. 2003). The toxicological tests can be conducted with bacteria, cells (in vitro), or with higher evolved organisms (in vivo). Besides, experimental test settings can vary in different parameters as for example: time (i.e., acute vs. chronically), kind and number of investigated species (single organism vs. microcosm), and analyzed end-points (e.g., growth inhibition test, toxicity, etc.).

Well-known margins of exposure for linear dose-response relations are the no-(observed-adverse)-effect-level (N[OA]EL). The margin describes the bioavailable concentration (i.e., dose) that does not cause an observable effect in the analyzed test system. The experimental test systems often have different limitations in terms of varied and considered parameters and represent only an abstract of the natural system. Additionally, the results for an organism are not necessarily transferable to another organism. This is the case when results from a lower evolved organism are adapted to higher developed organisms, for instance. However, if relevant data are missing, no broadly agreed approach on how to deal with uncertainty exists, so far (Renn et al. 2003).

Therefore, assessment factors are used in the REACH regulation to deal with such uncertainties. The determined margin of exposure is divided by the assessment factor to reduce the acceptable exposure concentration depending on the applied tests and investigated species (IPCS 2004; Van Leeuwen et al. 2007). The REACH framework R.10 defines different assessment factors ranging from 10 for long-term results from at least three species of the aquatic compartment to 10,000 for lowest short-term L(E)50² of three taxonomic groups for marine water compartment (ECHA 2012a). These adapted values are named predicted no effect level (PNEL) or derived no effect level (DNEL) that are applied in the subsequent risk evaluation step. With regard to the environmental hazard assessment, the extrapolated margin of exposure is named predicted no effect concentration (PNEC) (Van Leeuwen et al. 2007). Moreover, assessment factors also reduce efforts regarding experimental time and costs as well as ethical issues due to experiments. Finally, these values (PNEC or NOAEL) will be related to the (predicted) environmental concentration to assess the risk quotient, which both will be described in the following subchapter.

2.4.3 Definition and determinants of exposure

The focus of this thesis is on the environmental release and exposure assessment, which is why the term “exposure” and its influencing factors have to be introduced to provide the basis for a common understanding.

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Lethal (L) or effect (E) concentration (C) that can be observed at 50% of the population/organisms (ECHA 2012a).

Similarly to the risk term, the definition of exposure varies in different disciplines. Due to the variety of definitions and interpretations of the term exposure, the World Health Organization (WHO) started a harmonization project in 2000 in the context of the International Program on Chemical Safety (IPCS) and thereby acknowledged the increasing relevance of exposure assessment. The WHO project collected several definitions from 57 glossaries concerning risk assessment terms and created a meta-glossary with 39 definitions of general terms. The proposed definitions were evaluated by an interdisciplinary expert group and improved accordingly. The meta-glossary was proposed for interdisciplinary use to the International Society for Exposure Assessment (ISEA) that had finally agreed (Zartarian et al. 2005). These standardized definitions should support the knowledge exchange between the exposure research disciplines. Thus, the IPCS meta-glossary will be used as a basis in this thesis.

In the literal meaning, “exposure” can be understood as “being unprotected” or “to be in contact with something” (PONS 2015). Thereby, exposure is not only restricted to the contact with elements, but can be also extended to (harmful) influences or impacts with commonly biological, chemical, or physical (particularly radioactive) origin. The exposed entities are individual, organisms, (sub)populations, or (sub)systems that are generally called receptor, target organism, or exposed system. Therefore and depending on the context of the analysis, “exposure to a substance or influence” represents different situations with a single influence or combined influences on the receptor/target. The exposure is always linked to duration or time intervals as well as to a surface area. The exposed surface area is also named exposure surface.

As a result, the IPCS has defined exposure as (IPCS 2004, p.12):

“A concentration or amount of a particular agent that reaches a target organism, system or (sub-)population in a specific frequency for a defined duration.”

Furthermore, exposure can also be differentiated in “outer” (i.e., outside of the organism) and “inner” (i.e., inside of the organism) exposure. These terms are synonymously used as “concentration” and “dose”, respectively. The *concentration* is associated with the surrounding system or medium to which the potential receptor or target is exposed. In contrast, “dose” defines the bioavailable concentration, which is often lower compared to concentration due to different uptake mechanisms. The relation of the concentration (dependent on time “t” and quantity “q”) and the bioavailable dose is depicted in Figure 3.

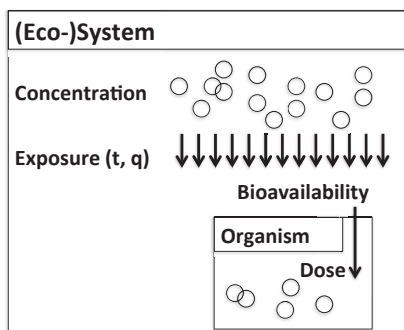


Figure 3. Relation of concentration and dose in exposure assessments. (own illustration)

The IPCS proposed the following definitions that will be applied in this thesis (IPCS 2004, p.12):

Concentration: Amount of a material or agent dissolved or contained in an unit quantity in a given medium, or system.

Dose: Total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population.

In order to understand the mechanism of exposure, it is helpful to have a look on the origin of the agent. Generally, before an entity is exposed to an agent, several steps have to be passed. These steps include the emission (or release), transmission of an agent, the exposure to an agent (cf. Figure 4).

At first, the *emission* of an agent is the source of exposure (IPCS 2004). The emission or release of an agent can be related to industrial manufacturing facilities or to products, which contain the agent. Following Fissan et al. (2013), the emission is best described by a factor that is defined as number, surface area, and/or mass (volume) released to the environment *per unit of time* in the context of industrial manufacturing facilities. In contrast, the release is best described by a release (factor) that is defined as number, surface area, and/or mass (volume) released to the environment *per unit of mass of produced or treated (nanostructured) material* (Fissan et al. 2013). Thus, the main difference of both terms is the relation to the denominator: per unit of time (i.e., emission) and per produced or treated (nanostructured) material (i.e., release). However, emissions and releases discharge the agent into the environment as a starting point of potential exposure. In the following chapters, the term release will be only used to describe the discharge of NOAAs into the environment related to the product matrix material.

Second, the released agent is discharged into a technical or environmental compartment. The released agent is transmitted and likely transformed (e.g., in the case of NOAAs due to hetero- or homoaggregation, or dissolution as described in chapter 2.6.2) or degraded in different compartments and transported to the final compartment(s) where it resides. This process is named *fate and behavior* of an agent, which also includes intercompartmental transfers. While technical compartments generally comprise wastewater treatment, waste incineration, and landfill to treat or store potential environmental releases (i.e., potential future releases in form of wastes), the environmental compartments are in turn differentiated in primary and secondary compartments. Within the primary and secondary environmental compartments the released agents can be transported and distributed in and between the compartments. The primary environmental compartments are the directly exposed compartments surface and marine water, soil, and atmosphere. In contrast, secondary environmental compartments are sediments and groundwater that are usually exposed to the agent only by intercompartmental exchange transfers. Third, after the transmission step, released agents may be transported (in pristine or transformed/degraded form) to the final compartmental system in which receptors are exposed to the released and transformed agent (see Figure 4).

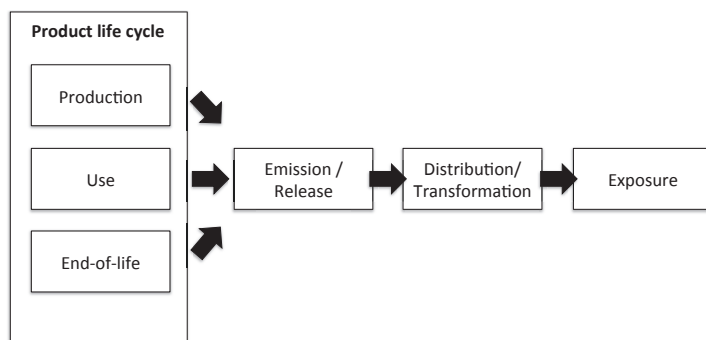


Figure 4. The origin of exposure from different product life cycle stages (own illustration)

Furthermore, when considering releases from products, the product life cycle stage has also relevant influences on the release and final exposure. Each life cycle stage (i.e., production, use, and EOL) is characterized by specific contexts. Particularly, when products are regarded, the life cycle stage and related contexts are major determinants of the exposure. For instance, safety measures in production systems, product design and corresponding use activities may have significant influence on release points and released species of the agent. Subsequently, release points determine the exposure pathways that are crucial information for later performed exposure route analyses (uptake mechanism by organisms, as for example oral, dermal, inhalation) (Lioy 2010). Therefore, it is helpful to additionally consider

the life cycle stage of the product/agent enabling the characterization of the later transported and, if possible, transformed agent.

Consequently, it is important to identify the relevant parameters determining exposure (IPCS 2004). A major influencing factor is the release source that influences the environmental concentration causing an exposure. Thereby, the product constitution (e.g., matrix material), applied safety measures (e.g., air filtration), and waste treatment influence the strength of the environmental release (Wigger et al. 2015a). Besides, also the product constitution can have significant influence on the exposure source. Particularly with regard to NOAA releases, it is relevant to gain knowledge on the released NOAA species as well as its further environmental transformations, since it is very likely that NOAAs will not be available in the pristine species at the point of exposure due to transformations (Mitrano et al. 2015).

The transformation of the agent depends on several factors. Hereby, the mobility and persistence of an agent are relevant aspects. The mobility allows agents to spread to various locations, whereas a higher persistence increases the long-range transport potential as well as the residence time of an agent. Together, both factors influence the exposure likelihood towards an agent. Finally, exposure assessments have to consider the environmental background concentration together with the additional agent to account for the complete exposure (IPCS 2004).

2.4.4 Exposure assessment as part of risk assessment

The exposure assessment is embedded in the second step of risk assessment and is usually conducted after or parallel to the hazard assessment. As the previous section has shown, exposure assessment can focus on different kind of receptors and target organisms with which the objectives vary. Furthermore, during the literature survey on the definition of exposure and its assessment, it became apparent that these terms are differently used depending on the respective scientific discipline. Therefore, the attempt was made to structure the connotations in Figure 5 to illustrate an overview on the used terms in the field of exposure science.

A general definition of exposure assessment is given by the IPCS as (IPCS 2004, p.12):

"The process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, pathways, routes, and the uncertainties in the assessment."

In addition, it has to be noted that not only a single agent can be investigated, but also combinational effects by several agents can be considered. This represents a more realistic scenario for environmental compartments and related exposure (Streffer et al. 2000).

In the context of risk assessment, exposure assessment can be differentiated into two main focal points: the human exposure assessment (HEA) and the environmental exposure assessment (EEA). The traditional HEA focuses on the direct exposure of workers (i.e., occupational health) and consumers (i.e., consumer health). The occupational health exposure assessments analyze work places in companies and attempt to evaluate the handled substances in order to limit potential exposure, if necessary. On the other hand, consumer products are investigated concerning potential releases (and exposures) in the context of consumer health. Besides, these subfields can also support hazard assessments by providing explanatory models for adverse effects, which are caused by the different exposure routes oral, dermal, and inhalative as well as the biodistribution. Due to this objective, HEA is closely related to human toxicology in risk assessment. Similarly, the EEA focuses on the same objectives, but analyzes different organisms that are exposed to the agent in environmental compartments. Thus, the EEA is related to ecotoxicology, where the effects of direct exposures are determined in experimental test settings (cf. Figure 5).

Another aspect of the EEA considers the environmental chemistry of substances such as chemicals or NOAAs (see Figure 5). The main objective of EEA is to analyze the agent's environmental fate and behavior. Furthermore, environmental concentrations are estimated for the compartments water (marine and surface water), soil, atmosphere as well as technical compartments, which is proposed by the REACH R.18 framework (ECHA 2012c). The environmental concentration is the indirect (or potential) exposure of organisms in the respective compartment.

Thereby, environmental concentrations are relevant for the human and ecologic related exposure assessment for experimental tests. Moreover, the potentially exposed receptor in a system, (sub)population, or organism must be identified within the HEA or EEA by modeling relevant exposure routes.

It has to be noted that wastewater treatment and sewage sludge are particularly relevant (see Figure 5), because the WWTP is a crucial point for the fate of released substances. For instance, agents can settle down as sediments into the sewage sludge. This sewage sludge can be applied as fertilizer to agricultural soils in several European countries, which may lead to other relevant exposure scenarios.

Field	<i>Human health (toxicology)</i>	<i>Environmental chemistry</i>	<i>Environment (ecotoxicology)</i>
Exposure focus	Direct Exposure	Indirect Exposure	Direct Exposure
Receptor/ target	Worker / Consumer	Compartment / Exposure pathway	Organism
Exposure routes	Dermal Oral Inhalative	Water Wastewater treatment Soil Atmosphere	Dermal Oral Inhalative
Kinetics	Biodistribution	Fate and Behavior	Biodistribution

Figure 5. Overview on aspects of exposure science with regard to different research fields, their foci, and interrelations. (own illustration)

Therefore, it is important to investigate and to evaluate the life cycle of agents (or products) as well as to determine qualitatively and quantitatively

- the release points and release amounts of the agent,
- the transport and exposure pathway,
- relevant transformations of the agent, and
- the (predicted or measured) environmental concentrations in the compartments.

In order to determine environmental concentrations, two principle approaches are available determining the measured environmental concentration or the predicted environmental concentration (PEC). Both are limited to a time frame and spatial area (Van Leeuwen et al. 2007; Lioy 2010). Likewise, both numbers represent the retrospective and prospective approach of exposure assessments, respectively (Mekel et al. 2007). As stated in section 1.2, the measurement of concentrations in environmental compartment is conducted after the release in a retrospective view (Lioy 2010). Thereby, retrospective approaches focus on already released agents, which is not in the sense of a precautionary strategy. Furthermore, retrospective assessments are used for biomonitoring, which is usually applied in human toxicology for determining past exposures (Paustenbach 2000; Lioy 2010). These methodologies are well developed for already known agents (Paustenbach 2000). However, they are not calibrated for analyzing new emerging substances.

Besides, exposure assessments also estimate concentrations by applying corresponding models in a prospective view (Paustenbach 2000). These models contain a model structure reflecting the relations between different entities and apply mathematical equations based on physical, chemical, or thermodynamical principles (e.g., fugacity approach from (Mackay

et al. 1992) to describe the relations between the entities. However, such exposure models cannot be easily validated. The most exact way would be if an environmental release has really occurred and can be measured (Dahme 1997). Therefore, the results have to be evaluated with regard to the model purpose and the assumed parameters (Berding et al. 1998; Cullen and Frey 1999). The modeling approach is further discussed in chapter 3.

Models can be further differentiated in deterministic and probabilistic models differing by their strategy to deal with uncertainties (Mekel et al. 2007). The former applies point estimates for parameters, whereas the latter uses probability distributions (Mekel et al. 2007). In the beginning, probabilistic modeling was mainly acknowledged in the U.S., but it also was increasingly credited and adopted later in Europe (Schümann 2000; Gottschalk et al. 2009). During the 1990s rather small and very specific models were developed, but with the turn of the millennium comprehensive environmental models were programmed for the risk assessment such as EUSES in the EU or CalTox in the U.S. (Lioy 2010). Nevertheless, the challenge to assess multiple agents in a test system in order to represent environmental relevant exposure (even in low dose level range) still prevails (Streffler et al. 2000; Callahan and Sexton 2007; Backhaus and Faust 2012; Altenburger et al. 2013).

2.4.5 Significance of exposure assessment in risk regulation and REACH

The previous section has already indicated an increasing relevance of exposure assessment in risk governance not only due to the development of comprehensive models, but also with the implementation of exposure aspects and the precautionary principle in the REACH regulation.

REACH provides a multilayered categorization scheme for chemicals, where companies have to register chemicals and provide the corresponding data for the risk assessment. Interestingly, with introduction of the REACH regulations in 2007, the conventional priorities in the risk assessment have explicitly shifted from hazard to exposure assessment at least equally emphasizing both aspects in the risk assessment of chemicals (Lioy 2010). This shift is implemented in REACH by the principle “*no data, no market*” (i.e., for hazards and exposures), which implies the registration, authorization, and evaluation (and eventually restriction) of new substances. Thereby, companies are obliged to deliver information on the substance depending on the production volume, if they want to sell new substances in the European market. In doing so, in a first step, REACH emphasizes two aspects, which were not regulated so far. First, REACH shifts the burden of proof from the state to the applying companies (Williams et al. 2009). Second, the exposure assessment attains a higher significance compared to the hazard assessment (in a first step) due to the connection of the required data with the production volumes of a substance (Schaafsma et al. 2009). The production volume determines the overall release and exposure potential. In REACH, the

annual production volumes are categorized into 1-10 tons, 10-100 tons, 100-1000 tons, and more than 1000 tons. During the registration process, companies have to deliver information on hazard and exposure, whereby the data requirements for hazard assessment increase with the production volume. For production quantities below 10 tons less extensive experiments are required. Above this level of 10 tons, the required data for hazard assessments throughout the complete life cycle is differentiated for several cases, which is also named “exposure-based waiving” or “exposure-triggered testing” (ECHA 2011).

Additionally, categories of reasons for concern are implemented addressing also exposure relevant issues. Particular reasons for concern are substances that are very persistent and very bioaccumulative (vPvB) or are very persistent, bioaccumulative, and toxic (PBT) (Vermeire et al. 2010; ECHA 2014). The assessment of PBT and vBvP properties has to be conducted for all substances with a production volume more than 10 tons (ECHA 2014).

The exposure assessment in REACH is a two-tier approach where the applicant first has to define possible exposure scenarios. Based on this, the second step focuses on the exposure estimation (Schaafsma et al. 2009). The exposure scenarios describe potential situations of exposure throughout the life cycle of the substance. For this purpose a categorization scheme with more than 50 descriptors was developed that standardizes potential exposure scenarios and applies also generic data sets (if measured data is not available). Thereby, several main descriptors were defined representing and summarizing standard activities with the corresponding exposure data. These main descriptors are classified in the economic sector of use, chemical product category, process category, article category as well as the ERCs (ECHA 2012e). The standard values are derived from the Technical Guidance Document of the European Chemical Bureau, ECETOC Targeted Risk Assessment³, ConsExpo (consumer exposure), NACE⁴, and OECD emission scenario documents (ECHA 2012e). Altogether, worst-case values for potential releases and exposure are provided with the focal points on production and use of chemicals. These values can be accordingly corrected, if risk management measures are applied or exposure data is available (ECHA 2012e).

By applying this approach in REACH, the aspects of prospective exposure assessments became relevant by adapting the required data for hazard assessments depending on exposure scenarios. Nevertheless, despite the streamlined risk assessment process, the number of substances that still have to be tested is comparably high, which is why different strategies for improving the REACH framework are discussed (Bunke et al. 2006; Marquart et al. 2006; Bruinen de Bruin et al. 2008; Schaafsma et al. 2009; Blainey 2009). However, in the

³

European Center for Ecotoxicology and Toxicology of Chemicals

⁴

Nomenclature Générale des Activités Economiques dans les Communautés Européennes

(European) regulation of nanomaterials several challenges exist, since the established frameworks for chemicals do not necessarily pertain for nanomaterials (cf. chapter 2.7)

2.5 Nanomaterials as technological innovation

The following sections will describe the applied definition of nanotechnologies and nanomaterials, which will act as the common basis for this thesis. Furthermore, the material properties of both IONPs and AgNPs will be determined regarding the nano-specific as well as bulk material characteristics. Finally, an overview on applied synthesis routes will be given.

2.5.1 Definition of nanotechnologies and nanomaterials

In the course of the last years, several definitions were formulated to determine nanotechnologies and nanomaterials, which additionally differed among the institutions and organizations (Boverhof et al. 2015). While nanotechnologies can be understood as a platform of diverse enabling techniques (Gleich et al. 2008; Miller and Wickson 2015), nanomaterial-specific definitions mostly agreed on the size of below 100 nm in one dimension of nanomaterials (Palmberg et al. 2009; Boverhof et al. 2015). However, definitions are distinct in covering natural and artificial particles as well as agglomerates and aggregates (Boverhof et al. 2015).

The European Commission (2011) recommended the following definition for nanomaterials that should be an orientation for stakeholders:

“A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm. By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.”

With this definition, the European Commission also includes natural nanomaterials and implemented the size distribution as another relevant aspect, because it is unlikely that samples contain 100% nanoparticles. However, the public review for this definition was conducted in 2015 and the concluding results are expected in the course of 2016 (European Commission 2016).

The International Standard Organization (ISO) applies another definition with focus on engineered nanomaterials. ISO/TS 80004:2015 defines a nanomaterial as:

“...a material with any external dimension in the nanoscale of 1 nm – 100 nm or having internal structure or surface structure in the nanoscale including nano-objects and nano-structured material, as well as aggregates and agglomerates of these materials (NOAA).”

The term **nano-object** includes not only the commonly known spherical nanoparticles, but also other primary particles such as nanocubes, nanopyramids, nanowires, nanostructures (two-dimensional), nanorods, quantum dots, for instance. Furthermore, nanoobjects can form **agglomerates**, which consist of a “collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components” (European Commission 2011). In contrast, **aggregates** are formed “by strongly bounded or fused particles” (European Commission 2011).

This thesis will focus on engineered metal and metaloxide nanoparticles, which is why the ISO definition will be applied throughout the chapters. The following sections will now characterize the two selected materials silver and iron oxide and their related material properties in bulk and nano-size.

2.5.2 Properties of iron oxide in bulk- and nanosize

Iron is an abundant element in nature and accounts for the fourth most common element in the Earth’s crust (Fleischer 1953; Wedepohl 1995). Iron oxides can be classified into sixteen mineral forms (Cornell and Schwertmann 2003c). The most frequent forms are magnetite (Fe_3O_4) and hematite ($\alpha\text{-Fe}_2\text{O}_3$) (Cornell and Schwertmann 2003c). Both are distinct by the degree of oxidation. In contrast, zerovalent iron, that is non-oxidized iron, only exists in certain natural conditions and is thus very rare (Cundy et al. 2008). Consequently, iron occurs in environmental compartments often as chemical compounds together with an oxygen group and/ or a hydroxyl group (Cornell and Schwertmann 2003c; Cundy et al. 2008). Magnetite (Fe_3O_4), maghemite ($\gamma\text{-Fe}_2\text{O}_3$), and hematite ($\alpha\text{-Fe}_2\text{O}_3$) are the most relevant mineral forms of iron for technical applications (Teja and Koh 2009).

Classical applications of iron oxide are listed below with decreasing relevance (Cornell and Schwertmann 2003a), for example:

- pigments for the paint and construction industry,
- magnetic pigments and ferrites,
- catalysts for industrial synthesis (Haber-Bosch, Fischer-Tropsch process),
- raw materials for the iron and steel industry,
- adsorbents for water and gas purification as well as for the decontamination of low level radioactive waste, and
- ferrofluids.

Besides, iron oxides are used in several research disciplines due to their abundance and bio(chemical) properties and the involvement in several essential biological processes (Cornell and Schwertmann 2003c). Figure 6 illustrates the variety of research disciplines. For example, in medicine iron (oxide) is analyzed regarding the cause of the iron overload syndrome (defective iron storage) and the related polynuclear-organic complexes (Siddique and Kowdley 2012). Iron (oxide) is also investigated with regard to biomineralization processes of bacteria communities in biology (Miot et al. 2014). Furthermore, the protein ferritin plays a major role in transport processes, iron storage, and hemoglobin synthesis (Finazzi and Arosio 2014) as well as the navigation sense of animals and organisms (Wiltshcko and Wiltshcko 2013). In environmental chemistry studies, iron (oxide) is also investigated with regard to the role in sorbents and oxidants (Guo et al. 2016). Iron oxides are also involved in the research of crystal chemistry (structure of crystals and the associated properties) and sorbants (Leblanc et al. 2015). The applied research mainly investigates iron (oxides) for pigments, tapes, and catalysts (Ziebart et al. 2012). Moreover, research on iron (oxides) in soil sciences focuses on sorbents, redox buffering (constraining oxygen fugacity), aggregation, plant nutrients, pedogenesis (soil evolution); the iron content serves as a criterion for soil classification (Colombo et al. 2013). The geology sciences carry out research on rocks, palaeomagnetism, and ores (Schmidt 2014b). Finally, mineralogy studies are interested in the crystal structure, properties, and the formation of iron oxides (Kaminsky 2012; Ayris and Delmelle 2012).

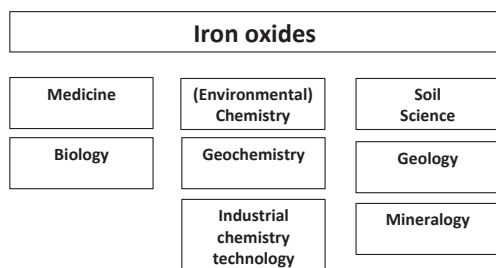


Figure 6. Applications of iron oxides in several research disciplines. Adapted from (Cornell and Schwertmann 2003c)

In material science perspective, iron oxides show different material properties. The magnetic moment of iron oxides differ between ferromagnetic and antiferromagnetic depending on the crystal structure and oxidation state (Cornell and Schwertmann 2003c). The magnetic properties are primarily used in magnetic tapes (data storage) in which pigments of iron oxide are embedded. Furthermore, iron oxides can be used in wood color (or other façade color) to affect an UV-blocking (or blocking of electromagnetic waves) due to reflection, scattering, and absorbing mechanisms (Cornell and Schwertmann 2003a). Generally, each element has a specific refraction index leading to the blocking of different ranges of wavelength. Nevertheless, iron oxides are less used in cosmetics, for example, in which

titanium dioxide and zinc oxide prevail due to their optical properties. Both titanium dioxide and zinc oxide are able to absorb a broader range of wavelengths (Weber and Schulmeister 2007). Besides, iron oxides offer a wide range of colors that are used in the color and lacquer industry (Cornell and Schwertmann 2003a). Iron oxides have also catalytic properties, which are applied as industrial catalysts (Cornell and Schwertmann 2003a).

Properties of iron oxide nanoparticles

Compared to the bulk material (i.e., iron oxide in non-nanometer size), IONPs have several advantages by showing enhanced or novel material properties (Deng et al. 2005; Jorand Sartoretti et al. 2005; Liang et al. 2006; Teja and Koh 2009), which emerge with smaller particle sizes. Interestingly, IONPs show a superparamagnetic behavior. Superparamagnetism represents a state of IONPs in which no magnetization and remanence (i.e., without a naturally remaining magnetization) is present. Thus, the superparamagnetic property enables an on-demand magnetization by applying external magnetic pulses (Wigger et al. 2015a).

The observed superparamagnetism results from different randomly orientated magnetic domains (i.e., Weiss-fields). Depending on the material characteristics, the average magnetic moment is equal to zero during the measurement interval without an applied external magnetic field (Kolhatkar et al. 2013). The superparamagnetism is caused by thermal fluctuations in the nanoparticle, which is equal to or greater than the energy barrier for the moment reversal, and is usually above the material specific blocking temperature (Kolhatkar et al. 2013). The magnetic moments accordingly flip and neutralize each other in the measurement interval, which defines a superparamagnetic behavior (Kolhatkar et al. 2013). The superparamagnetic effect depends on several factors such as particle size, particle shape, blocking temperature, and material compositions (Chalasani and Vasudevan 2011; Kolhatkar et al. 2013). In particular, the particle size and the superparamagnetic properties are material dependent (Kolhatkar et al. 2013). For instance, Mandarano et al. (2010) observed the superparamagnetic effect when the ferromagnetic domain is smaller than the hydrodynamical diameter. Other studies showed that the maximal particle diameter of approximately 30 nm is sufficient to create a superparamagnetic effect, whereas the critical particle size was determined with 15 nm (Gupta and Gupta 2005; Corot et al. 2006). Additionally, the group of Neuberger et al. (2005) identified a particle size of 10 nm as critical diameter for superparamagnetic effects at room temperature.

Besides, the magnetic properties of IONPs vary compared to the bulk counterpart. IONPs have a low Curie temperature (i.e., the loss of ferromagnetic moments and the beginning of paramagnetic properties), high coercivity (i.e., the ability to resist an external magnetic field

without being demagnetized), and a high magnetic susceptibility (i.e., the degree of magnetization in response to an external magnetic field) (Wu et al. 2008).

Moreover, IONPs have enhanced (conventional) material properties compared to the bulk material. The optical and catalytic properties can be enhanced due to the nanometer size of iron oxide (Kelly et al. 2003; Sohn and Cohen 1997; Shi et al. 2007). As a reasonable explanation for the enhanced reactivity, El-Sayed (2001) suggested that the electron density at the particle surface area affects these material properties. This is because with decreasing particle size, a higher amount of electrons are located at the surface area, which potentially interact with surrounding substances. The electron density depends on the morphology. For example, triangular particles have a higher electron density at the edges than spheric particles, which leads to a higher reactivity (El-Sayed 2001; Teja and Koh 2009; Zhen et al. 2011). With regard to optical properties, IONPs appear transparent in the nanometer range in thin-films (Ziolo et al. 1992). Table 2 summarizes characteristics of iron oxide in bulk- and nanosize, respectively.

Table 2. Comparison of chemical, physical, and mechanical properties of iron oxide in bulk- and nanosize.

	Chemical		Physical / Optical		Mechanical	
Bulk	catalytic effect	(Cornell and Schwertmann 2003c)	coloring effect	(Cornell and Schwertmann 2003c)	abrasion resistant	(Cornell and Schwertmann 2003c)
	binding of heavy metal ions or organic chlorides		blocking of ultraviolet waves and electro-magnetic fields			
			thermal conductive			
			electric conductive			
			(anti-)ferromagnetic			
Nanosize	enhanced catalytic properties	(Shi et al. 2007)	transparent (e.g., in thin-films)	(Ziolo et al. 1992)	structure reinforcing	(Li et al. 2006)
			low Curie temperature	(Wu et al. 2008)		
			high coercivity			
			high magnetic susceptibility			
			superparamagnetic	(Gupta and Gupta 2005; Corot et al. 2006)		

Reference: (own illustration)

2.5.3 Properties of silver in bulk- and nanosize

The concentration of silver amounts to 0.07 ppm in the Earth's crust, which is relatively low compared to iron oxide, whereas copper has a higher concentration with 25 ppm (Wedepohl 1995). Consequently, silver costs more than copper on the market. Copper has similar

material properties like silver and therefore copper can often substitute silver in many applications (Brumby et al. 2011). Silver is available in natural ores as oxides or sulfide compounds (Brumby et al. 2011). The production of silver from primary silver resources (i.e., ores) prevails, and, however, is completed by the production from secondary resources of recycling processes (Silver Institute 2013). In the primary production, silver is extracted in genuine form, but it is also extracted as a by-product in the copper, zinc, and lead production (Silver Institute 2013).

Bulk silver is known for its outstanding material properties in terms of electrical and thermal conductivity. Silver's electrical conductivity is the second best with 61.36×10^6 A/Vm, whereas the thermal conductivity is reported with 430 W/mK. Thus, silver has also a very low electrical resistance, which is why silver is frequently used in electronic industries. Moreover, silver is applied as a catalyst in the epoxidation of ethylene to ethylene oxide (Goncharova and Paukshtis 1995). Ethylene oxide is a raw material for the production of chemical substances such as ethylene glycol or polyester.

Furthermore, silver is known for its optical properties, which are used in mirror surfaces. In the analogous photography silver pigments are implemented in light sensitive papers for the film development, but it has shown a decreasing trend with the rise of digital photography (Silver Institute 2013).

Besides, silver is antimicrobially effective against several pathogens. The antimicrobial property was also used in silverware, tableware, and drinking water, since the medieval times in order to reduce exposures against potential diseases (Bhattacharya and Mukherjee 2008). So far, the mechanism of the antimicrobial effect of bulk silver, but also AgNPs, is not fully clarified (Reidy et al. 2013). It is supposed that dissolved silver ions cause these antimicrobial effects (Reidy et al. 2013). Besides, it is assumed that silver ions interact with thiol groups (-SH) at the cell wall of bacteria, which likely lead to the inhibition of essential cell processes. This is often regarded as the main mechanism of the antimicrobial activity (Reidy et al. 2013). Furthermore, silver ions can also link to the DNA and interfere with metabolic processes due to its strong sulfur affinity (as almost every metal) (Cho et al. 2005; Silvestry-Rodriguez et al. 2008).

Properties of silver nanoparticles

AgNPs show not only enhanced but also novel properties in the nanometer scale. Nevertheless, the antimicrobial effects seem to be the most discussed aspect in the scientific (risk assessment) literature. Thereby, the enhanced antibacterial effects were shown against bacteria and fungi (Navarro et al. 2008; Kittler et al. 2010). Also, antiviral effects (e.g., against HIV-1 virus) of AgNPs were reported (Elechiguerra et al. 2005). Since the mechanism of the antimicrobial effect is not completely understood, the theories about the mode of the

effect are focused on nanoparticles and silver ions. Sotiriou and Pratsinis (2010), for instance, assumed that both components contribute to the antimicrobial effect. Interestingly, higher toxicities were reported at lower concentrations and particle sizes (Beer et al. 2012). A reasonable explanation for this phenomenon would be the higher dissolution rate of ions due to the smaller particle size, which supports the silver ion theory (Le Ouay and Stellacci 2015). Especially, the particle properties and the media (environmental, human media, etc.) have to be thoroughly characterized to enable a comparison of different research studies (Bouwmeester et al. 2011; Beer et al. 2012). However, a final conclusion was not yet drawn (Beer et al. 2012; Reidy et al. 2013; Hadrup and Lam 2014).

Moreover, it was shown that dissolved silver ions can lead to the formation of reactive oxygen species causing oxidative stress in cells that lead to inflammatory reactions (Loza et al. 2014; Gaillet and Rouanet 2015). Additionally, AgNPs are more mobile than bulk silver particles. Therefore, it is expected that AgNPs can distribute easier to other biological locations by passing membranes (Hadrup and Lam 2014). Furthermore, AgNPs can also serve as a silver ion depot, whereby AgNPs are present in the cell and act as a reservoir with slowly dissolving silver ions leading to a long-term exposure. In this context, also the Trojan horse effect is discussed (Park et al. 2010; Hsiao et al. 2015). The Trojan horse effect is related to the transport of AgNPs from the extracellular into the intracellular space as for example shown by Hsiao et al. (2015).

Besides, AgNPs have remarkable plasmonic properties. The plasmonic properties result from the collective oscillation of electrons that interact with light waves. This effect can be used for visualization in biosensing or novel data storage mechanisms (Lal and Link 2007; Sotiriou et al. 2010; Sotiriou et al. 2011a). Furthermore, researches focus on the size-dependent optical properties of AgNPs for colors (Emory et al. 1998)

Table 3 illustrates an overview on the discussed properties of both the silver in bulk form and AgNPs.

Table 3. Comparison of chemical, physical, and mechanical properties of silver in bulk- and nanosize.

	Chemical		Physical / Optical		Biological	
Bulk	catalytic effect	(Goncharova and Paukshtis 1995; Brumby et al. 2011)	electrical conductive	(Brumby et al. 2011)	antimicrobial	(Navarro et al. 2008; Kittler et al. 2010)
			thermal conductive		antibacterial	
					fungicidal	
					antiviral	
Nanosize	enhanced catalytic effect	(Jana et al. 1999; Brumby et al. 2011)	other optical properties (size-dependent colors)	(Lal and Link 2007; Brumby et al. 2011; Sotiriou et al. 2011b)	enhanced antimicrobial	(Elechiguerra et al. 2005; Navarro et al. 2008; Kittler et al. 2010)
			plasmonic properties		enhanced antibacterial	
					enhanced fungicidal	
					enhanced antiviral	

Reference: (own illustration)

2.5.4 Synthesis of nanomaterials

The synthesis of NOAAs can be conducted in a top-down or bottom-up strategy (Laurent et al. 2008; Qiao et al. 2009). According to Mahmoudi et al. (2010) and Tran et al. (2013) the top-down approaches are comparably less investigated in the scientific literature. Such approaches follow the strategy to decompose (bulk) material by physical means in several iterations to receive the material in the desired size. Examples for top-down approaches are: pulsed laser ablation, laser induced pyrolysis, and powder ball milling (Mahmoudi et al. 2010; Tran et al. 2013). Generally, the physical strategies are not prevailing due to their rather polydisperse results and less modification options (e.g., particle size and shapes as well as coatings). Hence, the chemical bottom-up approaches are dominant that allow producing batches with monodisperse size distributions due to the better control of the crystal growth (Laurent et al. 2008; Mahmoudi et al. 2010). Besides, the bottom-up approach can better control the design of the particle morphology and coating especially in liquid media (Mahmoudi et al. 2010). The third approach category is based on the biomimetic synthesis routes. For this purpose, magnetotactic bacteria, proteins, and fungi organisms were analyzed. However, this synthesis approach is still not reliable due to the low production volumes and polydisperse particle size distributions. Consequently, Mahmoudi et al. (2010) identified only some studies applying biomimetic approaches.

In general, the nanomaterial has to fulfill different demands that are related to the application. In consequence, the research on nanoparticle synthesis routes has also broadened the perspective on potential surface modifications. Several kinds of surface modification strategies exist aiming at the particle stability to avoid agglomeration or precipitation in different media. Additionally, particle surfaces can be intentionally designed to control material properties and environmental behavior in specific media (Wu et al. 2008;

Laurent et al. 2008; Gao et al. 2009). Different kinds of materials can be used for surface modifications of NOAAs. Wu et al. (2008) have differentiated potential surfactants into organic and inorganic substances. Organic surfactants comprise small molecules, polymers, and biological molecules. Especially for IONPs, small molecules with oil-soluble, water-soluble, or amphilic characteristics are investigated in terms of the synthesis control, particle stabilization, and additional properties. Examples for such surfactants are oleic acid, lactic acid, different alkyl phosphates, and silanes (Wu et al. 2008). Typical polymers can have both natural origin such as dextran, starch, and chitosan, or artificial origin such as polyethyleneglycol, polyvinylpyrrolidone (PVP), and polyacrylic acid. Additionally and in particular for drug delivery systems, biological molecules like DNA or proteins are bounded to the particle surface to create a specific transport behavior in the human body (Wu et al. 2008; Laurent et al. 2008; Gao et al. 2009). Moreover, Wu et al. (2008) gave examples for inorganic surfactants such as metals (e.g., silver, gold, or different kinds of quantum dots), non-metals (e.g., carbon), and metal oxides (e.g., zinc oxide, magnesium oxide, etc.).

However, it has to be noted that modified surfaces will drastically change the characteristics of the nanomaterial. Besides, the environmental fate and behavior is influenced by these modifications (Mitrano et al. 2015). The aspect of the environmental behavior will be discussed in section 2.6.2.

2.6 State-of-the-art in the assessment of NOAA exposures

Generally, scientific studies considering the exposure to NOAAs can be differentiated into experimental tests and theoretical models. Experimental tests investigate single aspects of environmental fate and behavior of NOAAs as well as environmental releases from a nano-enhanced product. In contrast, theoretical models apply and combine the knowledge gained within experimental studies. Thereby, models theoretically represent certain stages of the product regarding potential NOAA releases. If no data is available, reasonable assumptions can be implemented in the model to estimate the environmental concentration of NOAAs.

This section summarizes the state-of-the-art in the EEA of NOAAs with special focus on AgNPs and IONPs, which are the selected NOAAs for this thesis. Thereby, the aspects of release, fate and behavior as well as integrated models will be described in more detail. Finally, this section closes with the description of existing challenges in the EEA of NOAAs.

2.6.1 Scientific studies on environmental NOAA releases

As stated in section 2.4.3, the source of exposure is the environmental release of NOAAs. Thereby, the occupational safety and health aspects received a lot of attention in the early years of scientific research by investigating potential releases at work places (e.g., production, handling, and formulation). Since the thesis will focus on environmental releases from products, the reader is referred to following articles on occupational safety and health

aspects: Maynard and Kuempel (2005), Brouwer (2010), Koponen et al. (2010), Kuhlbusch et al. (2011), and Tsai et al. (2011) as well as Kaminski (2015), Brenner et al. (2015), Brouwer et al. (2013), and Pietroiusti and Magrini (2014).

In contrast, the number of studies that investigated the NOAA releases from products increased only in the last years. Consequently, only some knowledge regarding the releases from products were gained, primarily due to the early stage of research and development of nanotechnologies (Wigger et al. 2015a). In general, these studies investigated single mechanical, thermal, or chemical influences affecting the NOAA-enhanced product during usage. Typical investigated materials were titanium dioxide, zinc oxide, carbon nanotubes, silver nanoparticles, cerium dioxide, copper, and silica as well as their integration in composites (Froggett et al. 2014). Reasons for these selected NOAAs are the likely high production volumes or an expected toxicological potential. In contrast, IONPs have not yet received great attention in environmental exposure assessments. An exception is the application of zerovalent IONPs for ground water remediation (Fu et al. 2014). The number of field studies with regard to AgNPs containing products was comparably higher. These studies on AgNP-enhanced products considered surface coatings, food packaging, sprays, and textiles (Lorenz et al. 2011; von Goetz et al. 2013b; Mitrano et al. 2014; Wigger et al. 2015a).

Thereby, textiles were among the most analyzed applications regarding AgNPs. One reason is that previous studies on clothing textiles have shown controversial results, since very high as well as very low release rates of AgNPs were reported (Benn and Westerhoff 2008; Geranio et al. 2009; KEMI 2012; Wigger et al. 2015a). Another reason may be that clothing textiles containing AgNPs are already available in consumer stores. The potential environmental releases throughout the product life cycle depend on several factors. Benn and Westerhoff (2008) and KEMI (2012) analyzed several kinds of clothing textiles as well as other textile products and discovered that release rates can vary considerably. Thus, it was concluded that the type of incorporation influences the release potential to a high degree (Benn and Westerhoff 2008; Som et al. 2010b). Furthermore, it was summarized that most of NOAAs are likely to end up in wastewater (Lorenz et al. 2011; von Goetz et al. 2013b; Mitrano et al. 2014), if no other release points are relevant during the product usage (Wigger et al. 2015a). Also, waste management systems (WMS) with their exports can play a major role in the final (geographical) fate of the NOAAs (Wigger et al. 2015a). Additionally, Geranio et al. (2009) analyzed the release forms of NOAAs from clothing textiles, since the released species significantly determine the further fate and behavior of NOAAs. They analyzed that the major fraction of the released AgNPs occurred as agglomerates with a size bigger than 450 nm after laundering processes.

Besides the laundering process, Kulthong et al. (2010) and Yan et al. (2012) investigated the influence of perspiration on AgNP releases from clothing textiles using artificial liquids. Thereby, Kulthong et al. (2010) identified quite diverse ranges of quantities released. The quantities depended on the perspiration liquid composition (that varies in different human body regions), fabric quality, and AgNP content. Yan et al. (2012) examined the released AgNP species with regard to the perspiration solution. They concluded that AgNPs are transformed to ionic state in alkaline perspiration solution. In contrast, AgNPs mainly remain in particulate state in saline perspiration solutions, whereas AgNPs agglomerate to sub-micrometer particles and also dissolve in acid perspiration liquids (Yan et al. 2012).

Moreover, façade coatings were investigated by Kaegi et al. (2008) and Kaegi et al. (2010). The façade was coated with a paint containing titanium dioxide nanoparticles (Kaegi et al. 2008) and in a second study also mixed with AgNPs (Kaegi et al. 2010). The coated façades were exposed to weathering influences and the runoff was collected and analyzed. A significant fraction of TiO_2 was identified in the collected runoff having a size below 100 nm. The second study on AgNP façade coatings measured release rates with $145 \mu\text{g/l}$. Thereby within one year; approximately 30% of the AgNPs were released with a particle size below 15 nm. However, the released AgNPs were agglomerated and bonded to the organic binder. Finally, the released AgNP debris was later transformed to Ag_2S – a less toxic form of silver (Kaegi et al. 2010).

Furthermore, cosmetics and sprays were analyzed regarding quantities and species of NOAAs released. Hagendorfer et al. (2009) and Lorenz et al. (2011) showed that the spray mechanism has a major impact on the presence and dispersion of NOAAs in the sprayed aerosol. This effect was observed with sprayers that use gas cartridges for the nebulization compared to manual pump-based sprays (Lorenz et al. 2011). The type of spray mechanism is relevant for the inhalation exposure route. Cosmetics were directly investigated by Lorenz et al. (2010) and Gondikas et al. (2014). Lorenz et al. (2010) set up a qualitative framework for exposure estimation of NOAAs used in cosmetics by considering several factors that affect the exposure likelihood. Gondikas et al. (2014) experimentally analyzed the titanium level at the Old Danube Recreational Lake in Austria, which is frequently used for bathing in summer time. Due to the challenging measurement and differentiation of nano- TiO_2 from bulk titanium, the elemental level of titanium was compared to environmental levels of other elements in order to make relative changes visible (Gondikas et al. 2014). The investigations showed a small increase in the elemental titanium level compared to the background concentration (Gondikas et al. 2014). Finally, Gondikas et al. (2014) supposed a rather short residence time of the TiO_2 nanoparticles in the surface water (Gondikas et al. 2014).

Besides, polymer composites with embedded NOAAs were also investigated in the last years. The studies had primarily focused on TiO_2 and SiO_2 , two typical additives for paints (Gheerardyn et al. 2010; Koponen et al. 2010; Golanski et al. 2011). Furthermore, carbon nanotubes composites were analyzed in other studies (Wohlleben et al. 2013; Kingston et al. 2014; Harper et al. 2015). So far, all conducted studies state that NOAAs will be not released as pristine particles, and will likely stay embedded in, or bounded to the matrix material (Gheerardyn et al. 2010; Koponen et al. 2010; Golanski et al. 2011). This also pertains for CNT modified polymer composites (Kingston et al. 2014; Harper et al. 2015). However, it is assumed that the main release of NOAAs within the life cycle happens in the production and formulation stage, whereas the use stage has a rather low likelihood to release NOAAs (Kingston et al. 2014). Abrasion and degradation are understood as major influences affecting release of NOAAs in the use stage. However, in current applications only low material impacts are expected (Harper et al. 2015). Thus, a release of NOAAs seems to be rather unlikely (Kingston et al. 2014). This may pertain for hard matrix materials. Nevertheless product releases are depending on the matrix material properties and a certain combination of use activities. So, soft matrix materials can have higher release potentials (Wigger et al. 2015a). Furthermore, degradation processes can be the initial step for an environmental release, but they do not necessarily lead to emissions of NOAAs (Nowack et al. 2013).

2.6.2 Environmental fate and behavior of NOAAs

This section deals with the potential distribution and transformation of NOAAs in environmental compartments and gives a basic overview on the scientific literature. For the interested reader a more in detail review can be found in Gottschalk et al. (2013) and Wagner et al. (2014).

The crucial information for exposure and hazard assessment is the NOAA species and their quantities that are present in the environmental compartment. NOAAs can be very mobile and can undergo various transformations (Harper et al. 2015). Unlike chemicals, NOAAs are present in a solid particulate form and thus show a different environmental behavior. For NOAAs, Hartmann et al. (2014) categorized potential transformation varieties, which are differentiated in physical, chemical and (photo)chemical transformation processes, interaction with other substances and surfaces as well as biological transformations.

Physical transformation processes

Physical transformations cover homo- and heteroagglomeration/-aggregation as well as sedimentation or deposition (Lowry et al. 2012; Hartmann et al. 2014; Wagner et al. 2014). Also, biological mediated processes initiated by organisms can lead to a transformation of the initially released NOAAs (Lowry et al. 2012; Hartmann et al. 2014). For all potential

transformation processes it pertains, the environmental fate and behavior is determined not only by the physico-chemical properties of NOAAs, but also by the chemistry of the surrounding system (Wagner et al. 2014).

Aggregated particles consist of several primary nanoparticles (i.e., the pristine particle), which are strongly bounded having the same crystal structure. The surface area of aggregated particles is relatively smaller than the surface area of single primary particles (Walter 2013). Aggregated particles have a strong bonding and can be separated when high-energy processes are applied. Compared to aggregation, agglomeration represents only a rather loose assemblage of primary particles, which can be easily separated without high-energy inputs. The relative surface area is similar to the summarized surface area of the primary particles (Walter 2013). Aggregation can occur with the same kind of particles or with distinct particles. The former aggregation type is named homoaggregation, whereas the latter is called heteroaggregation. Homoaggregation is one major mechanism in saturated media (Wagner et al. 2014). However, due to the unsaturated status of natural systems regarding NOAAs (Wagner et al. 2014), it is very likely that heteroaggregation kinetics will play a major role (Dale et al. 2015a).

Generally, Brownian motion, fluid motion, and differential settling are the main aggregation mechanisms, where the Brownian motion is the most relevant for particles smaller than 300 nm (Wagner et al. 2014). Furthermore, attractive and repulsive forces, as well as hydrophobic interactions, steric repulsion, polymer bridging, magnetic and hydration effects drive the aggregation behavior (Wagner et al. 2014). Especially, regarding soil and sediments, the physical sorption is relevant due to the presence of natural organic matter (Hartmann et al. 2014). Natural organic matter such as humic acid, fulvic acid, and proteins are also existent in aquatic compartments (Wagner et al. 2014). Additionally, the sorption with other substances will influence and change the surface chemistry of a particle, which in turn will likely lead to a different environmental behavior (Wagner et al. 2014; Dale et al. 2015a; Hartmann et al. 2014). The review article from Wagner et al. (2014) pointed out that the pH-value, ionic strength (i.e., concentration of ions in the solution), electrolyte valence (quantity of dissolved substances), and the particle coating (e.g., particularly organic substances) determine the aggregation behavior of NOAAs.

The aggregation also influences the sedimentation/deposition properties of NOAAs, since bigger particles tend to settle down faster than smaller particles. In aquatic and soil compartments, key parameters are the aggregation, solubility, dissolution and dispersion as well as sedimentation that determine the environmental fate and behavior of NOAAs, which still needs to be understood (Meesters et al. 2013). While the dispersed particles maintain their solid state in an aqueous medium regards particles, dissolved particles and their solubility depends on several chemical processes.

Chemical and biological transformation processes

The chemical transformation reduction-oxidation (redox) reaction and dissolution are often interrelated. The redox reaction describes the exchange of electrons between two (or more) atoms or molecules. In a reduction reaction an atom or molecule receives electrons, whereas in the oxidation reaction the atom or molecule donates electrons. Thus, both processes are always coupled and often reversible (Wagner et al. 2014). The redox potential is determined by the availability of reductants or oxidants as well as the pH-value. Moreover, it is supposed that the redox state has an influence on the toxicity of NOAAs as it is discussed for AgNPs and silver ions (Hartmann et al. 2014; Louie et al. 2014; Wagner et al. 2014).

Moreover, redox processes are the basis for dissolving substances in liquids (Hartmann et al. 2014). Dissolution is described as the property of a substance to dissolve homogenously in a solvent and is represented by the solubility limit saturation concentration (Fechner et al. 2007). Particle and solution properties drive the dissolution potential. Several dissolution processes are known and illustrated in Figure 7. Following Wagner et al. (2014), the dissolution potential is characterized by the solubility constant, chemical speciation, and the specific surface area (i.e., also particle size). Furthermore, the dissolution is influenced by surface strain (i.e., relative displacements of surface atoms), crystallinity, crystal phase, structural anomalies, particle size, and temperature (Wagner et al. 2014). Besides the dissolution of ions in the surrounding media, dissolved NOAAs can also link to other ligands and complexes (i.e., natural organic matter). AgNPs have a high affinity for chlorides (AgCl) or sulfides (Ag₂S). These kind of AgNP species have a lower dissolution potential with a different surface chemistry in turn (Louie et al. 2014). Consequently, the environmental behavior of formed complexes with natural organic matter will change as well. However, it was also reported that dissolved metal ions (as well as ligands) can re-precipitate in certain conditions (Wagner et al. 2014; Louie et al. 2014).

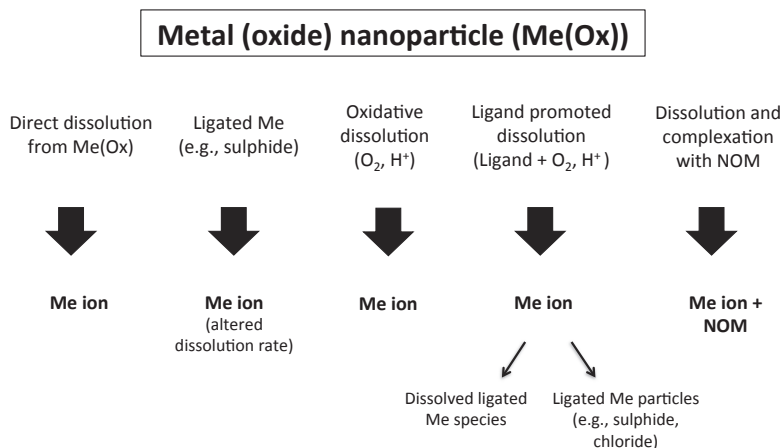


Figure 7. Possible metal (Me) and metal oxide (MeOx) nanoparticle dissolution and ligation processes. Adapted from Louie et al. (2014). NOM = natural organic matter

Biological mediated processes are related to living organisms that degrade or modify NOAA compositions. For instance, a known process is the biomineralization of silver or iron by bacteria. However, Hartmann et al. (2014) concluded a rather unlikely relevance of such biological processes despite some indications given.

Photochemical transformation processes

(Photo)chemical transformations comprise the (photo)chemical degradation, dissolution, (re)precipitation, as well as reduction and oxidation (Lowry et al. 2012; Hartmann et al. 2014; Wagner et al. 2014). Thereby, photocatalytic processes are induced by incident light leading to excitation of photocatalytic material such as titanium dioxide or zinc oxide (Hartmann et al. 2014). The exposure to light triggers chemical reactions (i.e., such as redox reactions or dissolution) or can degrade the surrounding polymers (Hartmann et al. 2014).

Transformation processes in the air compartment

Concerning the fate and behavior of NOAAs in the air compartment, knowledge gained from former fine particulate matter studies can be used, although some major issues need to be analyzed in order to understand the compartmental behavior (Hartmann et al. 2014). Diffusion processes of NOAAs in the atmosphere are dependent on size, structure, and morphology (Mädler and Friedlander 2007), that is why the different particle characteristics should be considered. NOAAs in smaller sizes have a higher mobility (Hartmann et al. 2014). Nevertheless, atmospheric NOAA releases are generally expected to settle down rather fast via wet or dry deposition processes (Lowry et al. 2012; Meesters et al. 2013; Sun et al. 2014).

Additionally, atmospheric released NOAAs can be altered not only by physical processes such as coagulation and condensation, but also by photochemical degradation processes in the ambient atmosphere (Meesters et al. 2013).

Table 4 summarizes and evaluates the potential relevance of NOAA transformations in the environment for non-coated particles (Hartmann et al. 2014). It has to be noted that the evaluation depends on the material of considered NOAAs as well as on their surface modifications.

Table 4. Relevance for inclusion of environmental transformation processes in NOAA fate modeling.

Environmental transformation process		Compartments			
		Air	Water	Sediment	Soil
Chemical and photochemical processes	Photochemical reactions	++	+	-	-
	Redox reactions	-	++*	++*	+*
	Dissolution/speciation	-	-/++*	-/++*	-/++*
Physical processes	Aggregation/agglomeration	+	++	+	+
	Sedimentation/deposition	+	++	-	-
Interaction with surfaces / substances	NOM adsorption	-	+	++	+
	Sorption to other surfaces	-	+	++	++
Biologically mediated processes	Biodegradation	-	-/++*	-/++*	-/++*
	Biomodification	-	-/+*	-/+	-/+

++: Highly relevant for inclusion in NOAA fate modeling; +: relevant for inclusion in NOAA fate modeling; -: low/no relevance for inclusion in NOAA fate modeling; *: highly dependent on the NOAA chemical composition; NOM = natural organic matter Reference: (Hartmann et al. 2014)

2.6.3 Environmental models for assessing NOAA exposures

In the EEA of NOAAs several approaches exist that attempt to estimate the PEC. Generally, exposure models implement data from analytical studies or in case of lacking data corresponding assumptions have to be made. The models currently developed differ in several aspects. Gottschalk et al. (2013) differentiated approaches into deterministic or stochastic models. Deterministic exposure models consider several scenarios in which different sets of data and assumptions on production volumes, environmental releases and behavior are subsumed for the PEC estimation. On the other hand, stochastic models consider the inherent model and data uncertainties with stochastic methods.

Besides, the recently developed models also differ in model structure and their foci. Thereby, the exposure models vary also regarding the considered compartments with an analysis of single or multimedia compartments (cf. e.g., (Gottschalk et al. 2009; O'Brien and Cummins 2011; Sun et al. 2014)), as well as the focus on natural and/or technical compartments (e.g., (Hendren et al. 2013a; Walser and Gottschalk 2014), and different geographical boundaries like Europe and Switzerland (Sun et al. 2014), Denmark (Gottschalk

et al. 2015) or Germany (Hund-Rinke et al. 2008; Wigger et al. 2015a). Typically a mass-balance approach combined with a life cycle thinking approach is used in environmental exposure modeling (Wigger et al. 2015a). The PEC of the respective compartment is determined by balancing input and output flows for each process in every stage of the life cycle (Wigger et al. 2015a). A key parameter is the overall production volume of NOAAs, which is usually not easily available. Therefore, the production volume estimations are mostly based on early publications in this field: Blaser et al. (2008), Mueller and Nowack (2008), Gottschalk et al. (2009), and Piccinno et al. (2012). The production volume of a specific material is allocated to a geographical area of interest by using weightings based on the population or economic power of these regions (Hendren et al. 2013b; Wigger et al. 2015a).

In general there is a severe lack of knowledge on products and their NOAA contents as well as the fate and behavior of released NOAAs. In particular, the latter aspect is rather complex, because NOAAs can transform and thus change their properties during their life cycle (Mitrano et al. 2015). Therefore, currently existing fate and behavior models used for organic chemicals need to be adapted (Westerhoff and Nowack 2013).

Such a modified approach using for example partition coefficients (octanol-water coefficient) can estimate the distribution of NOAAs in environmental compartments and major exposure pathways in risk assessment (Westerhoff and Nowack 2013). Consequently, several studies focus on the applicability of partition coefficients for NOAAs to predict their environmental behavior (Praetorius et al. 2014; Cornelis 2015). However, recent findings have highlighted that partition coefficients are probably not applicable for NOAAs and thus alternative methods are needed (Praetorius et al. 2014; Cornelis 2015). This is mainly because the specific transport and behavior of NOAAs in environmental compartments represent a major determinant of exposure (Praetorius et al. 2012; Praetorius et al. 2014; Meesters et al. 2014).

Current studies showed that not only natural, but also technical compartments are relevant regarding predicted environmental release points and concentrations. Consequently, the EOL stage gets an increased attention, because NOAAs will likely end up in wastewater treatment plants (WWTPs), or waste incineration plants (WIPs), and landfills, as shown by Gottschalk et al. (2009), Keller and Lazareva (2013), and Sun et al. (2014). Therefore, scientific studies mainly focus on the identified technical compartments.

The WWTP is an important starting point for environmental exposure. The first studies of Burkhardt et al. (2010) and (Kaegi et al. 2011) supposed the sulfurization of AgNPs to Ag₂S in WWTPs and thereby the almost complete removal of AgNPs (>90%). Moreover, Doolette et al. (2013) pointed out that for example AgNPs coated with PVP also transform to Ag₂S after

the anaerobic digestion without an influence on the nitrification performance. Nevertheless, Ag₂S can affect the sub-dominant wastewater microbial communities (Doolette et al. 2013). These observations were confirmed by Impellitteri et al. (2013) and also by King et al. (2015). Due to this results, King et al. (2015) supposed an efficient removal of the AgNP contaminants in the primary wastewater treatment, despite the influences of anionic and non-ionic substances (i.e., the influence of anionic PVP-coated AgNPs and non-ionic polymer poly-sodium 4-styrene sulphonate in the wastewater). Impellitteri et al. (2013) analyzed incinerated biosolids enriched with AgNP species and showed that a fraction of spiked silver (30-50%) is transformed to elemental silver and to Ag-S complexes as for example Ag₂SO₄ (up to 25%) as well as sulfhydryl groups (26-50%).

First models were developed to predict the fate and behavior of NOAAs in WWTPs. Hendren et al. (2013a) applied a Monte-Carlo modeling approach for the prediction of the behavior of four different kinds of AgNPs in a WWTP. The simulation results showed that AgNPs distributed differently in the sewage sludge and effluent depending on the considered particle surface coating. However, the biggest fraction of AgNPs was bounded to biosolids (Hendren et al. 2013a). Another WWTP related study was conducted by Lazareva and Keller (2014). They analyzed potential environmental releases of different kinds of NOAAs from WWTPs in the local areas of New York, London, and Shanghai by applying a life cycle perspective. The study considered the influence of geographical differences in the calculation of PECs. Lazareva and Keller (2014) concluded that despite high data uncertainties the calculated concentrations are in the same order of magnitude in the considered locations of WWTPs.

Besides the WWTP, the pathway from the household sewer to the WWTP can have a relevant influence on the transformation of released NOAAs. Kaegi and co-workers analyzed the fate and behavior of NOAAs (AgNP, AuNP, and AgCl) in the wastewater stream towards the WWTP (Kaegi et al. 2013; Kaegi et al. 2015). Generally, they discovered that the sulfurization of AgNPs to Ag₂S is strongly dependent on the available concentration of sulfides in the sewage channel (Kaegi et al. 2013). Furthermore, the experimental tests showed an efficient transport of AgNPs to the WWTP. As shown in previous studies, Kaegi and co-workers stressed the efficient removal of AuNPs and AgNPs via the biosolids (>90%) in the WWTP. Finally, only low amounts of AgNPs are emitted into the surface water. The settled AuNPs and AgNPs were present in a hetero-aggregated form. Furthermore, Kaegi et al. (2013) subsumed that the AgNP and AuNP removal efficiency was high and not dependent on particle size, coating, or type of the core material, although the AgNP sulfurization process is strongly influenced by the size (distribution) and structure (crystallinity) (Kaegi et al. 2013). In a newer study, Kaegi et al. (2015) investigated the fate and behavior of AgCl (a likely transformation product after laundering of textiles) in the

sewer channel and subsequent wastewater treatment. Also, the AgCl species were transformed to a high extent in the sewer channels (two-third were transformed to nanoparticulate Ag₂S). One third of the AgCl fraction entered the WWTP system and was finally transformed to Ag₂S (Kaegi et al. 2015).

The combustion of disposed wastes enriched with NOAAs or NOAA-products has recently received a higher attention in the research. So far, only a few studies have investigated the waste treatment of cerium oxide during incineration, where the main fraction ended up in the slag residues (81%) and fly ash (approximately 19%) (Walser et al. 2012). The results were not that surprising, since the WIP combustion conditions range from 850°C – 1150°C and cerium oxide has a comparably high melting temperature of approximately 2,400°C (Wiesner and Plata 2012). Walser et al. (2012) ruled out possible transformations and emphasized the point of an efficient air filtration system. The air filtration will work independently of the agglomeration or enclosure by other substances. Nevertheless, even if optimal combustion parameters are kept, other substances can enclose nanoparticles or either NOAAs can be incompletely transformed or transformed to new nanoparticles and finally released (Wiesner and Plata 2012). Also Mueller et al. (2013) and Walser and Gottschalk (2014) applied a stochastic fate analysis of NOAAs in WIPs in order to calculate and to predict environmental concentrations.

The export and recycling of disposed NOAA-products is only discussed by two recent studies. Caballero-Guzman et al. (2015) extended the probabilistic model of Sun et al. (2014) by the recycling processes of NOAA-products for Switzerland. They concluded that most of the NOAA-products would be landfilled or combusted. Due to these results, Caballero-Guzman et al. (2015) do not expect the dissipation of NOAAs in other product streams after the recycling processes. In contrast, Wigger et al. (2015a) compared two different WMSs (Germany and Sweden) for textiles. In their study they showed a significant influence of the product lifespan and the established WMS on environmental releases. Particularly, the export of disposed clothing textiles can lead to the negligence of other important exposure scenarios (e.g., export to countries with less established WMSs) (Wigger et al. 2015a).

The landfilling of disposed or combusted NOAAs is rather rarely investigated so far. Yang et al. (2012b) have shown that pristine AgNP releases will not significantly influence the methanogenesis in low concentration of 1 mg Ag/kg. However, they also emphasized that higher concentrations at 10 mg Ag/kg inhibited the anaerobic digestion and reduced the biogas production indicating the need for further studies (Yang et al. 2012). On the other hand, it is supposed that PVP-coated AgNPs or other silver species like AgCl or Ag₂S may have a lower influence on the performance of landfills due to the reduced number of silver ions causing a comparably reduced toxicity (Bolyard et al. 2013; Gitipour et al. 2013).

2.7 Challenges and needs for prospective assessment of NOAA exposures

The previous sections pointed out multiple challenges in the assessment of risks and in particular of NOAA exposures, which are apparent throughout every life cycle stage of nano-enhanced products. Against the background of accelerating innovation cycles with intensified global competition and the existing knowledge gaps regarding risks (cf. chapter 0), regulators and decision-makers have to act despite significant uncertainties and ignorance prevail. The following sections will review the regulatory challenges, which are strongly related to the current state-of-the-art. Finally, the need for prospective assessments will be discussed.

2.7.1 Regulatory challenges in REACH

The REACH framework constitutes a regulation in which NOAAs can be registered and evaluated, despite the fact that nanomaterials are not explicitly addressed. However, the discussions on the appropriateness of REACH regulation for NOAAs are still ongoing, whereas it is agreed that NOAAs have to be specifically considered (ECHA 2016). Consequently, several limitations exist in REACH with regard to NOAAs (Hansen and Baun 2012; Schwirn et al. 2014). In particular, the current mass-based regulation does not pertain for NOAAs, which in general are produced in very low masses. Furthermore, despite that bulk testing strategies are performed by following REACH guidelines (GCA 2013), NOAAs can fundamentally differ with regard to adverse effects and environmental behavior due to their nano-specific properties (GCA 2013; Schwirn et al. 2014). In addition, information on production volumes and relevant information along the life cycle of products are not accessible (e.g., product lifespans and environmental releases) due to manufacturer's secrecy and non-disclosure policies (Hansen and Baun 2012).

Concerning the exposure scenarios for substances that have to be defined during the registration and evaluation process in REACH, other challenges prevail. Generally, the default ERCs may not pertain for NOAA exposures and specified environmental release categories (spERCs) are urgently required for NOAAs to set up exposure scenarios (Nowack et al. 2012; Meesters et al. 2013).

Since 2010, several industrial associations have been working on the improvement of ERCs using the industrial expert knowledge for realistic release factor estimation of chemicals. Reihlen (2014) firstly analyzed the transparency and comprehensibility of available spERCs for chemicals and identified several shortcomings. In particular the derivation of release factors and respective risk management measure efficiencies were poorly documented or the justification for analogical assumptions was not available (Reihlen 2014). Furthermore, the substance properties were neglected in the release factor derivation despite of their potential impact on release and exposure characteristics (Reihlen 2014). Even if the report of Reihlen (2014) is related to chemicals, analogies to NOAAs and their uses in products are

reasonable. Such investigation was not taken into account for the release and exposure assessment of NOAAs, so far. Thus, the estimation of release factors remains rather speculative and the necessity of modeling and measurement techniques are demanded for sound exposure assessments (Nowack et al. 2012; Meesters et al. 2013).

However, by applying a case-by-case approach for release and exposure estimation, the amount of product applications and potential NOAA species tends to have no limits and aggravates the exposure assessment. This challenge applies also to conventional chemicals that still remain for testing in REACH (Schaafsma et al. 2009). Additionally, the retrospective analysis (i.e., focus on commercially available products, and measurements after environmental releases) does not sufficiently contribute to prospective assessments in terms of precaution. To encounter this challenge of complexity, Praetorius et al. (2013) proposed an approach for assessing exposures by using scenarios and informed simplifications. Especially in regulation context simplified approaches are sufficient and pragmatic approaches are needed as Meesters et al. (2013) also emphasized it.

2.7.2 Challenges for the assessment of NOAA releases and exposures

The previous section already highlighted several obstacles in the assessment of NOAA releases and exposures, which is why only a short conclusion for the three major challenges is given. At first, obstacles are present in the analytics and measurements of NOAAs. Thereby, experts have mandatorily formulated profound characterizations of the analyzed NOAAs in the respective test system. The thoroughly characterization of the material in a standardized approach is required to allow a comparison between research studies due to the fact that only single NOAA properties can change the toxicity and environmental behavior significantly (Wagner et al. 2014). Moreover, the diversity in NOAA characterization protocols applied in experiments and the lack of reference materials complicate predictive hazard estimations (Schafer et al. 2013; Wigger et al. 2015a). However, the characterization of NOAAs is still technically challenging, particularly in complex environmental media, where background concentrations may influence the results correspondingly (Aschberger et al. 2011; Wagner et al. 2014).

Second, section 2.6.1 recapitulated that only some studies on NOAA releases from products were performed, so far. Correspondingly, several knowledge gaps are present in this regard. Especially, the interrelation of NOAAs and product matrix materials and their influence on release potentials should be examined to track released NOAA species and quantities. This knowledge on the released NOAA species is necessary for the subsequent exposure assessment focusing on the fate and behavior of NOAAs. Particularly, NOAAs can interact with substances and undergo multiple transformations in environmental media (e.g., AgNPs likely is transformed to Ag₂S). Finally, these NOAA species are actually needed for the hazard and exposure assessment to investigate potential adverse effects and exposure scenarios. In addition, the determination of the environmentally transformed species is complicated due

to the high variety of pristine NOAAs and their surface modifications as well as the actual released NOAA species along the product life cycle.

Besides, the modeling and estimation of environmental concentrations is a key concept that is already applied for chemicals. Hence, the environmental exposure models for chemicals are well developed (Scheringer et al. 2014), but they need to be adapted (Westerhoff and Nowack 2013; Wigger et al. 2015a). For instance, in aqueous media NOAAs are mainly present as a solid-liquid system and thus behave differently compared to conventional liquid-liquid systems of chemicals (Westerhoff and Nowack 2013; Scheringer et al. 2014).

Third, another challenge is associated with the data availability. For exposure modeling often the key information is not available in most cases, such as production volumes, products, and their content of NOAAs. Consequently, estimations in this regard have to be made in order to design environmental exposure models for predicting environmental concentrations.

2.7.3 Demand for prospective approaches

In the light of the summarized challenges, it becomes apparent that other more pragmatic approaches are needed to give an orientation for exposure assessment (Meesters et al. 2013), risk management, decision-making, and for regulation. In almost all life cycle stages of NOAAs, a severe lack of knowledge and several open questions prevail, which hampers a regulation and the choice of risk reducing measures, also in terms of precaution. Applying the precautionary principle means to take preventive actions or decisions, even though there is considerable scientific uncertainty and ignorance with regard to the cause-and-effect relations and/or probability and degree of exposure (Wigger et al. 2015b). Thus, also in precautionary perspective knowledge about adequate risk management measure is needed in order to act twofold by avoiding a moratorium (i.e., to stop innovation) and by providing a precautionary framework for future development. This precautionary approach can use indications that are provided by the characteristics of the technology (Gleich 2013; Gleich et al. 2013).

Consequently, an approach for estimating potential releases from products based on indications would facilitate further research and first precautionary regulations. Furthermore, this approach can not only enable the release and exposure assessment of passive nanostructures, but also act as a basis for the next generations of nanotechnologies (i.e., active nanostructures, integrated nanosystems, and converging technologies) (Roco 2011), which may even comprise other challenges and consequences (Hansen and Baun 2012).

Therefore, this thesis will focus on current and future products by applying the life cycle concept in a prospective view to estimate potential environmental NOAA releases and thereby consider the precautionary principle. In doing so, potential release hot spots can be identified enabling the relation of exposure to different use and release scenarios. Finally, this will allow for a prospective exposure and risk assessment and for the conceptualization and examination of specific product design alternatives to minimize potential hazards, exposures and risks in a precautionary manner (Wigger et al. 2015a).

Environmental Release of and Exposure to Iron Oxide
and Silver Nanoparticles
Prospective Estimations Based on Product Application
Scenarios

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