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Development of comparative toxicity potentials of TiO$_2$ nanoparticles for use in life cycle assessment

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18

Abstract

20 Studies have shown that releases of nanoparticles may take place through the life cycle of products

21 embedding nanomaterials, thus resulting in potential impacts on ecosystems and human health.

22 While several life cycle assessment (LCA) studies have assessed such products, only a few of them

23 have quantitatively addressed the toxic impacts caused by released nanoparticles, thus leading to

24 potential biases in their conclusions. Here, we address this gap and aim to provide a framework for

25 calculating comparative toxicity potentials (CTP) for nanoparticles and derive CTP values for TiO$_2$

26 nanoparticles (TiO$_2$-NP) for use in LCA. We adapted the USEtox 2.0 consensus model to integrate

27 the SimpleBox4Nano fate model, and we populated the resulting model with TiO$_2$-NP specific data.

28 We thus calculated CTP values for TiO$_2$ nanoparticles for air, water and soil emission

29 compartments for freshwater ecotoxicity and human toxicity, both cancer effects and non-cancer

30 effects. Our results appeared plausible after benchmarking with CTPs for other nanoparticles and

31 substances present in the USEtox database, while large differences were observed with CTP values

32 for TiO$_2$ nanoparticles published in earlier studies. Assumptions, which were performed in those

33 previous studies because of lack of data and knowledge at the time they were made, primarily

34 explain such discrepancies. For future assessment of potential toxic impacts of TiO$_2$ nanoparticles

35 in LCA studies, we therefore recommend the use of our calculated CTP.

36

37 **TOC**

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39

1. Introduction

40
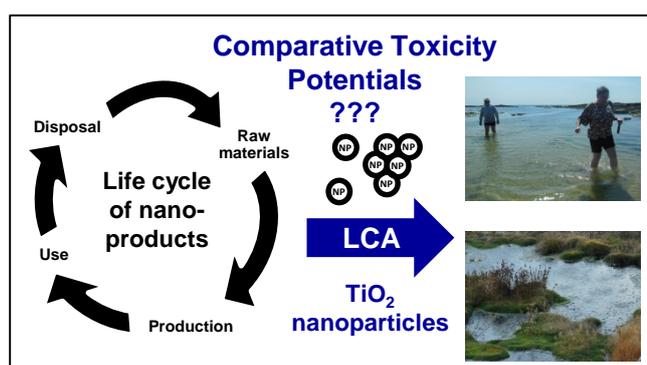
41   Owing to their physicochemical properties, such as high surface areas and small sizes,

42   nanomaterials have been increasingly applied in various commodities over the past decade, bringing

43   optimized strengths and efficiencies compared to conventional products. When embedding

44   nanomaterials in product matrices, their emissions might occur through the life cycle of the

45   resulting nano-products.[1–4] Direct releases during the manufacturing of the nanomaterials may thus

46   take place.[5] Likewise, depending on the type of location of the nanomaterial in the product matrices,

47   e.g. suspensions in liquids or surface-bound, and on the type of handling, the use and disposal of the

48   nano-products may also lead to potential releases of nanoparticles.[1,4,6] Several studies have reported

49   the risks and potential impacts to humans and the environment that such releases may cause.[7–14] To

50   comprehensively assess the environmental impacts of nano-products, it is therefore necessary to

51   quantify the impacts on ecosystems and human health stemming from these releases over the entire

52   life cycle of the nano-products.[2,3,15,16]

53   To address this need, the most prominent tool is life cycle assessment (LCA). LCA is a tool, which

54   aims at quantifying all relevant environmental impacts of a product or system taken in its life cycle

55   perspective, i.e. from extraction of the raw materials through its production and use up to its final

56   disposal.[17] In practice, inventories of pollutant emissions aggregated over the system life cycle are

57   translated into potential impact indicators using characterization factors from life cycle impact

58   assessment (LCIA) methods. These LCIA methods rely on models describing the cause-effect chain

59   from the emissions of a substance to its resulting impacts on ecosystems or human health. To

60   characterize the impacts caused by the toxicity of emitted substances on freshwater ecosystems

61   (termed "freshwater ecotoxicity" in the following) and human health (termed "human toxicity"), the

62   European Commission's International Reference Life Cycle Data System (ILCD) and the US

63   Environmental Protection Agency recommended the USEtox model as best LCIA practice.[18–20] The

64   USEtox model is a consensus-based model, which allows calculating globally-applicable

65   characterization factors or comparative toxicity potentials (CTP) for assessing freshwater

66   ecotoxicity and human toxicity differentiated into cancer effects and non-cancer effects.[21,22]

67   To date, more than fifty studies have applied LCA to nano-products.[15,23] However, most of them

68   have left out the assessment of potential impacts from released nanoparticles.[15,24] Until now, only

69   twelve studies have investigated the characterization of toxic impacts caused by released

70   nanoparticles. Among these studies, five addressed nanosilver and only accounted for the dissolved

71   fractions thus neglecting potential impact of pristine particles.[25–29] Three studies focused on CTP for

72   freshwater ecotoxicity of carbon nanotubes,[30] graphene oxide[31] and copper nanoparticles.[32] Four

73   studies developed CTP for TiO$_2$ nanoparticles for freshwater ecotoxicity[28,33,34] and for human

74   toxicity[35] (only for airborne emissions). Most of these studies focus on a specific toxic impact

75   category and/or emission compartment, and none provides CTP for both ecotoxicity and human

76   toxicity impacts and for all emission compartments (air, water, soil), all being necessary for the

77   conduct of comprehensive LCA studies. Taken altogether, the four publications focusing on TiO$_2$

78   nanoparticles come close to cover all impacts and emission compartments; however, inconsistencies

79   were identified in the determination of the CTP proposed in them, compromising their usefulness in

80   case studies –see Sections 3.5 and 3.6. Considering the large number of nanoproducts on the

81   market,[4,36–39] the overall limited number of studies addressing the comprehensive derivation of

82   nano-specific comparative toxicity potentials is therefore alarming. Even though science lags

83   behind to adequately assess the toxicity of nanoparticles, there is a need to build experience in

84   developing LCIA of nanoparticles and in applying the resulting CTPs to case studies.[24]

85   In this context, we therefore aim to (i) adapt the USEtox modelling framework in its currently

86   available version (v.2.0), including the integration of recent advances in environmental fate

87   modelling of nanoparticles, to allow for impact assessment of nanoparticles; and (ii) apply the

88   adapted USEtox model to TiO$_2$ nanoparticles to calculate consistent CTPs for freshwater

89   ecotoxicity and human toxicity (both cancer and non-cancer effects) for emissions to air, water and

90   soil compartments that can replace published values. The selection of TiO$_2$ nanoparticles was made

91   as it is one of the most used nanomaterials on the market and one of the most studied nanoparticles

92   in toxicology,[36,39] and it also requires updating of the CTP values proposed in recently-published

93   studies by Salieri et al.[33], Miseljic and Olsen[23], Hischier et al.[34] and Pini et al.[35] (see Sections 3.3-

94   3.5 and 4).

95

96   **2.   Methods**

97   **2.1.   USEtox framework**

98   The USEtox model (http://usetox.org) is set up as a framework which combines matrices relating to

99   the fate, exposure and effects of a given substance.[21,40,41] In this study, these matrices were

100   determined by identifying relevant data in relation to the exposure and effects of nanoparticles and

101   by altering the fate modelling to account for specific nanoparticle behavior. The version 2.0 of

102   USEtox was used as basis in that effort, and the CTPs were calculated according to Equation 1.

103

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

105

106   The fate factors (FF) represent the substance residence time in a given compartment in unit of time

107   (in days). The exposure factors (XF) relate a substance concentration to its actual intake (in day^{-1}

108   for human intake; dimensionless for ecosystems exposure factor). The effect factor (EF) for

109   freshwater ecotoxicity characterizes the fraction of species potentially affected from exposure to the

110   substance and is expressed as a potentially affected fraction of species (PAF) over a volume per

111   mass of exposed substances (in PAF.m^3/kg-exposed or m^3/kg-exposed). The EFs for human toxicity

112   relate the amount of substance taken in by the population via inhalation or ingestion to the

113   probability of adverse effects (carcinogenic or non-carcinogenic effects) of the substance in the

114   human body; they are expressed in the unit of cases/kg-intake. The resulting CTPs are expressed in

115   potentially affected fraction of species (PAF) over time and volume of water per mass of emitted

116   substances for freshwater ecotoxicity (in PAF.m³.d/kg-nanoparticles emitted) or in number of

117   potential cancer or non-cancer cases per mass of emitted substances for human toxicity (cases/kg-

118   nanoparticles emitted).

119   In the following subsections, each factor is individually and critically evaluated and adapted to

120   account for the complexity of the nano-specific properties. Some of the factors may be size-

121   dependent. Wherever possible, the particle size was differentiated, and a default (arbitrary) primary

122   size of 21 nm (diameter) was considered in the calculation of the comparative toxicity potentials;

123   this size is commonly found in particles tested in toxicological studies (e.g. see Table S4).

124

125   **2.2. Fate factors**

126   The FF determines the concentration in a given compartment to the quantity released by applying

127   multimedia mass balance modelling.[21] USEtox fate modelling for conventional substances accounts

128   for removal processes, like degradation, burial into sediment, leaching, and intermediate transports

129   between compartments, which are either diffusive or advective.[42] However, as discrepancies

130   between the fate of conventional chemicals and nanomaterials have been reported, e.g. in water[43],

131   the fate modelling requires adaptation.[44] Two main approaches for modelling the fate of

132   nanoparticles have been proposed in the literature, with the fate and transport of the nanoparticles

133   being modelled either through models relying on partition coefficients or via the use of kinetic

134   models and attachment efficiency α. On-going discussions remain on which approach is better

135   suited for providing parsimony and accuracy (see for example refs. 45–48). In the present study, we

136   have used the Simplebox4nano (SB4N) model, which relies on the Smoluchowski equation to

137   derive attachment rates between ENPs and the natural particles occurring as colloidal particles in

138   soil and sediment pore waters and for both the colloidal and non-colloidal natural particles that are

139   suspended in surface waters.[49,50] This choice was motivated by the ability of the model to

140   scientifically capture nanoparticle-specific fate and transport aspects while ensuring compatibility

141   and a relatively easy integration into the USEtox fate modelling framework. The USEtox-defined

142   dimensions of the continental and global boxes were thus adapted to the dimensions of the SB4N

143   model.

144   SB4N is an extension of the chemical multimedia fate model SimpleBox[51] that calculates chemical

145   concentrations by performing mass balance equations for transport and degradation processes

146   across air, rain, surface waters, soil and sediment. The model matrix of SimpleBox has been

147   extended to that of SB4N, in which (i) the environmental fate of pristine nanoparticles is simulated

148   as well as that of nanoparticles hetero-aggregated with natural colloid particles (<450 nm) and

149   nanoparticles attached to larger natural particles; (ii) dissolution is treated as a removal mechanism

150   because once a nanoparticle has been dissolved, it is no longer a nano-scaled solid particle; and (iii)

151   the rates at which the nanoparticles strive at thermodynamic equilibrium are represented by

152   dissolution, aggregation and attachment rates.[49]

153   The most significant transformation process for nano-TiO$_2$ is the aggregation/agglomeration

154   process.[52] This process is modeled in SB4N by applying the Derjaguin Landau Verwey Overbeek

155   (DLVO) theory, which calculates the interactions between particle surfaces in dispersions. It should

156   be noted that the experimental ecotoxicological studies have so far mostly been performed on

157   aggregates of suspended nanoparticles, which is often termed homo-aggregation. In the

158   environment, nanoparticles will interact with biota, organic and inorganic entities and form what is

159   known as hetero-aggregates. Until now, a distinction in the ecotoxicity exerted by individual, homo-

160   and hetero-aggregated nanoparticles have not been determined experimentally,[53,54], and more

161   environmentally-relevant studies are still required to provide insights into that question.[55]

162   Therefore, in the absence of further information, the free and homo- and hetero-aggregated particles

163   are assumed to be bioavailable in the derivation of the fate factors.[50] Full documentation of the

164   modelling of the aggregation mechanisms and the associated input parameters is available in

165   Supporting Methods and Table S1.

166

167   **2.3.   Exposure factors**

168   The exposure factor (XF) for freshwater ecotoxicity of conventional substances is calculated as the

169   dissolved fraction of the chemical in freshwater.[42] For nanoparticles, the consideration of both free

170   and aggregated particles as bioavailable in freshwater environment makes XF for freshwater

171   ecotoxicity set to 1 (see Section 2.2). With regard to human exposure, several intake pathways exist

172   and are subdivided into direct and indirect exposure in the USEtox model –see Supporting Methods.

173   Direct exposure can occur through inhalation of contaminated air or ingestion of contaminated

174   drinking water, and the modelling of these impact pathways rely on USEtox landscape parameters,

175   which were left unchanged in the model. Dermal exposure, which is a relevant route to address for

176   exposure to nanoparticles,[56] e.g. via the use of sunscreen[57] or textiles[58] containing nanoparticles, is

177   not encompassed in the USEtox 2.0 model and hence was disregarded in the current study. Indirect

178   exposure covers the ingestion of agricultural produce (divided into above- and below-ground

179   produce), meat, dairy products and fish[40], and bioaccumulation factors (BAF) corresponding to

180   these exposure pathways are needed.[42] To the authors' knowledge, no studies reporting

181   biotransformation factors (BTF) for meat or milk exist. Therefore, these two exposure pathways

182   were neglected, and only bioaccumulation factors for fish (BAF$_{fish}$), above-ground produce

183   (BAF$_{above-ground}$) and below-ground produce (BAF$_{below-ground}$) were addressed here.

184   BAF for fish is determined as the ratio of the concentration in the organism over the concentration

185   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$_{below-ground}$ can be determined based on the root concentration factor (RCF) with the formula:

189   BAF$_{below-ground}$ = (ρ_{soil}/ρ_{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$_{above-ground}$ 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$_{above-}$

200   $_{ground}$, 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$_{above-ground}$ value was therefore assumed identical to the BAF$_{below-ground}$.

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

209   of the geometric over the arithmetic means being justified by the need to find best estimates in

210   LCIA modelling and the stronger robustness in cases of limited data sets.[64,65]

211   To derive EFs for nano-sized TiO₂, a critical literature review of studies testing ecotoxicity of TiO₂

212   nanoparticles was first conducted (see Supporting Methods). To ensure quality of the data, this step

213   was complemented by shortlisting the retrieved studies according to 3 conditions: (1) only studies

214   stating an EC50; (2) only studies using tests following standardized test methods (ISO, OECD,

215   ATSM etc.); and (3) excluding tests with severe alterations. A final classification of the retained

216   studies into five different sets (some of them being subsets of others) depending on a number of

217   criteria was performed to test the nano-specificities of the EF. Supporting Methods provide detailed

218   descriptions of these sets of studies, each of them leading to the determination of a corresponding

219   EF, which was interpreted as part of a sensitivity analysis (see Section 3.3).

220

221   **2.5.   Effect factors for human toxicity**

222   In the USEtox model, the EFs for human toxicity are distinguished between carcinogenic and non-

223   carcinogenic effects, each of them being further differentiated between inhalation and ingestion

224   routes.[21] The effect factor relies on the assumption of linearity in a concentration-response curve up

225   to the point where the lifetime disease probability is 0.5, and is defined as EF = 0.5/ED50, with

226   ED50 (in kg-intake/person over lifetime) being the lifetime intake dose resulting in a 50 %

227   increased probability of effects.

228   To determine ED50 for non-carcinogenic effects of TiO₂ nanoparticles, the study conducted by

229   Laurent et al.[66] was used. In this study, a critical review of *in vivo* studies was performed and

230   relationships between non-observed adverse effect levels (NOAEL) and the primary particle sizes

231   of the particles were investigated. Statistically-significant associations were identified, although

232   some uncertainties reside in the numerical estimates due to the inability to capture other possibly

233 influential physicochemical properties, e.g. surface coatings.[66] Expressions of NOAEL for humans

234 as a function of the particle size were thus derived and recommended for use in LCIA of TiO$_2$

235 nanoparticles until new knowledge allows further refinement.[66] Effect factors for both inhalation

236 and ingestion routes, considering a default particle size of 21 nm (see Section 2.1), were derived

237 using Equations S9 and S10. Further details are available in Supporting Methods.

238 To derive the EF for carcinogenic effects of TiO$_2$ nanoparticles via ingestion route, the critical

239 review by Jovanovic[67] focusing on public health regulations regarding oral ingestion of TiO$_2$ was

240 used. With regard to cancer effects via inhalation, the intake dose reported by Heinrich et al.[68] on

241 rats was used as inputs to derive an EDx.[69] Assuming linearity in the dose-response curve, as

242 demonstrated between carcinogenic effects and low effect doses by Crettaz et al.[69], an effect factor

243 defined as EF = (x/100)/EDx, was then derived. Detailed calculations are reported in Supporting

244 Methods.

245 In EF for both cancer and non-cancer effects, it is important to note that, in addition to the lack of

246 data (e.g. only one usable study for cancer effects via inhalation), most extrapolations (e.g. from

247 animal to humans) stem from conversion factors derived from chemical toxicological studies, and

248 discrepancies may occur when addressing specific nanoparticle behaviors. Considering the lack of

249 insight into this source of uncertainties, we therefore followed the conventional methodology for

250 deriving EF as performed in the USEtox model. Further research is however needed to test these

251 assumptions for nanoparticles and refine the derived EF.

252

253 **3. Results and discussion**

254 The different factors for the fate, exposure and effects of nano-TiO$_2$ as well as the resulting

255 comparative toxicity potentials were derived. These factors are presented and discussed individually

256 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

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

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

280   exposure in the aquatic environment is thus typically neglected in studies, resulting in the

281   determination of bioconcentration factors (BCF) instead of a BAF.

282   In the current study, two BAF proxies were therefore determined based on BCF values. A first BAF

283   proxy of 21.4 was determined based on the geometric mean of several identified BCF values –see

284   Table S2. A second BCF of 35.3 was derived based on the study by Yeo & Nam[78], who set up a

285   microcosm including several trophic levels. Although the use of BCF values as BAF proxies can be

286   acceptable in the absence of better data, Zhu et al. showed that the body burden for *D. rerio* was

287   higher when exposed to nano-TiO₂ contaminated *D. magna* compared to aqueous exposure

288   indicating that the dietary exposure could play a significant role in the uptake of nanoparticles.[79]

289   Therefore, the BCF value of 35.3 derived from the study by Yeo & Nam,[78] who included exposure

290   through both water and diet, was selected as expected to be a closer proxy to an actual BAF.

291   For below-ground produce, the $BAF_{below-ground}$ was calculated as the geometric mean of several BAF

292   values obtained for different plants, for which accumulation and uptake of nano-TiO₂ were

293   investigated[80,81] –see Table S3. A $BAF_{below-ground}$ of 2.9 was thus determined. This value appears

294   very low in regards to typical ranges of bioaccumulation factors, thus suggesting that the

295   bioaccumulation of nano-TiO₂ in roots, and hence in the below-ground produce, may be very

296   limited.

297   As indicated in Section 2.4, due to lack of data, the $BAF_{above-ground}$ was estimated from the BAF for

298   below-ground produce. They were assumed equal, resulting in a $BAF_{above-ground}$ value of 2.9. This

299   assumption seems acceptable as little or no translocation between roots, leaves and fruits have been

300   reported in the majority of studies identified.[82–85] If no translocation of particles takes place, the

301    $BAF_{above-ground}$ in relation to the soil compartment can be argued to be equal to the concentration in

302   the roots of the plants and thus be equal to the $BAF_{below-ground}$. It should however be noted that

303   translocation were evidenced for other nanoparticles (e.g. Ag, Zn, Cu, Co, etc.) indicating that the

304   behavior of nanoparticles in both soil and plant medias is particle-specific and likely depends on

305   their physicochemical properties (e.g. solubility).[82,86–88]

306

307   **3.3.   Effect factor freshwater ecotoxicity**

308   From the literature review, a total of 65 relevant publications was identified covering 22 different

309   species –see Table S4. Results for the five sets of EFs are provided in Table S5 and range between

310   9.4 and 26.9 PAF.m^3/kg-exposed (trophic level). The EF value of 26.9 PAF m^3/kg is recommended

311   for use as it relies on studies, which were identified as adequately testing ecotoxicity of

312   nanoparticles, i.e. specific requirements were fulfilled in relation to the distinctive behavior of

313   nanoparticles (based on Lützhøft et al.[89] –see Supporting Methods).

314   Two studies can be used for comparison with this finding. Miseljic and Olsen[23] identified 12

315   studies, which cover data published up to 2011 and resulting in 27 possible endpoints, and reported

316   an EF of 26.1 PAF m^3/kg for freshwater ecotoxicity of TiO$_2$, while Salieri et al.[33], who identified 32

317   studies covering data published up to 2013 and resulting in 30 possible endpoints, reported an EF

318   value of 28.1 PAF.m^3/kg. The value recommended in our study is nearly identical to the values

319   reported in those two sources, which may thus indicate a high consistency.

320   To put the results in perspective, the recommended EF value was compared to the existing EFs in

321   USEtox for both organic and inorganic chemicals (amounting to ca. 2500 chemicals) along with the

322   values reported by Salieri et al.[33] and Miseljic and Olsen[23] –see Figure S1. The recommended EF

323   for TiO$_2$ is observed to be in the lower range of EF values for both organic and inorganic chemicals.

324   TiO$_2$ has been showed to exert low toxicity compared to other metal oxides, like ZnO or CuO.[90,91] It

325   therefore makes plausible the relative positioning of nano-TiO$_2$ among other chemicals reported in

326   USEtox, and thus our recommended EF value.

327   The relative variability in the EF value, ranging 9.4-26.9 PAF m^3/kg across the 5 sets at the trophic

328   level (see Table S5) can primarily be explained by the influence that highly sensitive species may

329   have on the results (e.g. protozoa). These observations therefore call for developing specific data

330   selection guidelines to derive consistent EFs for nanoparticles in future studies. Until such

331   guidelines emerge, a 2-step procedure should be followed, using the nano-specific criteria set by

332   Lützhøft, et al.[89] to shortlist the studies before applying the methodology described in Larsen and

333   Hauschild.[64,65]

334

335   **3.4.   Effect factors for human toxicity**

336   The recommended effect factors for human toxicity, cancer and non-cancer effects, are reported in

337   Table 1. Background documentation pertaining to their determination is available in Supporting

338   Methods.

339

340

341

342   **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	

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

344

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

370 value of 0.15 case/kg-inhaled (Table 1). This estimate by Pini et al.[35] is also observed to range

371 among the top carcinogenic substances in the EF for organics and to be well above any EF of metals

372 reported in USEtox 2.0 for cancer effects (see Figure S3). This is regarded as unrealistic

373 considering the IARC classification of TiO$_2$ as possibly carcinogenic to humans[92], in contrast to

374 substances like arsenic, nickel or beryllium, all of them being classified as carcinogenic to humans

375 and reported in USEtox 2.0. Based on the study by Laurent et al.[66], who used the National Institute

376 of Occupational Safety and Health (NIOSH) exposure thresholds[93], as did Pini et al.[35], an EF value

377 of 7.4E-2 cases/kg-inhaled should be found when applying the methodology reported by Pini et al.[35]

378 With respect to the ingestion pathway, Jovanović[67] showed that although nano-TiO$_2$ has the

379 potential for absorption and storage in various organs by mammals, no study has demonstrated that

380 ingestion of TiO$_2$ could induce carcinogenic effects.[67,92] Therefore, the EF value for carcinogenic

381 effects through ingestion was set to 0 cases / kg-ingested (see Table 1). For non-cancer effects, no

382 comparative study could be done as, to the authors' knowledge, no studies have investigated this

383 exposure route yet.

384 As indicated in Table 1, a particle size differentiation could only be considered for the EF values for

385 non-cancer effects, following the work by Laurent et al.[66] When applying Equations S9 and S10,

386 which can be used to determine EF as a function of the size, a decrease of the EFs for non-cancer

387 effects by a factor of ca. 6 was observed between TiO$_2$ nanoparticles with primary size of 10nm and

388 100-nm TiO$_2$ particles. Although not investigated further in this study, such results suggest the

389 relevance to consistently include size differentiation when determining CTP values for

390 nanoparticles. To a larger extent, a differentiation accounting for relevant physicochemical

391 properties of the nanoparticles, e.g. surface treatment or coatings, which may influence the fate,

392 exposure and effects of the nanoparticles, and thus the resulting CTP values, need to be further

393 explored. Such explorative studies, which should additionally match the actual properties of the

394   nanoparticles released to the environment, however remain currently hampered by the lack of

395   comprehensive and transparent reporting of the tested nanoparticles in toxicological studies.[39,55,66,94]

396

397   **3.5.   Comparative toxic potentials for freshwater ecotoxicity**

398   Table 2 shows the comparative toxicity potentials for freshwater ecotoxicity resulting from the

399   combination of the recommended fate, exposure and effect factors described in Sections 3.1-3.3.

400

401   **Table 2**. Comparative toxic potentials (CTPs) for freshwater ecotoxicity of TiO$_2$ nanoparticles

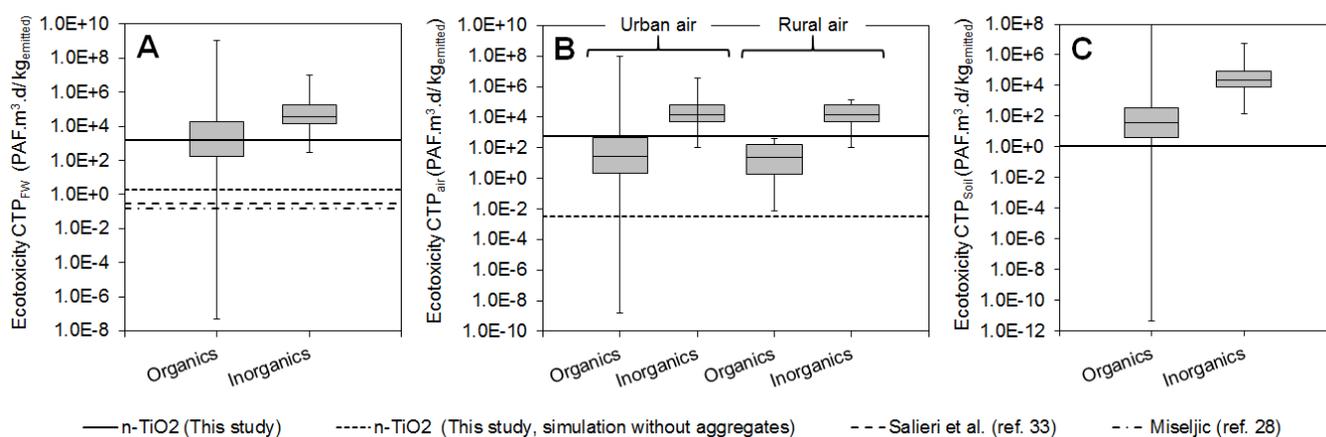| Emission compartments	Comparative Toxic Potentials (CTUe or PAF.m^3.d/kg$_{emitted}$)
Emission to air	6.05E+02
Emission to freshwater	1.55E+03
Emissions to soil	1.19E+00

402

403   The recommended CTP of 1.55E+03 PAF.m^3.d/ kg-emitted for emissions to freshwater (see Table

404   2) can be compared to the values derived by Salieri et al.[33] and Miseljic[28], who reported CTP values

405   of 2.8E-01 and 1.48E-01 PAF.m^3.d/ kg-emitted, respectively. These published factors are 3-4 orders

406   of magnitude smaller than the CTP developed in the current study –see Figure 1A. This large

407   difference is caused by the inclusion of the toxic impacts of aggregated particles in our model,

408   unlike those of Salieri et al.[33] and Miseljic[28]. By simulating the disregard of aggregates, the

409   recommended CTP value virtually drops by 3 orders of magnitude to 1.82 PAF.m^3.d/ kg-emitted

410   (see Figure 1A). Both studies by Salieri et al.[33] and Miseljic[28] modelled aggregation as a removal

411   process in the fate of the nanoparticles, which result in largely underestimated fate factors (and

412   hence CTP values) since a large fraction of the emitted nanoparticles, i.e. all aggregated

413   nanoparticles, end up being removed and are thus not bioavailable to cause effects in the exposed

414   organisms. When conducting ecotoxicity testing on nanoparticles, several studies have reported that

415   the species take up both the pristine and the aggregates,[95,96] and most of the current toxicological

416 studies, which are used in the determination of EF, are based on suspensions covering both pristine

417 particles and aggregates.[97,98] Therefore, he inclusion of both states of the particles when deriving the

418 CTPs for nanoparticles, as done in the current study, is strongly recommended.

419 This is also in line with the study by Eckelman et al.[30] who derived CTP for freshwater ecotoxicity

420 for CNT. The only removal process considered in the latter study was the advection in the ocean,

421 which resulted in a conservative CTP of 2.9E+04 PAF.m^3.d/ kg-emitted to freshwater, thus in a

422 similar range to the CTP derived in our work (ca. 20 times higher than that of TiO$_2$; see Table 2). In

423 two additional studies, Deng et al.[31] determined a CTP of 7.89E+02 PAF.m^3.d/ kg-emitted to

424 freshwater for graphene oxide, thus approximately twice lower than our CTP for TiO$_2$

425 nanoparticles, while Pu et al.[32] determined a CTP of 5.96E+03 PAF.m^3.d/ kg-emitted to freshwater

426 for CuO nanoparticles (with regional variation ranges of 3.87-11.1E+03 PAF.m^3.d/ kg), hence four

427 times higher than our estimate for TiO$_2$. Although the modelling in these studies vary (e.g. fate), the

428 CTP values are within same orders of magnitude and consistent with reported toxicity rankings (e.g.

429 CuO nanoparticles being more toxic than TiO$_2$ nanoparticles[99]), suggesting a relatively good

430 precision of these studies.

431 In the same manner as the effect factors (see Sections 3.3 and 3.4), the obtained comparative

432 toxicity potentials for nano-TiO$_2$ were benchmarked against existing CTP present in the USEtox

433 database for organic and inorganic chemicals –see Figures 1A, 1B and 1C for air, freshwater and

434 soil emission compartments, respectively. The drop of the CTP derived by Salieri et al.[33] and

435 Miselic[28] for freshwater emissions at the bottom of the entire USEtox CTP database, which amounts

436 to ca. 2500 organic and 27 inorganic substances, confirms the likelihood that these CTP are largely

437 underestimated (see Figures 1A). In contrast, the CTP values obtained in our study fall within the

438 lower range of CTPs for inorganics and the median or higher range of CTPs for organics, which is

439 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).

459   As observed in Table 3, because the EF via ingestion for carcinogenic effects was estimated to be

460   null (see Section 3.4) and because nanoparticles do not volatilize, the CTPs for carcinogenic effects

461   for freshwater and soil emissions are equal to zero. For the remaining CTP values of Table 3,

462   comparisons with the CTP values reported in Pini et al.[35] for inhalation exposure (outdoor) and with

463   the CTP database in USEtox v.2.0 can be made –see Figure 2.

464   For non-cancer effects, the CTP values from Pini et al.[35] plotted in Figure 2B reveal the strong

465   influence of the underestimated EF value, in which ingestion data were used for estimating the

466   inhalation effect factor (see Section 3.4). With regard to cancer effects, abnormally high EF values

467   (see Section 3.4) suggest largely overestimated CTP values in Pini et al.[35], although some of these

468   overestimations are compensated by lower intake fractions due to different geographical settings

469   (Pini et al.[35] adapted the USEtox model landscape and population parameters to Swiss conditions)

470   and a different particle size (Pini et al.[35] considered a particle size of 10 nm).In contrast, the CTP

471   values estimated in our study fall in the range of CTPs for organics and below the range for

472   inorganics. Such results seem consistent asTiO$_2$ and titanium in general are not reported to be

473   strongly bioaccumulative nor strongly toxic substances compared to other metals and metalloids

474   (e.g. Ag).[100–102]

475

476
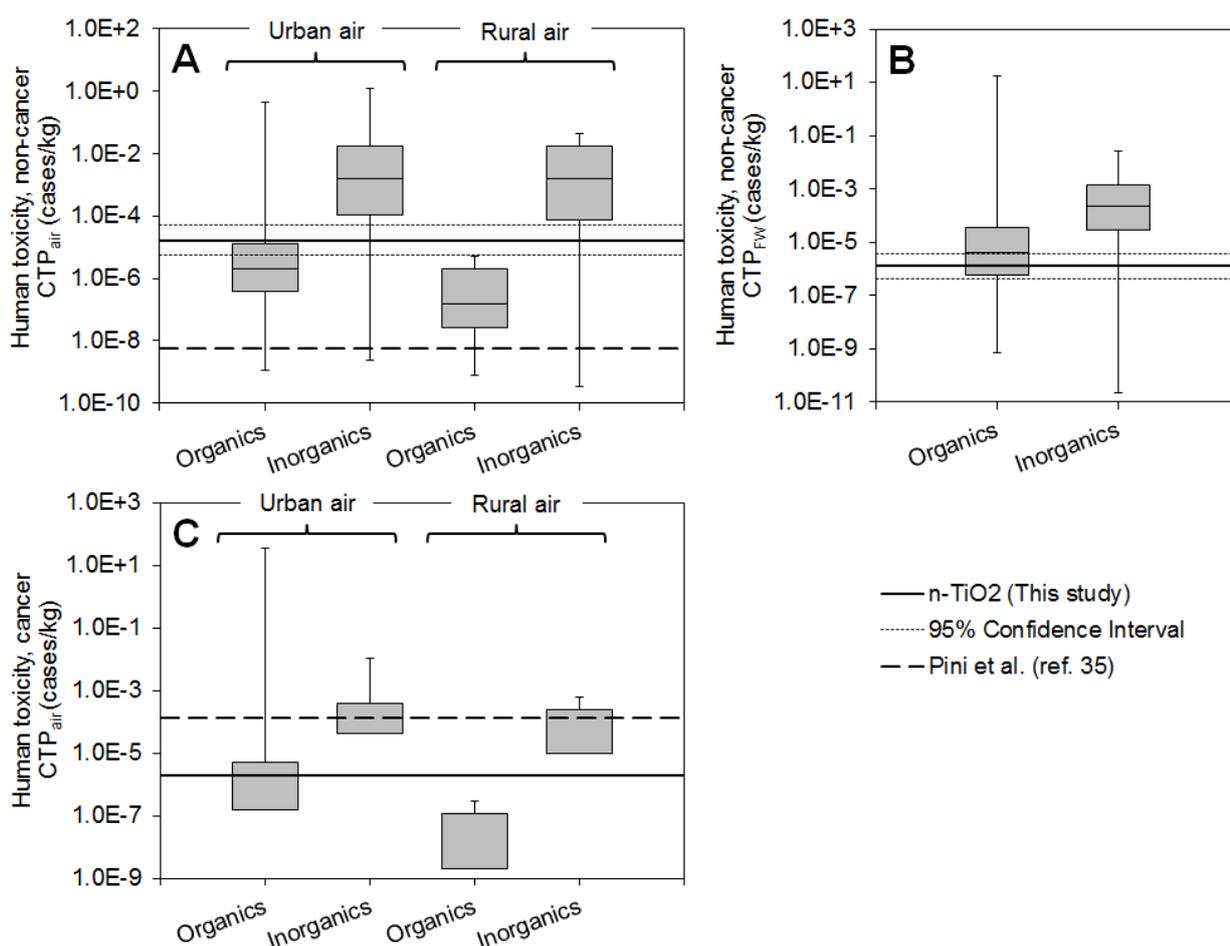
Figure 2. Comparative Toxic Potentials (CTP) for human toxicity of TiO$_2$ nanoparticles plotted against existing USEtox CTP database for (A) non-cancer effects – emissions to air (differentiated between urban and rural air compartments), (B) non-cancer effects – emissions to freshwater, and (C) cancer 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.

506

507 **4. Associated content**

508 Supporting Information Available: Contains (1) the adapted USEtox model to derive CTP for

509 nanoparticles, (2) a PDF of Supporting Information containing Supporting Methods documenting

510 the detailed methodology and background data for the determination of the fate, exposure and effect

511 factors for freshwater ecotoxicity and human toxicity as well as Supporting Figures and Tables to

512 complement the section Results and Discussion of the manuscript.

513

514 **5. Acknowledgements**

520

521 **6. References**

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