> Human and Ecotoxicity of Synthetic Nanomaterials

Initial insights for major accident prevention

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> Abstracts

Nanotechnology is a rapidly growing research and development area with increasing importance for the economy, research and society. The present study addresses the question as to whether new criteria for the determination of the quantity thresholds quoted in the Ordinance on Protection against Major Accidents may result from the accident potential or possible new hypothetical accident scenarios related to the human and ecotoxicity of synthetic nanomaterials. The literature study carried out concludes that at present, insufficient fundamental data are available to draw final conclusions on this question. However, knowledge gained until now does not suggest a need for immediate specific regulations to be included in the Ordinance on Protection against Major Accidents where nanomaterials are concerned.

Keywords:
Major accident prevention, nanotechnology, synthetic nanomaterials, human and ecotoxicity

Die Nanotechnologie ist ein rasch wachsendes Forschungs- und Entwicklungsgebiet mit zunehmender Bedeutung für Wirtschaft, Forschung und Gesellschaft. Die Studie befasst sich mit der Frage, ob sich aufgrund des Gefahrenpotenzials oder möglicher neuartiger Störfallszenarien in Zusammenhang mit der Human- und Ökotoxizität von synthetischen Nanomaterialien neue Kriterien für die Bestimmung der Mengenschwellen in der Störfallverordnung ergeben. Die durchgeführte Literaturstudie hat gezeigt, dass zurzeit zu wenige Grundlagendaten für eine abschliessende Beurteilung dieser Fragestellung vorliegen. Bisherige Erkenntnisse geben aber keinen Anlass dazu, sofort spezifische Regelungen für Nanomaterialien in den Bereichen Human- und Ökotoxizität in die Störfallverordnung aufzunehmen.

Stichwörter:
Störfallvorsorge, Nanotechnologie, synthetische Nanomaterialien, Human- und Ökotoxizität

La nanotechnologie est un domaine de recherche et de développement en expansion rapide. Son importance croît pour l'économie, la recherche et la société. Les nanomatériaux synthétiques sont source de dangers potentiels pour l'homme et l'environnement. Vu ces dangers, et sur la base de possibles scénarios d'accidents majeurs d'un genre nouveau, la présente étude cherche à déterminer s'il faut fixer de nouveaux critères pour l'établissement des seuils quantitatifs fixés dans l'ordonnance sur les accidents majeurs. En étudiant la littérature existante, il est apparu que les données actuellement disponibles ne permettent pas de tirer des conclusions définitives à ce sujet. Dans l'immédiat, au vu des connaissances actuelles, il n'y a aucune raison de doter l'ordonnance sur les accidents majeurs de réglementations spécifiques en matière de toxicité des nanomatériaux pour l'homme et l'environnement.

Mots-clés:
Prévention des accidents majeurs, nanotechnologie, nanomatériaux synthétiques, toxicité pour l'homme et l'environnement

La nanotecnologia è un settore della ricerca e dello sviluppo in rapida espansione e sempre più importante per l'economia, la ricerca e la società. Il presente studio esamina se dal potenziale di pericolo o da possibili nuovi scenari di incidenti rilevanti dovuti alla tossicità umana e all'ecotossicità dei nanomateriali sintetici possano scaturire nuovi criteri sulla base dei quali fissare i quantitativi soglia nell'ordinanza sugli incidenti rilevanti. L'analisi della letteratura scienitica svolta mostra che, al momento, i dati di base disponibili sono insufficienti per consentire una valutazione definitiva. Dai risultati ottenuti sinora si evince che l'adozione immediata di norme specifiche nell'ordinanza sugli incidenti rilevanti volte a disciplinare i nanomateriali negli ambiti della tossicità umana e dell'ecotossicità non sarebbe giustificata.

Parole chiave:
Incidenti rilevanti, nanotecnologie, nanomateriali sintetici, tossicità umana ed ecotossicità

> Foreword

The purpose of the Ordinance on Protection against Major Accidents (OMA) is to protect the public and the environment from serious damage resulting from major accidents, which can occur during the operation of industrial facilities. The principal themes of the OMA include, among other things, the quantification of the risk to the public and the environment, which may result from the handling of substances, preparations, and special wastes. Where the enforcement of the OMA is concerned, the FOEN has the responsibility for overall control. In its control function, it monitors continuously developments involving chemical risks, lends its support to unified enforcement of the OMA in the whole of Switzerland, and prepares guidelines in cooperation with representatives of the responsible cantonal enforcement authorities, industry and science.

Nanotechnology is a rapidly growing research and development area with increasing importance for the economy, science and society. Over and above the opportunities it offers, it is important to detect possible risks to humans and the environment in good time, and, where necessary, to take appropriate protection measures. As of 9 April 2008, the Federal Council approved the "Synthetic Nanomaterials" Action Plan, whose purpose is to prepare the basis for a secure nanotechnology, and decided to extend it to 2015.

Part of the Action Plan is to investigate whether the hazard potential or hypothetical new accident scenarios make it necessary for specific regulations on nanomaterials to be included in the OMA. This problem was clarified by the FOEN in the field of fire and explosion properties in the published packet, Environmental Studies, in 2010. The present study provides initial insights into this question for the fields of human and ecotoxicity. The study shows that the fundamental data available at the present time are very limited and are not adequate to enable general conclusions to be drawn. Nonetheless, initial insights for major accident prevention could be won, and a perspective on important pending questions given. The FOEN's objective is to encourage the research institutions and industry to take up these questions.

The FOEN section responsible for major accident prevention will continue to follow the national and international developments in this field, to put it in a position to introduce the necessary measures when necessary.

Andreas Götz
Vice Director
Federal Office for the Environment (FOEN)

> Summary

The purpose of the Ordinance on Protection against Major Accidents (OMA) is to protect the public and the environment from possible major accidents. In order to ensure the necessary level of protection, the FOEN, which has responsibility for overall control of the enforcement of the OMA, monitors the development of new technologies and substances, so that the OMA can be amended whenever necessary. Nanotechnology is rated as a rapidly expanding research and development area. Even at the present day, a whole range of nanomaterials are on offer on the market in very diversified products, and new fields of application are constantly being discovered. As part of the Swiss "Synthetic Nanomaterials" Action Plan, an investigation is therefore to be performed as to whether nanomaterials are adequately covered by the OMA. To this purpose, in the present study, data taken from human toxicological and ecotoxicological studies on a range of nanomaterials were analysed, and a selection of companies were visited to obtain knowledge on their production facilities and the processing of nanomaterials.

The visits to companies made it clear that the quantities of nanomaterials produced and processed in Switzerland are small. Moreover, no nanospecific release routes are to be expected. The existing safety measures in the chemical industry are also suitable for nanomaterials – this applies in particular to the separate storage of solvents and the provision of retention basins where nanosuspensions are involved. The risk of the release of nanomaterials in powder form is greater than for nanosuspensions, but this can be minimised by the application of safety measures from the field of conventional powders.

The studies consulted on human and ecotoxicology show that, as yet, no conclusive statement on the (eco)toxicity (i.e. human and ecotoxicity) of nanomaterials can be made. Compared to traditional substances, the (eco)toxicity of nanomaterials can differ not only in relation to their chemical composition but also to their functionalisation, size, form, and other parameters. The existing studies indicate that the (eco)toxicity of nanomaterials is comparable to that of the corresponding microparticles (titanium dioxide) or to the corresponding ions (e.g. silver and zinc). An exception to this is photocatalytically active titanium dioxide, which displays higher toxicity to aquatic microorganisms.

It is absolutely essential that the manufacturers of nanomaterials should honour their duty to prepare a Safety Data Sheet, on which they must supply the necessary data for categorisation of the nanomaterials, enabling the enforcement authorities in the cantons to determine the nanospecific quantity threshold.

Owing to the present limited fundamental data, the conclusions drawn in the present report must be regarded as initial insights. Not until standardised tests for the determination of the toxicity of nanomaterials are available, and it is clear from what point onwards nanomaterials must be declared in Safety Data Sheets, it is advisable for the purposes of major accident prevention to perform monitoring of "high production volume" nanomaterials at regular intervals, and to check whether the conclusions drawn in the present report still remain valid.

> Résumé

L’ordonnance sur les accidents majeurs (OPAM) a pour but de protéger la population et l’environnement des accidents majeurs potentiels. Afin de garantir un bon niveau de protection, l’OFEV observe l’évolution des nouvelles technologies et substances en sa qualité d’autorité de haute surveillance pour au besoin adapter l’OPAM. Or, la nanotechnologie est un domaine de recherche et de développement en expansion rapide. Les nanomatériaux sont déjà utilisés dans différents produits commercialisés et les applications se multiplient dans les domaines les plus divers. Dans le cadre du plan d’action suisse «Nanomatériaux synthétiques», il convient d’examiner si l’OPAM prend en compte les nanomatériaux de manière adéquate. La présente étude s’est donné pour but de répondre à cette question par l’analyse des résultats d’autres recherches sur la toxicité de différents nanomatériaux pour l’homme et l’environnement et par des visites d’entreprises de fabrication ou de traitement des nanomatériaux.

Les visites d’entreprises ont montré que les quantités de nouveaux nanomatériaux produits et transformés en Suisse sont faibles. Qui plus est, il n’y a pas de risque particulier de dissémination lié à ces matériaux. On peut leur appliquer les mesures de sécurité déjà connues dans l’industrie chimique, en particulier le stockage séparé des solvants et l’utilisation des bassins de rétention pour les nanomatériaux en suspension. Ceux-ci sont moins sujets à une dissémination accidentelle que les nanomatériaux sous forme de poudre, par lesquels le risque peut toutefois être minimisé grâce à des mesures de sécurité identiques à celles prises pour les poussières traditionnelles.

Quant à l’analyse de la littérature scientifique, elle montre qu’aucune conclusion définitive ne peut encore être tirée quant à la toxicité des nanomatériaux pour l’homme et l’environnement. Contrairement aux substances classiques, la toxicité des nanomatériaux dépend non seulement de leur composition chimique, mais aussi de toute une gamme de variables (structure, taille, forme, etc.). Les études actuelles semblent indiquer que les nanomatériaux présentent le même degré de toxicité que les microparticules (dioxyde de titane) ou ions (argent, zinc) des mêmes composés. Le dioxyde de titane utilisé dans la photocatalyse fait exception, car il présente une toxicité plus élevée pour les micro-organismes aquatiques.

Les producteurs de nanomatériaux doivent impérativement respecter leurs obligations et établir une fiche de données de sécurité avec les indications nécessaires pour classer les nanomatériaux. Les autorités d’exécution cantonales seront ainsi en mesure de déterminer les seuils quantitatifs spécifiques.

Les données à disposition étant encore limitées, les conclusions de ce rapport ne constituent qu’un premier jalon dans le domaine. Tant que des tests uniformisés permettant de déterminer la toxicité des nanomatériaux n’auront pas été développés et qu’il n’aura pas été clairement décidé à partir de quand les nanomatériaux doivent être notifiés sur les fiches de données de sécurité, il faut, pour prévenir les accidents majeurs, procéder à des contrôles réguliers des nouveaux nanomatériaux produits en grands volumes (high production volume). En outre, il s’agira de vérifier régulièrement la validité des conclusions du présent rapport.

1 > Introduction

1.1 Background

Ordinance on Protection against Major Accidents

The purpose of the Ordinance on Protection against Major Accidents (OMA)[1] is to protect the public and the environment from serious damage resulting from major accidents. A company is subject to the OMA if substances are stored on its premises in quantities exceeding the quantity thresholds for substances, preparations or special wastes according to OMA. The quantity thresholds for substances and preparations can be determined by means of the list of criteria contained in Annex 1.1 Nb. 4 OMA in relation to their properties or (for certain substances and preparations) directly from the list of exceptions. In this, the determination of the quantity thresholds is based on the method which relates the properties of a substance to its mass. Companies that are subject to the OMA must submit to the enforcement authority a summary report containing an estimate of the extent of possible damage due to major accidents. As specified in Handbook I on the OMA[2], the estimate must be based on accident scenarios. In selecting these, the type of establishment, the danger potential present in the individual installations in the company, as well as the possible accident causes and sequences of events based on a reasoned assessment must be considered. Where substantial damage to the public (more than 10 fatalities outside the company premises) or damage to the environment cannot be excluded, the enforcement authorities must require the owner of the establishment to submit a quantitative risk study based on accident scenarios for their approval.

The OMA[1] differs from the regulations on workplace and consumer safety in that it attempts to protect the public and the environment from serious damage resulting from exceptional events. In this, only persons outside the premises of the establishment subject to an isolated exposure are taken into account. Chronic effects are not considered.

Synthetic Nanomaterials Action Plan

Nanotechnology is a rapidly growing research and development area with increasing importance for the economy, research and society. It is therefore important to investigate possible risks comprehensively and if necessary to take measures to protect humans and the environment. The current discussion on the risks involved is concentrated on the synthetic nanomaterials used in nanotechnology. The purpose of the Confederation in issuing the "Synthetic Nanomaterials" Action Plan[3] is to lay down the procedures for the safe use of nanotechnology. Owing to their small size and for other reasons, synthetic nanomaterials display altered properties, and for this reason cannot be regarded as equivalent to larger particles. A separate assessment of the quantity thresholds and assessment criteria is necessary in order to take proper account of the new characteristics of nanomaterials.

1.2 International activities

Fire and Explosion Properties of Synthetic Nanomaterials

An assessment of the situation in neighbouring countries shows that there is disagreement as to whether nanomaterials are adequately covered or not in existing legislation on the prevention of major accidents. Up till now, the authors of the present report are not aware of any studies with the exception of the FOEN report on the fire and explosion properties of synthetic nanomaterials[4]. The European Commission has stated that nanomaterials with major accident potential can be categorised in this sense under the EU Seveso II directive[5]. More hard-and-fast regulations do not exist at present, despite the fact that the theme of major nano-accidents has been recognised as significant in various countries[6–8]. As an exception, the attitude of the British Parliament differs from this in that it regards nanospecific regulations as superfluous. The question has not yet been considered by the European Parliament[9].

OECD Working Group

The British Standards Institution (BSI)[10], the Canadian Research Institute for Public Health (IRSST)[11] and the German Federal Centre for Workplace Protection and Occupational Medicine BAuA[12] have published guidelines on the safe handling of nanomaterials. In the BSI document, fundamental measures for major accident prevention are listed. For example, the BSI demands for firms that work with synthetic nanomaterials should prepare an emergency plan of action for hypothetical accidents, which lists the precise sequence of events and the measures which must be taken in the case of an incident or major accident. All persons that may be involved in such an event should be correspondingly informed and trained in the handling of nanomaterials. Furthermore, measures must be taken to prevent the dispersion of nanomaterials in case of an incident. The main focus of the IRSST document is on hygienic recommendations for the workplace. The theme of major accidents is not mentioned. The OECD has appointed its own working group on synthetic nanomaterials with the objective of lending support to international cooperation in the field of toxicity and ecotoxicity of these materials[13]. The revised draft of the report of the working group contains detailed information on risk determination of nanomaterials. However, neither does this report consider the theme of major accidents. A specific report on major accidents involving nanomaterials is in preparation[14]. The Swiss delegation in the OECD working group has purposed the establishment of a workshop on this subject.

1.3 Definition

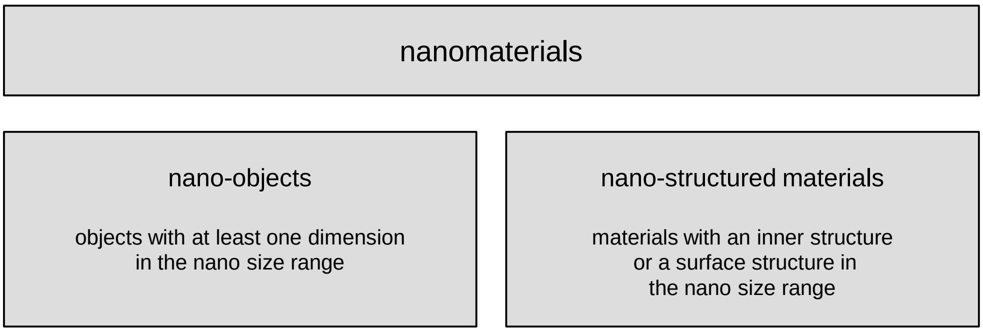
Definition "synthetic nanomaterial"

There are several different definitions of nanotechnology in current use[15]. Most of these define a size range of 1–100 nm. An exception is the Swiss "synthetic nanomaterials" Action Plan[3], which adopts a bandwidth of 1–500 nm. In October 2011, the EU tabled the following suggestion for a definition[16]:

"A nanomaterial means 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 1–100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%."

A generally well accepted definition and nomenclature was introduced by the ISO (International Organisation for Standardisation)[17]. In this, among other things, a distinction is made between nano-objects and nano-structured materials (fig. 1).

Fig. 1 > Definition of nanomaterials according to ISO[17]



ISO/TS 80004–1

In the present report, the terminology is based on the ISO definition[17], and the term "Engineered nano-objects" (ENO) used to designate all synthetic nano-objects with at least one dimension in the nano size range. Despite this, the size range is defined analogously to the Swiss Action Plan[3], since biologically relevant properties of ENO (e.g. ready absorption, novel material properties, larger surface) cannot precisely be limited to 100 nm, but depending on material and effect, can continue to arise up to a size of several hundred nm. An extension of the nano size range to 1–500 nm is therefore justified. The size range refers to the primary particles. Agglomerates with corresponding primary particles are therefore expressly included. Composite materials, on the other hand, from which ENO can only be separated with significant energy expenditure are rated as nano-structured and do not come under the term ENO in the sense of the present study.

The framework for the classification is provided by the Safety Data Sheets (SDS), in which it should be made mandatory to enter the corresponding information. Unfortunately, however, it has not been made mandatory to declare the quantity of substances contained, but a statement of the chemical compound suffices. Therefore, companies that further process the substances receive no information as to whether the product contains nanoscale substances. In many cases, the nanosubstance in question does not even exceed the threshold concentration of 1%, so that it must not even be included in the list of substances contained. A clear obligation to declare the size of nanoscale substances in the SDS should be prescribed, ensuring that in future the necessary data will be included in the SDS.

1.4 Questions covered and procedure

Questions covered

The main focus of the present work is the assessment of the human and ecotoxicity of ENO in the case of a major accident in comparison to conventional chemicals. The question is addressed as to whether the quantity-based approach adopted in the OMA for the determination of the quantity thresholds may also be used for ENO, and which major accident scenarios must be taken into account in connection with human and ecotoxic ENO. To address these questions, for one, a comprehensive literature study on toxicity and ecotoxicity was performed; for another, visits to companies that produce or use ENO were made to provide a basis for the preparation of major accident scenarios. Generic exposure estimates provided data on the distribution of ENO in the environment following a major accident.

It is clearly apparent that it would neither be possible nor reasonable to perform an analysis of the complete range of synthetically manufactured, nanoscale objects. The present report therefore concentrates on the following four selected substances, that, for one, are widely distributed, used or produced in larger quantities, and for which, for another, data are available on their ecotoxicity (in the list below, the customary abbreviation is cited):

Synthetic nanomaterials (ENO): 4 examples

> Titanium dioxide (nano-TiO_2)
> Zinc oxide (nano-ZnO)
> Carbon nanotubes (CNT)
> Silver (nano-Ag)

The present report is intended to provide an assessment of the human and ecotoxicity of ENO as a basis for a corresponding regulation in the OMA[1].

1.5 Fields of application of the synthetic nanomaterials studied

As mentioned above, the ENO selected belong to the group of frequently used nanomaterials, that are therefore used in larger quantities. In comparison to the corresponding conventional materials, the quantities used still remain very limited. Thus in 2009, for example, a quantity of 4,68 million t of titanium dioxide was produced worldwide, the quantity of nano-TiO_2 produced amounted, however, to less than 1% of this quantity. As this example shows, the nano fraction of the total quantity produced is relatively small. This also applies to silver, zinc oxide and CNT, whereby the annual world production of CNT amounts to an estimated 100 to 200 t, whereby some references quote a use of several thousand t[18].

Conventional TiO_2 is used in many different applications and particularly as white pigment in paints. Basically, TiO_2 is only weakly soluble and chemically inert. It occurs in three different crystal structures: anatas, rutile and brookite, whereby brookite is not commercially relevant. The areas of application of anatas and rutile differ in relation to their different properties: nano-TiO_2 with an anatas crystal structure is photocatalytically active and is used for this reason in or on inorganic matrices with selfcleaning properties, whilst (coated) rutile-nano-TiO_2 is used in (organic) coagulants as a pigment and UV absorber. The most well-known example is in sun creams. Owing to its diverse applications as UV absorber and photocatalyst, nano-TiO_2 is the most well-studied ENO. Although conventional TiO_2 pigments used in paints contain a certain fraction of nanoscale TiO_2 particles, till now no negative effects have been reported.

As with titanium dioxide, zinc oxide also has a very broad and diverse spectrum of use, extending from technical applications via cosmetics up to pharmacy. Zinc oxide is also used in the production of rubber, cement, and also in dispersion and artwork paints. When used in cosmetics, zinc oxide has UV absorbing properties, and in many medical products (ointments, pastes, wound treatment products), it also has positive effects on the immune system and on the regeneration of the skin. In principle, its protective effect against UV radiation may be enhanced by the addition of nanoparticles, and this effect is exploited for example in textiles, varnishes for wood and furniture, and also in transparent plastics and plastic films (plastic glasses).

By contrast, carbon nanotubes, which are a completely new form of carbon, have very interesting properties that are generally technical in nature. The tubes are extremely stable in relation to their tensile strength. For example, the tensile strength of a multi-walled plastic nanotube was found to be 63 GPa, corresponding to approximately a factor of 50 greater than that of steel. In relation to their electrical properties, carbon nanotubes can have insulating, semi-conducting, or metal-like, conducting properties. Depending on how they are produced, these properties can be set at will, enabling very diverse uses to be conceived. Examples of this are: transistors of nanotubes, nanotube storage, nanotubes for the improvement of plastics, and in measurement technology. CNT are not presently used in biology and medicine, but a series of studies have already been performed on this.

Silver was already used in prehistoric times, and has since been used in many applications. Although its use in the photographic industry declined significantly following the development of digital photography, silver continues to be relevant in electronics. Alongside its main application in the jewellery industry, silver is used as a biocide, and was already used by our predecessors as a disinfectant and conservation agent for drinking water. In the form of nanoparticles (colloidal), silver is mainly used owing to its antibacteriological properties, and has been used for a hundred years, for example in private swimming pools as an algicide and biocide, and owing to these properties is also gaining increasing importance in textiles and medicine.

2 > Toxicity and ecotoxity of engineered nano-objects (ENO)

2.1 Comparison between microparticles and ENO

Comparison between microparticles and nanoparticles

Various studies draw attention to the circumstance that the particle size (nano or micro) is an important determinative factor in absorption and distribution in the organism, and toxicity. Particles with a diameter up to 2.5 µm can be transported into the deep regions of the lung, where the air/blood barrier is only several µm thick. It has been shown in animal tests that nanoscale particles administered in high doses are well able to overcome this barrier and to enter the blood[32]. The quantity of nanoparticles overcoming the barrier is small in comparison to the dose administered, and depends on the physical and chemical properties of the ENO. Nevertheless, the ENO have the potential to more readily overcome the barrier, and thus to gain access to tissues and cells that would not be affected by larger particles. Through this mechanism alone, different reactions of the tissues can be expected.

In a study by Gaiser et al.[19], the mortality rates of daphnia in the presence of nano-Ag in comparison to micro-Ag were measured, and a significantly higher acute toxicity for nano-Ag than for micro-Ag was found, although both the nano and the microparticles were present in aggregated form and had a comparable secondary particle diameter. In a study by Zhu et al. the nano-TiO_2 particles were approx. eight times more toxic than the microparticles[20]. These results were confirmed by Xiong et al.[21]. Although the particle sizes of the aggregates of nano-TiO_2 were comparable to those of the microparticles, no toxicity was found for the microparticles, even at high concentrations. By contrast, this study found comparable toxicity of nano-ZnO and of micro-ZnO[21]. Also, further authors could not detect any significant difference in the toxicity of nano- and micro-ZnO[20,22,23]. Differing results can be found in Ma et al.[24] for the phototoxicity of ZnO. Their study showed a significantly higher toxicity of nano-ZnO. Yet another study discovered that nanoscale metals released ions more readily than microparticles[25].

Despite conflicting results in certain cases, it can therefore be assumed that ENO can display higher toxicity than larger particles having identical chemical composition. Even among the ENO, particles of different size can have differing values of toxicity. This difference is particularly noticeable with inhaled CNT. Whilst fibres up to 5 µm in length can be eliminated without difficulty by guard cells in the body (macrophages), larger fibres can lead to cell proliferation through mechanical irritation of the lung epithelium. This phenomenon is referred to as the fibre paradigm. Notwithstanding this, till now, neither with CNT nor with asbestos could it be demonstrated that this effect also occurs with isolated doses. With algae exposed to nano-TiO_2, the comparison of different particle sizes in relation to their (photo) toxicity gave a critical particle size of 4–30 nm[26].

2.2 Comparison between ions and ENO

Comparison between nanoparticles and ionic dissolution

With soluble ENO, it is important to compare the toxicity of the ENO with the toxicity of the corresponding ions. In doing so, it is, for example, important to be aware that all preparations of nano-silver are already contaminated with silver ions, as this cannot be avoided for methodical reasons. It is important for this fraction to be quantified in the studies and included in the assessment. Gaiser et al.[19] determined the toxicity of nano-Ag having a solubility below 1%. Owing to the acute toxicity of these barely soluble particles, the authors concluded that the dissolution of ions cannot provide the only explanation for the toxicity of nano-Ag. The results of a study with bacteria support this conclusion[27]. Similar results were also found in the studies of Poynton et al.[28], Yu et al.[22], Ji[29] and Ma et al.[24], which also concerned soluble ZnO. These studies show that only part of the ENO are transformed to ionic Zn^{2+}, and that this fraction cannot entirely explain the toxicity of nano-ZnO. The same results were also found with algae[29] and invertebrates (D. magna[28]), and also with fish (zebrafish[22]). Control experiments of Ji et al.[29] showed that the toxicity of Zn^{2+} via nano-ZnO and micro-ZnO declined at a concentration below 50 mg/l; but that at higher concentrations, the toxicity of nano-ZnO was greater than that of zinc ions. In this, blackout effects could be excluded. A possible explanation could be the deposition of nanoparticles on the surface of the cells. Furthermore, in the study of Ma et al.[24] on the phototoxicity of ZnO, the dissolution of the particles played a subordinate role. However, the study by Xiong et al.[21] comes to a conflicting conclusion, whereby no difference in the toxicity of nano-ZnO and Zn^{2+} was found. Proven explanations for the different toxicity mechanisms of nano-ZnO and ionic zinc are not yet available. A recent published study by Shaw & Handy[30], however, draws attention to the fundamental difference in the bioavailability and the absorption mechanisms of dissolved metal ions and particulate metals, whereby this also applies to human cells, and had also been found earlier[31]. Distribution and excretion pathways of nanometals are still largely unknown. Although nanometals can release ions, their acute toxicity is not always entirely explicable by the toxicity of the metal in dissolved form[30]. Notwithstanding this, the different effects of ENO in comparison to the corresponding metal in ionic form might also be explicable by their different distribution in tissues. Nanoparticulate metals can accumulate in cells/tissues that are not accessible to ions, and therefore function as so-called "nanotrojans", leading to massively increased local concentrations with corresponding effects. Under these conditions, special treatment of the ENO – also in relation to the precautionary principle – is justified. However, further studies are advisable to enable a sufficiently well-founded conclusion to be drawn.

"nanotrojans"

2.3 Modification and functionalisation of ENO

ENO can be doped with foreign elements to achieve certain properties. For example, nano-TiO_2 can be enriched with nitrogen, boron or other elements to increase the light absorption spectrum. In doing so, the original particles are modified by foreign elements, so that the chemical composition differs from non-doped nano-TiO_2. Alternatively, ENO can also be functionalised at their surface with various organic or inorganic compounds. Such coatings are under certain circumstances reversible (this can apply, for example, to organic coatings). The determinative factor in describing the particle is therefore the particle core. Nevertheless, these coatings also have a decisive influence on the behaviour or the properties of the corresponding ENO. Using coatings of SiO2 or aluminium oxide (which form so-called "core-shell particles"), it can be prevented that nano-TiO_2 becomes photocatalytically active. The most frequent reason for the functionalisation of ENO is to prevent their agglomeration.

In the absence of the necessary coating, ENO tend to agglomerate to larger particles. It is therefore difficult to bring non-functionalised ENO into suspension. In medicine, ENO can be functionalised to make them more readily water-soluble or fat-soluble, and in this way the distribution in the body and excretion can be influenced. Similarly, differently functionalised ENO can also display different (eco)toxicity. It is problematical that products mostly contain modified ENO, whereas in (eco)toxicity studies, unmodified ENO were mostly used.

2.4 Human toxicity

Human Toxicity

Owing to their small size and large specific surface, the toxicity of ENO differs in comparison to larger particles with respect to (a) absorption pathways and (b) toxicity. The principal absorption pathways of ENO in our body are inhalation and oral uptake, whilst the skin only plays a subordinate role. As opposed to the lung, which is the most vulnerable entry port for ENO, healthy skin fundamentally represents an efficient barrier. For this reason, powdery ENO present a higher risk of acute toxicity. As yet, only few studies have been carried out on chronic toxicity. A carcinogenic or mutagenic effect, or toxicity of ENO to the reproduction system – in particular nano-TiO_2, nano-ZnO, nano-Ag and CNT, that are manufactured on an industrial scale – cannot therefore be generally confirmed or excluded at the present time.

2.4.1 Nano-TiO_2

Nano-TiO_2

It could be shown in animal tests that inhaled nano-TiO_2 can reach the deepest regions of the lungs, i.e. the alveoles. There, the ENO are largely absorbed by guard cells (macrophages). There are, however, indications that a small part of the nano-TiO_2 administered can breach the tissue barrier, and therefore be carried into the bloodstream, and distributed in the whole body[32,33]. Exposed lung tissues or lung cells only display minor signs of stress (after very high doses [≥ 10 mg/m³]) such as inflammation[34], but not, however, genotoxic effects[35]. The human toxicity of nano-TiO_2 can therefore be described as low.

"Overload" studies

"Overload" studies and studies in which quantities far exceeding the maximum quantities released in major accidents were not considered, since the effects observed could no longer be related to substance or size properties. This overload situation had already been described in the early 1990s, in which an isolated quantity of 3 mg of particles or dust was found to overload the lungs of rats[36]. In this case, this results in increased mortality independently of the substance administered (in some cases through suffocation) owing to the unrealistically high administered dose.

2.4.2 Nano-ZnO

Nano-ZnO

Non-modified ZnO dissolves partly or wholly in the watery milieu of the human organism, and zinc ions are released. This dissolution process is specific to the particle type and depends on the composition of the watery solution in which the zinc oxide particles are dissolved. Zinc itself is an essential element (15 mg or 12 mg/d recommended dose for men or women respectively), and the immune system, for example, must be provided with zinc in order for it to perform its function. Large quantities of zinc are, however, toxic, and a painstaking assessment of nano-ZnO is therefore necessary at the workplace or in its administration. Several in vitro tests indicated damage to cells in the form of reduced cell vitality and infective reactions right through to the death of the cell[37–39]. In these older studies, no unambiguous distinction could be made between particle-versus-ion effects. The study by Bürki-Thurnherr et al.[40] provided for the first time the experimental basis enabling a nano-ZnO effect to be excluded, at least for the nano-ZnO particles used in the tests[39,41].

Zinc has an acute effect when inhaled as zinc-oxide smoke, as could be observed, for example, during welding work. Although in such work, it was seldom possible to detect any absorption in the bloodstream, the local concentrations in the lung are sufficient to trigger systemic effects via inflammatory mediators[42–44]. This effect could also occur in the course of a major accident and the further distribution of ZnO nanoparticles. For this, the concentrations would have to rise significantly above 50 mg/m^3, since in trails on test persons, no serious consequences could be observed at concentrations up to 33 mg/m^3[45].

2.4.3 CNT

Carbon nanotubes (CNT)

Much attention has been devoted to CNT, not only owing to their exceptional material properties, but also due to their needle-like appearance that is similar to asbestos. In the past 10 years, over 550 articles have been published on possible toxic effects[46], although discussion on the mechanism of this effect has been very controversial. Basically, CNT belong to a substance class having many different types and, depending on the manufacturing process, with differing metallic catalysts such as Ni, Co, Fe and Y, which renders it practically impossible to compare the studies. Irrespective of the effects of impurities[47], the agglomeration state of the tubes has a large influence on cell vitality, since the higher the degree of agglomeration, the more toxic the CNT becomes in cell tests[48].

Over time, and in connection with the work of Donaldson and collaborators[49,50], the fibre paradigm has become established. The fibre paradigm states that only the longer (> 20 µm) and stiff CNTs, which cannot be eliminated from the lungs through natural filter processes, as with asbestos, can induce pleural mesotheliomas. It can also be concluded from this that short and contorted CNTs can cause hardly any damage to the tissues, or no damage at all. Even so, CNTs can also be present in functionalised form. As a result of chemical modifications, functional groups can be attached covalently to the graphene structure, and in this way alter the original hydrophobicity for selected groups of tubes in the direction of hydrophilicity. The CNTs, which in this way become more readily water-soluble, and, through the modification of their physical and chemical properties, become significantly less toxic in comparison to the non-functionalised CNTs if the fibre paradigm is valid. Depending on the modification (see Chapter 2.3), developments are in progress to apply CNTs for diagnostic and therapeutic purposes[51].

Following inhalation or instillation[1] of CNTs in the lungs of test animals, although more pronounced inflammation and increased formation of granulomas were detected[52,53], a conclusive assessment on the biological effect of CNTs in general cannot, however, be given. To do so, CNTs are, for one, too varied and, for another, the results of previous studies too divergent.

2.4.4 Nano-Ag

Nano-Silver

As opposed to microorganisms, silver is only toxic to humans and mammals in larger quantities (LD50 500–5000 mg/kg[54]. Nanoscale silver is now increasingly being used as an antibiotic substitute. Through nanoformulation, the release of silver ions can be more readily preset, and in this way the best possible effect at very low material expenditure achieved[55]. With the increasing use of Nano-Ag, nanotoxicological studies are being increasingly performed. There are indications that following inhalation, nano-Ag spreads to the whole organism[56]. Cell tests using high doses of nano-Ag have shown that mitochondria activity is adversely affected[57,58], or the DNA can be damaged[59]. To what extent this is due to a nano- or Ag-ion effect is not yet clear, and is the subject of current research.

2.4.5 Comparison of the human toxicity of ENO to that of the corresponding microparticles

In the Ordinance on Protection against Major Accidents, the following criteria for the determination of the quantity thresholds are prescribed in relation to toxicity[1]:

1 Instillation is a method by which a predefined dose of a material can be deposited using a tube or cannula directly in the lung at a predefined position. This method is very simple and low-cost (in comparison to inhalation), but it has a series of decisive disadvantages, e.g. an overdose at the position treated, whilst the remaining parts of the lung remain untreated.

- EU classification
- Acute toxicity, orally, dermally oral, dermal and inhalative
- SDR classification

Micro versus Nano

A comparison between traditional chemicals (e.g. microparticles and powders) with ENO based on these criteria is limited to the “acute toxicity” criterion, since ENO do not have their own EU or SDR classification. In Tab. 1, the risk potential of ENO in comparison to traditional materials is summarised.

Tab. 1 > Risk potential of ENO in comparison to traditional materials (microparticles)

ENO	Risk potential			notes
	acutely toxic	long-term effects	difference micro-nano	
TiO_2	very slight	slight	1 to 10	Although titanium dioxide is assigned to Class 3 of the carcinogenic materials (based on a poor animal test study), the general toxicity is only slight, as could be shown in recent studies on several occasions. Although there exists a difference in the effects of large and small particles, this fact is of only minor importance for a dispersion scenario in a major accident.
ZnO	yes; concentrations from approx. 5 mg/m³ air $\Rightarrow$ zinc fever	slight	tend to be slight	The injection of fine or nanoscale ZnO particles into the lungs of mice or rats causes a heavy, but only transitory inflammatory reaction. Surprisingly, both the intensity and also the progress of this reaction were practically identical for fine and nanoscale ZnO. The acute consequence of inhaling zinc dust is zinc fever, but even here, to produce serious consequences (mortality), the concentrations must be well above 5 mg/m³.
CNT	tend to be slight	high	-/-	Depending on the type of CNT (physical and chemical properties, e.g. single-walled, multi-walled, long/short, among others), long-term effects must be taken into account as for asbestos (mesothelioma?), if the conditions applying to “WHO fibres”(length $> 5\mu m$, diameter $< 3\mu m$ and a length/diameter ratio over 3:1) are applicable.
Silver	tend to be slight	slight	tend to be slight	For many decades, silver has also been used in the form of nanoparticles (colloidal). There are no indications of acute intoxication with risk to life; except in the case of exposure to ultrahigh concentrations. Since silver nanoparticles tend only to be used in small quantities in products, the production and transported quantities tend to be slight, and therefore a major accident with serious consequences due to nano-Ag is not to be expected.

2.5 Ecotoxicity

Ecotoxicity

The potential ecotoxicity of nanomaterials did not become a principal object of research until recent years. In consequence, there are usually only few studies available for each ENO – often with conflicting results, since standardised test methods are still largely lacking. A further challenge is that the toxicity values depend not only on the substance and species, but may also vary in relation to functionalisation and method of suspension of the ENO. The experiments of Schwab et al.[60] show, for example, that even the age of an ENO suspension may have an influence on ecotoxicity. As is well-known, the exposure time also plays a significant role. Kim et al.[61] detected a seven-times higher mortality of daphnia (D. magna) with constant nano-TiO_2 concentration, when the exposure time was extended by a factor of 10.

2.5.1 Nano-TiO_2

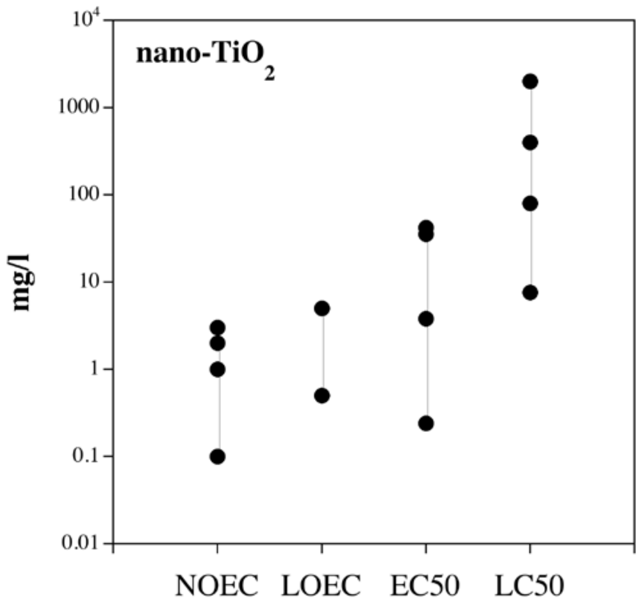
Nano-TiO_2

Particularly the photocatalytic activity of TiO_2 in the crystal structure of anatas is relevant to the ecotoxicity of nano-TiO_2. Whilst (uncoated) anatas particles become photocatalytically active in the presence of light, and thereby display higher toxicity, the (coated) particles in rutile form are less toxic. The study of Ji et al.[29] demonstrated that rutile nano-TiO_2 (as for SiO_2 and Al_2O_3) are not toxic to green algae (chlorella sp.), whilst for anatas an EC_{30} of 30 mg/l was observed. The following values are available for the test organisms (daphnia and fish) quoted in the criteria list of the OMA: Hall et al.[62] measured the toxicity of nano-TiO_2 for the fathead minnow (P. promelas) and determined an LC_{50} of 0.5 mg/l. For the zebrafish, Xiong et al. determined an LC_{50} of 124 mg/l[21]. The NOEC was determined to be 1 mg/l[63].

For the daphnia species C. dubia, the LC_{50} is 7.6 mg/l[62] or 400 mg/l[64], for D. magna 20 000 mg/l[65], and for D. pulex 9.2 mg/l[62]. The very high value of toxicity of nano-TiO_2 to D. magna may be explained by the test conditions (darkness) during the study. Owing to its photocatalytic activity, the toxicity of nano-TiO_2 is principally induced by light. The toxicity varies in relation to the radiation intensity. Depending on the particular study, exposure time and test organism, the NOEC values lie between 0.1 mg/l[66] and 1–3 mg/l[23,63,67,68] and at 20 000 mg/l in the study without light[65]. For C. dubia, Li et al. determined an EC_{50} value of 42 mg/l[69], Zhu et al. 35.3 mg/l[20] and Dabrunz et al. a value between 0.24 mg/l and 3.8 mg/l depending on the exposure time[70]. In addition, the study of Wang et al. indicates that combined effects of different substances may occur[64]. The authors detected a significantly higher toxicity of arsenic (As(V)) in the presence of a low concentration of nano-TiO_2[64]. Fig. 2 shows the bandwidth of the values found in the toxicity studies with daphnia.

Fig. 2 > Range of scatter of the toxicity values (LC_{50}, EC_{50}, LOEC, and NOEC) of daphnia

The data were obtained in different studies with various different nano-TiO_2 particles and different species of daphnia.



The data scatter is high. This may be explained by the following deviations in the test conditions:

- > Different species of daphnia
- > Different duration times
- > Different nano-TiO_2 particles
- > Different illumination

Further differences in the test conditions, as for example the method of suspension, which may lead to other agglomerate sizes

Apart from individual data points, Fig. 2 shows a general increase in the values of NOEC via LOEC and EC_{50} in the direction of LC_{50}. It can therefore be assumed that the values represent the dose-effect relationship. The relatively large scatter of the data mirrors the variability of the toxicity in relation to the factors mentioned above.

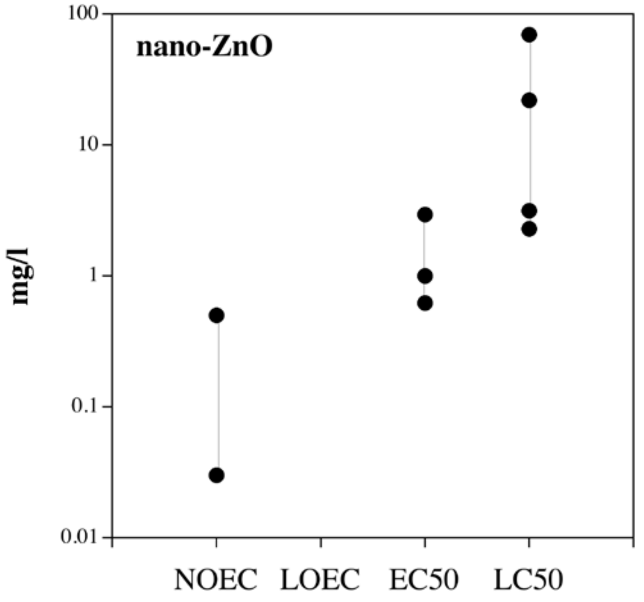
2.5.2 Nano-ZnO

As described below for silver, zinc oxide is also known to have a biocide effect, whereby the toxicity – likewise comparable to silver – must at least partly be attributed to the dissolved Zn2+ ions. Franklin et al. determined an LC_{50} value of 0.055 mg/l for algae (P subcapitata)[71]; the NOEC values for different species of algae varied between 0.017 mg/l and 5 mg/l[29,72,73]. For daphnia, LC_{50} values between 3.15 mg/l for T. platyurus[74], 22 mg/l for D. magna[28] and 2.3 mg/l[75] and 70 mg/l for C. elegans[24] were measured. The available EC_{50} values lie between 0.622 mg/l[20], 1 mg/l[23] und Nano-ZnO

3.95 mg/l[74], die NOEC values between 0.03 mg/l and 0.5 mg/l[65]. For zebrafish (D. rerio), experimental LC_{50} values of 1.8 mg/l[76], 3.97 mg/l[22] and 4.9 mg/l[21] were found. Fig. 3 summarises the ecotoxicity values of nano-ZnO for the daphnia species used in the criteria list of the OMA.

Fig. 3 > Overview of the various nano-ZnO toxicity values (LC_{50}, EC_{50}, NOEC) of daphnia

The data were obtained in different studies with different nano-ZnO particles and various different species of daphnia.



The scatter in the data may be explained by the use of different species of daphnia, different exposure times, different nano-ZnO sources and further differences in the test conditions (e.g. method of suspension). Fundamentally, an increase in the concentration of NOEC via EC_{50} in the direction of LC_{50}, and thus a dose-effect relationship, may be observed.

2.5.3 CNT

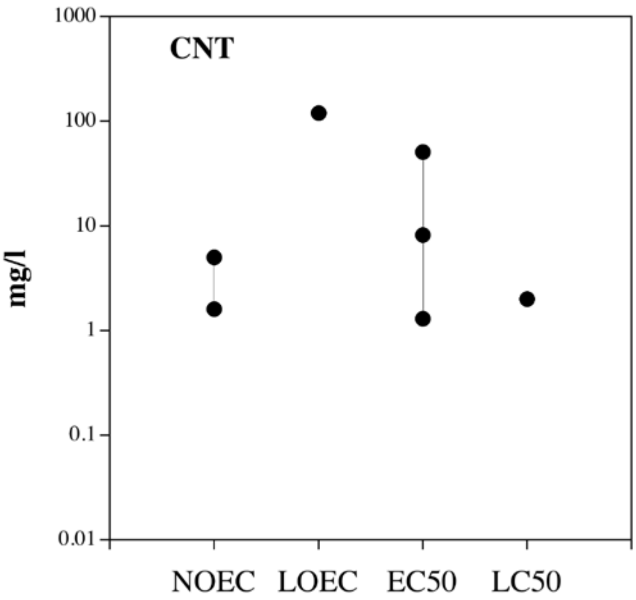
Owing to their similarity to asbestos, CNT were recognised early on as toxic, and therefore studied intensively in the field of human toxicology. In ecotoxicology, however, only very few studies exist. Schwab et al. investigated the toxicity of CNT suspensions with C. vulgaris and found significantly different NOEC values, although only the method of suspension was changed[60]. The values oscillated between 0.042 mg/l in a fresh suspension with finely distributed particles and 3 mg/l in a fresh suspension with aggregated particles[60]. Edington et al. measured an LC_{50} value of 2 mg/l for D. magna[77]. The other studies only detected certain effects (for EC_{50}) or no effects at all (for NOEC). For daphnia (D. magna), a NOEC of 5 mg/l was found[78], for A. tenuiremis the NOEC was 1.6 mg/l[79]. For C. dubia, the EC_{50} was 50.9 mg/l[80] and for single-walled CNT 1.3 mg/l and for multi-walled CNT 8.7 mg/l[20]. For the zebraf-

carbon nanotubes (CNT)

ish (D. rerio), Asharani et al. found a NOEC of 40 mg/l[81]. For the zebrafish, the study by Cheng et al. found a LOEC of 120 mg/l[82].

Fig. 4 > Range of scatter of various toxicity values (LC_{50}, EC_{50}, LOEC, NOEC) of daphnia

The data were taken in different studies with different CNT particles, and various different species of daphnia.



Owing to a lack of studies, no general dose-effect relationship for CNT could be obtained up till now. However, Zhu et al. determined a dose-effect relationship for specific single-walled and multi-walled CNT[20].

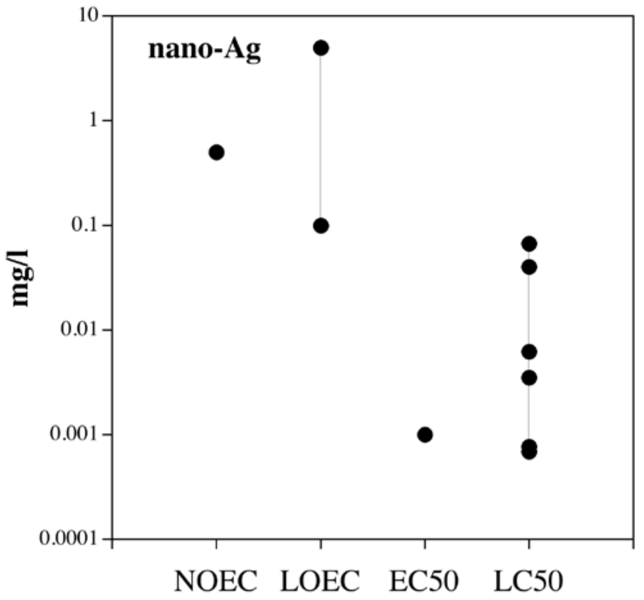
2.5.4 Nano-Ag

Nano-Silver

In comparison to human toxicity, silver is very much more toxic to certain organisms, and this also applies to nano-silver. The ecotoxicity of nano-silver was found in studies with daphnia. For C. dubia, LC_{50} values between 0.00069 mg/l and 0.067 mg/l were found[83,84]. The LC_{50} values for D. pulex (0.04 mg/l[83]) and D. magna (0.003 mg/l[85]) lay in a similar range. According to Zhao et al. for D. magna, the NOEC is 0.5 mg/l[86]. However, Kim et al. detected an effect with 50% of the daphnia[87] at a NOEC of as low as 0.001 mg/l. The LOEC values for C. elegans lie between 0.1 and 5 mg/l[88,89]. The studies on the ENO toxicity to fish determined LC_{50} values between 0.025 mg/l[90], 0.084 mg/l[91] and 7.07 mg/l[83] for D. rerio, and between 1.25 and 10.6 mg/l for P. promelas, depending on whether the particles were brought into suspension by stirring or by sonication[92] and 0.028 mg/l for O. latipes[87]. It should, however, be mentioned that all of the nano-Ag suspensions contained a fraction of dissolved silver ions. This fraction can vary between < 1% to more than 40%, and therefore have a decisive effect on the toxicity. Fig. 5 summarises the results of different studies on the toxicity of nano-Ag to daphnia.

Fig. 5 > Overview of the toxicity of nano-Ag to daphnia

The data were taken in various studies with various nano-Ag particles (different solubility) and different species of daphnia.



At present, no dose-effect relationship can be derived for nano-Ag. Further studies are necessary to enable a well-founded statement to be made.

2.5.5 Comparison of the ecotoxicity of ENO to that of the corresponding microparticles

The OMA[1] specifies the EC_{50} value (inability to swim after one day) as the criterion for the assessment of the ecotoxicity to daphnia and the LC_{50} value for fish (after 2–4 days). The only quantity threshold associated with ecotoxicity is stated as 2 tonnes for an EC_{50} value of ≤ 10 mg/l for daphnia or an LC_{50} value for fish, likewise of ≤ 10 mg/l.

Micro versus Nano

The following tables (Tabs. 2 and 3) compare the threshold value in the OMA[1] with the ecotoxicity values for selected examples in nano or bulk form for the two assessment criteria taken from the OMA. The values for microparticles are taken from the Safety Data Sheets (SDS) of commercial products. For ZnO, the data for EC_{50} differed in the SDS from standard ZnO for daphnia between 0.17 mg/l[93] and > 1000 mg/l[94,95]. For this reason, the value from the study by Wiench et al.[23] was used as a comparison. Published values for dissolved Zn are of the same order of magnitude[96,97]. For CNT, no comparison is possible.

Solubility plays a major role in the assessment of the toxicity of ENO in comparison to microparticles. Nanoparticles of readily soluble compounds such as zinc oxide and copper oxide, and metals that form ions (Ag/Cu) following oxidation, rapidly dissolve because of their smallness and the associated increased surface (in relation to any existing surface coatings). Their toxicity is therefore comparable to that of the corresponding metal ions (Ag^{+}, Zn^{2+}, Cu^{2+}). The most important difference is that ENO accumulate in cells and tissues, and may lead locally to massively raised concentrations of the corresponding metal ions, whereas the readily water-soluble ions are more evenly distributed or excreted.

Tab. 2 > Comparison of the EC_{50} values (mg/l) for daphnia for various ENO in nano versus micro form

EC_{50} daphnia [mg/l]	ENO (lowest measured value)	Larger particles or dissolved ions of the same chemical composition[1]	Ratio of nano:micro[1] (rounded)
Ag	0.001[87]	0.001[5][97]	1:1
CNT	1.8[20][2]	-	-
TiO_2	0.24[70][3]	> 3[94]	1:10 (for the photocatalytically active form)
ZnO	0.62[20][4]	1.8[6, 7][96]	1:1

[1] For readily soluble silver, the comparison is based on the corresponding metal ions.
The value for micro silver particles therefore corresponds to the EC_{50} for ionic silver.
[2] Further values: 50.9[80]
[3] Further values: 3.8[70], 35,3[20], 42[69]
[4] Further values: 1[23], 3.95[74]
[5] Further values 0.002[98]
[6] Mean value of the 48h EC_{50} for dissolved Zn (range 0.3–3 mg/l)
[7] Further values (for micro-ZnO): 1[23]

Tab. 3 > Comparison of LC_{50} values (mg/l) for fish for various ENO in nano versus bulk form

LC_{50} fish [mg/l]	ENO (lowest measured value)	Larger particles or dissolved ions of the same chemical composition[1]	Ratio of nano:micro[1] (rounded)
Ag	0.025[90][2]	0.003[97][5]	10:1
CNT	LOEC: 120[82]	-	-
TiO_2	124.5[21][3]	> 100[99]	1:1
ZnO	1.8[76][4]	16,7[96]	1:1

[1] For readily soluble silver, the comparison is based on the corresponding metal ions.
The value for micro silver particles therefore corresponds to the EC_{50} for ionic silver.
[2] Further values: 0.028[87], 1.25–1.36 or 9.4–10.6[100], 7.07[83]
[3] Further values: 500[62]
[4] Further values: 4.92[21]
[5] Further values 0.006[98]
[6] Mean value of the 30d EC_{50} for dissolved Zn (range 0.3–1.9 mg/l)
[7] Further value 1.1[94]

The only critical ENO among the four analysed compounds (Ag, CNT, TiO_2, ZnO) is therefore photocatalytically active (anatas)-TiO_2 owing to its toxicity to daphnia and other microorganisms. For Ag, CNT and ZnO, no significant difference in the ecotoxicity can be determined from the current state of knowledge.

3 > Release to the environment

3.1 Major accident potential of ENO

A major accident can occur at any location where larger quantities of a potentially toxic substance are present. This can be the case both with the production and processing, and also with the storage or transport of a substance. At present, the quantities of ENO produced or handled in Switzerland are, with few exceptions, below one tonne[101,102]. An increase in the production volumes and/or quantities handled is, however, to be expected. The study by Schmid & Riediker[64] also showed that larger quantities of ENO are not produced in Switzerland. All companies that handle significant quantities of ENO belong to the processing industry. Examples of this are the use of several hundred tonnes of nano-$CaCO_3$ in paper production, and the employment of organic pigments (about 100 t) in the paint industry. These examples do not, however, apply to ENO in the sense of new materials, but of traditional materials. In total, just under 600 (confidence interval: 145–1027) companies in Switzerland work with ENO[101].

The major accident scenarios are heavily dependent on the ENO present and on other chemicals, and also on the specific situation and installation. For example, among other things, on the:

- Form of the ENO: in suspended or powder form
- Presence of readily flammable or explosive substances (e.g. metallic Nanoparticles or organic solvents)
- Accident risks on transport routes Fig. 6
- Safety measures.

Fig. 6 > Accident risks on transport routes

The lorry containing 23 tonnes of zinc oxide waste crashed on 12 April 2012 on motorway no. 8 in the area of Ulm. Following the busting of a tyre, the vehicle together with its trailer began to swerve, crashed into the central safety barrier and finally rolled on its side, as reported by the police. The zinc oxide, which was packed in sacks, tumbled onto the road. As the goods carried were classified as hazardous materials, the fire service arrived at the scene complete with protective masks. A special service firm was called to aid the rescue operations. There was no endangerment of humans and the environment, as was reported. The motorway was closed for several hours in both directions. As the material in question was zinc oxide waste, it is not clear what its composition was, particularly concerning particle size.

Source of text: «Schwäbische Zeitung»; Photo: Thomas Heckmann

It can fundamentally be assumed that the major accident potential is considerably higher when powdery ENO are involved, since these can be more readily dispersed than suspended ENO[103]. The accident potential is likewise raised through the (unprotected) storage of readily flammable or explosive substances in the vicinity of the ENO.

The ZEMA (Zentrale Melde- und Auswertestelle für Störfälle und Störungen in verfahrenstechnischen Anlagen) of the German Umweltbundesamt[104] investigated 23 events reported in 2008 (the year evaluated for report purposes) as major accidents or disruptions of normal operation. No major accidents involving nanomaterials have been reported till now. The ZEMA identified as likely starting points of a major accident in general the process itself (11 events, 44%). Further critical operations are handling/loading (4 events, 16%), arrival/departure (3 events, 12%), and maintenance/repair (2 events, 8%). Storage, decommissioning and transport each account for one event (4%). Between the remaining two major accidents, the process causing the major accident is unknown. The risk from natural events such as lightning, earthquake and flooding must also be considered as causative factors of major accidents[105,106].

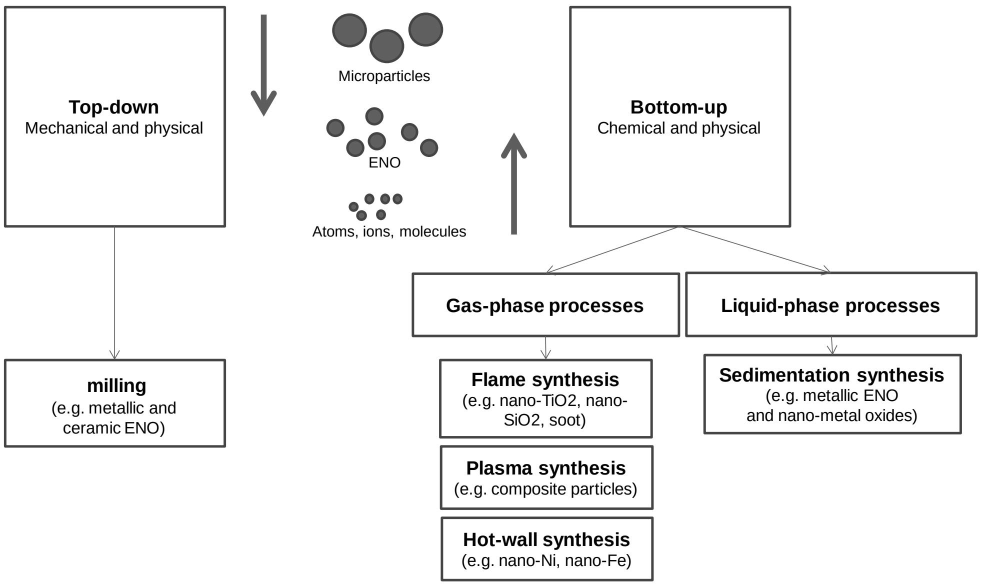
The following release scenarios are rated as realistic causes of major accidents:

3.1.1 Possible causes of major accidents during the production process

Causes of major accidents in production processes

ENO are manufactured in very different production processes[107]. Basically, a distinction is made between the mechanical and physical "top-down" processes and the chemical and physical "bottom-up" processes (Fig. 7). In the first case, the ENO are manufactured from larger particles through milling, in the second, they are formed from selected atoms, ions and/or molecules. The milling process is chosen for the manufacture of metallic or ceramic ENO with a relatively large particle size distribution. Chemical and physical synthesis processes have the advantage that the form and size of the particles can be relatively well predetermined. Among the possible processes are sedimentation reactions (liquid phase) and flame, plasma or hot-wall syntheses (gas phase).

Fig. 7 > Overview of the most important ENO manufacturing processes



In grinding operations, a major accident with consequences for the public can be practically excluded. Since this process takes place in a suspension and is usually only performed with ceramic materials or metal oxides, an explosion can be excluded. In case organic solvents are in fact employed as suspension medium, the process takes place in a protected environment; even so, the quantities are so small that it can be assumed that then the risk to the public can be excluded. Despite that, for gas-phase processes, a deflagration, and when using readily flammable solvents in liquid-phase processes, a fire cannot be excluded. Nevertheless – provided the necessary measures are taken (see Chapter 4) – a concatenation of various circumstances would be necessary to cause release of the ENO beyond the establishment premises.

A possible scenario is the explosion of distillation equipment and resulting fire. In this case, organic solvents explode in the distillation apparatus. A fire breaks out, whereby the entire quantity of nanoparticles present in the affected area is released. Depending on the safety measures, the quantities stored and the particular circumstances, larger quantities of ENO can be released to the air or wastewater (if a connection is present). It must further be considered that carbon-based ENO are in large measure burnt, whilst metallic ENO are oxidised.

3.1.2 Possible causes of major accidents during transport by road and rail

Causes of major accidents during transport

The transport of toxic substances is subject to comparatively high risk, since, for one, accidents during transport are relatively frequent (cf. Fig. 6), and, for another, readily flammable liquids (e.g. petrol) can be released. Despite that, the quantities transported are only limited (at present at most several hundred kg), particularly since in Switzerland larger quantities of ENO are as yet seldom manufactured. The quantities of ENO transported in Switzerland in the course of goods transport are unknown to the authors. Although, till today, no nanospecific obligation to declare has existed, according to the information from various companies, ENO are labelled for safety reasons as hazardous goods, and stored in containers of the highest safety level.

An accident during transport could lead to leakage of a suspension, or even to a fire. By this means, ENO could be released to the air, to waste water or to nearby ground and surface waters.

3.1.3 Possible causes of major accidents during processing and storage

Causes of major accidents during processing and storage

In the processing or storage of ENO, a fire can break out, whereby ENO can be released both to the air (mainly powdery ENO), and to ground and surface waters (ENO suspensions). The causes of major accidents can be both internal (technical malfunction), and also external (natural causes) factors. Even so, the quantities of ENO stored are as yet very small (at most several hundred kg), both at the manufacturing and processing companies. A deflagration is conceivable in the processing of metallic particles. For this reason, however, metallic particles are processed/stored in suspension or in an inert atmosphere (N_2).

3.2 Dispersion and behaviour in the environment

Behaviour in the environment

Based on the scenarios described, a primary release of ENO to all three environmental compartments (air, water, soil) is possible. Furthermore, a secondary exposure of the soil and of surface waters through sedimentation from the air is likely. It must also be considered that indirect contamination of surface waters may occur through discharge from waste water treatment plants. A secondary pollution of groundwater can be disregarded in the case of ENO, since the mobility of the particles in the soil is only slight[108].

Till today, no major accidents involving ENO have been reported. Therefore no experience is available on the dispersion of ENO in the environment following a major accident. Also, till now no simulation models are available to simulate the dispersion of ENO in the environment in the local area. Various simulation experiments and measurements were performed for workplace situations[109–112]. In one study, the dispersion of ENO in the case of a major accident in a laboratory production installation for gas-phase synthesis of ENO was measured and simulated[113]. The authors concluded from the measurements that the coagulation of the ENO, except immediately in the neighbourhood of the source, is negligible[109,113]. The measurements and calculations were, however, limited to the production room, and are not, therefore, unreservedly applicable to environmental conditions or major accident scenarios.

3.2.1 ENO in the air

Dispersion in the air

During a major accident, powdery ENO can be relatively easily released in larger quantities to the air. Suspended particles are not volatile, and are therefore only released to the air in case of an explosion or fire through the vaporisation of the solvent. The first stage of the elimination process is primarily the agglomeration due to the Brownian motion. Owing to the small dimensions of the particles, gravitation does not play a primary part, but comes into effect following agglomeration of the particles. Agglomerates with a diameter of approx. 1 µm have the longest persistence time in the atmosphere. Owing to the agglomeration, it is improbable that isolated ENO could remain as such in the air[114].

The concentration in the air is of primary importance for human exposure following a major accident. In this, the weather conditions prevailingat the time of the accident (windspeed, wind direction and rainfall) play a major part. However, these factors cannot be considered in a generic scenario. The following simulation parameters are suggested in the Technical Guidance Document[115] for calculations of the local exposure outside the works premises:

> The entire emissions are distributed radially symmetrically around the source (radius 1 km).
> The source is at a height of 10 m.
> The average distance from the source to the perimeter of the works premises is 100 m.
> The concentration declines linearly from the source to the distribution limit (1 km).

These assumptions for the calculation of local concentrations of chemicals are very generic and are not intended for the simulation of a major accident scenario.

3.2.2 ENO in ground and surface waters

Input to ground and surface waters

The release of ENO to ground and surface waters following a major accident can take place in three ways:

1. Direct release to a surface water through drainage systems along roads (following a transport accident) or in the case that ground or surface water is present in the immediate vicinity of the major accident: in this case it must be assumed that only part of the entire emissions are released directly to the ground or surface waters. The probability of a direct release to surface waters is greater with suspended ENO. However, washout of powdery particles by rain or quenching water cannot be excluded.
2. Release of ENO to the waste water treatment system with indirect release to a ground or surface water: previous studies show that insoluble ENO are eliminated in treatment plants at an efficiency of up to 98%[117]. Possible process mechanisms are agglomeration and sedimentation, or, in the case of soluble ENO, dissolution. Even so, the release of a bactericidal ENO (e.g. silver), if too high, can have an adverse effect on the bacterial population of the treatment plant and can, under certain circumstances, lead to a shut down of the treatment plant.
3. Sedimentation from the air: in this case, the input quantity is dependent on the surface of the water. Owing to the continuous sedimentation process, flowing waters are less at risk than standing waters.

When entering a ground or surface water, the ENO are diluted. The dilution factor depends on the water level or the size of the ground or surface water, and can take values between 1 and 100 000[115]. The TGD[115] proposes a dilution factor of 10 in case no more precise data are available. Further dilution can occur through quenching water.

Any water contamination that may occur depends on the local situation. This is even more the case than for emissions to the air. The probability of contamination of a ground or surface water that qualifies as a major accident therefore depends on the proximity of the establishment or the transport route to a (larger) ground or surface water. This factor must be considered in assessing the outer limits of the accident area. According to the assessment criteria I of the OMA[118], serious damage is present when in a water volume of 10^6 m^3, the LC_{50} and/or the EC_{50} for fish or daphnia is exceeded. This volume corresponds approximately to a surface water of the size of the Katzensee (Canton of Zurich). For an $EC(50)_{daphnia}$ of 1 µg/l[87] for nano-Ag and homogeneous distribution within the water volume, the release of just 1 kg of nano-Ag would suffice to cause an equivalent concentration. However, in doing so, relevant elimination processes such as the formation of stable silver sulphide (Ag_2S) and silver chloride (AgCl) are neglected. Furthermore, a homogeneous distribution in a standing water is improbable owing to the temperature-dependent stratification of the water, and also depends on the size of the water and time of year. As a result, massively higher concentrations can occur locally.

The contamination of ground and surface waters can lead to a secondary exposure to humans through bioaccumulation via fish as food source. Long-term impairments of this nature are not, however, considered here.

3.2.3 ENO in the soil

Input to the ground

The direct release of ENO to the soil is only to be expected with transport accidents on country roads and railway lines. Indirect release, on the other hand, may occur via wet or dry sedimentation from the air. Although following a major accident, the local ENO concentration in the soil can temporarily take on very high values, serious impairment of the environment can be practically excluded (a) owing to the very low particle mobility[108] and (b) the possibility of *ex-situ* soil regeneration. Therefore, no dispersion models are required.

4 > Safety mesures

Particular attention should be paid to the safety measures, as these can contribute considerably to major accident prevention, this is particularly important, among others, in the processing industry. Whilst suitable provisions are usually standard practice in production, uncertainty in the handling of ENO in processing can lead to an increased, albeit unintentional, risk of release[8,119,120]. In this connection, one very important measure is the training of the personnel. Safe handling of ENO requires nothing other than careful handling of powders and conventional chemicals.

During visits to companies made in connection with this study it was observed that the companies fullfil the high safety standards pertaining. These are determined by the chemicals (e.g. solvents) used in the process, making necessary the application of high safety standards. Particular attention must be paid to those works having no experience in the handling of chemicals that were founded as pure “nano-works”.

Processing establishments must be regarded as critical, particularly if they dispose of no other information on the ENO than that contained in the SDS, and because at present the SDS mostly contain no nanospecific data. Since these establishments (owing to the high activity of the ENO) only keep small quantities in stock, these factors are only seldom relevant in an accident context.

4.1 Structural measures

Structural measures are indispensable for the safe handling of ENO. Notwithstanding this, the usual measures in the chemical industry are adequate. The measures should differ in relation to the aggregate state of the ENO. In the production, processing and storage of suspended ENO, a retention basin should be provided. The room or the rooms in the establishments must not be connected to the sewage system, or any connection existing must be fitted with a retention mechanism for use in the event of an accident (e.g.: stop valve). With powdery ENO, the ventilation system and the design of the building shell are of central importance. These elements are decisive as to whether in the case of a major accident ENO can be released to the environment through a damaged roof/window or via the ventilation. Apart from that, in both cases, the main factors are fire protection measures such as fire protection doors, separate storage rooms for organic solvents and separate fire compartments.

4.2 Technical measures

Various technical measures can prevent or limit a major accident. These are, for example, among other things, sprinkler equipment in the store room, pressure-controlled installations and ventilation switch off in case of a major accident. These measures are, however, not nanospecific, but are part of the standard accident prevention measures for readily flammable substances stored in the same room. When these traditional measures are consistently applied, they are also effective for ENO.

To prevent the dispersion of ENO in the case of a major accident, ENO should whenever possible be present in suspended form.

4.3 Organisational measures

Administrative measures such as restriction of access and the thorough training of personnel represent simple but effective measures. All co-workers that work with ENO must be suitably trained and, when necessary, have suitable personal protection equipment available. Unauthorised persons should only have access to the room or rooms when authorised, and in the company of a trained co-worker. Furthermore, the responsible (works) fire brigade should be informed about the ENO and on suitable fire protection measures.

5 > Conclusions

The quantity thresholds and criteria in the OMA[1] are based on the mass of a substance or preparation. Owing to the smallness of the particles and the resulting heavily increased surface, the adoption of the mass basis for ENO is called in question by various authors. A study by Oberdörster et al.[121] showed comparable toxicity values of traditional and nanoscale particles, if the particle concentration was normalised to the surface. The comparison of the human and ecotoxicity for the ENO considered in this report and given in Tabs. 1 and 2 shows, however, that the mass-based method is appropriate.

It is, however, in all cases essential that the manufacturers of ENO should honour their obligation to prepare a Safety Data Sheet and enter in this the necessary data for the categorisation of the ENO, in order for the subsequent processing works and the enforcement authorities in the cantons to determine the nanospecific quantity threshold.

The ENO investigated in this report are attributed the following quantity thresholds based on the limiting tolerance values:

> 2 000 kg: ZnO, TiO_2, Ag
> Not mentioned in the list: CNT

For CNT, an assessment must be performed based on the criteria in the OMA[1] and the data on toxicity provided in the SDS by the owner.

Owing to the still limited basic data, the conclusions drawn in the present report must be understood as initial insights. Until standardised tests for the determination of the toxicity of ENO are available, and it is clearly defined from what point onwards ENO must be declared in the Safety Data Sheets, it is advisable for the purposes of major accident prevention to perform monitoring at regular intervals for “high production volume ENO”, and to determine whether the conclusions drawn in the present report continue to remain valid.

It can be generally concluded that ENO, where their chemical reactivity is concerned, are significantly less critical than other chemicals (e.g. solvents and highly active substances) and can be dealt with similarly to pigments or other powders. The OECD also states in its current report that the acute toxicity of ENO according to the majority of experts is not the central concern in risk research on ENO[114]. It is, however, important to mention that this assessment applies only to major accidents and not to workplace protection, e.g. exposure within the establishment premises or consumer exposure to the ENO contained in products.

6 > Perspectives/need for action

The most important basis for establishing new regulations for ENO in the OMA is to provide a clear definition of the terms ENO and nanomaterial. It is the task of legislation to provide such a definition to determine the quantity thresholds, which can then be used in the OMA. In this, the definition must accord with the needs of diverse requirements to avoid over-regulation. For example, it should be clearly stated that only those companies that work with discrete particles are subject to the (nano) legislation. As soon as the ENO are bound to a fixed matrix, the risk of their release is significantly reduced. It is also necessary to proceed cautiously in the case that materials that till now have been treated as traditional materials (e.g. SiO_2 in toothpaste), must "suddenly" be classified as ENO on the basis of new knowledge. On the basis of this definition, ENO should also be declared in the SDS, even with minimum additives. The SDS should wherever possible contain nanospecific data on (eco)toxicity.

There is a considerable need for scientific research to determine the (eco)toxicity or the toxicity mechanisms of ENO. In this, the studies must be based on standardised experimental methods to improve comparability. In particular, many of the studies on nanotoxicity so far lack important information on the chemical and physical parameters of the materials tested[122,123]. Such parameters are, however, absolutely essential in providing reliable information on materials.

Nevertheless, particularly for the materials addressed in the present report, there exists a large number of studies with pertinent results, which for the most part do not indicate any specific need for action in the near future for nanomaterials. The acute risks of nanosubstances in connection with major accidents do not differ from those of traditional substances, so that the regulations in the current OMA also cover the relevant field for nanomaterials.

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> Abbreviations, figures and tables

Abbreviations

CNT
Carbon nanotubes

EC_{50}
Effect concentration (concentration at which 50% of the organisms show an effect)

ENO
Engineered nano-object (synthetically manufactured nano-object according to ISO definition)

ISO
International Organisation for Standardisation

LC_{50}
Lethal Concentration (concentration which leads to the death of 50% of the organisms)

LOEC
Lowest Observed Effect Concentration (lowest observed concentration at which an effect occurs)

Nano-Ag
Synthetically manufactured silver particles in the nano size range

Nano-TiO_2
Synthetically manufactured titanium dioxide particles in the nano size range

Nano-ZnO
Synthetically manufactured zinc oxide particles in the nano size range

NOEC

No Observed Effect Concentration (concentration at which no effect is observed)

OECD
Organisation for Economic Co-operation and Development

SDS
Safety Data Sheet

Figures

Tables