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Probabilistic modelling of nanobiomaterial release from medical applications into the environment

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ABSTRACT

Nanobiomaterials (NBMs) are currently being tested in numerous biomedical applications, and their use is expected to grow rapidly in the near future. Many different types of nanomaterials are employed for a wide variety of different applications. Silver nanoparticles (nano-Ag) have been investigated for their antibacterial, antifungal, and osteoinductive properties to be used in catheters, wound healing, dental applications, and bone healing. Polymeric nanoparticles such as poly(lactic-co-glycolic acid) (PLGA) are mainly studied for their ability to deliver cancer drugs as the body metabolizes them into simple compounds. However, most of these applications are still in the development stage and unavailable on the market, meaning that information on possible consumption, material flows, and concentrations in the environment is lacking. We thus modeled a realistic scenario involving several nano-Ag and PLGA applications which are already in use or likely to reach the market soon. We assumed their full market penetration in Europe in order to explore the prospective flows of NBMs and their environmental concentrations. The potential flows of three application-specific composite materials were also examined for one precise application each: Fe_3O_4PEG-PLGA used in drug delivery, MgHA-collagen used for bone tissue engineering, and PLLA-Ag applied in wound healing. Mean annual consumption in Europe, considering all realistic and probable applications of the respective NBMs, was estimated to be 5,650 kg of nano-Ag and 48,000 kg of PLGA. Mean annual consumption of the three application-specific materials under the full market penetration scenario was estimated to be 4,000 kg of Fe_3O_4PEG-PLGA, 58 kg of MgHA-collagen, and 24,300 kg of PLLA-Ag. A probabilistic material-flow model was used to quantify flows of the NBMs studied from production, through use, and on to end-of-life in the environment. The highest possible worst-case predicted environmental concentration (wc-PEC) were found to occur in sewage sludge, with 0.2 μg/kg of nano-Ag, 400 μg/kg of PLGA, 33 μg/kg of Fe_3O_4PEG-PLGA, 0.007 μg/kg of MgHA-collagen, and 2.9 μg/kg of PLLA-Ag. PLGA exhibited the highest concentration in all environmental compartments except natural and urban soil, where nano-Ag showed the highest concentration. The results showed that the distribution of NBMs into different environmental and technical compartments is strongly dependent on their type of application.

1. Introduction

A biomaterial is a natural or synthetic material designed to interact with biological systems for a medical purpose (Merriam-Webster, 2020). A nanobiomaterial (NBM) is a nano-sized material engineered to interact with the human body. Nano-sized drug formulations have several potential physical and biological advantages over conventional medicines, such as improved solubility and pharmacokinetics, enhanced efficacy, reduced toxicity, and increased tissue selectivity (Chaloupka et al., 2010). A common practice is to conjugate a therapeutically active agent with a nanoparticle, or encapsulate the agent within one, to alter its pharmacokinetics. Thus, nanoparticles can be designed to enable the active agent to reach previously impervious areas, circulate longer, and allow greater accumulation. More than 50 nanopharmaceuticals have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and are available for clinical practice. Even more are being investigated in medical trials (Ventola, 2017). Most of these, however, are conventional drugs formulated in a nano-form. Nano-form carrier particles are also used to a lesser extent. A large number of nanomaterials such as different metals or polymers is investigated for their use in nanomedicine (Priyadarsini et al., 2018; Ventola, 2017; Ferraris and Spriano, 2016; Patra et al., 2018; Calzoni

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et al., 2019). Two of the most commonly investigated nanoparticles are nano-silver (nano-Ag) and poly(lactic-co-glycolic acid) (PLGA) (Han et al., 2018; Singh et al., 2017).

Nano-Ag has been increasingly used in the medical industry due to its antibacterial, antifungal, antiviral, anti-inflammatory, and osteoinductive properties (Ge et al., 2014; Murphy et al., 2015). Silver's advantage over conventional antibiotics is that bacteria would need to undergo three separate mutations in three different bacterial systems in order to develop resistance to the element (Murphy et al., 2015). Nano-Ag is thus used in applications such as wound dressings, tissue scaffolds, protective coatings, and drug delivery (Burdușel et al., 2018).

PLGA is a copolymer composed of lactic acid and glycolic acid. It is approved by the FDA and EMA for medical applications and used in various conventional (non-nano) drug delivery systems (Danhier et al., 2012; Kim et al., 2019). PLGA copolymers degrade in the body into lactic and glycolic acids. These monomers can easily be metabolized by the body via the Krebs cycle and eliminated as carbon dioxide and water (Dinarvand et al., 2011). PLGA's degradation rate can be controlled by the ratio of lactic acid to glycolic acid. PLGA composed of higher numbers lactic acid moieties usually degrades more slowly than PLGA with a lower lactic acid content (Araújo et al., 2009). This is why PLGA is the most commonly used biodegradable polymer for the controlled release of encapsulated drugs. Nanoparticles present many advantages, such as increasing stability and protecting drugs from degradation. PLGA has thus been identified for use in improving cancer therapy (Mirakabad et al., 2014).

Because NBMs are increasingly being used in medical applications, their environmental release and the risks they pose need to be evaluated. Identifying hotspots along their life cycle is essential to mitigating the risks of NBM release. However, to identify these hotspots, their flows into different technical and environmental compartments must be quantified. As NBMs are used similarly to pharmaceuticals, looking at the distribution of pharmaceuticals in the environment is a good starting point. Pharmaceuticals excreted in urine and feces enter the sewage system; they are then transported to wastewater treatment systems where they are partially removed, and the rest is discharged to surface water (Chèvre et al., 2013). Pharmaceuticals have been found worldwide in surface water, groundwater, tap and drinking water, manure, and soil (Umwelt Bundesamt, 2018). It is thus also important to evaluate the possible flows and risks of NBMs in technical and environmental compartments.

Evaluating the environmental risk posed by a nanomaterial involves comparing the chances of exposure to it with how hazardous this might be. Several nanomaterial hazard assessments have been published, including for nanomaterials used in nanomedicine (Hauser et al., 2019; Wang and Nowack, 2018; Coll et al., 2016). The analytical determination of nanomaterials in environmental compartments is difficult, thus a modelling approach is often used (Nowack et al., 2015). Material flow analysis (MFA) is an established method to study material or energy flows into, through, and out of a system (Brunner and Rechberger, 2004; Graedel, 2019). Several MFAs have been published for engineered nanomaterials (ENMs) (Gottschalk et al., 2010, 2009; Mueller and Nowack, 2008; Sun et al., 2014, 2017; Wang, Kalinina, et al., 2016; Adam et al., 2018). The MFA approach has also been applied to pharmaceuticals, e.g., by Chèvre et al. (2013), to study the flows of four different drugs from Lausanne's hospitals into Lake Geneva. To date, only one study has been conducted to predict the flows of an NBM into the environment. Mahapatra et al. (2015) used MFA to evaluate the risk of environmental exposure to nano-gold (nano-Au) from medical applications in the United States and the United Kingdom. They used a probabilistic MFA model to calculate the environmental concentrations of nano-Au from the use and consumption of selected medical applications. Assuming a full market-penetration scenario, flows of nano-Au were modelled through sewage treatment, septic tanks, and waste to the soil, air, surface waters, and sediment. The study found that most of the nano-Au either stayed in the body, ending up in a cremation or burial, or it flowed through technical and environmental compartments until it was deposited in soils. Another study investigating NBMs, among other materials, used particle flow analysis (using particle numbers instead of particle mass) to trace nano-Ag in wound dressings, textiles, and electronic circuitry (Arvidsson et al., 2011). Its results indicated that electronic circuitry or textiles were much larger sources of nano-Ag than wound dressings. Lastly, a study by Pourzahedi and Eckelman (2015) evaluated the environmental impacts of commercially available nano-Ag-enabled medical bandages using a cradle-to-grave life cycle assessment. It found that even with a low Ag-loading, silver nanoparticles were the most significant contributor in all the impact categories considered. Additionally, their modelling results suggested that emissions from nano-Ag synthesis and bandage production were several times more impactful than emissions from bandage incineration.

Nonetheless, studies specifically investigating the flows of NBMs other than the nano-Au currently used in available or promising medicinal devices are still lacking. The environmental impacts of some specific medical applications of nano-Ag have been investigated previously. However, models evaluating the complete life-cycles of all nano-Ag's medical applications are still missing, as are any models analyzing organic materials. The present study therefore aimed to evaluate the complete flows of two materials for which nanomedicine has great expectations—nano-Ag and PLGA—using probabilistic material flow analysis. The three composite materials of Fe_3O_4PEG-PLGA, MgHA-collagen, and PLLA-Ag were also studied as examples for realistic representative materials which industry is currently developing for specific uses as NBMs. Fe_3O_4PEG-PLGA covers a combination of different intended uses in the field of cancer therapy for theranostic purposes: as a magnetic hyperthermia agent, an *in vivo* imaging/contrast agent (MRI), and an active targeting and drug delivery agent (Baldi et al., 2015). MgHA-collagen is used as a fibrous, scaffold bone substitute in orthopedic or spinal surgery (finceramica, 2020). PLLA-Ag contains electrospun poly-L-lactide (PLLA) microfibers doped with Ag nanoparticles, and it is being considered for applications such as topical wound dressings (Electrospinning Company, 2020).

2. Methods

2.1. Model description

An MFA model was developed to predict the emissions and worst-case predicted environmental concentrations (wc-PEC) of NBMs. The present study's geographical scope was the EU27 plus the United Kingdom, Switzerland, and Norway. The MFA was based on a life-cycle perspective and included the production of the NBMs, their application inside the body, waste treatment systems such as waste incinerators, landfills, and wastewater treatment plants, and environmental compartments such as the air, soil, and water (see Fig. 1). The elimination of organic polymers was also considered in some technical processes.

The present study was based on the MFA developed by Adam et al. (2018) for ENMs, with which they systematically evaluated flows of different forms of nano-Ag and nano-TiO_2 in Europe over one year. The model used probability distributions as transfer factors and described five different forms of those ENMs. Unfortunately, no data are available on the forms of the excreted NBMs (Berkner et al., 2016), and therefore the different forms could not be considered. The basic model was adjusted slightly to better represent the present study, and some transfer factors were adjusted when newer data were available. These adjustments refer to the inclusion of health care waste and subsequently to alternative treatments and hazardous waste incineration, hospital sewage, and the disposal of corpses via cremation or burial. All the NBM applications considered in the present study were administered in a hospital setting; home use was not considered.

The system boundaries included only the initial parent NBMs. This means that all the flows refer to the initial material, and as soon as a part of that material is transformed (e.g. an organic coating during

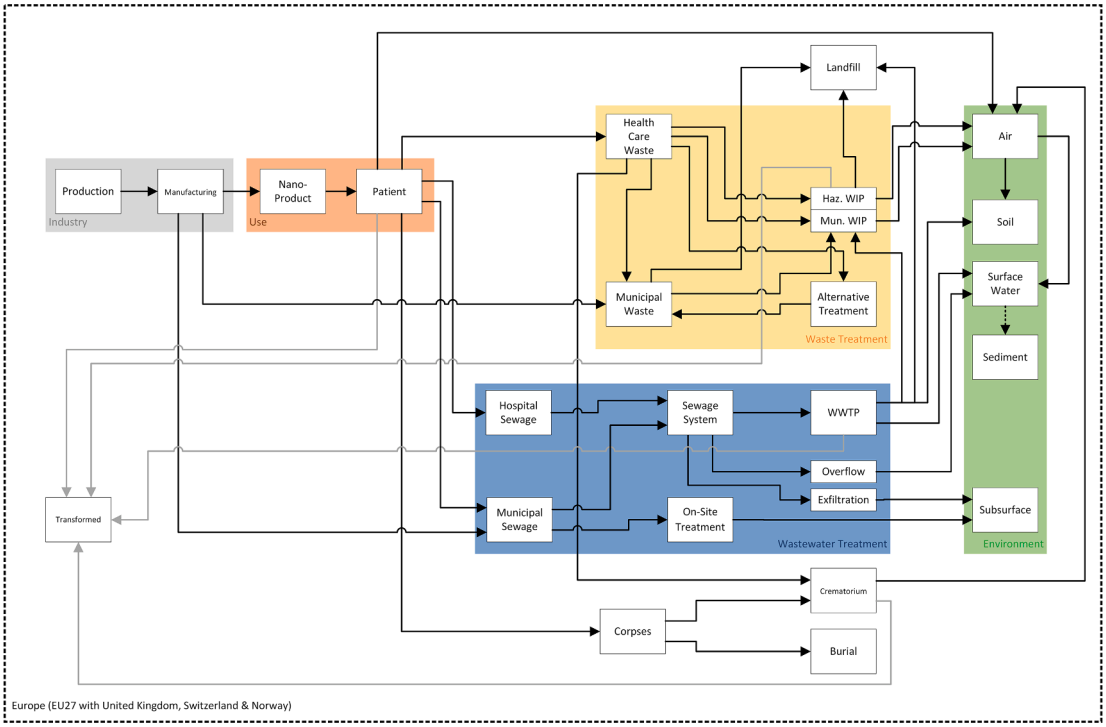

Fig. 1. Structure of the material flow model. The model tracks the nanobiomaterials through their entire life cycle from production and manufacturing to their incorporation into medical products and then through to their elimination via waste and wastewater treatment until they finish in the environment. (WWTP: Wastewater treatment plant; Haz. WIP: Hazardous waste incinerator plant; Mun. WIP: Municipal waste incinerator plant) (Modified after (Giubilato et al., 2020.))

incineration), the whole material was considered to have been transformed.

2.2. Applications of NBMs

The literature was searched for medical applications of the two selected NBMs. Only applications with two or more published articles from different research groups were considered. Applications where all the published articles were ten years old or more were discarded as their potential was deemed to be lost. Applications were classified into three categories—"realistic", "probable", and "unrealistic"—based on how likely the application was to reach the market. An application's potential to reach the market was classified as realistic if either a product of this kind containing nanomaterials was already on the market or a patent existed in Europe or the United States. Applications were classified as probable if either a patent existed in another country or several studies from different laboratories evaluating the same application were found in the literature. Lastly, market introduction potential was classified as unrealistic if the NBM was just one of many NBMs being tested for a specific application.

Similar to the works of Mahapatra et al. (2015) and Arvidsson et al. (2011), we developed an explorative full market penetration scenario. As a first step, currently available and potential medical applications of nano-Ag or PLGA were researched, as described above, for their chances of reaching the market. It was then assumed that these applications would reach a 100% market share within their product group. The scenarios developed here were therefore realistic as the applications were already on the market or were likely to reach the market soon. It could also be considered a worst-case scenario as we assumed full market penetration for the nano-product, with no other products for a specific application expected to exist.

Each application's consumption of NBM was calculated similarly to the approach used by Caballero-Guzman and Nowack (2018). The total number of units used in one application was considered in conjunction with that application's characteristics, including the weight per unit in kg and the NBM content. The calculation method is described by Eq. (1):

$$NBM_{consumption} = NanoApp_{used} * NanoApp_{weight} * NBM_{content} \quad (1)$$

$NanoApp_{used}$ represents the total units of an application used in Europe in one year, $NanoApp_{weight}$ represents the mass of that one application in kg, and $NBM_{content}$ represents the concentration of NBM in the material. By employing the total number of units used in Europe, we could calculate the maximum consumption of NBMs for each application, thus representing a full market penetration scenario and indicating an upper boundary to how much of this NBM might be used in Europe in one year.

Nano-Ag is used in catheters, wound dressings, dental and root canal fillings, adhesives for braces, bone cement, bone tissue engineering, coatings for implants and screws, and drug delivery. PLGA is used in the delivery of several cancer drugs. Compared to nano-Ag and PLGA, used in many different applications, each of the three application-specific composite materials only has one. Employing this approach, the major pathways used by a material with a specific application could be followed through the system. Fe_3O_4PEG-PLGA is used for drug delivery, MgHA-collagen is used in bone tissue engineering, and PLLA-Ag is used for wound healing.

2.3. Transfer coefficients

The model uses general transfer coefficients that are independent of the NBM in question and transfer coefficients that are material-dependent. Examples of general transfer coefficients include the treatment of health care and municipal waste, the sewage treatment connection rate, overflow and exfiltration rates, and the cremation rate. These general transfer coefficients are the same for all materials, and average European values were taken whenever possible. Most of these general transfer coefficients were adopted from Adam et al. (2018) unless newer data had been published since the base model (e.g., for waste treatment) or the compartments had not been present in the base model (e.g., health care waste and hospital wastewater). The major

changes made to the system are described below, and minor adjustments are explained in chapters 8 and 9 of the Supporting Information.

The other type of coefficient is the material-dependent transfer coefficient. Examples of this are NBM behavior inside waste incineration plants and the removal of NBMs in wastewater treatment plants. For nano-Ag, the transfer coefficients from Adam et al. (2018) were taken unless there were new data available (such as for wastewater treatment; see chapter 8.4 in the Supporting Information). For PLGA and the application-specific composite materials, transfer coefficients were derived from different sources, as explained below. An uncertainty coefficient of +/− 50% was applied to all parameters unless otherwise stated.

2.3.1. The use stage

Transfer coefficients from the use stage (application in the patient) to different waste treatment options or environmental compartments are application-dependent. Table 1 shows the transfer coefficients for nano-Ag for each application. References and details on how the transfer coefficients were derived can be found in chapter 5.2 of the Supporting Information. For intravenously administered particles used for drug delivery, excretion from the body was modelled based on the cumulative excretion profile for intravenously administered nanoparticles developed in our previous work (Fig. 5A in Hauser and Nowack, 2019). Of these excreted NBMs, 95% was assumed to end up in hospital sewage (excreted while the patient is still in hospital) and 5% in the municipal sewage (excreted after the patient returned home from hospital).

PLGA is used in the delivery of cancer drugs such as doxorubicin, paclitaxel, docetaxel, and cisplatin. The transfer coefficients for all these applications are thus the same as for the delivery of doxorubicin with nano-Ag. Fe_3O_4PEG-PLGA is also used in drug delivery, so the transfer coefficients were also the same as for drug delivery with nano-Ag. For MgHA-collagen, the coefficients are identical to bone tissue engineering from nano-Ag. For PLLA-Ag, the same coefficients as for wound healing with nano-Ag are taken. A table with the transfer factors and a description of how the coefficients were derived, as well as the underlying references for PLGA and the three application-specific materials, can be found in chapters 6.2 and 7.2, respectively, of the Supporting Information.

2.3.2. Waste treatment

The transfer coefficients for the waste treatment system were general transfer coefficients, mostly taken from Adam et al. (2018). On certain occasions, new data were available, as described by Rajkovic et al. (2020). If this was the case, they are described in chapter 8.1 of the Supporting Information. Certain aspects of the waste treatment systems relevant to hospitals had not been evaluated in previous studies. This specifically includes waste and wastewater treatment from hospitals. These additions are described below.

2.3.3. Health care waste

Health care waste (HCW) is defined as all wastes generated by medical activities (World Health Organisation, 2002). Due to its hazardous character, the management of HCW is strictly controlled. However, regulations differ within EU member states. The treatment of the HCW is determined by the category under which that waste is classified (Gaudillat et al., 2018). The EU distinguishes between the following categories: non-risk HCW, sharps, human anatomical waste, blood and body fluids, infectious waste, and chemicals. The transfer coefficients used were independent of the material. For a detailed description of waste categories and how transfer coefficients were derived, see chapter 8.2 in the Supporting Information.

2.3.4. Wastewater

Wastewater treatment was modelled following Rajkovic et al. (2020) as they provided a more detailed, updated approach than Adam et al. (2018). This specifically included the general transfer coefficients for sewage systems, on-site treatment, combined sewer overflow, exfiltration, primary, secondary, and tertiary treatment, and the treatment of sludge. Values for nano-Ag removal during wastewater treatment were taken from those published by Rajkovic et al. (2020). No studies have been published yet for organic or polymeric nanomaterials, so we took values from Frehland et al. (2020) and Wu et al. (2018). For more details, see chapter 8.3 in the Supporting Information.

2.3.5. Hospital wastewater

Hospital wastewater is defined as any water that has been adversely affected in quality during the provision of health care services. It is mainly liquid waste but may contain some solids produced during health-care-related processes or by humans (World Health Organisation, 2014). Today's hospital effluents are still generally considered to have the same pollutant characteristics as urban wastewater and are thus discharged into the public sewer system and transported to an urban wastewater treatment plants (WWTPs) (Verlicchi et al., 2015). We thus assumed that 100% of hospital wastewater was transported to the general WWTPs and treated there together with domestic wastewater.

2.3.6. Waste incineration

Two new studies (Quicker and Baran, 2017; Oischinger et al., 2019) on the behavior of nanomaterials in full-scale waste incinerators have appeared since the publication of the base model, thus we adapted it slightly. Our study also evaluates different partly-organic nanomaterials, which were assumed to be completely destroyed during incineration. As the system boundaries only included the initial composite material, a coating transformation was assumed to transform the whole material (see chapter 8.4 in the Supporting Information for details).

Mahapatra et al. (2015) used different transfer coefficients for flue gas treatment to air, depending on the type of incineration. UK and US

Table 1
Transfer coefficients in % for nano-Ag from the use stage to the waste treatment or environmental compartments for different products (for a detailed description of the calculations, assumptions, and underlying references, see chapter 5.2 in the Supporting Information. Parentheses show health care waste categories and sewage systems).

Application	Health Care Waste (HCW)	Sewage	Corpses
Catheter	85 (Sharps)	7.5 (Hospital Sewage)	7.5
Wound Healing	100 (Blood and Body Fluids)	0	0
Dental Fillings	10 (Non-Risk HCW)	5 (Hospital Sewage)	85
Root Canal Fillings	10 (Non-Risk HCW)	5 (Hospital Sewage)	85
Adhesives for Braces	10 (Non-Risk HCW)	5 (Hospital Sewage)	85
Bone Cement	63 (Non-Risk HCW)	0	37
Bone Tissue Engineering	10 (Non-Risk HCW)	0	90
Implant Coatings	0	0	100
Screw Coatings	0	0	100
Drug Delivery (Doxorubicin)	1 (Pharma Waste)	IV excretion profile from Hauser and Nowack (2019) • 95% to Hospital Sewage • 5% to Municipal Sewage	100-HCW-Excretion

hazardous waste incinerators were assumed to use less stringent air pollution control equipment than municipal waste incinerators. We, however, have found no evidence of this. The hazardous waste incinerator in Biebesheim, Germany, incinerates medical waste among other hazardous waste fractions in a rotary kiln. Its flue gas treatment consists of a spray dryer, an electrostatic precipitator, a quench, a scrubbing tower, and bag filters (HIM, 2016). The hazardous waste incinerator in Leverkusen-Bürrig, Germany, uses a rotary kiln, a quench, a rotary scrubber (acidic and alkaline), condensation exhaust gas recirculation, and selective catalytic reduction (Currenta, 2019). We therefore used the same coefficient for flue gas treatment to air for hazardous waste incineration and municipal waste incineration.

2.3.7. Cremation

A fraction of the NBMs administered to patients will accumulate in their organs and tissues. Therefore, after the patient's death, it will be important whether the body is buried or cremated. Cremation rates for certain European countries were available (The Cremation Societey, 2020) and were then scaled, based on population, to a European average. Values for 2017 were taken as data from more countries was available than for more recent years. An average European cremation rate of 55% was calculated, meaning 45% of corpses were buried. Organic materials (e.g., PLGA) are likely eliminated during cremation and were therefore assumed to be completely transformed (as with waste incineration). As crematoria generally only use basic flue gas cleaning, such as deacidification, deodorization, dedusting devices, or flue gas cooling (Xue et al., 2018), we used the transfer coefficients for hazardous waste incineration from Mahapatra et al. (2015).

2.4. Worst-case predicted environmental concentrations

Based on their flows into different environmental and technical compartments, worst-case predicted environmental concentrations (wc-PECs) of the NBMs were calculated for natural and urban soil, biosolid-treated soil (i.e., soil where sewage sludge is applied), surface water, sediments, WWTP effluents, and sewage sludge. wc-PECs represent the average concentrations in well-mixed receiving compartments, assuming no fate such as degradation or other removal processes. They therefore represent an upper boundary to how much NBM could end up in the environment. Sediment values represent a case with 100% sedimentation from water, whereas water values represent a scenario with no sedimentation. Compartment volumes were those described by Sun et al. (2014).

3. Results

3.1. Consumption volume

Nano-Ag is used in nanomedicine as an antibacterial agent. Catheters and wound dressings using nano-sized silver particles are already on the market so these applications were classified as realistic. A Chinese patent and several published articles were found for the application of nano-Ag in bone cement. Several articles were also found on using nano-Ag in dental fillings, bone cement, adhesives for braces, bone-tissue engineering, and the coating of implants and screws. All these applications were classified as probable. Lastly, some articles were found for the delivery of the cancer drug doxorubicin (Dox) with nano-Ag. However, cancer drugs are more commonly delivered with liposomes or polymers, therefore this application was classified as unrealistic.

The amount of silver used in catheters was calculated by multiplying the amount of silver used per catheter by the number of external ventricular drainage catheters, central venous catheters, and urinary catheter used in Europe per year. The amount of silver used per square centimeter of wound dressing was multiplied by the amount of wound dressing used in Europe. For dental fillings, root canal fillings, and adhesives for braces, the amount of material applied per application was multiplied by the concentration of silver and the number of applications performed per year in Europe. The amount of cement used per knee or hip replacement was multiplied by the concentration of silver in the cement and the number of hip and knee replacements performed in Europe each year. For bone tissue engineering, the number of bone grafts inserted in Europe per year was multiplied by the average amount of material used per bone graft and the concentration of silver in this material. The amount of silver used for implant and screw coatings was calculated by multiplying the amount of silver used in the coatings by the number of implants or screws used per year. We assumed that all the Dox currently used in Europe would be delivered with nano-Ag, thus we multiplied the amount of Dox used per year by the amount of silver needed for delivery. For detailed information on nano-Ag consumption volume calculations, see chapter 2 in the Supporting Information.

PLGA has been investigated for use as a carrier agent for many different drugs, such as anti-inflammatories, antibiotics, and treatments for Alzheimer's or Parkinson's disease. However, we often only found one article for each drug so these applications were not considered here. The most often-used application of PLGA is the delivery of cancer drugs. Several studies were found on improving the delivery of the existing cancer drugs like paclitaxel, doxorubicin, cisplatin, and docetaxel so these four applications were considered and classified as probable applications. PLGA consumption volume was calculated as previously described for nano-Ag consumption in Dox delivery. For more

Table 2
Consumption volumes per year and market introduction potential for nano-Ag, PLGA, and three application-specific composite materials (for detailed description of calculations and assumptions see chapters 2, 3, and 4 in the Supporting Information).

Material	Category	Application	Consumption (kg)	Market Potential
Nano-Ag	Catheter	Catheter	1.25	Realistic
	Wound Healing	Wound Dressing	3,710	Realistic
	Dental Application	Dental Filling	222	Probable
		Root Canal	2.30	Probable
		Adhesives	0.35	Probable
	Bone Healing	Bone Cement	1,710	Probable
		Bone Tissue Engineering	0.29	Probable
		Implants Coatings	2.28	Probable
		Screw Coatings	0.18	Probable
	Drug Delivery	Doxorubicin	2,000	Unrealistic
PLGA	Drug Delivery	Doxorubicin	4,000	Probable
		Paclitaxel	26,000	Probable
		Docetaxel	9,000	Probable
		Cisplatin	9,000	Probable
Fe_3O_4PEG-PLGA	Drug Delivery	Doxorubicin	4,000	Probable
MgHA-collagen	Bone Healing	Bone Tissue Engineering	58	Probable
PLLA-Ag	Wound Healing	Wound Dressing	24,338	Probable

information and details on calculating PLGA consumption volume, see chapter 3 in the Supporting Information.

Total consumption volume for the three application-specific materials was calculated based on the whole nano-formulation, i.e., the NBMs plus their coating but not including any drugs they might deliver to the body. Fe_3O_4PEG-PLGA is used for drug delivery and one study was found to use a very similar material (PFH/DOX@PLGA/Fe3O4–FA) for doxorubicin delivery (Tang et al., 2018). As their weights are very similar, we used the PLGA consumption volume for doxorubicin delivery for Fe_3O_4PEG-PLGA too. MgHA-collagen is used for bone tissue engineering similarly to nano-Ag, as described above. As nano-Ag is often used as an additive to a hydroxyapatite base, the same weight of base material was used as described for nano-Ag. The total consumption of MgHA-collagen is much higher than for nano-Ag because we considered the silver and the base material. Lastly, PLLA-Ag is used in wound healing. We used the same data as for nano-Ag, but not only considered the silver but also the mesh. For more details, see chapter 4 in the Supporting Information.

Annual consumption volumes and the market introduction potential

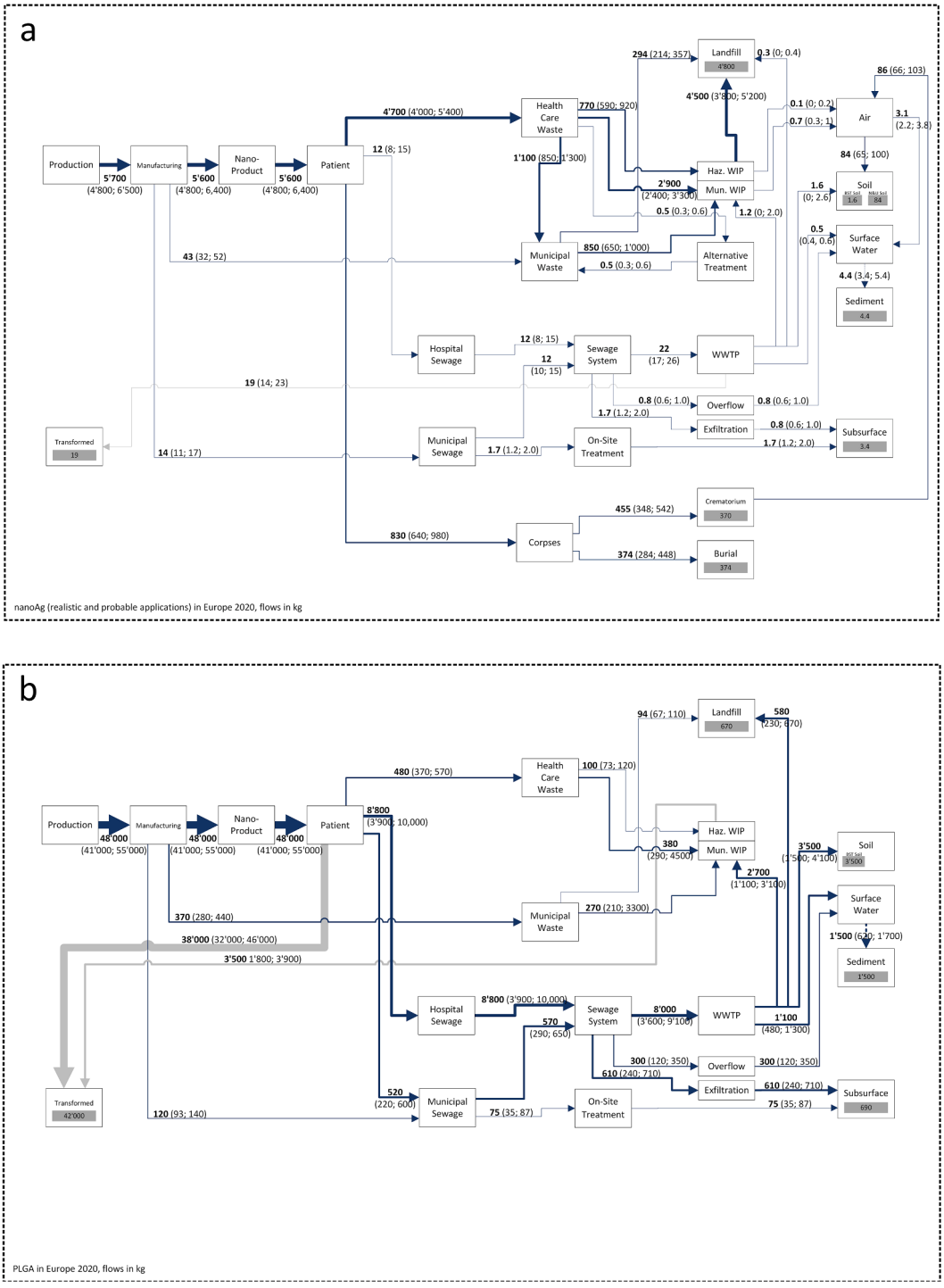

Fig. 2. Flow diagrams considering realistic and probable nano-Ag (a) and PLGA (b) applications in Europe assuming full market penetration of the considered applications (flows in kg). Bold: mean flow; In parentheses: Q25; Q75. WWTP: wastewater treatment plant, MWIP: municipal waste incineration plant, HWIP: hazardous waste incineration plant, N&U Soil: natural and urban soil, BST Soil: biosolid-treated soil.

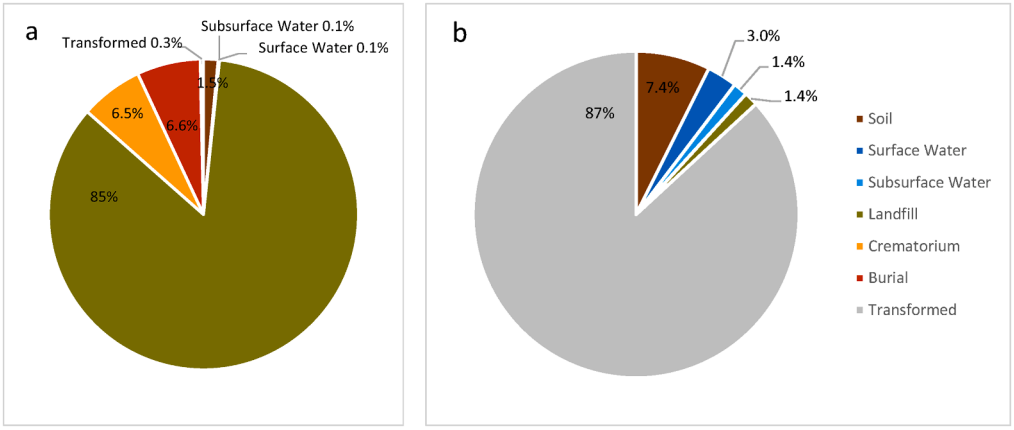

Fig. 3. Distribution of nano-Ag (realistic and probable applications) (a) and PLGA (b) to final sinks. Total amount of nano-Ag 5,650 kg, and total amount of PLGA 48,000 kg.

for nano-Ag, PLGA, and the application-specific materials are shown in Table 2.

3.2. Flow diagrams

NBM flows from production, application to patients, and through to release into environmental compartments were modelled using the consumption data given in Table 2. The mean realistic and probable material flows for nano-Ag and PLGA applications are shown in Fig. 2 in kilograms per year, Q25 to Q75 values in parentheses. The flow diagram for nano-Ag only shows realistic and probable applications (i.e., applications either already on the market or likely to reach it soon). Flow diagrams considering realistic nano-Ag applications only (i.e., already on the market) and all nano-Ag applications (i.e., including applications unlikely to reach the market soon or at all) are shown in chapter 10 of the Supporting Information.

Flows leaving the system, e.g., via rivers or export, were not considered. Arrow thicknesses are proportional to the total amount of material input into the system, however, thicknesses between the different figures or subfigures are not comparable.

Nano-Ag (Fig. 2a) was considered in nine different realistic or probable applications, each with its own specific pathways through the technical and environmental compartments. Thus, there are many different flows into the environment. Even though nano-Ag from one application might mainly end up waste, nano-Ag from another application might stay predominantly in the body. Nano-Ag takes many different routes through the system. The majority of nano-Ag, however, ends up in landfill, as can be seen in Fig. 3a. Only 13% stay in the body and eventually end up in the crematorium or burial. Trace amounts end up in soil, surface and subsurface water, or are transformed during wastewater treatment.

Four different PLGA applications were considered. Because they are all drug delivery applications, there is one prominent flow: the transformation of PLGA inside the patient. One main reason why PLGA is an often-used material in nanomedicine is its decomposition into lactic acid and glycolic acid within around five weeks (Gentile et al., 2014). The body then metabolizes lactic and glycolic acids into water and carbon dioxide (Dinarvand et al., 2011), leaving no PLGA in the body after one year. As shown in Fig. 3b, 87% of PLGA does not even reach environmental compartments. The rest ends up in wastewater, where half is removed with the sludge and then applied to soil. Smaller amounts end up in surface and subsurface water or landfill.

The relative distributions of Fe_3O_4PEG-PLGA and PLGA through the system were exactly the same as they are both used for the delivery of cancer drugs. Their relative distributions into final sinks were, therefore, also the same (see Figs. 3b and 5a). However, during metabolisation inside the body or transformation during incineration, only the organic parts of Fe_3O_4PEG-PLGA will metabolize; the iron oxide will stay intact. As our system boundary only considered the initial parent material, the total amount of the material was considered as being transformed, even though only parts of the material are actually affected. Depending on the organic content of the NBM, up to 290 kg iron oxide would stay in the bottom ash during incineration and end up in landfill.

MgHA-collagen (Fig. 4b) is used in bone tissue engineering and stays in the body. Therefore, the most prominent flow is into corpses and from there either to burial (40%) or cremation (48%). The organic part will be destroyed during cremation, which is thus not a final sink but a flow to transformation. A smaller amount is discarded before application in the body and ends up in landfill (3%).

PLLA-Ag (Fig. 4c) is used in wound dressings. Here, the NBM does not enter the body and, therefore, there is no flow into corpses. Wound dressings are discarded after use and end up in the waste stream, which is the most prominent flow for PLLA-Ag. Waste is then incinerated, destroying the PLLA but not the nano-Ag. Here, everything was modelled as being transformed because the material is not the initial material anymore. However, the nano-Ag would remain intact and end up in bottom ash, amounting to around 3,800 kg of nano-Ag.

3.3. Worst-case predicted environmental concentrations

wc-PECs are shown in Table 3 as means with upper and lower quantiles (Q25 and Q75) in parentheses. The concentration of all NBMs is highest in sludge, followed by biosolid-treated soil and sediments. PLGA showed the highest concentrations in all compartments except natural and urban soil. Nano-Ag was the only NBM evaluated with a release to natural and urban soil. PLGA, Fe_3O_4PEG-PLGA, MgHA-collagen, and PLLA-Ag showed no wc-PECs to natural and urban soils as NBMs are only deposited there from the air. Release to air happens either during waste incineration or cremation. As these are all partly organic materials, they will be destroyed at such high temperatures and no release to air will occur, and thus no deposition on soils can occur.

3.4. Relative uncertainty

The relative uncertainties of the NBM flows between different compartments were calculated by dividing the standard deviations of the probability distributions by their respective means, as previously done by Adam et al. (2018). A figure showing the uncertainties for these different flows can be found in chapter 10 of the Supporting Information. The uncertainties for PLGA and Fe_3O_4PEG-PLGA were both very high for flows into landfill, surface and subsurface water, and soil; only their flows into elimination showed low relative uncertainty. The

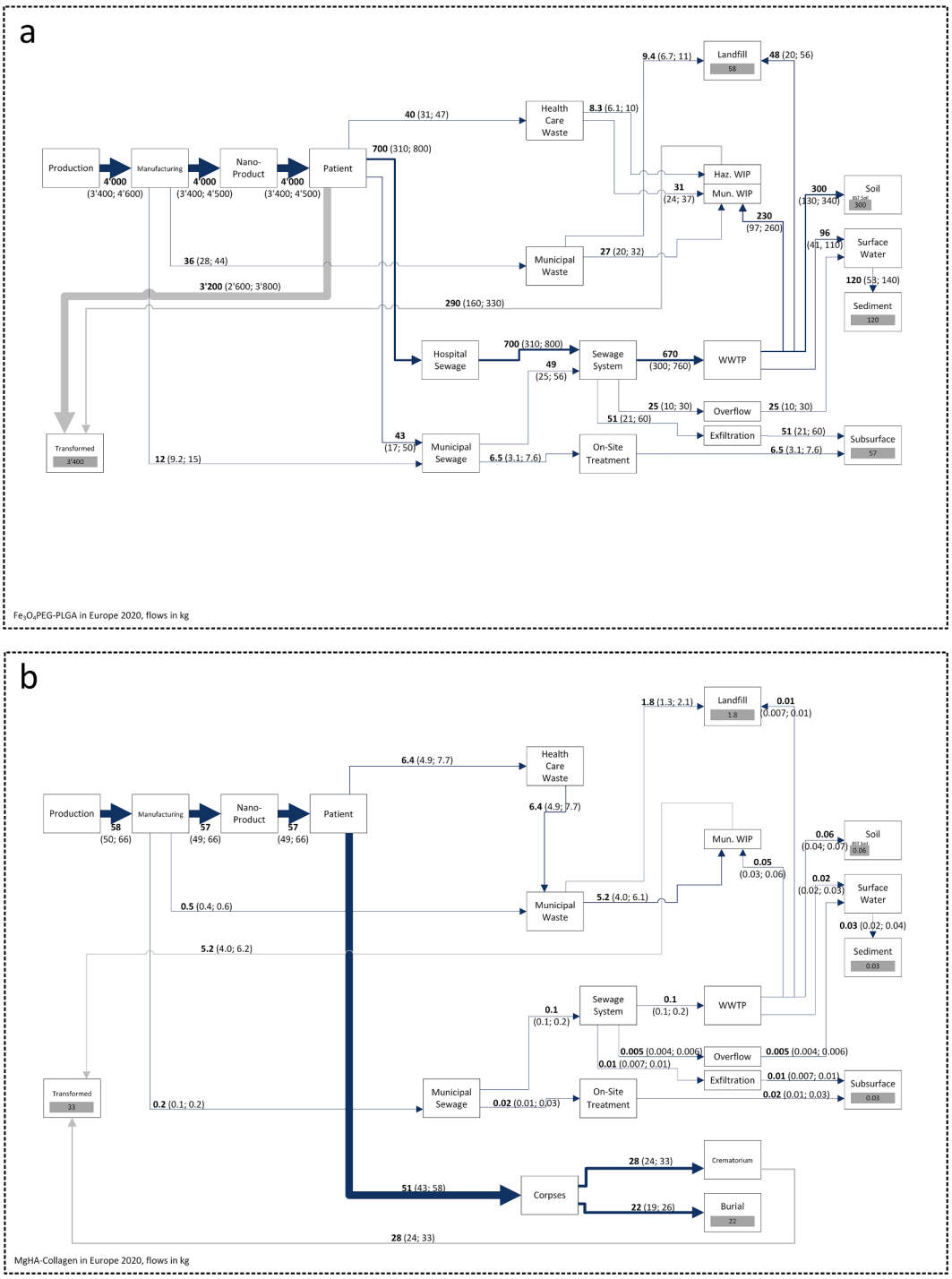

Fig. 4. Flow diagrams for the three application-specific materials: Fe_3O_4PEG-PLGA used in drug delivery (a), MgHA-collagen used in bone tissue engineering (b), and PLLA-Ag used in wound dressings (c) in Europe assuming full market penetration of the considered applications (flows in kg). Bold: mean flow; In parentheses: Q25;

uncertainties for these two materials were the same because both are used for drug delivery and, therefore, the same transfer coefficients were used. Nano-Ag, MgHA-collagen, and PLLA-Ag all showed very low relative uncertainties for all flows. MgHA-collagen and PLLA-Ag are only used for single applications with well-defined flows, resulting in low relative uncertainties.

4. Discussion

The first result that stands out when looking at the distribution of NBMs into different compartments is that they are very different depending on their application. Each application has its own unique distribution. For example, NBMs used in wound dressings are predominantly eliminated during incineration, whereas NBMs used in bone tissue engineering mainly remain in the body and are subsequently either buried or cremated. Thus, NBMs cannot just be lumped into one category but should always be evaluated separately and according to their application.

Of all the NBMs considered here, PLGA generally showed the highest concentrations in all compartments. This accords with the prospective production volumes estimated using the explorative full-market-

Q75. WWTP: wastewater treatment plant, MWIP: municipal waste incineration plant, HWIP: hazardous waste incineration plant, N&U Soil: natural and urban soil, BST Soil: biosolid-treated soil.

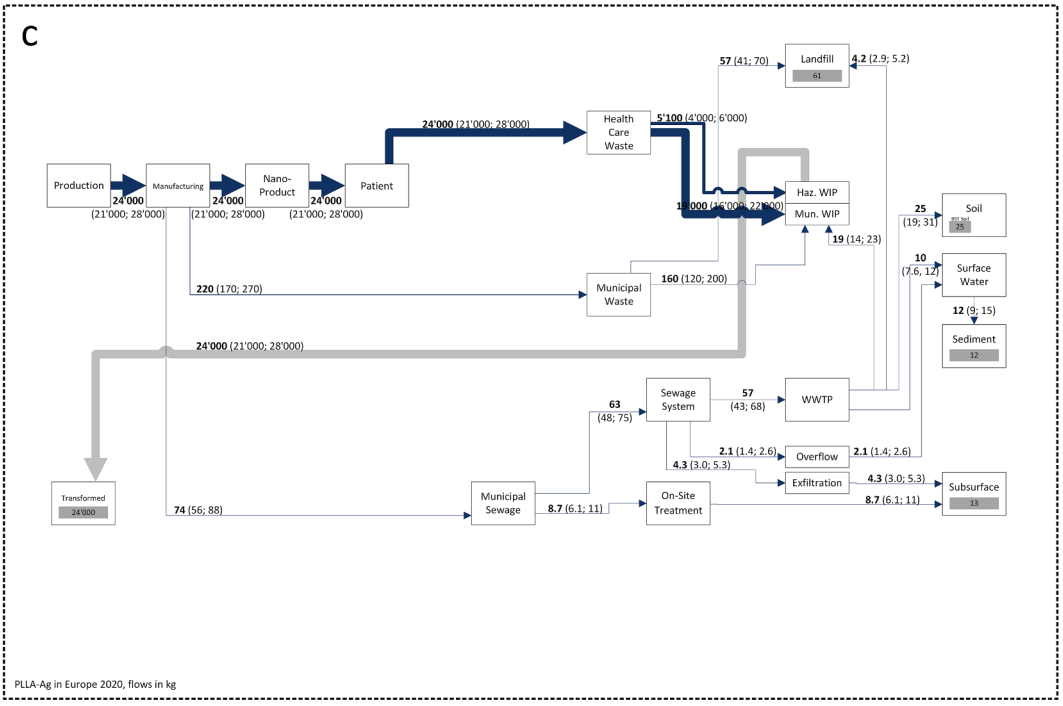

Fig. 4. (*continued*).

penetration scenario. PLGA has by far the highest potential production volumes of the NBMs evaluated here. Several other studies have also identified production volumes as an important factor for determining the magnitude of nanomaterial emission flows (Gottschalk et al., 2009; Wang, Deng, et al., 2016). The input volumes used here were calculated based on available research, but almost none of the applications considered is yet on the market. Therefore, although this work shows a current possible worst-case scenario, with the considerable research presently going on into the possible applications of NBMs in medical devices, this could change significantly in the near future. If more applications become available, the total input into different environmental concentrations will likely increase. However, it must be noted that our use scenario assumed the 100% market penetration of each NBM application considered. This is, of course, an oversimplifying assumption, and we must be aware that real production volumes will be much lower as other non-NBM applications will also remain on the market. The flows and wc-PECs presented in this work therefore constitute an upper boundary to what could be expected. Because the NBM market is changing quickly, there are large uncertainties regarding the market in five or even ten years. We therefore decided to assume a full-market-penetration scenario instead of extrapolating current data into the future, which would have led to even greater uncertainties than already exist now. Additionally, this work only shows the flows of realistic and probable applications, i.e., those already on the market or likely to reach it soon. Flows from unrealistic applications, such as using nano-Ag in drug delivery, are only shown in the Supporting Information because it is unlikely that they will reach the market soon or even at all.

Nine different realistic and probable nano-Ag applications were identified, but the total consumption volume is dominated by wound dressing and bone cement applications, constituting 65% and 30% of total nano-Ag consumption, respectively. The seven other applications only account for 5% of total possible consumption. Wound dressing and bone cement applications should receive the most attention with regards to their release and possible environmental impact. However, as the former are almost all thrown away as waste and the latter stay in the body, both applications have a low potential for release into the environment.

Previously, MFA studies for nano-Ag had only been conducted to

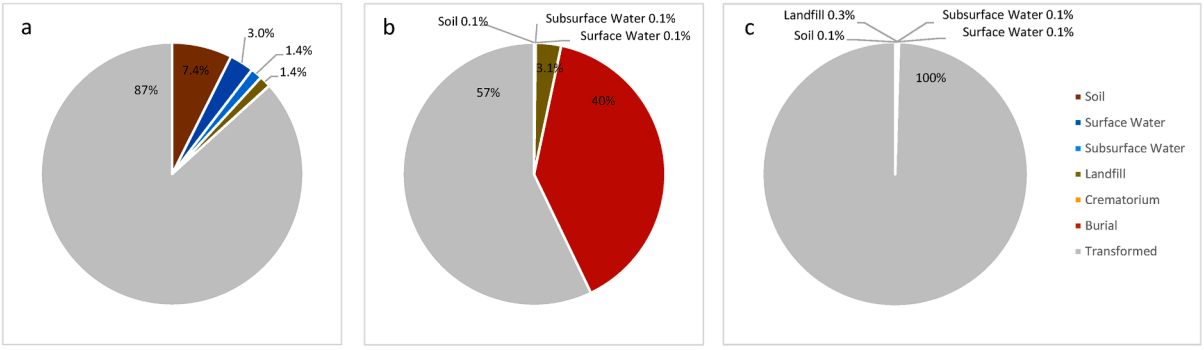

Fig. 5. Distribution of Fe_3O_4PEG-PLGA (a), MgHA-collagen (b), and PLLA-Ag (c) to final sinks. Total amount Fe_3O_4PEG-PLGA 4,000 kg, total amount MgHA-collagen 58 kg, and total amount PLLA-Ag 24,400 kg.

Table 3
Worst-case predicted environmental concentrations in different technical and environmental compartments. Shown as mean and Q25 and Q75 in parentheses. NA means no release to this compartment.

	nano-Ag (realistic & probable)	PLGA	Fe_3O_4PEG-PLGA	MgHA-collagen	PLLA-Ag
Natural & Urban Soil [pg/kg]	110 (85; 130)	NA	NA	NA	NA
Biosolid-treated Soil [ng/kg]	2.2 (0; 3.6)	4,800 (2,100; 5,500)	400 (180; 460)	0.08 (0.06; 0.10)	34 (25; 41)
Surface Water [pg/l]	12 (8.7; 14)	3,700 (1,600; 4,300)	310 (140; 360)	0.08 (0.06; 0.09)	32 (24; 39)
Sediments [ng/kg]	4.4 (3.3; 5.3)	1,400 (610; 1,600)	120 (52; 140)	0.03 (0.02; 0.04)	12 (9.1; 15)
WWTP effluent [pg/l]	18 (13; 22)	38,000 (16,000; 44,000)	3,200 (1,400; 3,700)	0.83 (0.60; 1.0)	350 (250; 420)
Sludge [µg/kg]	0.2 (0; 1.3)	400 (170; 460)	33 (14; 38)	0.007 (0.005; 0.008)	2.9 2.1; 3.4)

calculate their emissions into the environment. Sun et al. (2016) used a dynamic model to calculate nano-Ag flows from every available application in Europe. Although the production volume considered in this work of 50.1 tons/y is almost ten times larger than the predicted full-market-penetration scenario for NBMs, their calculated environmental concentrations were 100 to 40,000 times higher than what we calculated. Sun et al.'s (2016) concentrations for surface water and WWTP effluent were around 100 times higher than ours, and their concentrations for sediments was almost 40,000 times higher. Some applications considered in their study, such as paints, release nano-Ag directly into the environment during the use phase, which is something that does not occur in NBM releases. The increased use of nano-Ag in medical devices, therefore, should not considerably increase environmental concentrations of nano-Ag. Caballero-Guzman and Nowack (2018) used a similar approach to compare the potential emissions from future nanomaterial applications to existing flows of the same material. They investigated a wood coating containing CuO, a car bumper containing the organic pigment DPP or Fe_2O_3, polymeric car parts containing carbon nanotubes (CNT), and pancake mixture containing SiO_2. Only the use of the wood coating with CuO predicted an increase in the total flows of that material into the environment. As with the nano-Ag investigated in the present work, none of their other applications resulted in increased releases into the environment.

Our model did not distinguish between the different NBM surface coatings. In nanomedicine, nanomaterial coatings are very common, e.g., to avoid macrophage uptake (Weissleder et al., 2005). There is a wide range of different coatings available, but even for uncoated nanomaterials, data for many steps in their life cycle are rare. Our assessment therefore only considered generic nano-Ag and PLGA materials, not different coatings or functionalizations. By using a probabilistic-model approach, we managed to include the uncertainties about the coating's behavior to a certain extent. Once more data become available, this shortcoming should be corrected and specific MFAs for specific materials could be elaborated.

Our work was also unable to consider the different potential forms of excreted NBMs, and all of the material that ended up in the environment was considered to be in its original nanoparticulate form. It would, of course, be very useful to know the different forms of the materials released as this information would contribute to our knowledge of the behavior and toxicity of those materials in the environment (Adam et al., 2018). Once again, no data were available on the form of the NBMs released during use or from the human body (Hauser and Nowack, 2019).

However, more form-specific models could be developed for application-specific composite materials, i.e. models for one specific form of an NBM with a particular coating or part of a specific nanocomposite. The present work only evaluated flows of the initial materials and labelled them as transformed as soon as parts of the composite material were transformed, mainly after incineration of the composite's organic part. A more form-specific approach could give more insight into the flows of the transformed material parts, e.g., such as after incineration, when only the inorganic parts of the material remain. However, it is important to include these coating or matrix transformations in further risk assessments of the specific NBM because hazard and exposure data need to be available for the same nano-form. Hazard data from the pristine nano-form should not be used to obtain conclusions on the hazard of the transformed form.

During incineration, we assumed that organic materials would be destroyed completely. Müller et al. (2013) assumed that 94% of CNTs would be destroyed during incineration; the remaining 6%, mainly incorporated in other materials, would therefore not be destroyed because CNTs can be stable in the absence of oxygen even at temperatures above 1000 °C (Sobek and Bucheli, 2009). The organic materials evaluated in the present work, however, can be completely pyrolyzed and destroyed at prevailing furnace temperatures. Additionally, only data on the behavior of nano-CeO_2, nano-$BaSO_4$, and nano-TiO_2 (Oischinger et al., 2019; Walser et al., 2012; Quicker and Baran, 2017) inside waste incinerator plants are available. No data for nano-Ag is available and thus we have assumed that nano-Ag would behave in the same way as other metallic nanomaterials. This is an oversimplification as nano-Ag might melt during incineration and aggregate into larger particles. If this were the case, the release of nano-Ag into air would be smaller than we predicted. Because the present study attempts to establish an upper boundary for the amount of NBMs which could be released, we deemed this simplification acceptable.

Another simplification to the model was the assumption that non-pretreated hospital wastewater is treated together with domestic wastewater. Again, no data on any possible pretreatment was available in the literature. Besides, most municipal WWTPs employ a tertiary treatment step, which almost completely removes NBMs. Thus an additional pretreatment at the hospital would likely not significantly change the release into the effluent.

In general, waste treatment varies significantly between different countries, and we used average values whenever possible. We decided against focusing solely on countries where more data on waste treatment were available. No large flows of NBMs are modeled from waste treatment into the environment, therefore, we believe that using averaged European values represented the most robust input values.

One process which would likely decrease environmental concentrations of NBMs in environmental compartments was omitted from the present model: environmental fate. We only provide worst-case PECs, which do not include the fate processes inside environmental compartments, such as agglomeration, dissolution, or biodegradation. For example, PLGA has been used in medical devices, especially for its property of fast metabolization. Depending on the ratio of lactic to glycolic acid, PLGA has been shown to metabolize in the body in one to four weeks (Gentile et al., 2014). Similar metabolization or other fate mechanisms could also occur in the environment, causing a decrease of PLGA in environmental media. Our wc-PECs calculated are therefore a worst-case scenario and actual concentrations in the environment are likely to be smaller. The wc-PECs given for water and sediments also constituted another worst-case scenarios with no or complete sedimentation, respectively. The wc-PECs that we provided for technical and environmental concentrations could be used as input values for more sophisticated environmental fate models incorporating processes such as agglomeration and sedimentation.

The model presented here only considered a time span of one year and did not consider accumulation over time, as other recent models have (Sun et al., 2016; Bornhöft et al., 2016). A dynamic model is useful if NBM production trends are observable over time. However, the NBM

applications we considered were in early developmental stages and some are unlikely to reach the market in the near future. A dynamic model was not deemed appropriate, therefore, as the basic production and use data contained too much uncertainty. Using a dynamic model would indicate a level of certainty in the data that is not currently available. Using a probabilistic model that predicted a realistic worst-case scenario was the best way to represent current certainties and data availability.

Emissions during production and manufacturing were also considered and were assumed to be released evenly throughout Europe. However, the production of a certain medicinal product may be concentrated in a few factories or even a single site. Release from production and manufacturing is likely far more concentrated than release from the use stage in thousands of hospitals (Larsson, 2014). Furthermore, the waste and wastewater treatment differs from country to country; we assumed European averages for these transfer coefficients. One major difference between different European countries is their sewage sludge handling. Countries applying high proportions of sewage sludge to their soil will have much higher concentrations of NBMs in sludge-treated soil than countries which mainly incinerate their sewage sludge. To get a better understanding of country-specific or even local emissions, a more localized model would be necessary. Nevertheless, given the significant uncertainties in many of the model's underlying parameters, a Europe-wide evaluation of NBMs can be considered a first step towards highlighting critical materials and the compartments most affected by them.

To validate an emission model and evaluate its accuracy, modelled flows into the environment are usually compared to measured data. However, this is a critical aspect for all models predicting flows of engineered nanomaterials to the environment (Nowack et al., 2015). Current analytical methods and measurements are not yet sensitive and specific enough to be useful in exposure model validation. To date, measurements and models have provided different answers. Modeling and measurements can provide an different view of nanomaterials: modeling can provide estimates of the presence of nanomaterials in environmental compartments, whereas analytical measurements can provide physical characterizations of those nanomaterials, thus giving a suggestion of what the total nanomaterial concentration might be. There is one additional aspect to reflect on: we considered only very specific applications of particular nanomaterials used as NBMs, yet nano-Ag, for example, is not only used in medical applications, but also in a range of other commercial applications such as in plastics, cosmetics, paints, metals, and consumer electronics (Sun et al., 2014). In the environment, it is impossible to distinguish between the NBMs modelled in our present work and those originating from other applications. Our modelled data could therefore not be compared to measured data for the same NBMs even if such analytical data were available. Secondly, most of the applications considered here are still in the developmental phase and not yet on the market. Our model predicts possible future emissions which cannot be measured yet. MFAs nevertheless remain important for establishing where nanomaterials released into the environment might have come from. Once the source has been established, efforts can be made to reduce NBM emissions. Our model gives an insight into whether NBMs might pose a problem in the future, once their applications reach the market.

The wc-PECs provided in the present work could serve as a starting point for environmental risk assessments of these NBMs, with their toxicological threshold values—usually a predicted no-effect concentration (PNEC)—being compared to their predicted environmental concentrations. As a starting point, the present study's wc-PECs could be approximated as PEC values and compared to existing PNEC values for NBMs. Hauser et al. (2019) performed a hazard assessment of polymeric NBMs used for drug delivery. They searched the literature for data on chitosan, hydroxyapatite, polyacrylonitrile, PLGA, polylactic acid, and polyhydroxyalkanoates, but they could only obtain soil or freshwater data for the first three materials. To the best of our knowledge, no ecotoxicological tests have been performed on PLGA, polylactic acid, or polyhydroxyalkanoates. Using the PNEC for polyacrylonitrile—the NBM with the greatest resemblance to PLGA—and comparing it with our calculated wc-PEC for surface water and soil, its environmental risk quotients are extremely low, at 10^{-12} for freshwater and 10^{-8} for soil. Thus, polyacrylonitrile's environmental risk could be regarded as insignificant, even for this prospective worst-case scenario.

5. Conclusions

In this study, we used an explorative full-market-penetration scenario to calculate the potential flows of two promising NBMs (nano-Ag and PLGA) and three application-specific composite materials into the environment. We found that an NBM's application played an important role in its distribution to different technical and environmental compartments. We conclude that estimates of NBM releases to the environment cannot be generalized but instead require an evaluation for each individual application. We also compared releases of nano-Ag from medical applications with releases of nano-Ag from commercial applications, and we calculated that nano-Ag used as an NBM would not significantly increase concentrations of nano-Ag in the environment. Because PLGA is an organic material, it will be metabolized within the human body in weeks and will most likely cause no significant exposure in the environment. However, as NBMs are mainly used in hospitals, and these locations are concentrated in densely populated areas, NBM-release hotspots could be created. Classifying such hotspots could be the topic of a future study. The use of NBMs is very likely to increase as new applications emerge in the future, and this will likely lead to increased releases into the environment, no doubt necessitating updated release assessments in the near future.

Author contributions

MH collected, prepared, and evaluated the input data. MH also ran the model, created the figures and tables for the manuscript, and wrote the manuscript. BN supervised the study, gave inputs on the data and the model, and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Model availability

The codes are available at https://zenodo.org/record/4040435#.X4_crdAzaM8.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106184.

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