

REVIEW

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# How to consider engineered nanomaterials in major accident regulations?

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## Abstract

Major accident regulations aim at protecting the population and the environment from possible accidental releases of chemicals. To achieve this goal, the regulations need to be reassessed in light of the development of new technologies. A currently rapidly growing new technology is nanotechnology, and engineered nanomaterials (ENM) are already produced and used in commercial products. The aim of this work was therefore to evaluate the current knowledge on human and ecotoxicology of ENM and their release and behavior in the environment in the context of major accident prevention. Nano-specific release paths are not to be expected. The established safety standards in the chemical industry are also applicable to ENM, especially the separate storage of flammable solvents and detention reservoirs. The potential of a release to the environment of ENM in powder form is larger than for suspensions; however, it can be minimized by safety measures established for conventional dusts. The considered human toxicology studies show that to date not conclusive enough answers regarding the toxicity of ENM can be made. The effects are dependent not only on the material itself but more on the functionalization, surface reactivity, size, and form. The acute ecotoxicity of ENM seems to be similar to the one of the corresponding microparticles (TiO<sub>2</sub>) or the respective dissolved ions (Ag, Zn) with the exception of photocatalytically active nano-TiO<sub>2</sub>, which has an increased toxicity. In order to guarantee that all ENM are included in the existing major accident regulations, different classification options are possible and the advantages and disadvantages are discussed. An important step will be the compulsory inclusion of nano-specific data in the Material Safety Data Sheets that serve as the basic medium to transfer information from the manufacturer to downstream users and authorities. We also call for a regular monitoring of the production and uses for 'high production volume ENM' that could have the largest implications for major accident regulations.

**Keywords:** Nanomaterials; Major accidents; Toxicity; Ecotoxicity

## Review

### Introduction

The major accident prevention regulations have the goal to protect the general population and the environment from severe damage due to accidents. In Switzerland, a company has to fulfill the requirements of this regulation if they store compounds on their premises in amounts that surpass the thresholds given in the regulation [1]. The determination of these thresholds is based on an approach, which contrasts the properties of a substance to its amount used within the company. Companies that fall under this regulation have to report an estimation of possible damage and formulate scenarios. If major damage of the general population (more than

ten deaths outside the area of the company) or of the environment cannot be excluded, a quantitative risk estimation based on scenarios has to be prepared. The regulation for major accident prevention only considers major damages of people outside the area of the company and is therefore separate from occupational or consumer protection regulations. It only considers acute effects, and chronic effects or exposure is therefore not included in this scenario.

Nanotechnology is a rapidly growing research and application area with increasing importance for economy, research, and society. In line with the precautionary principle, it is therefore important to investigate possible risks and, if necessary, take measures to protect humans and the environment. In the focus of the risk discussion about nanotechnology are the engineered nanomaterials (ENM) because they can show - compared to larger

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materials - different properties and reactivity. Therefore, they cannot *a priori* be handled in the same way as larger particles. A separate determination of threshold values and criteria for evaluation is therefore necessary, to account for the new characteristics of ENM.

There is to date no international agreement on how to deal with major accident prevention of ENM. Two reports are available about the fire and explosive properties of ENM [2,3]. The European Commission states that ENM with potential for accidents can be categorized within the Seveso II directive [4]. Several countries have identified the issue of nano-accidents as relevant [5-7]. The English Parliament does not consider nano-specific regulation to be necessary [8].

In a document by the British Standards Institution (BSI) about guidelines for safe handling of ENM, also fundamental measures for preventive actions against accidents are listed [9]. BSI asks companies that work with ENM to develop emergency plans for possible accident scenarios and to list the exact sequence of activities and the measures that need to be taken in case of an accident. All persons that would be involved in such an accident should be informed and trained in handling ENM. Furthermore, measures should be taken to prevent the dissipation of ENM in case of an accident. A report of the OECD about major accidents with ENM is in preparation [10].

The basis for the assessment into the major accident regulation is the material safety data sheet (MSDS). However, there is to date no duty to declare the size of particles or indicate if the material contains a nanosized fraction. Downstream users of compounds therefore receive often no information if a product contains ENM. In many cases, the nano-ingredient does not even reach the required threshold value of 1% so that it does not even need to be listed in the MSDS. A clear definition what constitutes an ENM is therefore compulsory so that in the future, appropriate designations can be made on the MSDS.

The aim of this work is the assessment of the human toxicity and ecotoxicity of ENM within a major accident in comparison to conventional chemicals. We try to answer the question if for the determination of threshold amounts in the regulation a mass-based approach can be used for ENM and which major accident scenarios need to be considered for ENM. We performed this assessment using four typical ENM that are covering different classes and that are all produced and used in high quantities: nano-TiO<sub>2</sub>, nano-ZnO, carbon nanotube (CNT), and nano-Ag [11]. We use the Swiss regulation as an example but aim to provide general conclusions.

## Release into the environment

### *Potential of ENM for major accidents*

A major accident can happen whenever large amounts of a potentially toxic or reactive substance are present.

This can happen during production and manufacturing as well as during storage and transport. The scenarios for major accidents strongly depend on the used ENM and other chemicals on the same site as well as factors specific for the situation or the site:

- Form of ENM: suspended or as powder
- Presence of flammable or explosive substances (e.g., metallic ENM or organic solvents)
- Type of containment
- Risk of accident during transport
- Safety measures.

In general, we can assume that the potential for major accidents is higher when ENM are present as powder, because they are easier dispersible than suspended ENM [12]. This is due to the fact that in the regulation of major accidents, only the first 30 min after the accident are of interest and the acute loss of lives or acute damage of the environment is calculated [1]. As water and soil can be purified and thus major consequences in the long-term are not included in the regulatory measures of major accidents, the velocity of dispersibility of powders compared to presuspended ENM plays no important role in our considerations. The potential is also increased by the storage of easily flammable or explosive compounds in the vicinity of the ENM.

Of 25 major accidents or incidents that were reported in 2008 in Germany (no nano-related cases) [13], 11 occurred during production; 4 during handling; 3 during transport; 2 during maintenance; 1 each during storage, decommissioning, and delivery; and 2 with unknown activity. Also, natural hazards such as lightning, earthquakes, or flooding need to be considered as triggers of major accidents, in addition to man-made disasters such as explosions in neighboring factories or airplane crashes [14,15].

The following release scenarios are considered as realistic causes of major accidents for ENM:

- Major accident scenarios during production  
ENM are produced in very diverse operations [16]. In general, the mechanical-physical top-down approaches can be distinguished from chemical-physical bottom-up approaches. In top-down approaches, ENM are made from larger materials through milling; in bottom-up approaches, ENM are synthesized from atoms, ions, or molecules in a chemical reaction. Milling operations are used for metallic or ceramic ENM with a relatively wide particle size distribution. Chemical-physical approaches have the advantage that the form and size of the particles can be better controlled.

Possible reactions are precipitation and flame-, plasma-, or gas-phase synthesis.

During milling, a major accident with consequences for the general population can practically be excluded, because in this process, only small amounts (around 100 kg) of ENM are used, mainly in aqueous dispersion and of metallic or ceramic ENM; hence, explosions can be excluded. If the process is carried out in organic solvents, then this process needs to be carried out in explosion-proof systems, but due to the small amounts (batch volume of around 100 L with max 10-kg ENM), no hazard for the population is to be expected. In gas-phase processes, a deflagration and, with easily flammable solvents, a fire hazard cannot be excluded. Nevertheless, a chain of different events is necessary so that release of ENM beyond the fabrication site is possible.

A possible scenario is the explosion of a distillation equipment with subsequent fire during which all ENM in the same fire compartment are released. Depending on the safety measures, amounts stored, and situation-specific conditions, larger amounts of ENM could be released into air or wastewater. We also need to consider that carbon-based ENM could be combusted while metallic ENM could be oxidized.

- Accident scenarios during transport

Transport of toxic substances is connected with a rather high risk because traffic accidents are quite

common and because easily flammable substances can be released (e.g., fuel). However, the transported amounts of ENM are currently rather small, compared to the total amount of produced material in any size (compare 5 Mio t of produced  $\text{TiO}_2$  of which only 47,000 t are nano- $\text{TiO}_2$  [17], and this is one of the nanomaterials with the highest production amounts). Although there is currently no nano-specific obligation to label, we propose that the containers for transport of ENM should be labeled as a hazardous material and that containers of the highest safety standards be used. An accident during transport could lead to the spilling of dispersions/powder or a fire through which ENM could reach air, soil, wastewater, or natural waters (Figure 1).

- Accident scenarios during manufacturing and storage

During manufacturing or storage of ENM, fire is a possible hazard, which can result in the release of ENM into air (when stored as powder) as well as into water/wastewater (ENM dispersions). The cause for the accident can be internal (e.g., technical) as well as external factors. Deflagration is possible for metallic ENM, but they are usually stored in dispersion and/or under inert atmosphere. An example is nano-zero-valent iron for which also hydrogen production and the danger of hydrogen explosion need to be considered.



**Figure 1 Example of an accident scenario.** In 2011, a truck transporting several 750-kg bags of photocatalytic titanium dioxide ( $\text{TiO}_2$ ) has lost part of its cargo. Since  $\text{TiO}_2$  is not classified as a hazardous material, workers of the road maintenance department cleaned the road. (Photo from [18]; photographer: Arnaud Viry).

### **Release and behavior in the environment**

Based on the scenarios described above, a primary release of ENM into air, water, and soil is possible. A secondary exposure of soil and surface water through deposition from the atmosphere is likely. Also, the indirect contamination of surface water through the effluent of wastewater treatment plants needs to be considered, especially because a shock load of ENM may destroy the removal capacity of the activated sludge phase of wastewater treatment. The secondary pollution of groundwater can be neglected in the case of accidents because particle mobility in soils is generally rather low [19].

To date, no major accidents with ENM are known, and therefore, we do not have any experience with the dissipation behavior of ENM after an accident. Also, models are not yet available that are able to simulate the distribution of ENM in the environment on a local scale [20]. The only available models predict ENM concentrations on a regional scale [21,22]. In these models, the flows of ENM from production, use, and disposal through technical compartments to the environment are predicted and environmental concentrations are obtained assuming well-mixed environmental compartments. Measurements and modeling have been performed for workplace situations [12,23,24]. One study measured and modeled dispersion of ENM during a (purposely made) failure of ventilation in a laboratory-scale flame synthesis reactor [25]. The authors conclude that coagulation of ENM is negligible inside the room [23,25]. The measurements and calculations are restricted to the production room and can therefore not be transferred to environmental conditions during a major accident.

During a major accident, powdered ENM can be released in larger amounts into air. Particles are not volatile and therefore only be released during an explosion or fire. The first elimination step is primarily agglomeration and subsequently deposition of larger particles. Agglomerates with a diameter of 1  $\mu\text{m}$  have the longest residence time of particles in the atmosphere [26]. Due to agglomeration, it is not likely that single ENM persist in air [27].

The concentration in air is primarily relevant for human exposure after a major accident. The prevailing weather conditions during the accident play a major role (wind speed, wind direction, precipitation). These conditions cannot be considered in a generic scenario. The following generic model parameters are proposed for calculations of local exposure outside the industrial site in the ECHA guidelines [28]:

- The total emissions are distributed radial symmetrically around the source (radius 1 km).
- The height of the source is 10 m.

- The average distance from the source to the boundary of the site is 100 m.
- The concentration decreases linearly from the source to 1 km.

These assumptions are used to calculate a generic local exposure scenario and therefore cannot be used to model a major accident at a specific site. In addition, they are not particle specific.

The input of ENM into surface water can occur in three ways:

1. Release into surface water through storm water collection systems along roads or on the production site or directly into surface water if there is a close proximity of the site of accident and the open water. In both cases, we have to assume that only a fraction of the total emitted ENM amount reaches the water. The probability to reach the water is higher for suspended ENM. However, washing of powdered ENM during rain events or with firefighting water cannot be excluded.
2. Release of ENM into wastewater with direct connection to surface water. Studies have shown that ENM are removed during wastewater treatment with a high efficiency [29]. However, during a shock load of antimicrobial ENM (e.g., silver), the bacterial population may be compromised and therefore the removal efficiency of the water treatment process [30].
3. Deposition from air. In this case, the input is dependent on the surface of the water body. Due to faster dilution, rivers are less at risk than lakes.

The ENM are diluted upon entry into the water bodies. The dilution *de facto* depends on the size of the water body and can have values between 1 and 100,000 [28]. A dilution factor of 10 is proposed if no other data are available. An additional dilution can result from the firefighting water.

Water contamination is even stronger dependent on the local situation than the emission into air. The probability for a contamination of surface waters that has to be classified as a major accident is therefore dependent on the proximity of the site of accident to the next freshwater body. An accident is considered as major when in a water volume of  $10^6 \text{ m}^3$  the lethal concentration 50 ( $\text{LC}_{50}$ ) and/or the acute half maximal effective concentration ( $\text{EC}_{50}$ ) for fish or *Daphnia*, respectively, is surpassed [31]. With an  $\text{EC}_{50}(\text{Daphnia})$  of 1  $\mu\text{g/l}$  [32] for nano-Ag and homogeneous distribution already, a release of 1 kg of nano-Ag could lead to the corresponding concentration. This evaluation neglects relevant elimination processes such as dissolution and precipitation as AgCl; however, they may only play a role at longer time



scales that are not relevant for major accident regulations. The contamination of natural waters can result in a secondary exposure of humans through bioaccumulation into fish. However, such long-term effects are not considered in major accident regulations.

A direct release of ENM into soils is only expected during transport accidents. Indirect transfer can occur through wet or dry deposition from air. Although the local soil concentration can be very high after a major accident, a persistent damage of the environment can be practically excluded due to the low particle mobility [33] and the possibility for soil remediation (excavation and landfilling of polluted soil).

### Toxicity and ecotoxicity in the framework of major accident prevention

#### Human toxicity

In the Swiss Ordinance on Major Accidents, the following criteria are used to determine the threshold amounts [1]:

- EU classification
- Acute toxicity; oral, dermal, and inhalation toxicities
- Classification given on MSDS

The comparison of conventional chemicals (e.g., microparticles) with ENM based on these criteria is restricted to the criterion 'acute toxicity' as the ENM have no special EU or MSDS classification. Table 1 summarizes the hazard potential of ENM to humans in comparison with conventional materials.

The published data are very heterogeneous and do not provide a clear effect pattern for each of the materials. The measured endpoint of the experimental data is not the lethal dose concentration (LD<sub>50</sub>), but more subtoxic events such as inflammation, oxidative stress response, or gene expression profiling over different time scales were assessed, which make a sound comparison of the studies impossible. In addition, the three exposure routes (oral, dermal, and inhalation) provide different symptoms; therefore, the hazard potential of the selected materials is based more on an expert view than on standardized and comparable data sets.

#### Ecotoxicity

The ordinance of major accidents [1] uses as criteria for the evaluation of the ecotoxicity the EC<sub>50</sub> for *Daphnia* (swimming disability after 24 h) and the LC<sub>50</sub> for fish (after 2 to 4 days). The only threshold in the area of ecotoxicity is at 2 t of substance used at a site for an EC<sub>50</sub> (*Daphnia*) or LC<sub>50</sub> (fish) <10 mg/l. Tables 2 and 3 contrast EC<sub>50</sub> and LC<sub>50</sub> values for the nano- and microparticles (TiO<sub>2</sub>) or dissolved metals (Ag, Zn). This comparison evaluates if the overall toxicity of the traditional form and the nano-form is different from each other. It does not consider any difference in the mode of action but simply uses mass as a metric to compare materials.

The only compound that is more critical in its nano-form than as dissolved metal is therefore TiO<sub>2</sub> in its photocatalytically active form. For Ag and ZnO, we cannot see a difference between the toxicity of the nano-form

**Table 1 Hazard potential of ENM to humans in comparison with conventional materials (microparticles)**

ENM	Hazard potential <sup>a</sup>			Remarks
	Acute toxicity	Chronic effects	Difference (micro/nano)	
Nano-TiO <sub>2</sub>	Very low	Low	1:10	Although TiO <sub>2</sub> was placed in class 3 of the carcinogenic materials, its general toxicity is low as shown by many recent studies. There is a difference in the effects of smaller and larger particles, but this, for a release scenario during a major accident, is only of low relevance [34-39]
Nano-ZnO	Medium	Low	1:1	Application of micro- or nanoscale ZnO particles into the lungs of mice or rats causes a strong but intermediate inflammatory reaction. The strength as well as the course of this reaction is practically identical for micro- or nanoscale ZnO [40,41]. The acute consequence of inhalation of Zn dust is zinc fever; however, for severe effects (deaths), the concentration needs to surpass widely the permissible exposure limit of 5 mg/m <sup>3</sup>
CNT	Low	High	n.a.	Dependent on the type of CNT (physicochemical properties, e.g., single-walled, multi-walled, short/long), long-term effects similar to asbestos need to be considered (mesothelioma) [42] if the conditions like for 'WHO fibers' (length >5 μm, diameter <3 μm, and a length/diameter ratio of more than 3:1) are given. So far, most industrially produced CNTs are not considered to be WHO fibers [43-49]
Nano-Ag	Low	Low	1:1	Silver is used since many years in nanoparticulate form (colloidal silver). There is no indication for an acute intoxication of humans with life-threatening degree, unless there is exposure to ultrahigh concentrations. Because Ag particles are added in rather small amounts to products, also the produced and transported amounts are rather small and the risk of a major accident with fatal consequences is therefore limited [50-54]

<sup>a</sup>Acute toxicity: classification on the basis of EU Directive 67-548 Annex VI - medium = R 23/25, low = R 20/22, very low = no labeling; chronic effects: based on actual literature. n.a., not applicable.

**Table 2 EC<sub>50</sub> values (mg/l) for *Daphnia* for different ENM: comparison between nano-form and microform/dissolved metals**

	EC <sub>50</sub> <i>Daphnia</i>		
	ENM lowest reported value (mg/l)	Larger particles or dissolved ions <sup>d</sup>	Rounded ratio (nano/micro)
Nano-TiO <sub>2</sub>	0.03 [55] <sup>a</sup>	>100 [56]	>1:100 (for the photocatalytically active form)
Nano-ZnO	0.62 [57] <sup>b</sup>	1.86 [58] <sup>e</sup>	1:1
CNT	1.8 [57] <sup>c</sup>	-	-
Nano-Ag	0.001 [32]	0.0015 [59]	1:1

<sup>a</sup>Other values (in mg/l): 0.8 [60], 3.8 [61]; <sup>b</sup>other values (in mg/l): 1 [56], 3.95 [62]; <sup>c</sup>other value (in mg/l): 50.9 [63]; <sup>d</sup>for Ag and ZnO, the values for the dissolved metals were taken; <sup>e</sup>other value (in mg/l, for micro-ZnO): 1 [56].

compared to the dissolved metals based on the currently available data. For CNT, we cannot make this comparison due to a missing larger particle.

#### Preventive measures

In the prevention of a major accident, a special emphasis should be placed on safety measures. This is especially important with downstream users. Whereas high safety measures are normally standard at production sites, especially in the chemical industry, the handling of ENM in manufacturing of the final products is much less controlled and can result in a much higher possibility for release [7,72,73]. An important step in this context is the employee training. The safe handling of ENM does not require more action than needed for the handling of powders and conventional chemicals.

Production and manufacturing sites have to comply with existing high safety standards, which are determined by the chemicals (e.g., solvents) that are used during the process. Special emphasis has to be placed on those companies that have no experience in handling conventional chemicals but were founded as pure 'nano'-company. A critical issue is the fact that downstream users of ENM do

**Table 3 LC<sub>50</sub> values (mg/l) for fish for different ENM: comparison between nano-form and microform/dissolved metals**

	LC <sub>50</sub> fish		
	ENM lowest reported value (mg/l)	Larger particles or dissolved ions <sup>e</sup>	Rounded ratio (nano/micro)
Nano-TiO <sub>2</sub>	2 [55] <sup>a</sup>	>100 [64]	>1:10
Nano-ZnO	1.8 [65] <sup>b</sup>	1 [58] <sup>f</sup>	1:1
CNT	20 [66] <sup>c</sup>	-	-
Nano-Ag	0.025 [67] <sup>d</sup>	0.003 [59]	10:1

<sup>a</sup>Other values: 125 mg/l [68], 500 mg/l [69]; <sup>b</sup>other value: 4.92 mg/l [68]; <sup>c</sup>LOEC value, no LC<sub>50</sub> available; <sup>d</sup>other values (in mg/l): 0.028 [32], 1.25 to 1.36/9.4 to 10.6 [70], 7.07 [71]; <sup>e</sup>for Ag and ZnO, the values for the dissolved metals were taken; <sup>f</sup>average 30-day EC<sub>50</sub> for dissolved Zn (range 0.3 to 1.9 mg/l).

not have other information than those given in the MSDS, because these contain actually no nano-specific descriptions. However, these companies are likely to store only small amounts of ENM on their site - due to the high reactivity of the materials and the normally low concentrations used in final products - thus, the relevance for major accidents is seldom given.

#### Constructional measures

Constructional measures are indispensable for a safe handling of ENM. However, the established safety procedures used in the chemical industry are deemed to be sufficient. The procedural methods should be distinguished according to the specific form of the ENM. During production, manufacturing, and storage of suspended ENM, a detention basin is needed. The rooms should also not have any direct connection to the sewer system, or the connection needs to be equipped with a possibility for closure during an accident. For ENM in powder form, the ventilation and the configuration of the building envelope are central because they determine if ENM are released through damaged windows/ceilings or through ventilation into the environment. In both cases, fire prevention measures such as fire doors, separate storage rooms for organic solvents, and separate fire compartments are key.

#### Technical measures

Various technical measures can prevent or restrict a major accident. These include sprinklers in storage rooms, pressure-controlled equipment, and disconnection of ventilation in case of accident. However, these tools are not nano-specific but target the accident prevention of easily flammable compounds, which are stored in the same room. If these conventional measures are adopted consistently, they are also effective for ENM.

#### Organizational measures

Simple but effective organizational measures are access restrictions and sound employee trainings. All employees working with ENM should get an appropriate training and should be able to have access to personal protective equipment. The plant fire brigade or the local fire brigade should be informed about the presence of ENM and should be trained in suitable firefighting procedures.

#### First insights of nanomaterials in major accident prevention

The thresholds and criteria in the ordinance on major accident prevention [1] are based on the mass of the compound. Due to the small diameter of ENM, it is questioned if the approach of using a mass basis is adequate for ENM or if the particle number or specific surface area should be taken instead. However, we

consider a mass-based approach for ENM within major accident prevention regulation reasonable because data from (eco)toxicological studies are mainly mass-based. However, indispensable is in any case a clear definition of what an ENM and the proposition for a definition by the EU [74] clearly also influences the major accident regulation as this definition also covers natural and incidental nanomaterials and not only ENM [75,76].

Solubility plays a central role for the assessment of the toxicity of ENM in comparison to microparticles. Nanoparticles of easily soluble materials such as ZnO or metals that can be oxidized and then release ions (e.g., Ag) dissolve, due to their small diameter and the corresponding high surface area, much faster than larger particles. Their toxicity should therefore be compared to that of the corresponding metal ions, e.g., Zn<sup>2+</sup> and Ag<sup>+</sup>. The most important difference is that ENM can enter cells by additional pathways including passive entering into the cells comparable to the Trojan Horse mechanism. However, as shown in our evaluation of ecotoxicological data, the nano-form has overall not a higher toxicity than the dissolved form and thus, within the context of major accident prevention, the total mass of a compound, irrespective of its form, can be used.

In order to guarantee that all ENM are included in the existing major accident regulation, different options are possible (Table 4). In every case, the declaration of ENM on the MSDS is compulsory because without this information downstream users cannot assess if a company has reached a nano-specific threshold. It is also problematic that in certain intermediate products, the nano-content is so low that it does not need to be specified in the list of ingredients.

In our opinion, option 2 is the best option for the following reasons:

- Classification 4 in Table 2 includes all ENM that will be produced in the future. The exemption list given

in the Major Accident Ordinance does not need to be adapted continuously, and there is no danger that new, potentially toxic ENM are regulated by a too generic regulation not strict enough. The precautionary principle is applied.

- The classification is specific for each ENM. An over- or under-regulation is avoided and the specific properties of each ENM are considered. The importance of substance specificity is evident from the following considerations.

Despite a wide breadth of published studies, there are still many significant questions unanswered. The substance-specific factors that affect the toxicity of ENM have not yet been answered in a coherent manner [77]. In addition to the chemical composition, the following properties have been mentioned [78]: primary and secondary particle size; specific surface area; impurities or doting; surface properties (zeta potential, functionalization, coating); redox potential, reactivity; particle form; crystallinity; hydrophobicity/hydrophilicity; solubility; biopersistence; age of particles.

In order to make any conclusions, all these factors need to be characterized and controlled in the studies. Additionally, particle-specific factors such as particle size distribution play a role. These considerations make clear that the terms 'CNT' and 'nano-TiO<sub>2</sub>' stand for a whole group of materials which can have very different properties, mainly due to shape, surface functionalization, or doting with other elements. It is, for example, assured that the toxicity of nano-TiO<sub>2</sub> varies tremendously with changing mineral structure or surface coatings [77,79].

For practical reasons, it will be difficult to perform (eco)toxicity tests for each produced or imported ENM. Producers need to be obligated to include the relevant information about toxicity and ecotoxicity of their product in the MSDS.

Based on our evaluation of the ENM, there is no special need for a drastic change in the classification of the

**Table 4 Overview on possible classifications for considering ENM in major accident regulations**

Rule	Advantage	Disadvantage
1 All ENM have the same (eco)toxicity as larger particles with the same composition. Some specific ENM are placed in the exemption list	Simple rule; recognizes the higher risk potential of certain ENM	Insufficient data to select exemptions
2 Each manufacturer has to provide specific (eco) toxicological tests for each ENM, independent of the chemical composition of the ENM	The nano-aspect as well as the different properties of various ENM are considered	Problem of definition of ENM; expensive for companies that produce only small amounts or small variations of materials
3 Dispersions are classified like normal chemicals; for powders, a nano-specific regulation is implemented in addition to existing regulations for powders	The different risk of dispersions and powders is accommodated. Simple to define	Possible exemptions need to be formulated (see 1)
4 For ENM in powder form, the mass threshold is reduced by a factor of 10 to accommodate the higher surface area	The precautionary principle and the increased surface area of the nanoparticles are considered	Relatively unspecific
5 ENM are categorized (e.g., soluble/insoluble, metal oxides/metals/organic ENM) and assessed differently	Differences between particle types are considered	Material-specific properties are over-represented; many exemptions

materials, no matter if nano or not. According to the guidelines of the Major Accident Ordinance [80], currently, the following threshold values are valid for potentially nano-scaled compounds:

- 2,000 kg: ZnO, AgNO<sub>3</sub>
- No threshold: TiO<sub>2</sub>, SiO<sub>2</sub>
- Not on the list: CNT, CeO<sub>2</sub>, carbon black, CaCO<sub>3</sub>, metallic silver
- Case-specific evaluation needed: iron oxides, pigments

For CNT and all ENM for which their conventional counterpart is not on the list, we suggest that a case-specific classification has to be performed based on the criteria of the regulation [1]. The implementation of option 2 that is favored by us would result in a threshold limit of 2,000 kg for most nano-Ag and nano-ZnO compounds, corresponding to the currently effective limits for conventional Ag and ZnO. For CNT and nano-TiO<sub>2</sub>, different threshold limits according to the specific properties of the ENM would come into force. Photocatalytic nano-TiO<sub>2</sub> would get a threshold of 2,000 kg due to the increased toxicity against *Daphnia*. No threshold value would apply for non-photocatalytic nano-TiO<sub>2</sub>. For CNT, different thresholds would apply according to the length and stiffness of the fibers. Option 2 thus allows a differentiated regulation of all ENM, under the precondition that a clear definition for ENM and the duty for declaration in the MSDS exists.

## Conclusions

As a general conclusion, we can state that ENM are clearly less hazardous than many other chemicals, e.g., solvents or high-reactivity compounds such as certain pharmaceuticals, and can be treated similar to dusts or pigments. However, it is extremely important to note that this conclusion is only valid in relation to major accidents and not for occupational and environmental health or product safety, i.e., the exposure of workers inside the factory premises or of consumers due to products containing ENM. It also does not consider long-term environmental effects due to release during the use of the products. These issues are covered in separate regulations that are not part of our evaluation.

Due to the limited fundamental understanding of ENM fate and effects, our conclusions need to be taken with caution. Until standardized tests for the determination of ENM toxicity are available and the declaration of ENM on the MSDS is standard, it is recommended to perform at regular intervals a monitoring regarding new 'high production volume ENM' and to check if the statements made in this work are still valid. Nevertheless, the multitude of different studies that exist for the ENM considered

in this work and that report relevant results show in general no evidence for a specific need for action. The acute risks of ENM within a major accident are not significantly different from conventional compounds, implying that the current regulation for major accidents is also able to cover ENM.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

All authors contributed equally to this work. All authors read and approved the final manuscript.

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