Nanomaterials in Plant Protection and Fertilization: Current State, Foreseen Applications, and Research Priorities

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Ⓢ *Supporting Information*

ABSTRACT: Scientific publications and patents on nanomaterials (NM) used in plant protection or fertilizer products have exponentially increased since the millennium shift. While the United States and Germany have published the highest number of patents, Asian countries released most scientific articles. About 40% of all contributions deal with carbon-based NM, followed by titanium dioxide, silver, silica, and alumina. Nanomaterials come in many diverse forms (surprisingly often ≫100 nm), from solid doped particles to (often nonpersistent) polymer and oil–water based structures. Nanomaterials serve equally as additives (mostly for controlled release) and active constituents. Product efficiencies possibly increased by NM should be balanced against enhanced environmental NM input fluxes. The dynamic development in research and its considerable public perception are in contrast with the currently still very small number of NM-containing products on the market. Nanorisk assessment and legislation are largely in their infancies.

KEYWORDS: *agriculture, pesticides, fertilizers, risk assessment, regulation, legislation*

1. INTRODUCTION

Materials, whether of natural or manufactured origin, that possess one or more external dimensions in the range of 1−100 nm are defined as nanomaterials (NM)[1] and are increasingly used in a wide range of technical applications and consumer products due to the unique physicochemical properties emerging at the nanoscale. Key applications of NM can already be found for example in the areas of electronics, energy, textiles, pharmaceutics, cosmetics, and biomedicine. This trend is fueled by many hopes and promises, such as improved performance and new functionalities accompanied by a significant reduction in the use of resources and the generation of waste. Thus, NM are generally believed to increase profitability and sustainability.[2]

As a constantly growing world population is in demand for higher agricultural yields, and as important resources such as phosphorus and potassium are limited, more effective strategies to optimize agricultural practices are urgently needed. Hence, attempts to do so with the help of nanotechnology and NM are increasing.[3−9] The application of NM in agriculture aims to reduce applied amounts of plant protection products (PPP), minimize nutrient losses in fertilization, and increase yields through an optimized nutrient management.[4,6−12] Several factors that influence the efficiency of PPP and fertilizers could be addressed using NM. For example, active substances can be lost during application through drift, runoff, evaporation, photolysis and hydrolysis, and degradation by microorganisms. As additives, NM with a high surface area and appropriate sorption properties may minimize losses by reducing runoff and decreasing release kinetics. Specifically designed particles could furthermore protect active ingredients from photodegradation or enhance uptake into the leaves and other parts of the plant. Nanomaterials may also substitute hazardous organic (co)-solvents, present in some PPP, and facilitate their dispersion, e.g., on plant surfaces. As active ingredients, NM could reduce application rates through their enhanced reactivity.

Despite these expected positive impacts in various fields, some NM definitely have properties that classify them as potentially hazardous.[13] Therefore, a lot of attention is currently paid to the potential risks arising from these materials,[14] which has already led to a number of studies that examine their mechanisms of unintentional emission and toxicity.[15−17]

However, the use of NM in agriculture—and specifically in plant protection and fertilization—may pose unforeseeable risks, in particular because these applications comprise an intentional input of NM to the environment. This may lead to higher input fluxes than predicted to date (Table 1).[18] Consequently, human and environmental exposure due to NM residues in crops and soil might increase accordingly, with exposure routes including possible bioaccumulation of NM in the environment[19,20] and in the food chain.[21,22] Agriculture is aiming at a sustainable management of natural resources which is globally imperatively needed as set out by the EU Millennium Development Goals.[23] Therefore, the application of NM must be critically evaluated to guarantee their safe use for agriculture.

With nanotechnology related markets growing at an enormous speed, there is an urgent need to regulate products with nano content. This need for regulation is, however, in general—but also specifically for agriculture—adversely accompanied by a lack of knowledge on the current state. In addition, the unique properties of NM alone already pose many difficulties to the regulatory bodies, beginning with the

Table 1. Modeled Fluxes[a] of Different NM and Application Rates of PPP or Fertilizers, Selected from Scientific Literature and Patents

NM type	modeled flux into soil	ref	application rate and calcd flux from PPP/fertilizer[b]	ref	flux ratio[c]
TiO$_2$	realistic scenario: 0.4 μg kg^{-1} y^{-1}	134[d]	4.5–15 kg ha^{-1} ≈ 1607–5357 μg kg^{-1} y^{-1}	79	334–1116
	high exposure scenario: 4.8 μg kg^{-1} y^{-1}		7.5 g ha^{-1} ≈ 2.7 μg kg^{-1} y^{-1}	76	0.56
	0.28–1.28 μg kg^{-1} y^{-1} (US, EU, and CH)	80[e]	max 30 kg ha^{-1} ≈ 10714 μg kg^{-1} y^{-1}	49	2232
Ag NP	realistic scenario: 0.02 μg kg^{-1} y^{-1}	134[d]	15 g ha^{-1} ≈ 5.4 μg kg^{-1} y^{-1}	34	54
	high exposure scenario: 0.1 μg kg^{-1} y^{-1}				
	8.3–22.7 ng kg^{-1} y^{-1} (US, EU, and CH)	80[e]			
CNT	realistic scenario: 0.01 μg kg^{-1} y^{-1}	134[d]	3–12 g ha^{-1} ≈ 1.1–4.3 μg kg^{-1} y^{-1}	109	55–215
	high exposure scenario: 0.02 μg kg^{-1} y^{-1}				
	0.56–1.92 ng kg^{-1} y^{-1} (US, EU, and CH)	80[e]			

[a]Limited to those NM for which data due to usage in the anthroposphere was available. [b]Assuming an application volume of 300 L ha^{-1}, 20 cm plow depth, a soil bulk density of 1.4 g cm^{-3},[26] and an application once per year. [c]Calculated as flux from PPP/fertilizer divided by the value of the highest modeled flux. [d]Based on an annual substance flow analysis from products to soil in Switzerland. [e]Based on a probabilistic material flow analysis from a life cycle perspective of engineered NM containing products.

statutory definition of a NM.[24] Regulatory issues in this context were up to now only reviewed regarding NM in food production in general.[25]

Agricultural NM applications and their potential advantages are often mentioned in the literature. Although several authors briefly addressed diverse prospective agricultural NM applications, without being specifically focused and comprehensive on PPP and fertilizers[4,8,10] (for a compilation of reviews related to the field, see Supporting Information Table S1), a systematic compilation of NM in plant protection and fertilization, including a list of existing patents, is currently lacking.

In this review, we therefore would like to align the increasingly common perception of NM use and benefit for crop protection and cultivation with actual scientific facts and figures. To achieve this goal, we will first give an overview on the developments concerning nano-PPP and fertilizers since the beginning of the 21st century and of the current state in the Nano-Agro-Business. In the following, we will systematically discuss different nanomaterials and their properties that are envisioned to improve agricultural formulations, based on the scientific literature and published patents. To conclude, we identify specific research gaps related to the risk assessment of NM in agriculture and address relevant aspects of nano-legislation.

2. METHODOLOGY

For this compilation, the following databases and literature sources were used. (i) Scientific databases: Web of Knowledge, Google Scholar. (ii) Patent databases: World Intellectual Property Organization (WIPO, EU), Free Patents Online (EU+US), Web of Knowledge. (iii) Gray literature obtained from various sources. Literature used for this evaluation was selected when it referred specifically to the development, testing, and application of nanoplant protection and fertilizer products. Remediation applications were excluded, as they were out of the scope of this review. In total, we selected a total of 36 publications and 33 patents (listed systematically in Supporting Information Tables S2 and S3) that were published until the beginning of February 2012. In the following sections, these 69 articles will be looked at from different angles.

Furthermore, concerning input of NM into soils, we calculated application rates and fluxes resulting from such applications (Table 1). For the calculations, we assumed an application volume of 300 L ha^{-1}, 20 cm plow depth, an average soil bulk density of 1.4 g cm^{-3},[26] and one application per year.

3. EVOLUTION OF RESEARCH AND DEVELOPMENT ACTIVITIES FOR NM IN AGRICULTURE

Historically, the notion that NM could be of use in agricultural systems is a fairly new one and under development now for approximately a dozen years (Figure 1). Apparently, the US
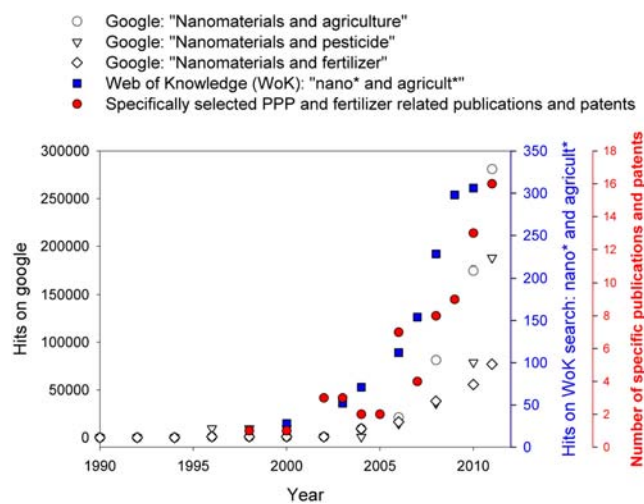

Figure 1. Temporal development of publication activity referring to NM in agriculture since 1990: as a rough search in the Web of Knowledge (WoK, right axis, blue squares), as publications and patents specifically selected (right axis, red dots), and as searches on Google (left axis, empty symbols). Searches were performed on November 20, 2011.

National Nanotechnology Initiative (US NNI) in the early 2000s[27] coincided with the onset of this new technology. The US NNI also invested in possible applications of NM in agriculture by supporting such research in the US Department of Agriculture (USDA), yet in 2005 with 0.5% of the total NNI funds only,[28] and remaining at this level until 2012.[29] The European Union (EU) funded nanoresearch as well since the beginning of this millennium with the FP6 (2002−2006) and FP7 (since 2008), however with no specific link to agriculture. In the field of NM and agriculture, the annual output of NM-related scientific publications is still drastically lower than in other fields: from 2000 to 2011 a general search using "(nanoparticle* or nanomaterial*) and (agricult* or agronom*)" yields 483 hits in Web of Knowledge, whereas "(nanoparticle* or nanomaterial*)" with the category refine-

ment "material science and engineering" yields 275,338 hits (search performed on May 16, 2012). Furthermore, there is a huge discrepancy between the still relatively small amount of published peer reviewed papers and patents on agricultural NM, and the public discussion and gray literature. Lagging behind scientific publications approximately 2−3 years, an exponential increase in open-source publication activity in this field started around 2006 (Figure 1). Google delivers 786 hits on the term "nanomaterials and agriculture" in the year 2000. In 2011, hits reached a number of 281,000. In more detail, the activities concerning "nanomaterials and pesticides" also increased exponentially (Figure 1), reaching 188,000 hits in 2011. Publications in the field of NM and fertilizers, however, are less prominently discussed, with 77,100 hits in 2011 (searches performed on November 20, 2011).

In 2004, the article "Down on the Farm" was released by the Action Group on Erosion, Technology and Concentration (ETC group),[28] which may constitute a turning point for the topic in public discussion and has been cited rather frequently (search on Google: "down on the farm ETC group": 1250 hits, search performed on November 18, 2011). It tackled a diverse list of topics, spanning from nanoencapsulated pesticides to nanosensors for pathogen detection and many more. Yet on the NM-pesticide topic, the focus was clearly on micro (or nano)-encapsulated pesticides, referring to already commercialized products of Syngenta (Primo/Banner MAXX with diameters down to 100 nm and ZEON) and some patents by BASF[30] and others. The main statements in this article were that NM applications in food production and agricultural industry are just emerging—therefore being overlooked even by nano-technologists—but may exceed the impacts of farm mechanization and the "green revolution". In 2005, an article concerning "applications of knowledge in development" was released by the Task Force on Science, Technology, and Innovation within the UN-Millennium Project.[31] This article stated that nanotechnology in agriculture would be especially interesting to developing countries, bearing the potential to reduce hunger, malnutrition, and child mortality. Thus, it may not be a coincidence that emerging economies with a large agricultural sector and population, such as China and India, are having a greater interest in using NM in agriculture as demonstrated by a relatively high output of publications (Figure 2). In this article, China, India, and Korea are declared
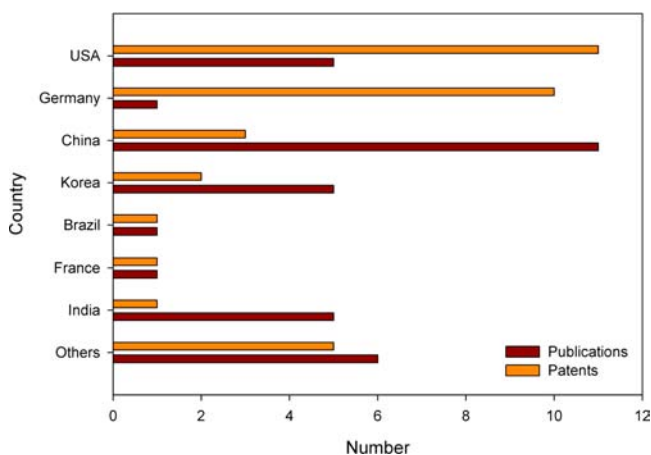
as the frontrunners in nanotechnology in the developing world, which seems to be reflected in Figure 2. Looking at institutions that contributed to publications in the field, it is surprising that both agriculture and nanospecific research institutes contributed only approximately 17% to the publications, whereas the majority originates from chemistry departments (19%). However, when it comes to the number of patented technologies, the leading countries are those of the Western World such as the United States and Germany. Most patents are held by companies (56%) that are mainly represented by smaller enterprises (Supporting Information Figure S1). However, BASF is holding 27% of all company patents and 15% of the total. Universities (29%) and individuals (15%) share the remainder. These are some indications that there is an increasing endeavor and progress, especially from industry, in the development of agricultural nanoformulations in recent years (Figure 1, also see Supporting Information Figure S1 and Table S3). This is, however, not yet reflected by data on commercialized products (Supporting Information Table S4), which is still very scarcely available and often not conclusive, regarding their actual NM content and speciation. Actually, almost no "nano" PPP seem to be currently on the market, unless there are some that are not declared.

4. CLASSES OF NM AND THEIR INTENDED PURPOSE IN AGRICULTURE

Generally, the elementary composition of NM in PPP or fertilizers (Figure 3) can be based on carbon (i.e., carbon
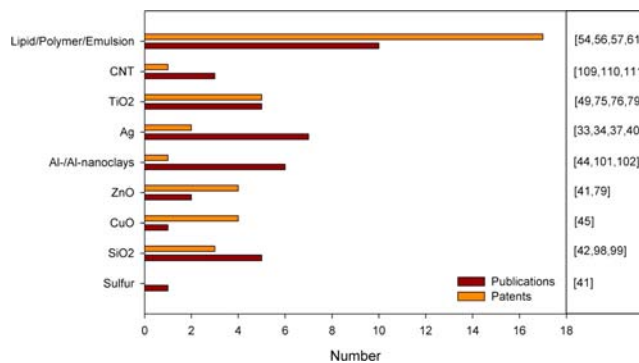

Figure 3. Number of different NM used in plant protection and fertilizer publications and patents, including selected references.

nanotubes (CNT), liposomes, organic polymers, etc.), metals or metal oxides (i.e., silver (Ag), zinc oxide (ZnO)), metalloids (silica), and nonmetals (sulfur (S)). The frequency of their application followed the following order: lipids/polymers/emulsions > titanium dioxide (TiO_2) > silver > silica (Figure 3). Note that the order changed to lipids/polymers/emulsions > TiO_2 > ZnO and copper oxide (CuO), taking into account the patents only. Nanomaterials can be present in formulations as solid particles or as nonsolid structures (Figure 4). The latter can be lipid or polymer (natural or synthetic) based structures or oil−water (O/W) emulsions. The size of such structures in both patented and published formulations varied mostly between 100 and 300 and between 300 and 2000 nm (Supporting Information Figure S2). In patents, this size range was even extended over 2 μm in a few cases. Size fractions below 100 nm could be found in 37% of the patents and 54% of the publications. This fraction is lower, however, if provided nominal sizes (size not confirmed in the actual
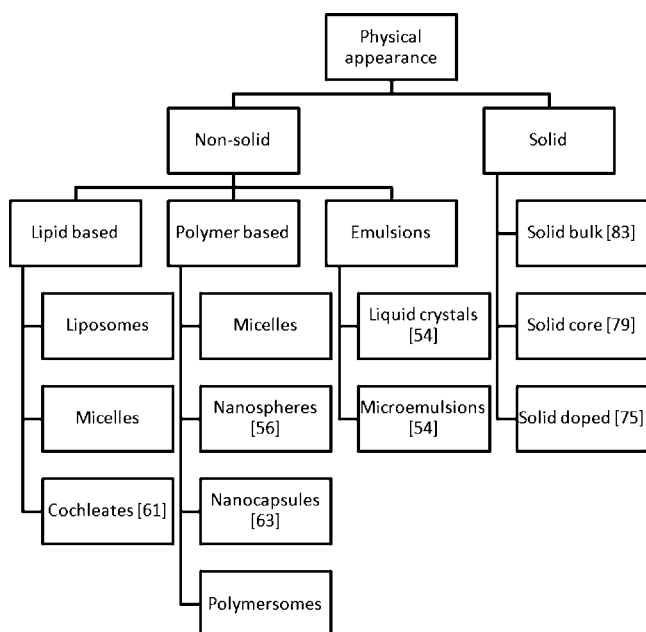

Figure 2. Countries active in research and development of nanoplant protection and fertilizer applications.

Figure 4. Physical appearance of NM in the analyzed publications and patents, classification adapted and adjusted from refs 9, 25, and 133, including selected references.

formulation) were excluded. Hence, a considerable fraction of the formulations indicated to be "nano" do contain size fractions extending beyond the "nano-range" (i.e., >100 nm[32]). With 74% of all papers, PPP prevailed over fertilizer products (Figure 5A). Overall, 35% of the PPP were planned to be used as fungicides, 33% as insecticides, and 27% even were considered for multiple categories (Figure 5B). In 41% of the PPP, NM were the active constituent (Figure 5C). This was especially the case for Ag and S NM applications, where the NM itself was used as a fungicide.[33−41] Further examples can be found in the case of silica[42,43] and alumina,[44] which were tested as insecticides. Another example is the BASF patent WO/2011/067186[45] based on nano-copper salts acting as a fungicide. However, in 57% of the PPP, NM were additives (Figure 5C) that acted as controlled release carriers (Figure 5D, 56%), protective (15%) or dispersing agents (11%) and

photocatalysts (11%). Apart from this, also milling of conventional crystalline solid pesticides to a sub-micrometer range was performed, improving biological efficiency.[46] Alternatively, emulsions can be spray dried to nanopowders and then be redispersed.[47] With the exception of nano-S, which was covered by one publication only,[41] in the following, individual NM will be discussed in the order of their frequency of application (Figure 3).

4.1. Nonsolid NM. Today's discussion on NM in general mostly refers to NM of a solid particulate nature. In agriculture (and maybe elsewhere as well), however, the most prominent fraction of NM is nonsolid, comprising nanoscale structures that may for example encapsulate an active ingredient in a PPP (Figure 3, 4). Active substances are often poorly soluble in water and at room temperature even solid or crystalline and therefore brought into solution with organic (co)solvents. To avoid the use of the latter, one method of choice is the use of O/W-based emulsions[48−52] (Figure 4), that enhance the solubility and thereby the loading capacity of the formulation for the active substance. Furthermore, this may also enhance coverage of the hydrophobic leaf surface and penetration of the active substance through the cuticula. However, nanoemulsions are metastable systems, which are prone to crystallization, agglomeration, and sedimentation. Stabilization is often achieved by sufficient amounts of suitable surfactants and additional protective colloids.[53] One example of a successful application of this technique is the BASF Patent WO2011138701.[54] Therein monoglycerides, i.e., hydrolyzation products from natural fats, are used as an amphiphile to form liquid crystal and microemulsion structures (Figure 4) that are able to incorporate up to 30−40% of water in the oil phase. The elements of such nanostructured O/W emulsions are thought to act as if they were the bulk substance. Structures created this way are quiet labile, as for example addition of ethanol can instantly destroy them. Furthermore, nanostructured monoglycerides also occur naturally in the gastro-intestinal tract, after action of the pancreatic lipase enzyme that hydrolyses triglycerides to monoglycerides.[55]

It is also possible to create amorphous solid organic NM by spray drying an O/W emulsion into a redispersible powder, as shown by Elek et al.[47] After redispersion, they found amorphous nanoparticles of novaluron in an O/W emulsion.
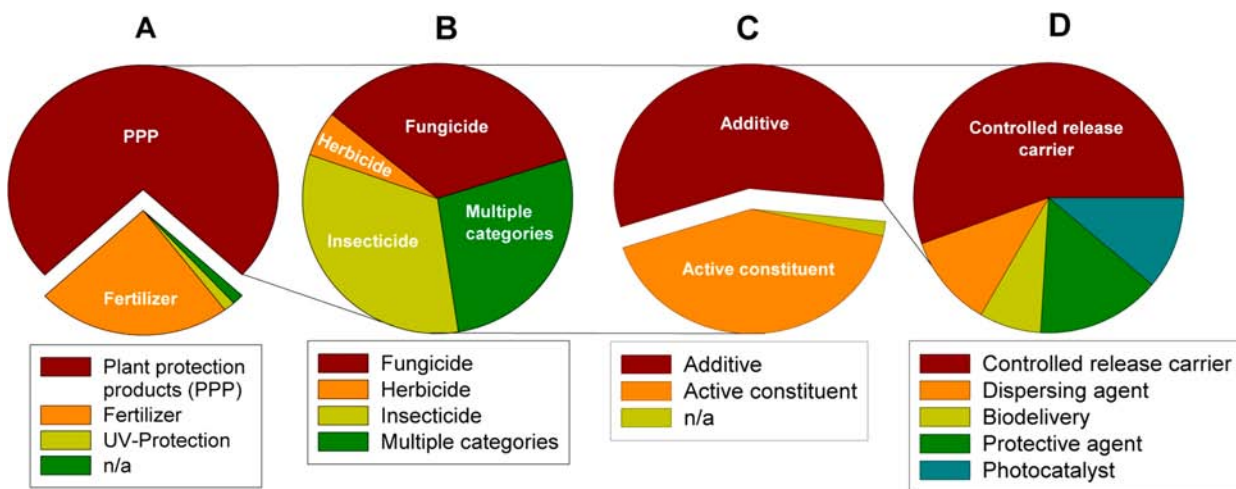

Figure 5. Purposes of agricultural NM applications (A), types of PPP containing NM (B), general functions of NM in PPP (C), and tasks of NM additives in PPP (D).

The nanoformulation of novaluron could, however, not surpass the activity of a commercial non-nano emulsion.

Examples of polymers used include nanospheres of polybutylcyanoacrylate,[56] polyethyleneglycol[57] or polyvinylpyr-rolidone.[58] Such materials are often used because they are already known from medical applications. However, substances approved for medical applications may involve higher risks than such approved for use in food.

Other nonsolid structures that can be used in this context are liposomes (Figure 4). Liposomes are spherical bilayer vesicles formed by dispersion of polar lipids in aqueous solvents. Liposomes have similarities to the structure of biological membranes, hence they are highly biocompatible and therefore usually biodegradable.[59,60] A special form of lipid based NM are cochleates (Figure 4), in which a lipid layer sheet is rolled up in a spiral fashion.[61] Another example for promising biocompat-ible substances considered for agricultural use is chitin derivatives.[62,63] Chitin is the most abundant natural amino polysaccharide[64] and is, together with its derivative chitosan, a very prospective molecule for encapsulation techniques. These nanocapsules (Figure 4) have very interesting possible applications, for example in cosmetics, food and nutrition, pollutant capture from wastewater, drug delivery, and many more,[64] and therefore seem worth further research. From an environmental point of view, they seem of no concern. Chitosan is a major component of the cell walls of common soil fungi and is produced by deacetylation of chitin. Chitosanase is known since the mid-1970s to be widespread among microbes.[65]

A company that attempts commercialization of such NM is Vive Crop (formerly Vive Nano Inc.[63]). With an actual budget of 16 million US $, they cooperate with major companies, incorporating their active ingredients into chitosan or poly-(acrylic acid) nanoformulations. However, until now, they state that none of their products has hit the market, but they are optimistic to reach a breakthrough in 2013.[66] One of the few examples of already commercialized formulations in this context is Banner MAXX[67] of Syngenta, belonging to the class of emulsions. In "Down on the farm" it was stated that this formulation contains "extremely small particles of about 100 nm". Again, concerning the above-mentioned structural specialty of emulsion-nanostructures, it may be misleading to use the term "particles" in this context. Moreover, Banner MAXX uses a biodegradable agent (tetrahydrofurfuryl alcohol) to dissolve the active ingredient.

4.2. Solid NM. *4.2.1. Titanium Dioxide (TiO$_2$).* Since its commercial production in the beginning of the twentieth century, TiO$_2$ in its bulk form has been widely used as a pigment, especially in paints.[68] In this context it is already used in agriculture to exert a marker effect during spraying of agricultural chemicals in amounts of 10 to 25% of weight.[69] In 1972, Fujishima and Honda discovered the phenomenon of photocatalytic splitting of water on a TiO$_2$ electrode under ultraviolet light.[70] Since then, a lot of research has been done to explore the potential of this material in its nano form especially in the categories "energy" and "environment". Concerning the latter, the main property of TiO$_2$ that has been exploited is its photocatalytic activity. It is generally regarded as a highly efficient environmentally benign photocatalyst.[68] Main applica-tions therefore also include degradation of pesticides or pollutants in soil remediation.[71,72]

However, one disadvantage of TiO$_2$ NM is that they are mostly active in the presence of UV light, due to their large band gap of approximately 3.2 eV.[73] This has implications for their use in agriculture, because the majority of sunlight consists of visible light and only to ~5% of UV light.[73] Modifying TiO$_2$ NM with different metals or other elements is a widely used technique to alleviate this problem and enhance photocatalytic activity by shifting the band gap response of TiO$_2$ NM to the visible region.[68,73] Materials that are used for this purpose are for example semiconductors with a more narrow band, metal or nonmetal ions, and others.[73] In this context, a bactericidal activity of TiO$_2$ due to light-induced oxidizing reactions has been shown in *Escherichia coli*[74] and has in that respect also been investigated for use in fungicide applications.[75] Lu et al.[75] reported the use of cerium (Ce)-doped TiO$_2$ NM as an active substance to control the downy blight disease occurring on litchi plants (*Litchi chinensis*) and powdery mildew on cucumber (*Cucumis sativus* L.). In lab experiments, they could show that the antifungal effectiveness of their NM was dependent on the available light source, decreasing in the order black light (315−380 nm) > sun light > indoor light. The results of their field experiments showed that the effectiveness of 1.0% Ce^{3+}-doped TiO$_2$ was able to exceed that of the commercially available Degussa P25.

In addition, the photocatalytic activity of (modified) TiO$_2$ NM can be used to reduce half-lives of pesticides, while ideally maintaining their effectiveness. This could be demonstrated by Guan et al., who reported two types of photodegradable insecticides.[76,77] In both cases, TiO$_2$ was used as a photocatalyst to enhance degradation of the used pesticides imidacloprid and avermectin respectively. The effectiveness of the nano-imidacloprid formulation was then tested against adults of a storage pest beetle (*Martianus dermestoides*) and found to be more effective than the conventional non-nano-imidacloprid (LC$_{50}$ 9.86 vs 13.45 at an application rate of 25 mg L^{-1}). Compared to other formulations, this application would cause the lowest of all calculated TiO$_2$ fluxes into soil (Table 1). Similar results could be obtained using tungsten-doped TiO$_2$ NM in the avermectin formulation. Following up on the imidacloprid study, the formulation was tested in the field,[78] where shorter imidacloprid half-lives in soil were observed for the nano-imidacloprid formulation compared to the non-nano-imidacloprid.

However, TiO$_2$ NM can also be used in the opposite way, protecting a system from photodegradation. This is achieved by employing the less photocatalytically active rutile as the crystal form and coating the particles with different functional moieties. Many active substances in PPP are sensitive to sunlight and therefore prone to photocatalytic degradation. Shielding the active substance from radiation is therefore believed to lower application rates of the PPP. An example for this is the BASF patent WO/2009/153231.[79] As a coating, an aluminum oxide (Al$_2$O$_3$) layer linked to a silicon containing polymer (dimethicone) is proposed. This particle, commonly known as TiO$_2$-M262 (Sachtleben Chemie/Kemira), is also used in sunscreens. The protected active substance was metaflumizone at 10 g ha^{-1}. The residual activity of the PPP was monitored for up to 10 days and found to be 21% (controls), 57% (common polymeric UV-protection agent), and 64% (the latter mixed with the coated nano-TiO$_2$). This would mean an increase in efficiency due to the addition of TiO$_2$ NM of only 7%. In the experiments described in the patent, TiO$_2$ concentrations of 15 to 50 g L^{-1} with application rates of 300 L ha^{-1} were employed. Thus, 4.5 to 15 kg of TiO$_2$ would be applied to 1 ha. This would imply a flux of 1607 to

5357 μg kg^{-1} per application, which is 4000-fold higher than the annual flux estimated by Gottschalk et al.[80] (Table 1).

Moreover, not only active substances in PPP are worth being shielded: Evonik-Degussa developed a "superspreading" agent containing TiO$_2$ as a photoprotective constituent to shield plant leaf surfaces from UV light.[81] This treatment then is intending to reduce sunburn damage in the plants and thereby loss of yield.

Apart from light based modes of action, TiO$_2$ can also be used as a dispersing agent, as demonstrated in a patent by Rhône-Poulenc.[49] Therein, up to 100 g L^{-1} TiO$_2$ in a size range between 100 nm and 1 μm is employed as a fine powder with a hydrophilic surface. A further described advantage of the use of TiO$_2$ NM in agricultural products is the enhanced growth of spinach after incubation with nanoanatase TiO$_2$, reported in several works.[82−86] The improved growth was related to a reduction of N$_2$ to NH$_3$ in the spinach leaves.

4.2.2. Silver (Ag) NM. Unique optical and physical properties have led to the use of Ag NM in catalysis, construction of highly sensitive and selective detectors, optical (bio)labeling, conductivity elements in electronics, sensing, and many more.[87,88] The antibacterial properties of Ag and even nano-Ag, however, have been known for centuries.[89,90] Products containing nanoscale Ag particles have been commercially available for over 100 years and were used in applications as diverse as pigments, photographics, wound treatment, conductive/antistatic composites, and catalysts, and as a biocide.[90] Several studies revealed that Ag NM may exhibit the same antimicrobial properties associated with ionic Ag, which lead to an increased use of Ag NM for disinfection purposes in a wide spectrum of consumer products such as fabrics, plastics, papers, and washing machines.[88] Above all, Ag ions are believed to have a low toxicity to animal cells.[89]

Concerning PPP and fertilizer applications, Ag NM are solely investigated as fungicides. For example, Jo et al.[33] tested Ag NM against two plant-pathogenic fungi, *Bipolaris sorokiniana*, which infests important agricultural crops such as *Hordeum vulgare* and *Zea mays*, and *Magnaporthe grisea*, a rice pathogen. They discriminated between Ag Ions and Ag NM by comparing AgNO$_3$ to Ag NM. The determined EC$_{50}$ values for the different applications were up to a factor of 5 lower for AgNO$_3$ than for Ag NM regardless of the pathogen species. The effective concentrations of Ag NM were approximately in the same range as in the study of Kim et al. (2008).[34] They tested the effectiveness of Ag NM against powdery mildew occurring on roses (*Sphaerotheca pannosa var. rosae*) in the field[34] and observed a decline in mildew infestation of 95% a week after the application of 15 g Ag NM ha^{-1}. According to ref 91 application rates of conventional fungicides against powdery mildew range from 105 g to 6 kg per ha. This shows that compared to other conventional fungicides, Ag NM could be applied in lower amounts, achieving the same effect. However, the flux arising from such an Ag NM application is still 54-fold higher than modeled for a high exposure scenario (Table 1), and even 245-fold higher than the maximum flux per year, as modeled by ref 80.

Alavi and Dehpour[37] could also show a higher efficiency of a commercial Ag NM product (Nanocid L2000) compared to a conventional fungicide. However, Ag—in concentrations occurring in sewage sludge—has the potential to severely affect microbial biomass in soils.[92] Silver NM are releasing Ag ions in the process of aging,[93] thus it is generally questionable

from an environmental point of view to introduce even more particles (Table 1), and consequently Ag ions, into soils.

4.2.3. Silica (SiO$_2$) NM. Silica NM have diverse applications, such as dye doped fluorescent probes in nanobioimaging[94,95] and in drug delivery.[96] They are highly hydrophilic and possess a good potential for surface modifications.[95] The main mode of action in agricultural formulations is taken over from pharmaceutical applications, where mesoporous silica NM are used as controlled release carriers in drug delivery.[97] Mesoporous silica NM are solid materials, which consist of a honeycomb-like porous structure with hundreds of empty channels (mesopores) that are able to be loaded with relatively large amounts of active substances. The unique properties, such as high surface area (>900 m^2 g^{-1}), large pore volume (>0.9 cm^3 g^{-1}), tunable pore size with a narrow distribution (2−10 nm), and good chemical and thermal stability of these materials, make them potentially suitable for various controlled release applications.[96] Li et al.[98] synthesized such mesoporous silica NM as controlled release carriers for the insecticide avermectin. With a larger shell thickness the particles could also act as UV shields. Increasing the shell thickness in a range of 5−45 nm also led to a more sustained release of the PPP. Also, these carriers had a high loading ability for the active substance (approximately 60.0% w/w). However, the efficiency of this formulation against target organisms was not tested.

In the case of slow release formulations, silica-composite NM have been proposed. For example, the University of central Florida patented a silica−copper nanocomposite formulation.[99] Therein, CuO NM were loaded onto a silica nanogel, which is claimed to be formed by "interconnection" of single silica NM, to release Cu in a sustained manner and to improve the stickiness to the plant surface. After two alternating spray applications and drying periods, 41 to 75% of the nanocomposite was still on the leaf surface, whereas only 1 to 5% remained of a conventional formulation.

Apart from controlled release, silica NM have also been proposed as active ingredients against insect pests. Since many insects, such as *Sitophilus* species that infest agricultural products during storage, have become resistant to a variety of active ingredients, which also remain as residues on the protected crops, Debnath et al. proposed the application of surface functionalized silica NM as an insecticide[43] to overcome the problem of resistance development to conventional insecticides. This idea mainly stems from the fact that the insecticidal use of inert dusts has a long history, from mammals and birds taking "dust baths" up to civilized nations as well as isolated tribes.[100] The main mode of action of such NM against insects is believed to lie in blockage of the trachea or impairment of the digestive tract. Another possible way is the disruption of the lipid−water barrier, that protects insects from desiccation.[100] In the study of Debnath et al.,[43] regardless of the mechanism of action, silica NM achieved up to 69% mortality of *Sitophilus* adults, whereas the bulk form only reached 23%, indicating the presence of a nanospecific effect.

4.2.4. Aluminum (Al) NM. Aluminum NM foreseen in agriculture mostly belong to the mineral class of Al silicates, as for example kaolin, that occur naturally in soils. Liang and Liu[101] describe one of the—currently—few nanofertilizer applications using a poly(acrylic acid)-*co*-acrylamide-kaolin nanocomposite powder as a slow release carrier for urea. However, the resulting formulation was not compared to a conventional urea fertilizer, so no statements on the benefits of use can be made. Another Al silicate slow release formulation is

described in the Patent US20080194406, filed by the company Natural Nano Inc.[102] Therein, nanoscale tubular structures are derived from Al silicates such as halloysite and serve to a sustained release of fertilizers as well as PPP. Unfortunately, also in this case, no additional comparisons or studies on the efficiency are presented.

Apart from Al silicates, Stadler et al.[44] proposed the use of "nanostructured alumina" as insecticides. These Al NM were based on Al_2O_3, a versatile ceramic oxide that has been used in a wide range of applications in electrical, engineering, and biomedical areas.[103] Two species that infest agricultural products during storage were used as model organisms, similar to the studies of Debnath et al.:[43] *Sitophilus oryzae* (L). and *Rhyzopertha dominica* (F.). Both species experienced significant mortality after 3 days of continuous exposure to treated wheat. Nine days after treatment, the LD_{50} observed ranged from 127 to 235 mg kg^{-1}.[44] However, mortality due to the Al NM was only "comparable" to that due to common insecticidal dusts.

4.2.5. Zinc Oxide (ZnO). Zinc oxide is a wide band gap piezoelectric semiconductor with many possible different morphologies such as rods, wires, sheets, and also hollow microspheres.[104] Zinc oxide NM have also been found to have superior UV blocking properties compared to their bulk substitute. This is one of the reasons why ZnO is often used in the preparation of sunscreen lotions.[105] Its UV-blocking properties are also one of the main modes of action in agricultural formulations. In patents of BASF (Patent WO/2009/153231[79]) and Evonik-Degussa (Patent WO/2007/014826[81]), ZnO is proposed as an alternative UV protection agent to the surface coated TiO_2 NM. Zinc oxide has also been investigated as an active ingredient for PPP: Goswami et al.[41] used ZnO NM as "dust" insecticides, similar to the study of Debnath et al.,[43] but found them to be less active against *Sitophilus oryzae* than the above-described nanosilica (33−65% mortality), indicating a material dependency of the effect.

Zinc oxide in its bulk form is also often incorporated into macronutrient fertilizers. However, the effectiveness of such fertilizers in providing plants with Zn in a Zn deficient soil is mostly governed by the solubility of the Zn source in the soil. As—in theory—solubility of particles depends on particle size, Milani et al.[106] very recently investigated Zn solubility and dissolution kinetics of ZnO NM and ZnO bulk particles coated onto selected granular macronutrient fertilizers. Surprisingly, the kinetics of Zn dissolution was not affected by the size of the ZnO particles applied for coating, possibly because solubility was controlled by formation of the same compounds irrespective of the size of the original ZnO particles used for coating.

4.2.6. Copper (Cu) NM. Copper has a long history as a fungicide, especially in vineyards and organic farming, where it is still used. The Cu ion (redox Cu^{2+} and Cu^{1+}) is responsible for the toxicity affecting the activity of several enzymes, thereby preventing germination of fungal spores. However, this application suffers from the high amounts of Cu that have to be applied (in the range of 500 to 1500 g ha^{-1}). In the BASF patent WO/2011/067186[45] nanoscale amorphous (i.e., non-crystalline) Cu-salt particles are mixed with a polymer to secondary particle sizes between 1 and 200 nm. In one example, such a mixture contained 6.5 g L^{-1} Cu as Cu acetate, sodium acetate, and polycarboxylate with particle sizes at 20 nm. One common non-nano Cu formulation is Cuprozin (Spiess Urania Chemicals) that contains 300 g L^{-1} Cu as Cu hydroxide. Compared to this formulation, at the same application dose of

150 ppm Cu, the nanoformulation could achieve an increase in efficiency of 8% against a phytopathogenic fungus on vines. The use of such a nanoformulation could thus reduce the amount of Cu introduced into agro-ecosystems.

4.2.7. Multiwalled Carbon Nanotubes (MWCNT). Multi-walled carbon nanotubes are NM composed of multiple layers of extensive sp^2 carbon atoms arranged in fused benzene rings (graphene). Their structure leads to exceptional electrical, chemical, and physical properties, which are in turn utilized in various applications[107] where unique structural, superconductivity, and mechanical properties as well as outstanding thermal and chemical stability are necessary. They have also been proposed as potential sorbents to remove organic contaminants due to their relatively high sorption capacity.[108]

The first to report positive effects of MWCNT on crops was the group of Khodakovskaya et al. in 2009.[109] Using an exposure concentration of 10 to 40 μg mL^{-1}, they observed increased germination rates in tomato seeds. The whole procedure has very recently been patented in WO/2011/059507.[110] The main mode of action is believed to lie in a mechanical penetration of the seed coat, thus enhancing water uptake and promoting seed germination. This publication has received a lot of attention in the public (search term "carbon nanotubes tomato seeds", 10,800 hits on May 7, 2012), and its findings were partially inflated into the grotesque, with open-source article titles such as "CNTs are super-fertilizers", "CNT make great tomatoes", "Want to growth über-Tomatoes really fast? Use CNTs as fertilizer", etc.

A similar experiment, but addressing growth rate, was conducted recently by Tripathi et al.[111] using water-soluble-CNTs (wsCNTs) as promoters of water uptake. A concentration of the wsCNT of up to 6.0 μg mL^{-1} was already sufficient to enhance the growth rate of common gram (*Cicer arietinum*) plants. Also, they provided evidence by optical, fluorescence, SEM, and TEM microscopy that these wsCNT were taken up by plants. Uptake was explained by comparing the outer diameter of wsCNT (10−30 nm) with that of the xylem (a few micrometers). Thereby, they presumed that the wsCNT may get introduced inside the lumen of tracheal elements. Due to the size difference between these two, wsCNT could be incorporated within the xylem according to the concept of the formation of a "large capillary". These wsCNTs can act then to form several new capillaries which increase the water uptake potential of the plant in addition to the natural flow.[111] They claim that this could be especially useful to enhance water transport and prevent water loss in agriculture. However, such CNT applications would also cause dramatically increased fluxes into the soil, compared to current estimations from unintentional release (Table 1). Organic contaminants have a high affinity to carbonaceous sorbents[112] such as CNT, and several studies postulate that CNT loaded with them could mediate a "carrier effect"[113] that may in turn lead to an increase in exposure to environmental micro-pollutants.[114] Therefore, such applications should be evaluated with great care.

5. RESEARCH PRIORITIES FOR A SAFE USE OF NM IN PPP AND FERTILIZATION

Intentional and enhanced input of NM into agricultural ecosystems (Table 1) is an intrinsic prerequisite for "nano-improvement" of PPP and fertilizers, yet many questions regarding the fate of these materials in the environment still have to be urgently answered. Despite the fact that soil is the

most important environmental compartment for agricultural production, very few studies investigated the behavior (e.g., mobility and stability) and the effects of NM in natural soils under environmental conditions. For example, size, charge, and agglomeration rate of Al NM allowed prediction of their mobility in soil.[115] Titanium dioxide NM easily passed columns with coarse soils and solutions of low ionic strength, but were significantly retained in soils with higher clay contents and salinities.[116] Carbon nanotubes were effectively retained by the soil matrix irrespective of the chemistry,[117] but may still undergo preferential flow under real conditions and were shown to be mobile in porous media when associated with natural organic matter.[118]

Only a few efforts have been made to date to assess NM effects on ecosystem services provided, e.g., by beneficial soil microorganisms. Silver NM for example were able to decrease mycorrhizal colonization of *Helianthus annuus*,[119] TiO$_2$ and ZnO NM negatively affected soil microbial communities,[120] and sublethal concentrations of quantum dots stimulated genes associated with nitrogen cycling for example in *Azotobacter vinelandii*.[121] Understanding the parameters governing NM mobility and effects on organisms in soils is essential for both risk assessment and design of sustainable agricultural NM applications.

From soils, NM may be taken up by plants. The current state of research has been reviewed by Rico et al.[122] and was found to be yet in its beginning. Contradicting results were found, and the differences might depend on several factors, such as species dependent effects, plant age and developing stage, NM concentration, surface area, and many more. For example, an uptake of <5 nm TiO$_2$ NM that were conjugated with alizarin red by *Arabidobsis thaliana* was reported by Kurepa et al.[123] The NM were distributed and accumulated in subcellular regions. In contrast, no uptake of TiO$_2$ NM in maize plants (*Zea mays*) was found by Asli and Neumann.[124] Nanoparticles used in the latter study were uncoated P25 (Degussa, Germany), and one may assume that a specific coating might facilitate uptake, for example by interaction with the mucilage surrounding the root. Regarding effects of NM on agricultural crops, also only few studies under environmental conditions exist. For example, TiO$_2$ NM negatively affected the growth of wheat and soil enzyme activities in a lysimeter study.[125]

Suitable analytical methods are lacking to quantify NM concentrations in water, soil, and air. This hampers risk assessment, where precise data on predicted environmental concentrations of relevant NM is essential to define exposure. Some efforts have been made to solve this gap by modeling environmental concentrations.[17,80] Several analytical techniques have been recently reviewed by von der Kammer et al.[126] General analytical difficulties include extraction and separation/ purification from the soil matrix and interfering constituents, as well as low analyte concentrations. Analysis of metallic NM is especially difficult, as many of them, such as TiO$_2$, have naturally occurring counterparts. However, promising techniques include hyphenated approaches, such as field-flow fractionation (FFF) coupled to ICP-MS, as well as X-ray based techniques. For carbonaceous NM such as CNTs, further development of chemothermal oxidation[127,128] and thermogravimetry–mass spectrometry[129] merits additional efforts.

In a classical risk assessment of organic compounds used as PPP, the PBT (persistence, bioaccumulation, toxicity) properties are evaluated. The evaluation of organic compounds is based on specific end points and parameters obtained from laboratory or field experiments. Persistence is evaluated considering the dissipation of 50% of the initial concentration, a decision on bioaccumulative properties of a compound is based on the octanol–water partition coefficient (K_{ow}), and to evaluate the toxicity criterion, the aquatic toxicity test results determining the intrinsic toxicity of the compounds are examined.

It is questionable if these procedures hold true for NM, since for example K_{ow} is not a suitable parameter to describe bioaccumulation for NM. Also in some cases, the determination of the intrinsic toxicity is difficult, especially for compounds which strongly agglomerate, so that test designs have to be adapted to the properties of the various NM. One parameter that could serve this purpose, however, is the reactivity of the NM, which is likely to be requested from regulatory bodies in the future.[130] This parameter could be rapidly determined and emphasize a need for regulatory action. For example, nonsolid NM such as emulsions or polymers have been classified as low redox or catalytically active, whereas solid metallic NM such as uncoated TiO$_2$ have been classified as highly active. However, these classifications still need a refinement, as the determining methods are not yet standardized.

6. NANOREGULATION AND ONGOING ACTIVITIES

The fast development of manufactured NM and their presence on some markets make it necessary to evaluate their environmental and health impacts. Due to safety concerns about some NM, and the problem of inappropriate generalization owing to the huge range of nanotechnological applications, it is urgently necessary to address this gap in the regulation of NM. It should be filled by using the findings of the ongoing projects in toxicity testing, decision making on material characterization and testing protocols, and exposure and data management of the Working Party on Manufactured Nanomaterials of the Organization for Economic Cooperation and Development, the European Committee for Standardization, and the International Organization for Standardization. Furthermore, an additional work program has been launched as part of the European framework program FP7 NMP (Nanosciences, nanotechnologies, materials and new production technologies),[131] named NANoReg. This intended proposal is aiming to establish collaboration among authorities of the European governments with regard to the knowledge required for appropriate risk management. The goal of this project is to provide legislators with a set of tools for risk assessment and decision making for the short to medium term, by gathering data and performing pilot risk assessment, including exposure monitoring and control, for a selected number of NM used in products. A second objective is to bring together the activities of national authorities responsible for worker protection, public health, and environment and create the basis for common approaches, mutually acceptable data sets, and risk management. At the current state, there has been an approach for declaration of nanopesticides in the US by the Environmental Protection Agency (EPA). In Europe, the European Chemicals Agency is currently reviewing the guidance documents to help registrants register nanoforms under REACH. It aims at sharing experiences with stakeholders on the type of information currently submitted by registrants on NM. Recently, the European Parliament decided on a new definition of a NM[1] and included this in a replacement of the Biocidal Products Directive 98/8/EC.[132] The updated directive states that there is a "scientific uncertainty" about the safety of

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NM. Hence, a nanoform of an active substance will not be included in the approval procedure, if not explicitly mentioned. To fill the gap before the current legislation can be adapted to the needs of NM regulation, a precautionary matrix has been published in Switzerland helping industry in self-controlling the possible impact of NM during the production process, taking into account environmental and health aspects.[130]

■ ASSOCIATED CONTENT

Supporting Information

Figure S1: Patents of nano-PPP and fertilizer applications. Figure S2: Particle sizes of nano-PPP and fertilizer applications. Table S1: Earlier reviews in related disciplines. Tables S2, S3, S4: Nanomaterials in PPP and fertilizer formulations: scientific literature, patents, and potentially NM containing products, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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