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Human health characterization factors of nano-TiO_2 for indoor and outdoor environments

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Abstract
Purpose The increasing use of engineered nanomaterials (ENMs) in industrial applications and consumer products is leading to an inevitable release of these materials into the environment. This makes it necessary to assess the potential risks that these new materials pose to human health and the environment. Life cycle assessment (LCA) methodology has been recognized as a key tool for assessing the environmental performance of nanoproducts. Until now, the impacts of ENMs could not be included in LCA studies due to a lack of characterization factors (CFs). This paper provides a methodological framework for identifying human health CFs for ENMs.
Methods The USEtox™ model was used to identify CFs for assessing the potential carcinogenic and non-carcinogenic effects on human health caused by ENM emissions in both indoor (occupational settings) and outdoor environments. Nano-titanium dioxide (nano-TiO_2) was selected for defining the CFs in this study, as it is one of the most commonly used ENMs. For the carcinogenic effect assessment, a conservative approach was adopted; indeed, a critical dose estimate for pulmonary inflammation was assumed.
Results and discussion We propose CFs for nano-TiO_2 from 5.5E−09 to 1.43E−02 cases/$kg_{emitted}$ for both indoor and outdoor environments and for carcinogenic and non-carcinogenic effects.
Conclusions These human health CFs for nano-TiO_2 are an important step toward the comprehensive application of LCA methodology in the field of nanomaterial technology.

Keywords Characterization factor · Exposure factor · Fate factor · Human toxicity factor · Intake fraction · Life cycle assessment (LCA) · Life cycle impact assessment (LCIA) · Titanium dioxide nanoparticles

1 Introduction

Engineered nanomaterials (ENMs) face increasing scrutiny for their potentially adverse effects on human health and the environment (Klaine et al. 2008; Krug and Wick 2011; Kahru and Ivask 2013). The release of ENMs into the environment could occur at any point in their life cycle: during their manufacture, use and end-of-life phases (Som et al. 2010). Nanoparticles may become a risk or danger if the hazard that they pose (in the form of their toxic effects) becomes a reality via exposure (due to their release and presence in the environment). Life cycle assessment (LCA) has been recognized and adopted as an essential tool for analyzing, evaluating, understanding and managing the environmental and health effects of ENMs (Hischier 2014). To date, only a few LCA case studies on ENMs have been published (Miseljic and Olsen 2014). However, they failed to properly assess toxic impact

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categories as per the ISO 140040-44 standard (Hischier and Walser 2012). This was mainly due to the lack of inventory information about the release of nanoparticles into environmental compartments and the lack of characterization factors for ENMs for both humans and the environment (Hischier and Walser 2012). Until now, only two papers on aquatic ecotoxicity CFs have been published: one for carbon nanotubes (Eckelman et al. 2012) and one for nano-TiO_2 (Salieri et al. 2015). No such factors have been proposed in the field of human toxicity—the determination of CFs for this toxic impact category seems imperative. The present paper proposes a first attempt at calculating CF for nano-TiO_2 for human health studies. The approach chosen was to combine a nano-specific fate model (SimpleBox4Nano, SB4N), developed outside the LCA framework, with the consensus model for the assessment of toxicological impacts, i.e. the USEtox™ model. For fate and exposure assessments, we suggest using nanoparticle categories based on different size ranges; these are based on those defined by the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) that propose a tiered approach with three defined categories (category 1, size >500 nm; category 2, 500 nm > size > 100 nm; category 3, 100 nm > size > 1 nm) (SCENIHR 2010). Few multimedia fate models dealing with nano-specific fate processes have been published (Meesters et al. 2014; Praetorius et al. 2012; Arvidsson et al. 2011; Garner and Keller 2014). The approach proposed above is applied to nano-TiO_2—a material widely used in a variety of different applications, such as self-cleaning and anti-fogging materials, photocatalysis, dye-sensitized solar cells, gas sensors, optical fibres, rubber, biomedical devices and a wide variety of consumer products ranging from cosmetics to textiles (Xu et al. 2014). Nano-TiO_2 is also the ENM expected to found in the highest environmental concentrations (Sun et al. 2014). Because nano-TiO_2 is so widely used, several toxicologists and scientific regulatory bodies have expressed their concerns regarding its potentially adverse health effects (Shi et al. 2013; Iavicoli et al. 2011).

2 Methods

The USEtox™ framework was applied to calculate the CF for nano-TiO_2 for the human toxicity impact category. USEtox™ defines the CF as a quantitative representation on how hazardous a substance is or impact potential related to the emission of a mass unit of a pollutant (Henderson et al. 2011). It is calculated as Eq. (1):

$$CF = FF*XF*EF*SF \quad (1)$$

The equation takes into account the fate factor (FF), exposure factor (XF) and effect factor (EF) of the emitted substance (Rosenbaum et al. 2008, 2011), together with its severity factor (SF), in order to obtain the endpoint characterization factor (Huijbregts et al. 2005). The FF and XF are aggregated into the so-called intake fraction (*iF*) [$kg_{intake}/kg_{emitted}$]. The EF can be interpreted as the increase in the number of cases of a given morbidity (e.g. cancerous or non-cancerous diseases) risk, in the exposed population, per unit mass ingested or inhaled [$cases/kg_{intake}$] (Rosenbaum et al. 2007). The CF can then be measured either in (disease) $cases/kg_{emitted}$ or as damage in disability-adjusted life years ($DALY/kg_{emitted}$) (Hofstetter 1998). DALY characterize severity by taking into account both mortality (years of life lost (YLL) due to premature death) and morbidity (years lived with disability (YLD)). It is calculated as DALY = YLL + YLD. In order to calculate damage in $DALY/kg_{emitted}$, we must add the severity factor (SF)—representing an increase in adversely affected life years as a consequence of an emission into the environment (Rosenbaum et al. 2007).

Despite oral and dermal exposure having been identified as the main routes for consumer exposure (Shi et al. 2013; Wang and Fan 2014), inhalation is likely to be the most relevant route of exposure to nano-TiO_2, especially in occupational settings (Shi et al. 2013). For this reason, the present study only considered inhalation exposure. Indeed, the majority of studies on TiO_2 address exposure of the lungs, as these have been identified as primary target organs for ENP exposure via inhalation in occupational settings (Wang and Fan 2014). Studies performed on pulmonary exposure to TiO_2 show that toxicity is primarily dictated by particle size and crystal structure: decreasing particle size and anatase forms of TiO_2 enhanced particle toxicity (Mikkelsen et al. 2011).

For indoor environments, a single-compartment box is recommended as the default model for LCA; this enables occupational and household exposure to be screened consistently against the existing models to assess outdoor emissions in a multimedia environment (Hellweg et al. 2009). For an outdoor *iF*, the present study also used a multimedia box model to account for the FF calculation for assessing the environmental fate of the ENM; the model considers all the transport and removal processes occurring in and across environmental media. Specifically, the SB4N multimedia model, developed by Meesters and co-authors (Meesters et al. 2014), was the model used here.

2.1 Intake fraction

2.1.1 Indoor intake fraction

To date, the health effects due to *indoor* exposure to ENMs have generally been neglected in LCA. However, this

omission is a significant shortcoming, as it may result in product or process optimization at the expense of workers' or consumers' health (Hellweg et al. 2009). The principal means of testing exposure to nano-TiO_2 in an occupational setting is via the respiratory route, as it is for other dusts. Here, the occupational setting was based on an indoor environment. Occupational indoor exposure was assessed as the corresponding indoor intake fraction (iF_i) and calculated using the formula proposed by Humbert et al. (2011) for defining the intake fraction for particulate matter:

$$iF_i = \frac{INH*POP_i}{V_i*m*k_{ex}} \quad (2)$$

where i is the index for the indoor (environment), INH is the daily inhalation rate of a male worker (a constant volume of 2.5 m^3/h, Hellweg et al. 2009), POP_i is the number of workers exposed, V_i is the indoor building volume (m^3), k_{ex} is the air exchange rate of the building volume in the exposure area, and m (unitless) is the mixing rate (defined as the abundance of one component of a mixture relative to that of all other components). For an industrial, occupational setting, the air exchange rate value of 10 h^{-1} represents ten changes of air volume per hour and m is set to 0.5 (see USEtox™ Model, version 1.10 beta 2013). Hence, to evaluate occupational exposure using volume per person ($V_{i\ \mathrm{person}}$) in an industrial building, we can use the ratio between V_i and POP_i (Eq. S1, Electronic Supplementary Material).

2.1.2 Outdoor intake fraction

The human outdoor intake fraction (iF_o) is calculated according to the USEtox™ methodology, using the chemical fate, also termed the fate factor (FF), and the human exposure factor (XF) (Fig. 1). The FF describes a chemical's fate in the environment, by taking into account environmental pathways for its removal, degradation and transport in and across environmental media. Portioning coefficients are used to describe the environmental fate and behaviour of organic chemicals; they are not valid for describing and quantifying the fate and behaviour of ENMs (Praetorius et al. 2014). Instead, for modelling the fate and behaviour of ENMs in environmental compartments, current practice uses first-order rate constants (k, day^{-1}) (Praetorius et al. 2012; Meesters et al. 2014; Liu and Cohen 2014). In this way, the FF can be calculated by applying the SB4N model's framework (Meesters et al. 2014). This is a multimedia box model, at steady state, where the transport and removal processes in and between environmental media are described by taking into account nano-specific processes (such as aggregation, attachment or dissolution) and are calculated as first-order rate constants (k, day^{-1}). Furthermore, the model takes into account the fact that an ENM (nano-TiO_2) can occur in different physicochemical forms, e.g. as free dispersive species, as hetero-agglomerates together with natural colloids, or attached to larger natural particles. The rate coefficients for nano-TiO_2 (radius of 10 nm, density of 4230 kg/m^3, Switzerland as a geographic unit: Table S1, Electronic Supplementary Material) proposed by Meesters were used to build our rate coefficient matrix $\overline{K}$ (day^{-1}) (Table S2, Electronic Supplementary Material) and subsequently to establish our FF matrix $\overline{FF}$ (Table S3, Electronic Supplementary Material). Next, iF_o can be calculated as follows (Rosenbaum et al. 2011):

$$\overline{iF}_o = \overline{FF}*\overline{XF} \quad (3)$$

The XF vector is calculated by considering Switzerland's population and the volume of air up to an altitude of 1000 m

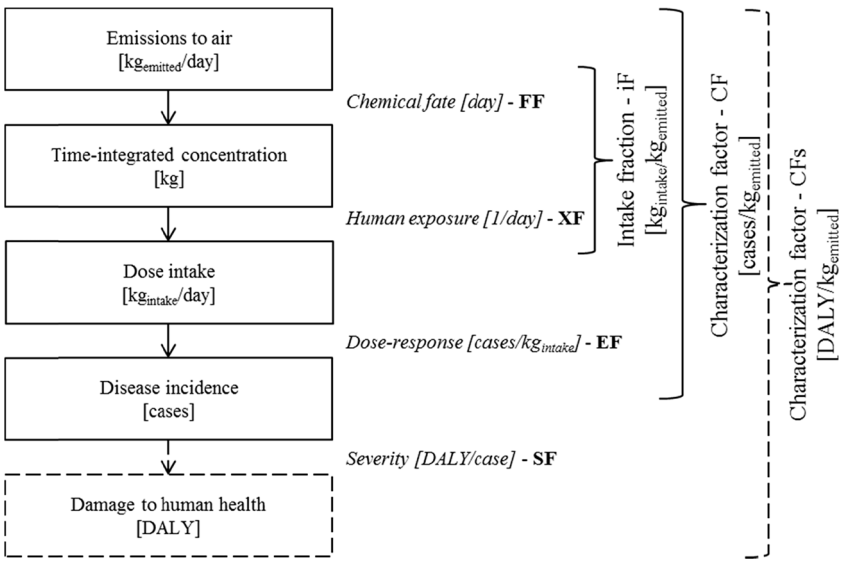

Fig. 1 USEtox™ framework for the assessment of human health impacts (Rosenbaum et al. 2011)

(for details, see Eq. S2, Electronic Supplementary Material). As this study focuses on direct human exposure by inhalation, so the intake fraction calculation only takes into account the part of the FF matrix related to air. The iF_o was calculated by summing the aggregated, attached and free species of ENM in the air, following a realistic approach.

2.1.3 Nano-specific uptake fraction

Size plays a key role in ENM toxicity. Once inhaled, particle distribution by size can be observed throughout different regions of the respiratory tract, namely the nasopharyngeal, tracheobronchial and alveolar regions. Some 90 % of smaller particles (1 nm) are deposited in the nasopharyngeal region and 10 % in the tracheobronchial region. ENMs of around 20 nm deposit in the alveolar region (50 %), whereas particles in the range of 1–5 nm deposit in all three regions. Particles ranging from 0.5 to 10 μm remain on the epithelial surface of the airway and alveoli (Simkó and Mattsson 2010). The importance of accounting the particle uptake (i.e. the amount of particles retained in the lung) within the exposure model has been recently underscored by Notter 2015. Walser et al. (2015) recently provided rough estimations with which LCA practitioners can calculate deposition and retention fractions for the nasopharyngeal, tracheobronchial and alveolar regions. Their information can be used for a first estimation of the uptake fraction when an ENM is inhaled. The same authors suggested that life cycle impact assessment (LCIA) frameworks for human toxicity assessments of ENMs should look at the actual nanoparticle dose in the target organ (i.e. lungs) for local effects or in the entire human body for systemic effects. However, calculating an actual dose is still not an easy thing to do due to the lack of such key information as the mass of the target organ in which a toxic effect is observed and the total lung retention fraction of the ENM concerned. Thus, a first approximation of particle uptake (in the lungs) could be made by multiplying the intake fraction by the fraction of the particles retained (Notter 2015) (i.e. 0.030 is the fraction of ENMs retained in the 10–100-nm range; for more details, see Walser et al. 2015, Fig. 4). Thus, we calculate uptake as follows:

$$\text{Uptake} = \text{Intake}^{*}rf \tag{4}$$

where rf [−] is the alveolar retention fraction for a class of particle sizes (10–100 nm), with a value of 0.030 (Walser et al. 2015). The intake factors for both indoor and outdoor environments (iF_i and iF_o) can be multiplied by the retention factor (rf).

2.2 Effect factors for carcinogenic and non-carcinogenic effects

The human toxicological EF is calculated according to the methodology applied in the USEtox™ model, which accounts for both non-carcinogenic and carcinogenic effects. For carcinogenic effects, the EF is based on the $ED_{50h}^{lifetime}$, which is the estimated lifetime dose that would generate a 50 % increase in human cancers [kg/lifetime]. For non-carcinogenic effects, the $ED_{50h}^{lifetime}$ can be extrapolated from the *no-observed-adverse-effect level* (NOAEL, see Electronic Supplementary Material). To date, the information required by the USEtox™ model is not available in the literature. Therefore, in the present study, we considered the *benchmark dose* (BMD) for particle surface area dose (m^2) per gram of lung, to be the dose extrapolated by National Institute for Occupational Safety and Health (NIOSH) from the Bermudez et al. (2004) study. This particular dose is associated with a pulmonary inflammation response (PIR) in rats of 0.0144 $m^2/g_{[rat\ lung]}$. Here, this value has been assumed as a daily exposure dose. Moreover, an equal sensitivity of rat lung surface area and rat body has been postulated. Considering the rat body weight of 417 g and the rat lung weight of 1.44 g (NIOSH 2011), the PIR value becomes 4.97×10^{-5} $m^2/g_{[rat\ body]}$. The value taken from the study by Heinrich and co-workers (Heinrich et al. 1995), of 48 $m^2/g_{[TiO2]}$, was then used here as the TiO_2 specific surface area (SSA). The BMD is the model's best estimate of the effective dose (ED) (DPR MT-2 2004). The benchmark response level associated to the BMD is a bronchoalveolar lavage fluid (BALF) containing 4 % of polymorphonuclear leukocytes (PMNs)—measuring elevated levels of PMNs is how NIOSH assesses pulmonary inflammation. Based on all these, an ED_4 value for human health *carcinogenic effects* can be calculated as follows:

$$\text{ED}_4^{\text{rat,s-c,inhalation}} = \frac{\text{PIR}}{\text{SSA}} = 1.036 \quad \mu\text{g/kg bw/day} \tag{5}$$

Equations S3 and S4 (see Electronic Supplementary Material) are adapted using this ED_4 value; i.e. a 4 % (instead of 50 %) effect increase in cancer response to the administered dose is used to calculate the EF and $ED_{50h}^{lifetime}$ values (see Eq. S6 and S7, Electronic Supplementary Material).

2.2.1 Non-carcinogenic effects

Landsiedel et al. (2014) estimated a *no-observed-adverse-effect-concentration* (NOAEC) value for coated nano-TiO_2 of 0.5 mg/m^3 (in a short-term inhalation study on rats). Unlikely, this value cannot be applied in USEtox™ framework where a daily dose value is required (i.e. mg/kg bw/day). The conversion from a NOAEC to a NOAEL value required detailed information (such as the volume of air respired or deposition efficiency) that is not usually reported in toxicity studies. To the best of our knowledge, this conversion has never been performed. Thus, for *non-carcinogenic effects*, we took a NOAEL value of 62.5 mg/kg-body weight/day from sub-chronic (s-c) oral study on mice (SCCS 2013) in order to

calculate the $ED_{50}^{mice,s-c,inhalation}$ value and, consequently, the $ED_{50h}^{lifetime}$ value (Eq. S5 and S4, Electronic Supplementary Material). Due to the lack of toxicological data, we had to use a NOAEL value based on oral exposure. However, this may lead to a reduction in the accuracy of the EF calculation.

3 Results and discussion

3.1 Intake fraction

The indoor intake factor, iF_i, for indoor occupational exposure, was calculated according to Eq. S1 (see Electronic Supplementary Material) and then multiplied by *rf* (Eq. 4), to give 3.41E−05 unit less.

Walser et al. (2015) stated that for indoor particle number concentrations greater than 10^6 per cubic centimetre (such as a situation of accidental pollution), the homogenous agglomeration and gravitational settling of the particles should be taken into account. In this case, a steady-state airborne concentration (C_{ss}) of ENMs can be approximated in a CF calculation such that

$$C_{ss} = \frac{E}{V + \left(k_{ex} + \frac{v_{ts}}{h}\right)} \quad (6)$$

where E is the emission rate (number s^{-1}), V is the volume of the exposure area (m^3), k_{ex} is the air exchange rate of the volume in the exposure area (s^{-1}), h (m), and v_{ts} is the terminal settling velocity.

To date, only a few studies have been carried out to monitor workplace air quality in ENM production facilities (Walser et al. 2012; Lee et al. 2011; Kuhlbusch et al. 2011; Brouwer 2010). Lee et al. (2011) monitored potential exposure to nano-TiO_2 and nano-silver in workplaces where employees handle these nanomaterials. The study reported gravimetric concentrations of TiO_2 ranging from 0.10 to 4.99 mg/m^3, particle number concentrations between 11,418 and 45,889 particles/cm^3 and a size range from 15 to 710.5 nm during the reaction phase. However, concentrations decreased to 14,000 particles/cm^3 when the reaction stopped. To the best of our knowledge, this is the only study to have reported the number concentration of nano-TiO_2 particles in a manufacturing workplace. With regard to that study, by Lee et al. (2011), the present study did not include the C_{ss} in the iF_i calculation. However, this must be decided upon a case-by-case basis.

The human intake factor is largely dependent on the emission rate, the manufacturing specifications, indoor activities, nanoparticle characteristics and personal protective equipment. Thus, a robust evaluation of the intake fraction requires a case-specific analysis. The resulting value for the outdoor intake fraction, iF_o (Eq. S2, see Electronic Supplementary Material), calculated using the retention factor *rf* (Eq. 4), was 7.6E−07, and this was determined by summing all the values of the resulting *iF* vectors, which take into account free, agglomerated and aggregated particles. Indeed, there is significant evidence to show that ENMs agglomerate rapidly and that they attach to the background aerosol when released in the air. Thus, human exposure to ENMs via inhalation is likely to be a mixture of free, agglomerated and aggregated particles (these *iF* vectors and their corresponding XF vectors are reported in detail in Tables S4 and S5, Electronic Supplementary Material). The difference between the iF_i and iF_o is of two orders of magnitude. This difference is mainly due to the calculation of the fate pathway of nano-TiO_2 in the environment. Indeed, for the iF_i, the fate of ENMs is mainly described by the exchange rate and the mixing factor (Eq. S1, Electronic Supplementary Material). Thus, nano-specific environmental fate processes such as degradation, attachment, aggregation and sedimentation are neglected indoors, and only the ventilation and mixing of air have been assumed as primary removal pathways. For the outdoor scenario, however, the fate pathway describes the environmental fate processes of attachment, aggregation, sedimentation within media (i.e. aggregation and attachment with an aerosol in air) and sedimentation between environmental media (i.e. from air to freshwater). Hellweg et al. (2009) calculated a similar difference in terms of orders of magnitude between the iF_i and iF_o. They reported a difference of two orders of magnitude between the iF_i for occupational exposure in the chemical industry and the iF_o for chemical intake of outdoor urban air.

3.2 Effect factor

Calculating the EF is complicated by the lack of epidemiological studies and/or toxicological data that can be applied to the LCA framework. To date, knowledge of nano-TiO_2 toxicity comes largely from a limited number of experimental animal (in vivo) or cell culture (in vitro) studies. These have required extrapolation to human exposure and toxicity (for details, see Electronic Supplementary Material). In vitro toxicity assays have been widely used to study ENM toxicity via the analysis of major cellular parameters such as cell viability and response to various stress factors. However, there are no guidelines for extrapolating such in vitro results to human health effects. Furthermore, selecting the most suitable in vitro methods to provide results that can be used for hazard identification is still a challenge. Appropriate cell lines with the standardized cytotoxicity and technical criteria for in vitro test systems suitable for ENM assays have only recently been put forward as relevant for ENM hazard identification (Landsiedel et al. 2010; Hirsch et al. 2011; Farcal et al. 2015). To date, the most relevant data with which to assess the health risks facing workers are the results from a chronic animal inhalation study using ultrafine (<100 nm) TiO_2; this showed a statistically significant increase in adenocarcinomas (Heinrich et al. 1995). This

was supported by a TiO_2 study that induced a pattern of response of persistent pulmonary inflammation in rats and mice (Everitt et al. 2000; Bermudez et al. 2004) and cancer responses for particles that were linked to their surface area. NIOSH has determined that exposure to ultrafine TiO_2 (including engineered nanoscale TiO_2) should be considered as exposure to a potential occupational carcinogen. Although NIOSH concluded that ultrafine TiO_2 is not a direct-acting carcinogen, its action through a secondary genotoxicity mechanism is not specific to TiO_2 but primarily related to particle size and surface area (NIOSH 2011). Evidence suggests that surface area matters more than particle mass when quantifying the lungs' inflammatory response to nanoparticle exposure, and this supports the concept that surface area is the dose measurement that best predicts pulmonary toxicity (Donaldson et al. 2004; Wittmaack 2007).

Table 1 shows the EF values for both carcinogenic and non-carcinogenic effects in indoor and outdoor environments. The EF_i and EF_o values were calculated starting from Eqs. S6 and S7 (see Electronic Supplementary Material). The indoor environment calculation used an *N* value representing the number of working days per year (240 potential exposure days/year, Council Directive 1999) and an LT value of a working lifetime of 45 years (NIOSH 2011). For the outdoor environment, *N* and LT were set to 365 days/year and a 70-year lifespan, respectively, in accordance with the USEtox™ model. Extrapolation factors for interspecies differences for rats and mice (4.1 and 7.3, respectively) and the transformation from sub-chronic to chronic exposure were also taken directly from the USEtox™ model.

The main difficulty in assessing the EF is calculating the $ED_{50}^{a,t,j}$ values required by the USEtox™ model. Indeed, as discussed above, no standardized toxicity data of ED_{50} exists for nano-TiO_2 performed using in vivo animal studies. The extrapolation of in vivo data from in vitro assays could be used with specific methods such as physiologically based toxicokinetic (PBTK) models (Krishnan and Peyret 2009). However, the application of these models to nanomaterials is affected by a lack of primary data and understanding, which leads to the fact that the results obtained by PBTK models are currently not validated. These perceptions may explain why these modelling approaches have not received rapid regulatory acceptance (Bessems et al. 2014). Thus, in the present study, this kind of extrapolation was not chosen. Instead, based on the only available data about occupational exposure limits for nano-TiO_2, published by NIOSH, an ED_4 was extrapolated in order to evaluate carcinogenic effects. So far, in this study, we have chosen to use an ED_4 even if the value is not belonging to a cancer effect. However, we are aware that the ED_4 extrapolated from non-carcinogenic effects can be representative also for carcinogenic effect following a precautionary approach. Indeed, NIOSH specified that the 4 % PIR, used as the benchmark response here, might be rather low—and thus highly protective for workers—stating that a somewhat greater inflammatory response is probably required for tumour initiation. It is also possible that the 25-fold uncertainty factor applied to the critical dose estimate for pulmonary inflammation is overly conservative because pulmonary inflammation happens early in the sequence of events potentially leading to lung tumours. NIOSH states that pulmonary, inflammation-based threshold exposure concentrations are expected to entirely prevent the development of toxicity secondary to pulmonary inflammation, thus resulting in zero excess risk of lung tumours due to exposure to TiO_2. In contrast, lung tumour-based exposure concentrations are designed to allow a small, but non-zero, excess risk of lung tumours due to occupational exposure to TiO_2. Hence, NIOSH has concluded that it is appropriate to base recommended exposure limits for nano-TiO_2 on lung tumours rather than pulmonary inflammation (NIOSH 2011). Regarding non-carcinogenic effects, we chose the NOAEL value obtained from the Scientific Committee on Consumer Safety report (SCCS 2013) and then converted it into ED_{50} value, following the USEtox™ model. Hence, due to the lack of robustness of in vivo results, the EF calculation needs to be improved, and therefore, standardization of nano-TiO_2 toxicological data is urgently required.

3.3 Characterization factor

By combining the exposure, fate and effects factors as in Eq. 1, midpoint CFs (CF_i and CF_o) for human toxicity impacts, expressed in disease cases per kilogram$_{emitted}$ [cases/kg$_{emitted}$], can be calculated for both indoor and outdoor environments, as well as for carcinogenic and non-carcinogenic effects. The CF for carcinogenic effects is calculated by taking the ED_4 toxicity value (i.e. by using Eq. S7, Electronic Supplementary Material); the CF for non-carcinogenic effects is calculated by taking into account the NOAEL toxicity values.

Table 1 Effect factors for indoor and outdoor environments

Human health effect	Toxicity value	Ref.	$ED_4^{a,t,j}$	$ED_{4h}^{lifetime}{}_i$	EF_i	$ED_{4h}^{lifetime}{}_o$	EF_o
Carcinogenic	ED_4	NIOSH (2011)	$ED_4^{rat,s\text{-}c,inh}$	9.55E−05	4.19E+02	2.26E−04	1.77E+02
Human health effect	Toxicity value	Ref.	$ED_{50}^{a,t,j}$	$ED_{50h}^{lifetime}{}_i$	EF_i	$ED_{50h}^{lifetime}{}_o$	EF_o
Non-carcinogenic	NOAEL	SCCS (2013)	$ED_{50}^{mice,s\text{-}c,inh}$	2.91E+01	1.72E−02	6.89E+01	7.26E−03

Where *s-c* sub-chronic, *inh* inhalation, *i* indoor and *o* outdoor

The nano-TiO_2 toxicity data selected and applied to this study were extrapolated from the review by NIOSH (NIOSH 2011) for their carcinogenic effects and from the scientific opinion of the SCCS (SCCS 2013) for their non-carcinogenic effects. To date, toxicity experiments have been carried out on a wide range of nano-TiO_2's physicochemical characteristics. These studies are thus intrinsically non-homogenous in terms of the size, surface area and structural properties of the nano-TiO_2 tested. Moreover, the great barrier for interpretation of those studies is that they use non-standardized test systems, which does not allow extracting the real physical-chemical properties of nano-TiO_2, which determine toxicity.

Our literature search focused on studies reporting acute, chronic and carcinogenic effects and on studies reporting EC_{50} or NOAEC values. Nano-TiO_2 sizes ranged from 5 to 40 nm—even up to ultrafine particles. Thus, the EF calculated is quite far from the FF calculated in terms of the dimensions of nano-TiO_2 particles. This may limit the robustness of the CF calculation. In our opinion, it is still impossible to link FF and EF based on the same particle size dimensions, just as it is impossible using other metrics of toxicity. Furthermore, with regard to the current state of the art, the choice of exposure route is of greater relevance than the type of organism tested. For this reason, because inhalation is the primary exposure route and the lungs are the target organs, toxicity data applied to hazard identification should, if at all possible, be derived from inhalation studies.

If the severity factor (SF) is added to the equation, it is possible to obtain endpoint characterization factors (CF_{Si} and CF_{So}), expressed in damage per $kilogram_{emitted}$ [$DALY/kg_{emitted}$]. We are aware that the uncertainty of the characterization factor values may be diluted further by adding this factor (SF). Nevertheless, we wanted to introduce a methodological approach, although still approximate, that should be adopted to calculate endpoint CF values, as soon as the epidemiological data concerning the severity of nano-TiO_2 will be available.

We adopted the damage SFs for the carcinogenic effects leading to *trachea*, *bronchus* and *lung cancer* and for the non-carcinogenic effects leading to *respiratory diseases*, as proposed by Huijbregts et al. (2005). For non-carcinogenic effects, the damage SF was obtained in the same way as the average DALY, i.e. weighted by the incidence of cases of respiratory diseases, namely *chronic obstructive pulmonary disease* and *asthma*. Therefore, for carcinogenic effects, there were 16.5 DALY, and for non-carcinogenic effects, there were an average of 2.5 DALY. Table 2 shows the human health CFs identified for indoor and outdoor environments, including the severity step. The CFs are again split into carcinogenic and non-carcinogenic parts.

Garcia et al. (2014) calculated CFs for human toxicity for single- and multi-walled carbon nanotubes (SWCNT and MWCNT) following the USEtox™ framework. They calculated a human non-carcinogenic CF in urban air for SWCNT and MWCNT of 7.5E−05 and 2.5E−03 $cases/kg_{emitted}$, respectively. To the best of our knowledge, no other CFs for human toxicity for ENM have been published. Moreover, making comparisons between organic or inorganic substances and their bulk materials is quite hard. Indeed, ENMs exhibit different environmental behaviours and properties and, therefore, different environmental fate descriptors (Praetorius et al. 2014).

Notter (2015) has recently performed a similar approach in LCA field. The author published human CFs for human toxicity for PM2.5 and PM10 expressed in DALY per kilogram and equal to 2.97E−05 and 1.31E−5, respectively. Notter defined the CFs on the basis of the size and chemical composition of particulate matter. Due to the similarities, in terms of environmental processes (i.e. coagulation and sedimentation) and physical state (i.e. particles, although some are ENM and some PM), it may be possible to define a comparison. The comparison among the $CF_{S,o}$ for nano-TiO_2 (outdoor environment) here calculated and the CFs for PM2.5 and PM10 shows that the CFs for particular matter are two order of magnitude lower and three higher than the CFs for nano-TiO_2 for carcinogen and non-carcinogen effect, respectively. This difference is intrinsic in the EF calculation for carcinogen and non-carcinogen effects.

3.4 The continental scale (an outdoor environment)

The USEtox™ model uses two geographic scales: the *continental scale* (distinguishing between air, urban air, freshwater, coastal marine water, natural soil and agricultural soil) and the *global scale* (with air, freshwater, ocean, natural soil and agricultural soil only). The aim of this further step was to eval-

Table 2 Human health CFs for both indoor and outdoor environments and carcinogenic and non-carcinogenic effects

Human health effect	Indoor environment		Outdoor environment	
	CF_i [$cases/kg_{emitted}$]	$CF_{S,i}$ [$DALY/kg_{emitted}$]	CF_o [$cases/kg_{emitted}$]	$CF_{S,o}$ [$DALY/kg_{emitted}$]
Carcinogenic (ED_4)	1.43E−02	2.36E−01	1.34E−04	2.214E−03
Non-carcinogenic (NOAEL)	5.85E−07	1.32E−06	5.5E−09	1.24E−08

Where *S* severity, *i* indoor and *o* outdoor

uate how outdoor CFs vary when the system's dimensions (such as area, height and volume of atmosphere) are modified, that is, by changing the geographic area considered from Switzerland to the continent (Europe). To do this, the first-order rate constant values for environmental transport and removal processes in the Swiss scenario were extended to the *continental* scale. Thus, the geographic area (1.14 −E8 km^2) and the number of inhabitants (9.98−E8 people) of Europe have been considered for the continental scenario; Table 3 shows the resulting midpoint and endpoint CFs for outdoor emissions calculated for this continental scale.

However, the entire continental scale FF matrix could be improved by using more adequate transport and removal rates, particularly by considering distinct input parameters for such a geographic area (e.g. nano-TiO_2 radius, mass density, aggregation and attachment efficiency). The authors recommend to adopt the CF values reported in Table 2; the environmental transport and removal processes for nano-TiO_2 considered in the present paper represent the rates calculated for geographic area studied, i.e. Switzerland.

4 Conclusions

USEtox™ was chosen as our characterization model because it is the currently recommended model for defining impacts related to ecotoxicity and human toxicity in LCA (Sala et al. 2011; JRC-IES 2010). One of the present study's general assumptions was the use of a one-box model (indoor compartment), direct human exposure via inhalation and steady-state conditions. The parameters considered for the indoor model (e.g. room volume or air exchange rates) may vary geographically because of climate conditions, cultural aspects, different ventilation practices and so on. Furthermore, a more sophisticated model using indoor spatial differentiation could also be used, if specific information about the spatial distribution of pollution sources and people in the room was available (Hellweg et al. 2009). The present study calculated iF_o for the atmospheric compartment based on the human inhalation rate. In order to take into account the specific characteristics of nanoparticles, the FF was calculated using the SB4N multimedia model (Meesters et al. 2014). The resulting values for the continental scale are one order of magnitude lower than for the Swiss scenario. Nevertheless, the authors recommend using the values from the Swiss scenario because the rate coefficient values, which represent the environmental transport and removal rate processes for nano-TiO_2, are here calculated considering the geographic area of Switzerland. Any possible application of our approach to other ENM therefore requires the availability of their fate models in the environmental media.

Current evaluations of toxicity data assume that nano-TiO_2 is released in a pristine form or produces the same effects as pristine nano-TiO_2. This can be clearly the case for occupational settings, where ENMs are produced or nano-products manufactured. However, for environmental exposure, the majority of the nano-TiO_2 first has to be released from the applications or processes in which it is used. It has been shown that the nano-TiO_2 released from paints only contains a small fraction of free nanoparticles, with the major part still embedded in matrix particles (Al-Kattan et al. 2014); the nano-TiO_2 is thus not exposed to the surrounding medium. The TiO_2 released from paints was not found to be toxic to human cell lines (Kaiser et al. 2013), and it induced much lower effects than the pristine TiO_2 when administered to mice (Smulders et al. 2014). Further research will be necessary to establish whether this lower toxicity is also observed for particles released from other applications. Finally, the characterization factor for indoor release is two orders of magnitude higher than for outdoor release (for both carcinogenic and non-carcinogenic effects). A similar trend was observed when the characterization was performed up to the endpoint level, since the SFs only multiply the CF values for both carcinogenic and non-carcinogenic effects.

Overall, the present study represents a first attempt at modelling human toxicity characterization factors of nano-TiO_2. This work shows that, despite limitations, CFs for ENMs can indeed be calculated following the LCIA framework. However, nano-specific issues have to be included; the fate module requires improvement, by considering rate coefficients as descriptors for environmental fate processes, for example. At the same time, several gaps still exist in the toxicity assessment of ENMs. There is an urgent need for a database comprising the results of all the toxicological tests carried out on these materials—a comprehensive set of information useful for studying the potential risks associated with specific ENMs (Iavicoli et al. 2011). This makes the calculation of the EF extremely hard, and we are aware that the EF

Table 3 Continental USEtox™ scale: human health CFs for outdoor environments and both carcinogenic and non-carcinogenic effects

	Outdoor environment	
Human health effect	CF_c [cases/$kg_{emitted}$]	$CF_{S,c}$ [DALY/$kg_{emitted}$]
Carcinogenic (ED_4)	5.98E−06	9.87E−05
Non-carcinogenic (NOAEL)	2.45E−10	5.51E−10

Where *S* severity and *c* continental

calculated in this study will require updating once a correct and standardized ED_{50} and NOAEL values for carcinogenic and non-carcinogenic effects are finally available. For the future, the human toxicity CFs for nano-TiO_2 developed in the present study should be applied to existing case studies dealing with this material, e.g. for façade coatings (Hischier et al. 2015), chemical synthesis (Pini et al. 2015) or functionalized building materials (Pini et al. 2012, 2013, 2014). To date, the case studies involving chemical synthesis and functionalized building materials have only made preliminary attempts to assess the impacts of nano-TiO_2 release on human health. However, a comprehensive and well-structured LCIA framework is mandatory for a complete assessment of the human health effects caused by nano-TiO_2 emissions. Furthermore, ENM LCIAs should also take into account the recently published freshwater ecotoxicity CFs (Salieri et al. 2015). Taking all these potential impacts into account as well will allow researchers to build a more comprehensive picture and present a more accurate evaluation of the safe fields of application for nano-TiO_2.

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Compliance with ethical standards This manuscript, entitled "Human health characterization factors of titanium dioxide nanoparticles for indoor and outdoor environments," has been approved by all its authors. It has not been previously published, nor is it under consideration for publication elsewhere. No data or figures have been fabricated or manipulated to support our conclusions. No data or text prepared by others have been presented as if they were the authors' own. Hence, the submission declaration has been complied with.

Conflict of interest The authors declare that they have no conflicts of interest. This research involved no animals.

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