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Development of comparative toxicity potentials of TiO_2 nanoparticles for use in life cycle assessment

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Abstract

Studies have shown that releases of nanoparticles may take place through the life cycle of products embedding nanomaterials, thus resulting in potential impacts on ecosystems and human health. While several life cycle assessment (LCA) studies have assessed such products, only a few of them have quantitatively addressed the toxic impacts caused by released nanoparticles, thus leading to potential biases in their conclusions. Here, we address this gap and aim to provide a framework for calculating comparative toxicity potentials (CTP) for nanoparticles and derive CTP values for TiO_2 nanoparticles (TiO_2-NP) for use in LCA. We adapted the USEtox 2.0 consensus model to integrate the SimpleBox4Nano fate model, and we populated the resulting model with TiO_2-NP specific data. We thus calculated CTP values for TiO_2 nanoparticles for air, water and soil emission compartments for freshwater ecotoxicity and human toxicity, both cancer effects and non-cancer effects. Our results appeared plausible after benchmarking with CTPs for other nanoparticles and substances present in the USEtox database, while large differences were observed with CTP values for TiO_2 nanoparticles published in earlier studies. Assumptions, which were performed in those previous studies because of lack of data and knowledge at the time they were made, primarily explain such discrepancies. For future assessment of potential toxic impacts of TiO_2 nanoparticles in LCA studies, we therefore recommend the use of our calculated CTP.

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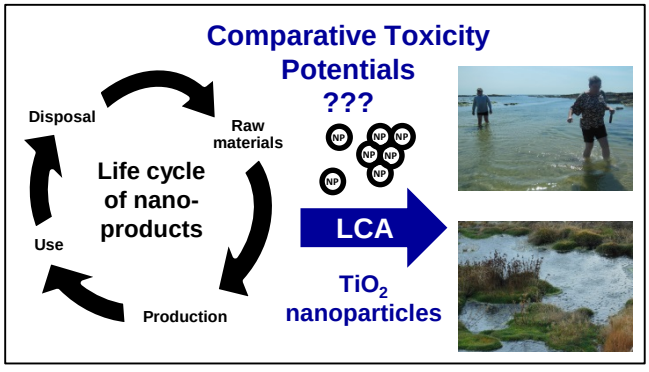

1. Introduction

Owing to their physicochemical properties, such as high surface areas and small sizes, nanomaterials have been increasingly applied in various commodities over the past decade, bringing optimized strengths and efficiencies compared to conventional products. When embedding nanomaterials in product matrices, their emissions might occur through the life cycle of the resulting nano-products.[1–4] Direct releases during the manufacturing of the nanomaterials may thus take place.[5] Likewise, depending on the type of location of the nanomaterial in the product matrices, e.g. suspensions in liquids or surface-bound, and on the type of handling, the use and disposal of the nano-products may also lead to potential releases of nanoparticles.[1,4,6] Several studies have reported the risks and potential impacts to humans and the environment that such releases may cause.[7–14] To comprehensively assess the environmental impacts of nano-products, it is therefore necessary to quantify the impacts on ecosystems and human health stemming from these releases over the entire life cycle of the nano-products.[2,3,15,16]

To address this need, the most prominent tool is life cycle assessment (LCA). LCA is a tool, which aims at quantifying all relevant environmental impacts of a product or system taken in its life cycle perspective, i.e. from extraction of the raw materials through its production and use up to its final disposal.[17] In practice, inventories of pollutant emissions aggregated over the system life cycle are translated into potential impact indicators using characterization factors from life cycle impact assessment (LCIA) methods. These LCIA methods rely on models describing the cause-effect chain from the emissions of a substance to its resulting impacts on ecosystems or human health. To characterize the impacts caused by the toxicity of emitted substances on freshwater ecosystems (termed “freshwater ecotoxicity” in the following) and human health (termed “human toxicity”), the European Commission’s International Reference Life Cycle Data System (ILCD) and the US Environmental Protection Agency recommended the USEtox model as best LCIA practice.[18–20] The USEtox model is a consensus-based model, which allows calculating globally-applicable

characterization factors or comparative toxicity potentials (CTP) for assessing freshwater ecotoxicity and human toxicity differentiated into cancer effects and non-cancer effects.[21,22]

To date, more than fifty studies have applied LCA to nano-products.[15,23] However, most of them have left out the assessment of potential impacts from released nanoparticles.[15,24] Until now, only twelve studies have investigated the characterization of toxic impacts caused by released nanoparticles. Among these studies, five addressed nanosilver and only accounted for the dissolved fractions thus neglecting potential impact of pristine particles.[25–29] Three studies focused on CTP for freshwater ecotoxicity of carbon nanotubes,[30] graphene oxide[31] and copper nanoparticles.[32] Four studies developed CTP for TiO_2 nanoparticles for freshwater ecotoxicity[28,33,34] and for human toxicity[35] (only for airborne emissions). Most of these studies focus on a specific toxic impact category and/or emission compartment, and none provides CTP for both ecotoxicity and human toxicity impacts and for all emission compartments (air, water, soil), all being necessary for the conduct of comprehensive LCA studies. Taken altogether, the four publications focusing on TiO_2 nanoparticles come close to cover all impacts and emission compartments; however, inconsistencies were identified in the determination of the CTP proposed in them, compromising their usefulness in case studies –see Sections 3.5 and 3.6. Considering the large number of nanoproducts on the market,[4,36–39] the overall limited number of studies addressing the comprehensive derivation of nano-specific comparative toxicity potentials is therefore alarming. Even though science lags behind to adequately assess the toxicity of nanoparticles, there is a need to build experience in developing LCIA of nanoparticles and in applying the resulting CTPs to case studies.[24]

In this context, we therefore aim to (i) adapt the USEtox modelling framework in its currently available version (v.2.0), including the integration of recent advances in environmental fate modelling of nanoparticles, to allow for impact assessment of nanoparticles; and (ii) apply the adapted USEtox model to TiO_2 nanoparticles to calculate consistent CTPs for freshwater ecotoxicity and human toxicity (both cancer and non-cancer effects) for emissions to air, water and

soil compartments that can replace published values. The selection of TiO_2 nanoparticles was made as it is one of the most used nanomaterials on the market and one of the most studied nanoparticles in toxicology,[36,39] and it also requires updating of the CTP values proposed in recently-published studies by Salieri et al.[33], Miseljic and Olsen[23], Hischier et al.[34] and Pini et al.[35] (see Sections 3.3-3.5 and 4).

2. Methods

2.1. USEtox framework

The USEtox model (http://usetox.org) is set up as a framework which combines matrices relating to the fate, exposure and effects of a given substance.[21,40,41] In this study, these matrices were determined by identifying relevant data in relation to the exposure and effects of nanoparticles and by altering the fate modelling to account for specific nanoparticle behavior. The version 2.0 of USEtox was used as basis in that effort, and the CTPs were calculated according to Equation 1.

$$\overline{CTP} = \overline{FF} \times \overline{XF} \times \overline{EF} \qquad \text{Equation 1}$$

The fate factors (FF) represent the substance residence time in a given compartment in unit of time (in days). The exposure factors (XF) relate a substance concentration to its actual intake (in day^{-1} for human intake; dimensionless for ecosystems exposure factor). The effect factor (EF) for freshwater ecotoxicity characterizes the fraction of species potentially affected from exposure to the substance and is expressed as a potentially affected fraction of species (PAF) over a volume per mass of exposed substances (in $PAF.m^3/kg\text{-exposed}$ or $m^3/kg\text{-exposed}$). The EFs for human toxicity relate the amount of substance taken in by the population via inhalation or ingestion to the probability of adverse effects (carcinogenic or non-carcinogenic effects) of the substance in the

human body; they are expressed in the unit of cases/kg-intake. The resulting CTPs are expressed in potentially affected fraction of species (PAF) over time and volume of water per mass of emitted substances for freshwater ecotoxicity (in $PAF.m^3.d$/kg-nanoparticles emitted) or in number of potential cancer or non-cancer cases per mass of emitted substances for human toxicity (cases/kg-nanoparticles emitted).

In the following subsections, each factor is individually and critically evaluated and adapted to account for the complexity of the nano-specific properties. Some of the factors may be size-dependent. Wherever possible, the particle size was differentiated, and a default (arbitrary) primary size of 21 nm (diameter) was considered in the calculation of the comparative toxicity potentials; this size is commonly found in particles tested in toxicological studies (e.g. see Table S4).

2.2. Fate factors

The FF determines the concentration in a given compartment to the quantity released by applying multimedia mass balance modelling.[21] USEtox fate modelling for conventional substances accounts for removal processes, like degradation, burial into sediment, leaching, and intermediate transports between compartments, which are either diffusive or advective.[42] However, as discrepancies between the fate of conventional chemicals and nanomaterials have been reported, e.g. in water[43], the fate modelling requires adaptation.[44] Two main approaches for modelling the fate of nanoparticles have been proposed in the literature, with the fate and transport of the nanoparticles being modelled either through models relying on partition coefficients or via the use of kinetic models and attachment efficiency α. On-going discussions remain on which approach is better suited for providing parsimony and accuracy (see for example refs. 45–48). In the present study, we have used the Simplebox4nano (SB4N) model, which relies on the Smoluchowski equation to derive attachment rates between ENPs and the natural particles occurring as colloidal particles in

soil and sediment pore waters and for both the colloidal and non-colloidal natural particles that are suspended in surface waters.[49,50] This choice was motivated by the ability of the model to scientifically capture nanoparticle-specific fate and transport aspects while ensuring compatibility and a relatively easy integration into the USEtox fate modelling framework. The USEtox-defined dimensions of the continental and global boxes were thus adapted to the dimensions of the SB4N model.

SB4N is an extension of the chemical multimedia fate model SimpleBox[51] that calculates chemical concentrations by performing mass balance equations for transport and degradation processes across air, rain, surface waters, soil and sediment. The model matrix of SimpleBox has been extended to that of SB4N, in which (i) the environmental fate of pristine nanoparticles is simulated as well as that of nanoparticles hetero-aggregated with natural colloid particles (<450 nm) and nanoparticles attached to larger natural particles; (ii) dissolution is treated as a removal mechanism because once a nanoparticle has been dissolved, it is no longer a nano-scaled solid particle; and (iii) the rates at which the nanoparticles strive at thermodynamic equilibrium are represented by dissolution, aggregation and attachment rates.[49]

The most significant transformation process for nano-TiO_2 is the aggregation/agglomeration process.[52] This process is modeled in SB4N by applying the Derjaguin Landau Verwey Overbeek (DLVO) theory, which calculates the interactions between particle surfaces in dispersions. It should be noted that the experimental ecotoxicological studies have so far mostly been performed on aggregates of suspended nanoparticles, which is often termed homo-aggregation. In the environment, nanoparticles will interact with biota, organic and inorganic entities and form what is known as hetero-aggregates. Until now, a distinction in the ecotoxicity exerted by individual, homo- and hetero-aggregated nanoparticles have not been determined experimentally,[53,54], and more environmentally-relevant studies are still required to provide insights into that question.[55] Therefore, in the absence of further information, the free and homo- and hetero-aggregated particles

are assumed to be bioavailable in the derivation of the fate factors.[50] Full documentation of the modelling of the aggregation mechanisms and the associated input parameters is available in Supporting Methods and Table S1.

2.3. Exposure factors

The exposure factor (XF) for freshwater ecotoxicity of conventional substances is calculated as the dissolved fraction of the chemical in freshwater.[42] For nanoparticles, the consideration of both free and aggregated particles as bioavailable in freshwater environment makes XF for freshwater ecotoxicity set to 1 (see Section 2.2). With regard to human exposure, several intake pathways exist and are subdivided into direct and indirect exposure in the USEtox model –see Supporting Methods. Direct exposure can occur through inhalation of contaminated air or ingestion of contaminated drinking water, and the modelling of these impact pathways rely on USEtox landscape parameters, which were left unchanged in the model. Dermal exposure, which is a relevant route to address for exposure to nanoparticles,[56] e.g. via the use of sunscreen[57] or textiles[58] containing nanoparticles, is not encompassed in the USEtox 2.0 model and hence was disregarded in the current study. Indirect exposure covers the ingestion of agricultural produce (divided into above- and below-ground produce), meat, dairy products and fish[40], and bioaccumulation factors (BAF) corresponding to these exposure pathways are needed.[42] To the authors' knowledge, no studies reporting biotransformation factors (BTF) for meat or milk exist. Therefore, these two exposure pathways were neglected, and only bioaccumulation factors for fish (BAF_{fish}), above-ground produce ($BAF_{above\text{-}ground}$) and below-ground produce ($BAF_{below\text{-}ground}$) were addressed here.

BAF for fish is determined as the ratio of the concentration in the organism over the concentration in the surrounding water, taking into account all exposure routes.[59] The more accurate and preferred

186 approach in USEtox is to use experimentally determined BAF_{fish} values.[40] A literature review was
187 therefore conducted to identify the most suited BAF_{fish} –see details in Supporting Methods.

188 $BAF_{below\text{-}ground}$ can be determined based on the root concentration factor (RCF) with the formula:
189 $BAF_{below\text{-}ground} = (\rho_{soil}/\rho_{plant})x(0.8\ RCF)$, where ρ_{soil} and ρ_{plant} are the bulk densities of soil and plant,
190 respectively.[40] As a standard methodology in USEtox, the RCF is determined based on the
191 substance octanol-water partition coefficient (K_{ow}).[40] However, as this coefficient is not applicable
192 for nanoparticles[60], an alternative approach was adopted based on correlation models for the transfer
193 of chemicals from soil solutions to roots developed by Briggs et al.[61] RCF can thus be determined
194 as the ratio of the particle concentration in the root and that in the soil water.

195 $BAF_{above\text{-}ground}$ is difficult to determine solely based on experimental data because of the complexity
196 behind the root uptake, air/plant uptake and translocation mechanisms. To measure the plant uptake
197 of organic chemicals, experiments have been conducted in exposure chambers under steady-state
198 exposure conditions. Unlike for organic chemicals,[62] for which experiments to measure plant uptake
199 have been conducted, no such study could be retrieved for nanoparticles. To predict the $BAF_{above\text{-}ground}$, mass balance modelling like that adapted in USEtox by Trapp and Matthies[63] is required.
201 However the strong dependency on K_{ow} in its current form renders it inapplicable to nanoparticles.[60]
202 In the present study, the $BAF_{above\text{-}ground}$ value was therefore assumed identical to the $BAF_{below\text{-}ground}$.
203 Further research to address this gap should be undertaken.

204

205 **2.4. Effect factors for freshwater ecotoxicity**

206 The EF is defined as: $EF = 0.5/HC50_{EC50}$, with $HC50_{EC50}$ being the hazard concentration, at which
207 50% of the species are exposed to a concentration above their EC50.[41] In USEtox, the HC50 value
208 is calculated as the geometric mean of all available EC50 values for the different species, the choice

of the geometric over the arithmetic means being justified by the need to find best estimates in LCIA modelling and the stronger robustness in cases of limited data sets.[64,65]

To derive EFs for nano-sized TiO_2, a critical literature review of studies testing ecotoxicity of TiO_2 nanoparticles was first conducted (see Supporting Methods). To ensure quality of the data, this step was complemented by shortlisting the retrieved studies according to 3 conditions: (1) only studies stating an EC50; (2) only studies using tests following standardized test methods (ISO, OECD, ATSM etc.); and (3) excluding tests with severe alterations. A final classification of the retained studies into five different sets (some of them being subsets of others) depending on a number of criteria was performed to test the nano-specificities of the EF. Supporting Methods provide detailed descriptions of these sets of studies, each of them leading to the determination of a corresponding EF, which was interpreted as part of a sensitivity analysis (see Section 3.3).

2.5. Effect factors for human toxicity

In the USEtox model, the EFs for human toxicity are distinguished between carcinogenic and non-carcinogenic effects, each of them being further differentiated between inhalation and ingestion routes.[21] The effect factor relies on the assumption of linearity in a concentration-response curve up to the point where the lifetime disease probability is 0.5, and is defined as EF = 0.5/ED50, with ED50 (in kg-intake/person over lifetime) being the lifetime intake dose resulting in a 50 % increased probability of effects.

To determine ED50 for non-carcinogenic effects of TiO_2 nanoparticles, the study conducted by Laurent et al.[66] was used. In this study, a critical review of *in vivo* studies was performed and relationships between non-observed adverse effect levels (NOAEL) and the primary particle sizes of the particles were investigated. Statistically-significant associations were identified, although some uncertainties reside in the numerical estimates due to the inability to capture other possibly

influential physicochemical properties, e.g. surface coatings.[66] Expressions of NOAEL for humans as a function of the particle size were thus derived and recommended for use in LCIA of TiO_2 nanoparticles until new knowledge allows further refinement.[66] Effect factors for both inhalation and ingestion routes, considering a default particle size of 21 nm (see Section 2.1), were derived using Equations S9 and S10. Further details are available in Supporting Methods.

To derive the EF for carcinogenic effects of TiO_2 nanoparticles via ingestion route, the critical review by Jovanovic[67] focusing on public health regulations regarding oral ingestion of TiO_2 was used. With regard to cancer effects via inhalation, the intake dose reported by Heinrich et al.[68] on rats was used as inputs to derive an EDx.[69] Assuming linearity in the dose-response curve, as demonstrated between carcinogenic effects and low effect doses by Crettaz et al.[69], an effect factor defined as EF = (x/100)/EDx, was then derived. Detailed calculations are reported in Supporting Methods.

In EF for both cancer and non-cancer effects, it is important to note that, in addition to the lack of data (e.g. only one usable study for cancer effects via inhalation), most extrapolations (e.g. from animal to humans) stem from conversion factors derived from chemical toxicological studies, and discrepancies may occur when addressing specific nanoparticle behaviors. Considering the lack of insight into this source of uncertainties, we therefore followed the conventional methodology for deriving EF as performed in the USEtox model. Further research is however needed to test these assumptions for nanoparticles and refine the derived EF.

3. Results and discussion

The different factors for the fate, exposure and effects of nano-TiO_2 as well as the resulting comparative toxicity potentials were derived. These factors are presented and discussed individually in the following sections, with provision of recommended values wherever relevant. The calculated

257 CTPs are based on a modified version of the USEtox model (from v.2.0), which accounts for all
258 developments made in this study and are available to LCA practitioners –see Supporting
259 Information.

260

261 **3.1. Fate factors**

262 The physiochemical data collected for the fate modelling for nano-TiO_2 are reported in Table S1.
263 These data are based on anatase and rutile crystal forms of TiO_2 nanoparticles with an average size
264 of 21 nm and a considered density of 4.23E+3 kg/m^3. In the adapted USEtox model (see Supporting
265 Information), it can be observed that the derived fate factors for the free and aggregated forms in
266 water is found equal to 6.33E-1 day and 4.48E+1 day, respectively. This reflects a strong influence
267 of including the aggregated fraction of nanoparticles on the FF (see also Section 3.5).

268 With the replacement of the USEtox fate model with the SB4N model, a number of relevant
269 differentiation of emission compartments as embedded in USEtox 2.0 are lost in the USEtox 2.0
270 adapted to nanoparticles, e.g. the industrial indoor air compartment (highly relevant for assessing
271 human toxicity).[70,71] Future works should therefore focus on developing a fate model, which
272 accounts for the nanoparticle specificities while embedding sufficiently differentiated emission
273 compartments to capture all emission situations that may occur in the life cycle of nanoproducts.

274

275 **3.2. Exposure factors**

276 Several studies have demonstrated the uptake of nano-TiO_2 in fish, including the uptake in gills,
277 brain, skin and other organs.[72–76] However, none of them have derived BAF values based on the
278 measured concentrations because of difficulties to address nanoparticle properties, in particular the
279 incomplete coverage of uptake routes needed to calculate the BAF.[77] The uptake from dietary

exposure in the aquatic environment is thus typically neglected in studies, resulting in the determination of bioconcentration factors (BCF) instead of a BAF.

In the current study, two BAF proxies were therefore determined based on BCF values. A first BAF proxy of 21.4 was determined based on the geometric mean of several identified BCF values –see Table S2. A second BCF of 35.3 was derived based on the study by Yeo & Nam[78], who set up a microcosm including several trophic levels. Although the use of BCF values as BAF proxies can be acceptable in the absence of better data, Zhu et al. showed that the body burden for *D. rerio* was higher when exposed to nano-TiO_2 contaminated *D. magna* compared to aqueous exposure indicating that the dietary exposure could play a significant role in the uptake of nanoparticles.[79] Therefore, the BCF value of 35.3 derived from the study by Yeo & Nam,[78] who included exposure through both water and diet, was selected as expected to be a closer proxy to an actual BAF.

For below-ground produce, the $BAF_{below\text{-}ground}$ was calculated as the geometric mean of several BAF values obtained for different plants, for which accumulation and uptake of nano-TiO_2 were investigated[80,81] –see Table S3. A $BAF_{below\text{-}ground}$ of 2.9 was thus determined. This value appears very low in regards to typical ranges of bioaccumulation factors, thus suggesting that the bioaccumulation of nano-TiO_2 in roots, and hence in the below-ground produce, may be very limited.

As indicated in Section 2.4, due to lack of data, the $BAF_{above\text{-}ground}$ was estimated from the BAF for below-ground produce. They were assumed equal, resulting in a $BAF_{above\text{-}ground}$ value of 2.9. This assumption seems acceptable as little or no translocation between roots, leaves and fruits have been reported in the majority of studies identified.[82–85] If no translocation of particles takes place, the $BAF_{above\text{-}ground}$ in relation to the soil compartment can be argued to be equal to the concentration in the roots of the plants and thus be equal to the $BAF_{below\text{-}ground}$. It should however be noted that translocation were evidenced for other nanoparticles (e.g. Ag, Zn, Cu, Co, etc.) indicating that the

behavior of nanoparticles in both soil and plant medias is particle-specific and likely depends on their physicochemical properties (e.g. solubility).[82,86–88]

3.3. Effect factor freshwater ecotoxicity

From the literature review, a total of 65 relevant publications was identified covering 22 different species –see Table S4. Results for the five sets of EFs are provided in Table S5 and range between 9.4 and 26.9 PAF.m^3/kg-exposed (trophic level). The EF value of 26.9 PAF m^3/kg is recommended for use as it relies on studies, which were identified as adequately testing ecotoxicity of nanoparticles, i.e. specific requirements were fulfilled in relation to the distinctive behavior of nanoparticles (based on Lützhøft et al.[89] –see Supporting Methods).

Two studies can be used for comparison with this finding. Miseljic and Olsen[23] identified 12 studies, which cover data published up to 2011 and resulting in 27 possible endpoints, and reported an EF of 26.1 PAF m^3/kg for freshwater ecotoxicity of TiO_2, while Salieri et al.[33], who identified 32 studies covering data published up to 2013 and resulting in 30 possible endpoints, reported an EF value of 28.1 PAF.m^3/kg. The value recommended in our study is nearly identical to the values reported in those two sources, which may thus indicate a high consistency.

To put the results in perspective, the recommended EF value was compared to the existing EFs in USEtox for both organic and inorganic chemicals (amounting to ca. 2500 chemicals) along with the values reported by Salieri et al.[33] and Miseljic and Olsen[23] –see Figure S1. The recommended EF for TiO_2 is observed to be in the lower range of EF values for both organic and inorganic chemicals. TiO_2 has been showed to exert low toxicity compared to other metal oxides, like ZnO or CuO.[90,91] It therefore makes plausible the relative positioning of nano-TiO_2 among other chemicals reported in USEtox, and thus our recommended EF value.

The relative variability in the EF value, ranging 9.4-26.9 PAF m^3/kg across the 5 sets at the trophic level (see Table S5) can primarily be explained by the influence that highly sensitive species may have on the results (e.g. protozoa). These observations therefore call for developing specific data selection guidelines to derive consistent EFs for nanoparticles in future studies. Until such guidelines emerge, a 2-step procedure should be followed, using the nano-specific criteria set by Lützhøft, et al.[89] to shortlist the studies before applying the methodology described in Larsen and Hauschild.[64,65]

3.4. Effect factors for human toxicity

The recommended effect factors for human toxicity, cancer and non-cancer effects, are reported in Table 1. Background documentation pertaining to their determination is available in Supporting Methods.

Table 1. Recommended EF for nano-TiO_2 for human toxicity, cancer and non-cancer effects.

Impact/impact pathway		Value[a]	Unit	Applicability
Human toxicity - cancer effects	Inhalation (nanosized)	1.54E-1 [-]	cases/kg-inhaled	Applicable for particle sizes between 15-40 nm
	Inhalation (microsized)	1.10E-2 [-]	cases/kg-inhaled	Applicable for particle sizes between 1.5-1.7 µm
	Ingestion	0 [-]	cases/kg-ingested	No cancer effects assumed
Human toxicity - non-cancer effects	Inhalation	1.15 [0.38; 3.48]	cases/kg-inhaled	Values set for 21 nm primary particle size (size dependency available in Equations S9 and S10)
	Ingestion	2.94E-2 [9.72E-3; 8.89E-2]	cases/kg-ingested	

[a] Confidence intervals were derived whenever possible and are provided in brackets

345 The obtained EF values from Table 1 were compared to Pini et al.[35], who published EF values for
346 indoor and outdoor inhalation exposure to TiO_2 nanoparticles for both non-cancer and cancer
347 effects. In addition, they were put in perspective with the USEtox 2.0 database of effect factors for
348 organics and inorganics (total of ca. 1000 EF values). Figures S2 and S3 illustrate those
349 comparisons for non-cancer effects and cancer effects, respectively.

350 For non-cancer effects, Pini et al.[35] report an EF value of 7.26E-3 cases/kg-intake, which is ca. 160
351 times lower than our EF value of 1.15 cases/kg-intake (see Table 1). This discrepancy can mainly
352 be explained by the assumption made by Pini et al.[35] to use a no-observed adverse effect level
353 (NOAEL) value for ingestion exposure when determining an EF for inhalation. As reported in
354 Laurent et al.[66], NOAELs differ by several orders of magnitude between the two exposure routes,
355 with regression analyses on available toxicological data for TiO_2 showing a factor of ca. 40 between
356 the two.[66] Provided that the extrapolations from NOAELs (expressed as daily chronic intake dose)
357 to ED50 and the subsequent calculations of the EF are the same between ingestion and inhalation
358 routes,[21,40] a difference observed in the NOAELs between the two routes is thus propagated to the
359 corresponding EF values (see for example the differences of factor ca. 40 between EFs for non-
360 cancer effects reported in Table 1). The observed underestimation is also suggested when
361 comparing with the EF for inhalation for organics and inorganics reported in USEtox 2.0, where
362 Pini et al.'s EF value falls in the lower 25 percentile of both organics and inorganics –see Figure
363 S2A. In contrast, our recommended EF values for inhalation of nano-TiO_2 fall close to the mean of
364 EFs for inorganic chemicals and just above the range of EFs for organic chemicals (Figure S2A).
365 For the ingestion pathway, the EF value provided in the present study falls close to the mean of the
366 organics and just below the inorganics (see Figure S2B). Such comparisons seem reasonable
367 considering the large number of organic and inorganic substances in the USEtox database.

368 With respect to cancer effects via inhalation, Pini et al.[35] reported an EF value of 1.77E+2 cases/kg-
369 inhaled (outdoor emission), which is more than 3 orders of magnitude higher than our reported EF

value of 0.15 case/kg-inhaled (Table 1). This estimate by Pini et al.[35] is also observed to range among the top carcinogenic substances in the EF for organics and to be well above any EF of metals reported in USEtox 2.0 for cancer effects (see Figure S3). This is regarded as unrealistic considering the IARC classification of TiO_2 as possibly carcinogenic to humans[92], in contrast to substances like arsenic, nickel or beryllium, all of them being classified as carcinogenic to humans and reported in USEtox 2.0. Based on the study by Laurent et al.[66], who used the National Institute of Occupational Safety and Health (NIOSH) exposure thresholds[93], as did Pini et al.[35], an EF value of 7.4E-2 cases/kg-inhaled should be found when applying the methodology reported by Pini et al.[35]

With respect to the ingestion pathway, Jovanović[67] showed that although nano-TiO_2 has the potential for absorption and storage in various organs by mammals, no study has demonstrated that ingestion of TiO_2 could induce carcinogenic effects.[67,92] Therefore, the EF value for carcinogenic effects through ingestion was set to 0 cases / kg-ingested (see Table 1). For non-cancer effects, no comparative study could be done as, to the authors' knowledge, no studies have investigated this exposure route yet.

As indicated in Table 1, a particle size differentiation could only be considered for the EF values for non-cancer effects, following the work by Laurent et al.[66] When applying Equations S9 and S10, which can be used to determine EF as a function of the size, a decrease of the EFs for non-cancer effects by a factor of ca. 6 was observed between TiO_2 nanoparticles with primary size of 10nm and 100-nm TiO_2 particles. Although not investigated further in this study, such results suggest the relevance to consistently include size differentiation when determining CTP values for nanoparticles. To a larger extent, a differentiation accounting for relevant physicochemical properties of the nanoparticles, e.g. surface treatment or coatings, which may influence the fate, exposure and effects of the nanoparticles, and thus the resulting CTP values, need to be further explored. Such explorative studies, which should additionally match the actual properties of the

nanoparticles released to the environment, however remain currently hampered by the lack of comprehensive and transparent reporting of the tested nanoparticles in toxicological studies.[39,55,66,94]

3.5. Comparative toxic potentials for freshwater ecotoxicity

Table 2 shows the comparative toxicity potentials for freshwater ecotoxicity resulting from the combination of the recommended fate, exposure and effect factors described in Sections 3.1-3.3.

Table 2. Comparative toxic potentials (CTPs) for freshwater ecotoxicity of TiO_2 nanoparticles

Emission compartments	**Comparative Toxic Potentials** (CTUe or PAF.m^3.d/kg$_{emitted}$)
Emission to air	6.05E+02
Emission to freshwater	1.55E+03
Emissions to soil	1.19E+00

The recommended CTP of 1.55E+03 PAF.m^3.d/ kg-emitted for emissions to freshwater (see Table 2) can be compared to the values derived by Salieri et al.[33] and Miseljic[28], who reported CTP values of 2.8E-01 and 1.48E-01 PAF.m^3.d/ kg-emitted, respectively. These published factors are 3-4 orders of magnitude smaller than the CTP developed in the current study –see Figure 1A. This large difference is caused by the inclusion of the toxic impacts of aggregated particles in our model, unlike those of Salieri et al.[33] and Miseljic[28]. By simulating the disregard of aggregates, the recommended CTP value virtually drops by 3 orders of magnitude to 1.82 PAF.m^3.d/ kg-emitted (see Figure 1A). Both studies by Salieri et al.[33] and Miseljic[28] modelled aggregation as a removal process in the fate of the nanoparticles, which result in largely underestimated fate factors (and hence CTP values) since a large fraction of the emitted nanoparticles, i.e. all aggregated nanoparticles, end up being removed and are thus not bioavailable to cause effects in the exposed organisms. When conducting ecotoxicity testing on nanoparticles, several studies have reported that the species take up both the pristine and the aggregates,[95,96] and most of the current toxicological

studies, which are used in the determination of EF, are based on suspensions covering both pristine particles and aggregates.[97,98] Therefore, he inclusion of both states of the particles when deriving the CTPs for nanoparticles, as done in the current study, is strongly recommended.

This is also in line with the study by Eckelman et al.[30] who derived CTP for freshwater ecotoxicity for CNT. The only removal process considered in the latter study was the advection in the ocean, which resulted in a conservative CTP of 2.9E+04 PAF.m^3.d/ kg-emitted to freshwater, thus in a similar range to the CTP derived in our work (ca. 20 times higher than that of TiO_2; see Table 2). In two additional studies, Deng et al.[31] determined a CTP of 7.89E+02 PAF.m^3.d/ kg-emitted to freshwater for graphene oxide, thus approximately twice lower than our CTP for TiO_2 nanoparticles, while Pu et al.[32] determined a CTP of 5.96E+03 PAF.m^3.d/ kg-emitted to freshwater for CuO nanoparticles (with regional variation ranges of 3.87-11.1E+03 PAF.m^3.d/ kg), hence four times higher than our estimate for TiO_2. Although the modelling in these studies vary (e.g. fate), the CTP values are within same orders of magnitude and consistent with reported toxicity rankings (e.g. CuO nanoparticles being more toxic than TiO_2 nanoparticles[99]), suggesting a relatively good precision of these studies.

In the same manner as the effect factors (see Sections 3.3 and 3.4), the obtained comparative toxicity potentials for nano-TiO_2 were benchmarked against existing CTP present in the USEtox database for organic and inorganic chemicals –see Figures 1A, 1B and 1C for air, freshwater and soil emission compartments, respectively. The drop of the CTP derived by Salieri et al.[33] and Miselic[28] for freshwater emissions at the bottom of the entire USEtox CTP database, which amounts to ca. 2500 organic and 27 inorganic substances, confirms the likelihood that these CTP are largely underestimated (see Figures 1A). In contrast, the CTP values obtained in our study fall within the lower range of CTPs for inorganics and the median or higher range of CTPs for organics, which is considered plausible (see Figures 1A-1C).

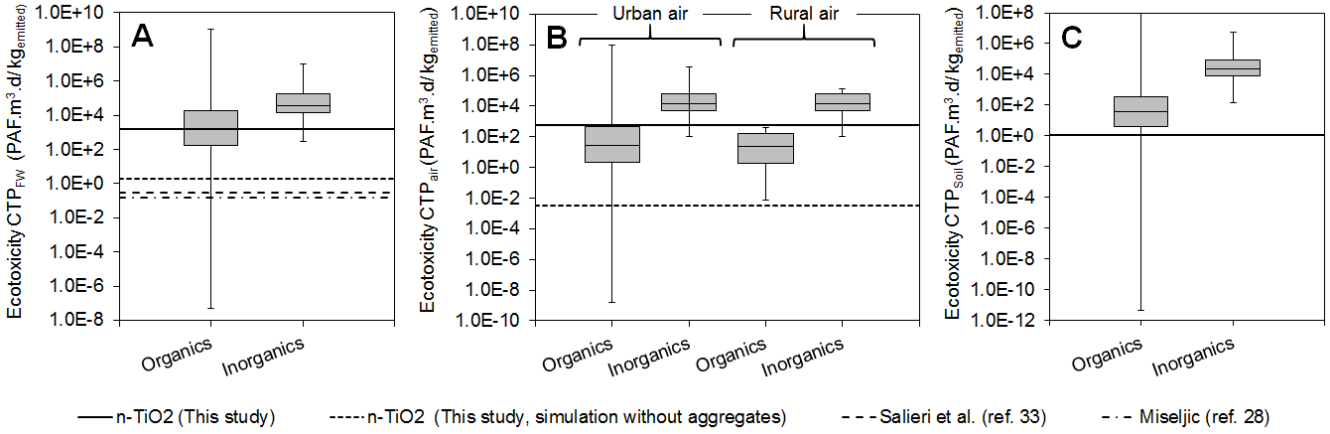

Figure 1. Comparative Toxic Potentials (CTP) for freshwater ecotoxicity of TiO_2 nanoparticles plotted against existing USEtox CTP database for emissions to (A) freshwater, (B) air (differentiated between urban air and rural air), and (C) soil compartments. The box plots represent the 25th to the 75th percentile of the CTPs and the upper and lower whiskers represent the maximum and minimum CTPs reported in USEtox (total of 2499 organics and 27 inorganics). Comparisons with Salieri et al.[33] and Miselic[28] can only be made for the freshwater emission compartment. Note that the CTPs are plotted on a logarithmic scale.

3.6. Comparative toxic potentials for human toxicity

The recommended CTPs for human toxicity for non-carcinogenic and carcinogenic effects are reported in Table 3 for air, freshwater and soil emission compartments. Additional sets of CTPs were also calculated for different scenarios to test the influence of variations in the BAF_{fish} derivations and the confidence intervals associated with the EF for human toxicity, non-cancer effects although relatively minor influences were observed (see Table S6).

Table 3. Comparative toxic potentials (CTPs) for human toxicity of TiO_2 nanoparticles

Emission compartments	**Comparative Toxic Potentials** (CTUh or cases/$kg_{emitted}$)	
	Cancer effects	Non-cancer effects
Emission to air	1.90E-06	1.70E-05 [a]
Emission to freshwater	0.00E+00	1.25E-06 [a]
Emissions to soil	0.00E+00	1.42E-08 [a]

[a] CTPs are given for a primary size of 21 nm (see Sections 2.1 and 3.4).

As observed in Table 3, because the EF via ingestion for carcinogenic effects was estimated to be null (see Section 3.4) and because nanoparticles do not volatilize, the CTPs for carcinogenic effects for freshwater and soil emissions are equal to zero. For the remaining CTP values of Table 3, comparisons with the CTP values reported in Pini et al.[35] for inhalation exposure (outdoor) and with the CTP database in USEtox v.2.0 can be made –see Figure 2.

For non-cancer effects, the CTP values from Pini et al.[35] plotted in Figure 2B reveal the strong influence of the underestimated EF value, in which ingestion data were used for estimating the inhalation effect factor (see Section 3.4). With regard to cancer effects, abnormally high EF values (see Section 3.4) suggest largely overestimated CTP values in Pini et al.[35], although some of these overestimations are compensated by lower intake fractions due to different geographical settings (Pini et al.[35] adapted the USEtox model landscape and population parameters to Swiss conditions) and a different particle size (Pini et al.[35] considered a particle size of 10 nm).In contrast, the CTP values estimated in our study fall in the range of CTPs for organics and below the range for inorganics. Such results seem consistent asTiO_2 and titanium in general are not reported to be strongly bioaccumulative nor strongly toxic substances compared to other metals and metalloids (e.g. Ag).[100–102]

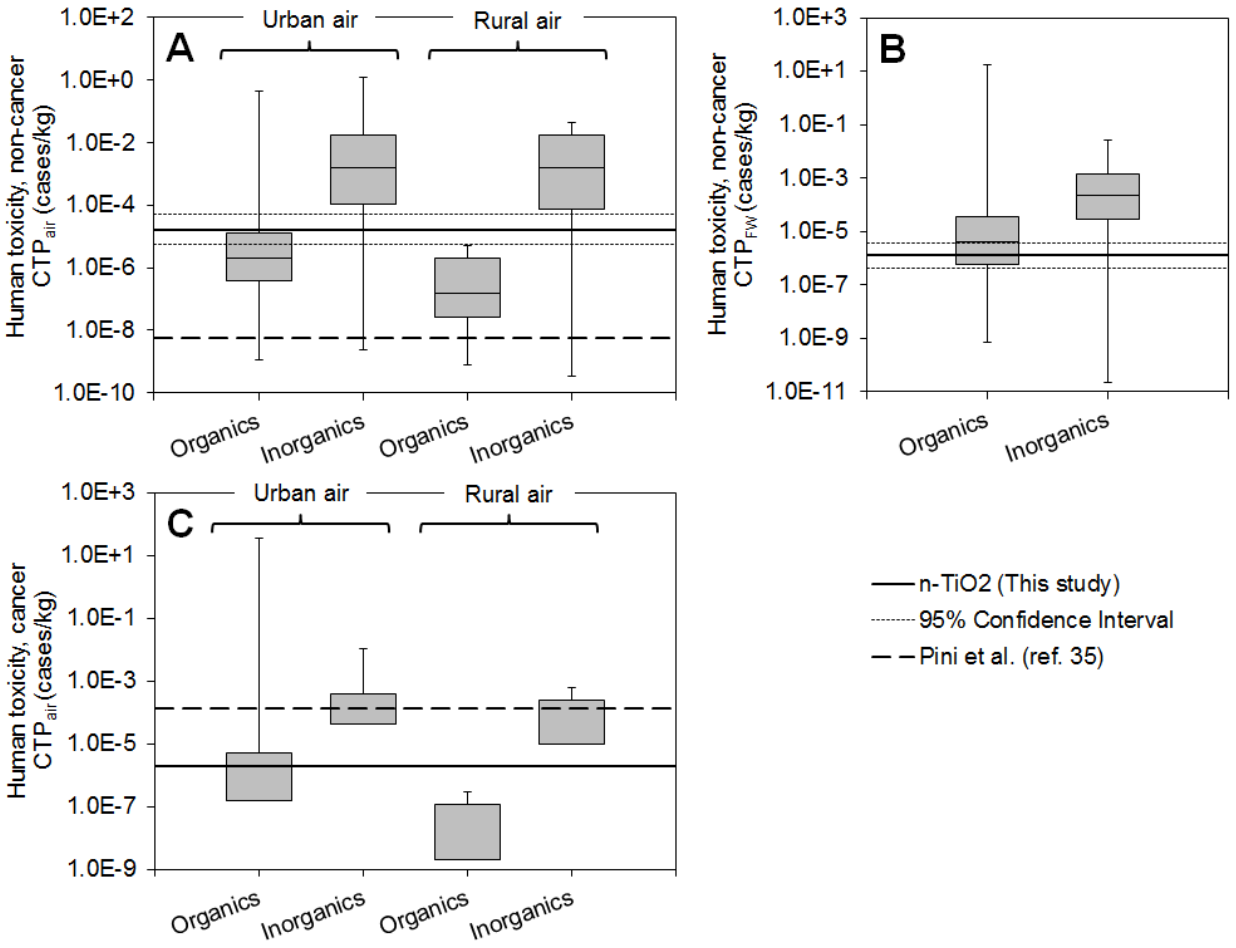

Figure 2. Comparative Toxic Potentials (CTP) for human toxicity of TiO_2 nanoparticles plotted against existing USEtox CTP database for (A) non-cancer effects – emissions to air (differentiated between urban and rural air compartments), (B) non-cancer effects – emissions to freshwater, and (C) cancer effects – emissions to air (differentiated between urban and rural air compartments). The box plots represent the 25th to the 75th percentile of the CTPs and the upper and lower whiskers represent the maximum and minimum CTPs reported in USEtox (total of 1024 organics and 15 inorganics for human toxicity, non-cancer effect, and 427 organics and 18 inorganics for cancer effects). No lower whiskers are plotted for cancer effects as some compounds are reported with CTP of 0 CTUh (non-carcinogenic substances). Note that the CTPs are plotted on a logarithmic scale.

3.7. Applications of CTP and recommendations

Using the adapted USEtox model, comparative toxicity potentials were developed for TiO_2 nanoparticles for characterizing freshwater ecotoxicity and human toxicity, both cancer and non-

491 cancer effects, resulting from emissions to air, water and soil compartments. These CTP values are
492 recommended for application in LCA studies in lieu of values published in earlier studies.[23,33–35]

493 Following the works by Eckelman et al.[30] and Deng et al.[31], the present study, and in particular its
494 methodological approach, can be considered as a first step towards more systematic and consistent
495 determinations of CTP for all emission compartments for nanoparticles using the USEtox model as
496 starting point and adjusting it (e.g. fate modelling, effect data, etc.) to integrate the specificities of
497 each nanoparticles. This will enable comparability with chemicals already characterized with the
498 model and thus allow performing life cycle assessment to gauge the potential impacts and relevance
499 of released nanoparticles compared to that of other contributing substances in the life cycle of
500 nanoproducts. To pursue efforts in this direction and enable LCA studies to include impacts of
501 nanoparticles, a number of recommendations for the LCIA modelling of nanoparticles and the
502 applications of derived CTPs are provided in Table 4.

503

504 **Table 4.** Recommendations to LCA practitioners and method developers for life cycle impact
505 assessment of nanoparticles.

Fate modelling
• Fate modelling should consider nano-specific transformations processes such as attachment efficiencies and dissolution and not be dependent on parameters driving the fate of conventional substances such as partitioning coefficients between dissolved organic carbon, suspended solids, sediment particles or soil particles and water used for the fate of conventional inorganics (see Section 2.2). • When deriving the final CTPs both the aggregated and the free/pristine particles should be considered bioavailable and thus included in the CTP calculation (see Section 2.2. and 3.5).
Exposure modelling
• Other exposure routes that are not included in the present USEtox model should be investigated. These include the dermal exposure to engineered nanoparticles present in cosmetics or health care products.
Effect modelling
• Data applied for deriving effect factors should be evaluated according to documentation of experimental conditions and nanomaterial properties such as aggregation, surface area, etc. (see Section 2.4 and 2.5); alternatively, they should follow the nano-specific guidelines published by OECD.[103]

• The possible influence of size on the human toxicity EF should be investigated in further details, particularly for the carcinogenic effects. The influence of other physicochemical properties on the CTP values should also be explored.
Overall CTP development and application in practice
• There is a need to develop CTPs for nanoparticles matching the actual properties of the released nanoparticles from nano-products. Several studies have evidenced a mismatch between the released nanoparticles and the pristine forms that are used in fate, exposure and effect modelling. The use of CTPs based on pristine nanoparticle data (as done in all existing studies) likely leads to overestimated impact results attributable to engineered nanoparticles, and should be considered with care by LCA practitioners when interpreting their results. • Owing to the different properties and behavior of each nanoparticle (e.g. carbon nanotubes vs. TiO_2 nanoparticles), further research is needed to consistently address the most important transformation processes in the fate modelling and the effects on ecosystems and human health.

4. Associated content

Supporting Information Available: Contains (1) the adapted USEtox model to derive CTP for nanoparticles, (2) a PDF of Supporting Information containing Supporting Methods documenting the detailed methodology and background data for the determination of the fate, exposure and effect factors for freshwater ecotoxicity and human toxicity as well as Supporting Figures and Tables to complement the section Results and Discussion of the manuscript.

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