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Estimating human exposure to TiO_2 from personal care products through a social survey approach

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Running head: Bottom-up approach assessing TiO_2 exposure from PCP

Keywords: Titanium dioxide, nanoparticle, social survey, human health, exposure routes

Conflicts of interest

There are no conflicts of interest to declare.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ieam.4197.

Acknowledgements

This work is supported by the National Science Foundation (NSF #1743891) and Wisconsin Alumni Research Foundation. The authors would like to thank the anonymous reviewers for their time and input.

Data Accessibility Statement

Please contact the authors Fan Wu and Andrea L. Hicks for any meta data or calculations not already provided.

Supporting information (SI)

SI contains the full survey and the validation criteria for the collected survey responds.

Abstract

Titanium dioxide (TiO_2) has been widely applied in personal care products (PCP), with up to 36% of TiO_2 found in PCP present at the nanoscale. Due to the large quantity produced and wide application of TiO_2, there is a great potential for human exposure through various routes and therefore elicit adverse impacts. This work utilizes a social survey to generate information and estimate TiO_2 (bulk and nanoparticle (NP)) exposure to individuals through the daily use of PCP. Households reside in the Madison, WI metropolitan area were surveyed about their PCP usage. Survey results were then combined with usage patterns and TiO_2 content in each PCP category to estimate human exposures. Results indicate sunscreen and toothpaste are major contributors to TiO_2 dermal exposure. The estimated daily dermal route of exposure ranges from 2.8 to 21.4 mg TiO_2/person-day. Toothpaste has the potential to be exposed though oral route, 0.15 – 3.9 mg TiO_2/day were estimated to be ingested when 10% toothpaste ingestion was assumed. The results generated in present case study are generalizable in predicting individual TiO_2 exposure from PCP when the usage pattern is available. In addition, this study can be further used for risk assessment and refine the use of TiO_2 in PCP.

Keywords: Titanium dioxide, nanoparticle, social survey, human health, exposure routes

Introduction

Titanium dioxide (TiO_2) is a naturally occurring metal oxide. The engineered TiO_2 nanoparticle (NP) is one of the most commonly used nanomaterials (with one or more dimension within 1-100 nanometers - nm) in consumer products (Shi et al. 2013). Global production of TiO_2 was approximately 6.1 million metric tons in 2016 and is projected to reach 7.8 million tons by 2022; furthermore, the global TiO_2 market is currently valued at $13.3 billion (USD) and is expected to grow at 8.9% annually through 2025 (Research and Markets 2016). With the current and projected future large production volume and widespread usage, some specific applications may pose a greater potential risk of TiO_2 exposure to humans (Zhang et al. 2015). Particularly, those applications that could lead to direct human exposure to TiO_2 via inhalation (e.g., cleaning aids, spray cosmetics, coatings), dermal exposure, such as personal care products (PCP), or oral ingestion through food and drink, such as soda, cheese, and chewing gum (Chen et al. 2013; Lomer et al. 2001).

PCP including lotion, shampoo, deodorant, toothpaste, etc., are often laden with chemicals, some of which are considered emerging contaminants. However, limited information is available to estimate TiO_2 exposure through the use of PCP, and specific usage of TiO_2 NPs is not transparently regulated in consumer products, especially in PCP. According to the literature, nearly 35% of manufactured TiO_2 is used in PCP (Keller et al. 2013), and up to 36% of TiO_2 is at the nanoscale in PCP (Weir et al. 2012). TiO_2 NPs are utilized in specific applications such as such as ultraviolet (UV) protection and preventing decoloration of products (Smijs and Pavel 2011). Consequentially, nanoscale TiO_2 in PCP could result in human exposure and release of this material into the environment (Keller and Lazareva 2013). Previously studied TiO_2 NP exposures focusing on human health impact still lacks systematic overviews and conclusions from both the exposure and toxicology aspects, making it a potential health concern to the public. Mechanistically, TiO_2 NP can elicit toxicity due to the generation of reactive oxygen species, affinity to attach to intracellular organelles and biological macromolecules, and cell membrane disruption (Shah et al. 2017). Although early studies suggest that TiO_2 NPs are toxic to some extent, the lack of sufficient *in vivo* chronic toxicity studies prevent conclusive results, and the potential chronic toxicity via various route of exposure may still pose concern to human health. Moreover, limited information exists on daily TiO_2 (including TiO_2 NP) exposure to humans through various routes, making it even more difficult to evaluate the relevant risks associated with TiO_2 usage.

In present the study, a social survey was utilized to generate personalized data and estimate TiO_2 human exposure on a household basis through the use of eight major PCP. This approach allows for a quantitative estimate of the exposure of TiO_2 at an individual level. The Madison metropolitan area was selected as the studied region. Results generated in this study can be utilized to potentially refine future regulations based on TiO_2 applications and pathways that are most likely to impact human health, refine the potential exposure concentrations for future TiO_2 risk characterization, and potentially decision-making.

Methods

Survey distribution and collection

This study employed an Institutional Review Board (IRB) approved social survey to collect information and estimate TiO_2 exposure at the household and individual level in Madison Metropolitan area. Survey was distributed through various avenues, such as mailing lists, science outreach events, online postings, and fliers. The survey was collected from April 3rd to December 22nd, 2018. The survey instrument was divided into multiple sections by PCP category including toothpaste, shampoo, conditioner, lotion/skin cream, sunblock/sunscreen, deodorant/ antiperspirant, shaving cream, other products, and a demographic section. The survey respondents were asked to check whether the PCP contain TiO_2 in the ingredient list, and then information was collected regarding the brand and number of products utilized. The demographics section asked for the respondent's gender, age, race, number of household members, and approximate household income. The full survey and details on its administration are provided in the Supporting Information (SI). The products listed by the respondents were then cross referenced with ingredient lists to confirm the presence or absence of TiO_2. Collected surveys needs to follow 4 criteria to be considered as valid:

1. Citizens reside outside the Dane county (Madison Metropolitan) area are excluded from this study. The full list of the district includes: city of Madison, Fitchburg, Middleton, Monona, Verona; town of Dunn - Kegonsa, Dunn, Pleasant Springs, Verona - Marty Farms, Verona, Westport; village of Cottage Grove, Dane, DeForest, Maple Bluff, McFarland, Shorewood Hills, Waunakee, and Windsor.

2. Incomplete survey will not be included in final data analysis, and the respondent will be at least 18 years of age.

3. Participants will have to ensure read the informed consent to be able to continue the survey, otherwise the survey will not be able to be completed.

Data analysis

Survey results were then combined with the daily usage and quantity of TiO_2 previously identified in various PCP to estimate the human exposure from the use of PCP. Table 1 contains the summary of the average usage for each PCP type, and the ranges of TiO_2 concentrations (both TiO_2/TiO_2 NP) detected in various PCP from a suite of research articles (Peters et al. 2014; Rompelberg et al. 2016; Warheit et al. 2015; Weir et al. 2012; Yang et al. 2014). Toothpaste and sunscreen are identified to have much higher concentrations than the other types of PCP. As the TiO_2 concentrations detected previously in PCP contain large range variations, lower and upper bound concentrations were used and estimated using the concentration compiled from multiple studies. In addition, research investigated the personal usage patterns of various types of PCP (Bennett et al. 2010; Biesterbos et al. 2013; Hall et al. 2011; Loretz et al. 2008; Loretz et al. 2005; Loretz et al. 2006). The average usage patterns were used to perform calculations in the present study.

Results and Discussion

Estimated concentrations of TiO_2 exposure

Based on a total of 401 household survey responses, 213 PCP have been identified to contain TiO_2. Figure 1 summarizes the estimated TiO_2 exposure from the daily use of PCP. Results suggests that TiO_2 exposures are emitted mainly through sunscreen and toothpaste. The majority of the PCP emissions clustered in the lower range, but higher TiO_2 were still observed when the higher bound concentrations are used (Figure 1b).

Figures 2a & 2b represent the low and high individual TiO_2 exposure when the results were sorted by household income, respectively. When comparing the exposure concentrations among varying household income (one-way analysis of variance) using SigmaPlot (Systat Software, Inc, San Jose, CA), no significant difference was found in the individual TiO_2 exposure among various household incomes, suggesting that household income does not affect the average TiO_2 exposure. Figure 2c demonstrates the distribution and brackets of individual TiO_2 exposure in low and high scenarios. Over 70% of individuals were exposed to TiO_2 in the range of 0 to 10 mg/day in low estimated concentrations (Figure 2a). When high estimate concentrations are used (Table 1), the distribution was more spread-out towards the higher concentrations. Taken together, results obtained from the surveyed population suggests that the majority of the population (over 80%) are likely exposed to TiO_2 through the daily use of PCP, mainly contributed from toothpaste, sunscreen, and bodywash. This finding is in line with the estimates from a survey study conducted by Keller et al. from a production perspective, where TiO_2 and other ENMs were used in sunscreen, cosmetics, and toothpaste (Keller et al. 2014).

TiO_2 and TiO_2 NP exposure to individual through various routes

The previous section estimated the overall exposure of TiO_2 from PCP because PCP serve as a major source of TiO_2 to directly interact with human bodies. However, TiO_2, especially TiO_2 NPs presented in these PCP, can reach various parts of the human body via exposure routes including inhalation, injection, dermal deposition and gastrointestinal tract absorption (Shi et al. 2013). Figure 3 estimates the source flow, quantity, and route of exposure from each surveyed PCP. Dermal route is considered as the dominant route for TiO_2 exposure through PCP usage, due to the dermal application of most products. Three TiO_2 exposure scenarios, low estimate (a), high estimate (b), and the worst-case scenario (c), were analyzed based on the different TiO_2 concentrations estimated in PCP (Figure 3). The maximum TiO_2 exposure is the worst-case scenario estimated based on the sum of the highest exposure value calculated in each PCP category (Figure 3c). Results suggest the estimated average TiO_2 exposure through dermal route ranges from 2.8 to 21.38 mg TiO_2/person-day, with a maximum exposure of 181.8 mg TiO_2/person-day. Sunscreen, toothpaste, and body wash are three of the biggest contributors for TiO_2 expose dermally. The average TiO_2 NP exposure concentrations from the use of PCP is within the personal disposal concentrations predicted by Keller et al. (2013). They estimated nanoscale TiO_2 released per person ranges from 1.95−22.70 mg/day at various locations. Researchers found the nanoscale TiO_2 fraction in PCP ranges from 10-36% (Peters et al. 2014; Rompelberg et al. 2016; Warheit et al. 2015; Weir et al. 2012; Yang et al. 2014). Based on the findings, the estimated TiO_2 NPs dermal exposure in our study likely range from 1 to 7.7 mg TiO_2 NP/person-day. Since PCP are the only source considered in our study, it is expected the concentrations are lower than the prediction by Keller et al. while other consumer products can contribute for TiO_2 NP releases.

Although ingestion is not considered as a major route for TiO_2 exposure through PCP usage, unintended exposure can still occur orally through ingestion of toothpaste, particularly for younger children (Shi et al. 2013). To estimate the oral route exposure, 10% toothpaste ingestion was assumed in the surveyed population average. Based on this assumption, 0.153 – 3.9 mg/day of TiO_2 (0.06 -1.4 µg/day of TiO_2 NP) was estimated being ingested. In comparison to a study conducted by Rampalberg et al., the estimated

TiO_2 exposed solely from toothpaste usage for children age < 6 years old can be up to 0.67 mg/kg body weight (bw)/day, while other older population mean intake ranges from 0.19-0.55 μg/kg bw/day (Rompelberg et al. 2016). Taking a person with 60 kg body weight for instance, the TiO_2 exposure from toothpaste varies between 0.012 and 0.033 mg/day. These concentrations are similar to the low average exposure estimated in present study (Figure 2b). In another study, the authors indicate global per capita TiO_2 ingestion depended on the geographical locations of the population, with the USA and the UK having an estimated consumption of ∼0.2–0.7 mg and ∼1 mg TiO_2/kg bw per day, respectively (Weir et al. 2012). The estimated concentrations in this study were lower than the ingestion concentrations estimated by Weir et al. (Weir et al. 2012), suggesting other source of TiO_2 ingested from food contributes to the oral route exposure.

TiO_2 NP impacts and discussion

In order to inform the design of environmental fate and toxicity studies on TiO_2, this study adapted a social survey to collect information on upstream anthropogenic behavior, and estimated and identified the potential TiO_2 exposure concentrations related to the corresponding routes. To simplify the estimation, previously quantified ranges of TiO_2 concentrations in PCP from the literature are used to estimate the potential daily TiO_2 exposure instead of quantifying Ti content in all the market available products (Peters et al. 2014; Rompelberg et al. 2016; Warheit et al. 2015; Weir et al. 2012; Yang et al. 2014). In addition, limited extraction and quantification methods to determine TiO_2 NPs fractions in these PCP are still very challenging. The estimated daily exposure concentrations through a citizen science approach can provide personalized exposure data, and could be used for future risk assessment with respect to each exposure route.

Our results suggest that dermal route exposure is the major concern for TiO_2 NP to interact with human through PCP usage. In the toxicology perspective, several studies suggest that TiO_2 NPs cannot penetrate the intact human skin (Crosera et al. 2015; Pflücker et al. 2001; Schulz et al. 2002), with no effect or even protect human skin against UV-induced adverse effects (Park et al. 2011; Schilling et al. 2010). However, others found small TiO_2 NPs can penetrate skin and damage different organs in animal models (Wu et al. 2009), and pass through hairy skin when applied as an oil-in-water emulsion (Bennat and Müller-Goymann 2000). While research shows conflicting findings and lack of evidence in significant dermal penetration of TiO_2 NP from PCP, evidence still found that TiO_2 NP may pose a health risk to human after dermal exposure over a relative long time period for inducing skin aging (Sadrieh et al. 2010; Wu et al. 2009). Although some studies indicate that TiO_2 NP only provoke toxicities at high concentrations, there is a common agreement that TiO_2 NP has greater potential to elicit adverse outcomes under specific environmental conditions, especially under UV inducement (Amiano et al. 2012). Other factors, such as the age of TiO_2 NPs, can impact the results due to the different morphology of the stratum corneum, and the oxidative activity and phototoxicity of TiO_2 NPs might create inflammatory with UV-induction, causing skin irritation and sensitization (Smulders et al. 2015). Since sunscreen typically has a long residence time on human skin, TiO_2 NP exposed dermally through using sunscreen is a major concern. This is particularly vital when interpreting the potential impact through dermal exposure such as when used as sunblock.

Although toothpaste ingestion is relatively low compared to food sources, studies have found that health risks from the ingestion of TiO_2 NPs via food, supplements and toothpaste are still possible (Heringa et al. 2016). A recent study observed a microbial composition shift from Proteobacteria to Firmicutes phyla in the presence of food and industrial grade TiO_2 (36 mg/L-day) (partially nanoscale), indicating that TiO_2 may have adverse impacts when considering exposure and risk (Waller et al. 2017). Moreover, Jovanovic reviewed oral ingestion and injection route of impacts for TiO_2 NPs (Jovanović 2015), and concluded that TiO_2 NPs can be absorbed by mammals after ingestion or injection, and stored in various organs (Sang et al. 2014; Sang et al. 2013). They also showed the potential to cause tissue damage, alter biochemical parameters (Ramsden et al. 2009), bioconcentrate, bioaccumulate, and biomagnify in animal bodies (Fouqueray et al. 2013). The estimated risk of ingested TiO_2 NP can be influenced by factors such as absorption, form of TiO_2, particle fraction, particle size and physicochemical properties in relation to toxicity, among others. This is challenging to investigate but should be tackled in order to refine the future regulations toward the application of TiO_2 NP in food and supplements.

TiO_2 exposure through PCP usage is limited in inhalation route; therefore, this route was not considered in present study. However, spray type PCP (e.g., sunscreen, and makeup) still enable respiratory route exposure. Several studies have concluded that there is no increase in toxicity, such as mortality (Fryzek et al. 2003), lung inflammatory response (Liao et al. 2009), or carcinogenic effect (Hext et al. 2005; Liao et al. 2008) associated with workplace TiO_2 exposure. However, conflicted results again suggests that when exposed to TiO_2 NPs, rats and mice experience significant lung inflammation (Ferin et al. 1992; Grassian et al. 2006; Gurr et al. 2005) and cell mutations (Trouiller et al. 2009). Previous study assessed the health risk of TiO_2 NP to workers from a chronic animal inhalation study with ultrafine TiO_2, where a statistically significant increase in adenocarcinomas was observed (CDC 2011; Heinrich et al. 1995). Research also investigated the inhalation impacts of P25 TiO_2 NPs to wistar rats and two different strains of mice at average concentration of 10 mg/m^3, where toxic effects were found on alveolar macrophages and alveolar lung particle clearance (Heinrich et al. 1995). In another study, Laurent et al. summarized no-observed-adverse-effect-level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values of TiO_2 NPs in various in vivo studies and predicted the LOAEL(NOAEL) concentrations to be 0.0836–4.05 (0.0171–10.5) mg/kg-body-weight/day for exposure through inhalation route. Tsang et al. used two studies and combining nano-TiO_2 and fine-TiO_2 to calculate carcinogenic ED50 (Bermudez et al. 2004; Heinrich et al. 1995), and obtained a value at 1.58 μg per g-wet lung (1.43 m^2/g-dry lung) (Tsang et al. 2017). These values provide specific evidence for potential risks elicited by TiO_2 NP inhalation. Moreover, the International Agency for Research on Cancer (IARC) designates TiO_2 as a carcinogen, largely due to studies that have found increased lung cancers due to inhalation exposure in animals (WHO 2010). Therefore, the use of TiO_2 in PCP should be carefully assessed and minimize direct inhalation.

Although this study was focused on the population residing in Madison, WI, there is a potential to project the results to a larger scale. The TiO_2 exposures estimated in present study are mainly dominated by the PCP usage pattern and PCP used in the household, data estimated in our study is generalizable whenever those two factors are available. Based on this study, individuals can also estimate their daily TiO_2 exposure through the amount of household PCP usage. Therefore, an easily accessible inventory including the amount of TiO_2 used in each household PCP is urgently required. This can not only project current results to a larger scale, but also refine the findings to be more beneficial for risk assessment, management, and regulation development.

Conclusion

This study estimated the heterogenous TiO_2 exposure from PCP via various routes. In addition, this work provided a better idea of the range of TiO_2 exposure instead of just a single average exposure value. The information generated in this study can be further used for risk assessment and refine the use of TiO_2 in PCP, specifically targeted on the dermal and oral routes of exposure. Although this is a regional case study, generalization is achievable when the usage pattern and the TiO_2 concentrations in PCP are more refined.

References

Amiano I, Olabarrieta J, Vitorica J, Zorita S. 2012. Acute toxicity of nanosized TiO_2 to *daphnia magna* under uva irradiation. Environ Toxicol and Chem. 31(11):2564-2566.

Bennat C, Müller-Goymann C. 2000. Skin penetration and stabilization of formulations containing microfine titanium dioxide as physical uv filter. Int J Cosmet Sci. 22(4):271-283.

Bennett DH, Ritz B, Cassady DL, Lee K, Hertz-Picciotto I. 2010. Usage pattern of personal care products in california households. Food Chem Toxicol. 48(11):3109-3119.

Bermudez E, Mangum JB, Wong BA, Asgharian B, Hext PM, Warheit DB, Everitt JI. 2004. Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. Toxicol Sci. 77(2):347-357.

Biesterbos JW, Dudzina T, Delmaar CJ, Bakker MI, Russel FG, von Goetz N, Scheepers PT, Roeleveld N. 2013. Usage patterns of personal care products: Important factors for exposure assessment. Food Chem Toxicol. 55:8-17.

CDC: Centers for Disease Control and Prevention. 2011. Current intelligence belletin 63: Occupational exposure to titanium dioxide.

Chen XX, Cheng B, Yang YX, Cao A, Liu JH, Du LJ, Liu Y, Zhao Y, Wang H. 2013. Characterization and preliminary toxicity assay of nano-titanium dioxide additive in sugar-coated chewing gum. Small. 9(9- 10):1765 -1774.

Crosera M, Prodi A, Mauro M, Pelin M, Florio C, Bellomo F, Adami G, Apostoli P, De Palma G, Bovenzi M. 2015. Titanium dioxide nanoparticle penetration into the skin and effects on hacat cells. Int J Environ Res Public Health. 12(8):9282-9297.

Ferin J, Oberdorster G, Penney D. 1992. Pulmonary retention of ultrafine and fine particles in rats. Am J Respir Cell Mol Biol. 6(5):535-542.

Fouqueray M, Noury P, Dherret L, Chaurand P, Abbaci K, Labille J, Rose J, Garric J. 2013. Exposure of juvenile danio rerio to aged TiO_2 nanomaterial from sunscreen. Environ Sci Pollut Res Int. 20(5):3340-3350.

Fryzek JP, Chadda B, Marano D, White K, Schweitzer S, McLaughlin JK, Blot WJ. 2003. A cohort mortality study among titanium dioxide manufacturing workers in the united states. J Occup Environ Med. 45(4):400-409.

Grassian VH, O'Shaughnessy PT, Adamcakova-Dodd A, Pettibone JM, Thorne PS. 2006. Inhalation exposure study of titanium dioxide nanoparticles with a primary particle size of 2 to 5 nm. Environ Health Perspect. 115(3):397-402.

Gurr J-R, Wang AS, Chen C-H, Jan K-Y. 2005. Ultrafine titanium dioxide particles in the absence of photoactivation can induce oxidative damage to human bronchial epithelial cells. Toxicology. 213(1-2):66-73.

Hall B, Steiling W, Safford B, Coroama M, Tozer S, Firmani C, McNamara C, Gibney M. 2011. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments part 2. Food Chem Toxicol. 49(2):408-422.

Heinrich U, Fuhst R, Rittinghausen S, Creutzenberg O, Bellmann B, Koch W, Levsen K. 1995. Chronic inhalation exposure of wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. Inhal Toxicol. 7(4):533-556.

Heringa MB, Geraets L, van Eijkeren JC, Vandebriel RJ, de Jong WH, Oomen AG. 2016. Risk assessment of titanium dioxide nanoparticles via oral exposure, including toxicokinetic considerations. Nanotoxicology. 10(10):1515-1525.

Hext PM, Tomenson JA, Thompson P. 2005. Titanium dioxide: Inhalation toxicology and epidemiology. Toxicol Sci. 49(6):461-472.

Jovanović B. 2015. Critical review of public health regulations of titanium dioxide, a human food additive. Integr Environ Assess Manag. 11(1):10-20.

Keller AA, Lazareva A. 2013. Predicted releases of engineered nanomaterials: From global to regional to local. Environ Sci Technol Lett. 1(1):65-70.

Keller AA, McFerran S, Lazareva A, Suh S. 2013. Global life cycle releases of engineered nanomaterials. J Nanopart Res. 15(6):1692.

Keller AA, Vosti W, Wang H, Lazareva A. 2014. Release of engineered nanomaterials from personal care products throughout their life cycle. J Nanopart Res. 16(7):2489.

Liao C-M, Chiang Y-H, Chio C-P. 2008. Model-based assessment for human inhalation exposure risk to airborne nano/fine titanium dioxide particles. Sci Total Environ. 407(1):165-177.

Liao C-M, Chiang Y-H, Chio C-P. 2009. Assessing the airborne titanium dioxide nanoparticle-related exposure hazard at workplace. J Hazard Mater. 162(1):57-65.

Lomer MC, Harvey RS, Evans SM, Thompson RP, Powell JJ. 2001. Efficacy and tolerability of a low microparticle diet in a double blind, randomized, pilot study in crohn's disease. Eur J Gastroenterol Hepatol. 13(2):101-106.

Loretz L, Api A, Babcock L, Barraj L, Burdick J, Cater K, Jarrett G, Mann S, Pan Y, Re T. 2008. Exposure data for cosmetic products: Facial cleanser, hair conditioner, and eye shadow. Food Chem Toxicol. 46(5):1516-1524.

Loretz L, Api A, Barraj L, Burdick J, Dressler W, Gettings S, Hsu HH, Pan Y, Re T, Renskers K. 2005. Exposure data for cosmetic products: Lipstick, body lotion, and face cream. Food Chem Toxicol. 43(2):279-291.

Loretz L, Api AM, Barraj L, Burdick J, Davis DA, Dressler W, Gilberti E, Jarrett G, Mann S, Pan YL. 2006. Exposure data for personal care products: Hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. Food Chem Toxicol. 44(12):2008-2018.

Park Y-H, Jeong SH, Yi SM, Choi BH, Kim Y-R, Kim I-K, Kim M-K, Son SW. 2011. Analysis for the potential of polystyrene and TiO_2 nanoparticles to induce skin irritation, phototoxicity, and sensitization. Toxicol In Vitro. 25(8):1863-1869.

Peters RJ, van Bemmel G, Herrera-Rivera Z, Helsper HP, Marvin HJ, Weigel S, Tromp PC, Oomen AG, Rietveld AG, Bouwmeester H. 2014. Characterization of titanium dioxide nanoparticles in food products: Analytical methods to define nanoparticles. J Agric Food Chem. 62(27):6285-6293.

Pflücker F, Wendel V, Hohenberg H, Gärtner E, Will T, Pfeiffer S, Wepf R, Gers-Barlag H. 2001. The human stratum corneum layer: An effective barrier against dermal uptake of different forms of topically applied micronised titanium dioxide. Skin Pharmacol Physiol. 14(Suppl. 1):92-97.

Ramsden CS, Smith TJ, Shaw BJ, Handy RD. 2009. Dietary exposure to titanium dioxide nanoparticles in rainbow trout,(oncorhynchus mykiss): No effect on growth, but subtle biochemical disturbances in the brain. Ecotoxicology. 18(7):939-951.

Research and Markets. 2016. Titanium dioxide (TiO_2) – a global market overview.

Rompelberg C, Heringa MB, van Donkersgoed G, Drijvers J, Roos A, Westenbrink S, Peters R, van Bemmel G, Brand W, Oomen AG. 2016. Oral intake of added titanium dioxide and its nanofraction from food products, food supplements and toothpaste by the dutch population. Nanotoxicology. 10(10):1404-1414.

Sadrieh N, Wokovich AM, Gopee NV, Zheng J, Haines D, Parmiter D, Siitonen PH, Cozart CR, Patri AK, McNeil SE. 2010. Lack of significant dermal penetration of titanium dioxide from sunscreen formulations containing nano-and submicron-size TiO_2 particles. Toxicol Sci. 115(1):156-166.

Sang X, Fei M, Sheng L, Zhao X, Yu X, Hong J, Ze Y, Gui S, Sun Q, Ze X. 2014. Immunomodulatory effects in the spleen-injured mice following exposure to titanium dioxide nanoparticles. J Biomed Mater Res A. 102(10):3562-3572.

Sang X, Li B, Ze Y, Hong J, Ze X, Gui S, Sun Q, Liu H, Zhao X, Sheng L. 2013. Toxicological mechanisms of nanosized titanium dioxide-induced spleen injury in mice after repeated peroral application. J Agric Food Chem. 61(23):5590-5599.

Schilling K, Bradford B, Castelli D, Dufour E, Nash JF, Pape W, Schulte S, Tooley I, van den Bosch J, Schellauf F. 2010. Human safety review of “nano” titanium dioxide and zinc oxide. Photochem Photobiol Sci. 9(4):495-509.

Schulz J, Hohenberg H, Pflücker F, Gärtner E, Will T, Pfeiffer S, Wepf R, Wendel V, Gers-Barlag H, Wittern K-P. 2002. Distribution of sunscreens on skin. Adv Drug Deliv Rev. 54:S157-S163.

Shah SNA, Shah Z, Hussain M, Khan M. 2017. Hazardous effects of titanium dioxide nanoparticles in ecosystem. Bioinorg Chem Appl. 2017.

Shi H, Magaye R, Castranova V, Zhao J. 2013. Titanium dioxide nanoparticles: A review of current toxicological data. Part Fiber Toxicol. 10(1):15.

Smijs TG, Pavel S. 2011. Titanium dioxide and zinc oxide nanoparticles in sunscreens: Focus on their safety and effectiveness. Nanotechnol Sci Appl. 4:95.

Smulders S, Golanski L, Smolders E, Vanoirbeek J, Hoet P. 2015. Nano‐ TiO_2 modulates the dermal sensitization potency of dinitrochlorobenzene after topical exposure. Br J Dermatol. 172(2):392-399.

Trouiller B, Reliene R, Westbrook A, Solaimani P, Schiestl RH. 2009. Titanium dioxide nanoparticles induce DNA damage and genetic instability in vivo in mice. Cancer Res. 69(22):8784-8789.

Tsang MP, Hristozov D, Zabeo A, Koivisto AJ, Jensen ACØ, Jensen KA, Pang C, Marcomini A, Sonnemann G. 2017. Probabilistic risk assessment of emerging materials: Case study of titanium dioxide nanoparticles. Nanotoxicology. 11(4):558-568.

Waller T, Chen C, Walker SL. 2017. Food and industrial grade titanium dioxide impacts gut microbiota. Environ Eng Sci. 34(8):537-550.

Warheit D, Brown S, Donner E. 2015. Acute and subchronic oral toxicity studies in rats with nanoscale and pigment grade titanium dioxide particles. Food Chem Toxicol. 84:208-224.

Weir A, Westerhoff P, Fabricius L, Hristovski K, Von Goetz N. 2012. Titanium dioxide nanoparticles in food and personal care products. Environ Sci Technol. 46(4):2242-2250.

WHO (World Health Organization) International Agency for Research on Cancer. 2010. Carbon black, titanium dioxide, and talc. IARC monographs on the evaluation of carcinogenic risks to humans. 93:1.

Wu J, Liu W, Xue C, Zhou S, Lan F, Bi L, Xu H, Yang X, Zeng F-D. 2009. Toxicity and penetration of TiO_2 nanoparticles in hairless mice and porcine skin after subchronic dermal exposure. Toxicol Lett. 191(1):1-8.

Yang Y, Doudrick K, Bi X, Hristovski K, Herckes P, Westerhoff P, Kaegi R. 2014. Characterization of food-grade titanium dioxide: The presence of nanosized particles. Environ Sci Technol. 48(11):6391-6400.

Zhang Y, Leu Y-R, Aitken R, Riediker M. 2015. Inventory of engineered nanoparticle-containing consumer products available in the singapore retail market and likelihood of release into the aquatic environment. Int J Environ Res Public Health. 12(8):8717-8743.

Figure 1. Summary of the estimated low (a) and high (b) TiO_2 concentration exposed daily from the usage of each type PCP. Each symbol in the figure represents an estimated TiO_2 exposure from corresponding PCP.

Figure 1.

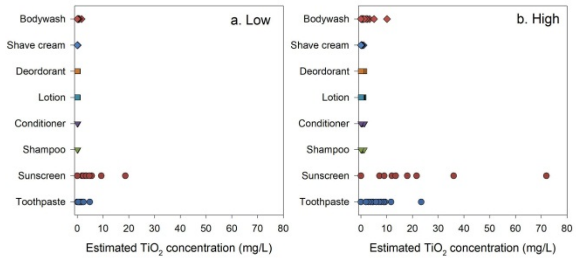

Figure 2. Estimated daily low (a) and high (b) individual TiO_2 exposure corresponding to the household income. Panel c shows the estimated exposure distribution of individual TiO_2 exposure of the surveyed population.

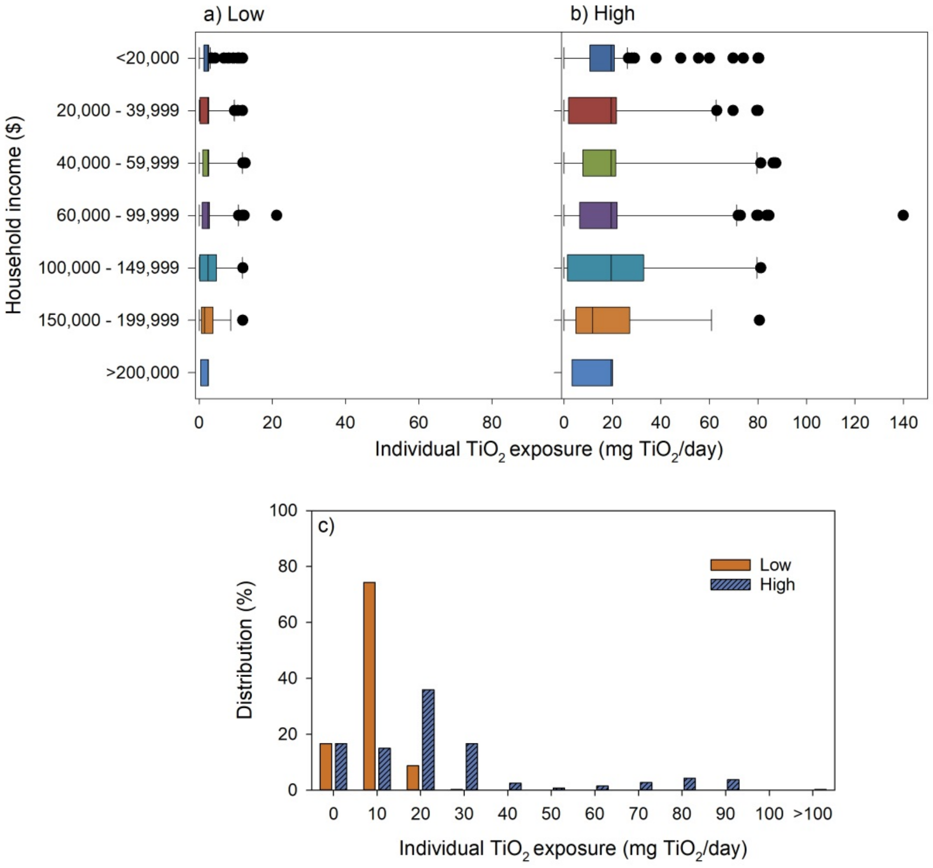

Figure 3. Estimated daily exposure of TiO_2 from the use of PCP (mg TiO_2/person-day): a) average low (2.91 mg TiO_2/person-day); b) average high (21.38 mg TiO_2/person-day); c) worst case scenario derived from the maximum values of each product (185.71 mg TiO_2/person-day). Oral route exposure was estimated based on assuming 10% of toothpaste is ingested to population at all ages.

Figure 3.

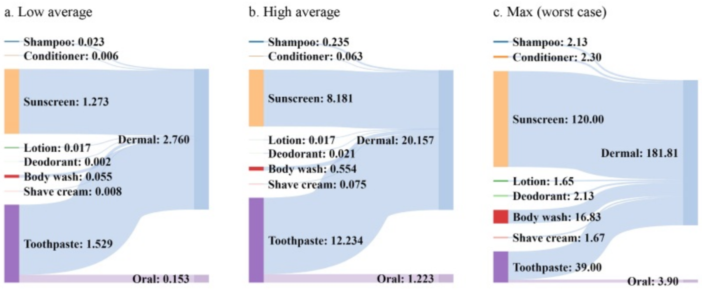

Table 1. Data used to calculate the concentration of TiO_2 used in each PCP category. PCP usage data and TiO_2 in PCP were gathered from the literature (Bennett et al. 2010; Biesterbos et al. 2013; Hall et al. 2011; Loretz et al. 2008; Loretz et al. 2005; Loretz et al. 2006; Peters et al. 2014; Rompelberg et al. 2016; Warheit et al. 2015; Weir et al. 2012; Yang et al. 2014).

	PCP usage (mean)	**TiO_2 in PCP (mg Ti/g)**	
Product	***g/person/day***	***Low Est. Con.***	***High Est. Con.***
Toothpaste	2.09	0.7	5.6

Sunscreen	0.4	14	90
Shampoo	11.76	0.01	0.1
Conditioner	13.1	0.01	0.1
Lotion	9.92	0.1	1
Deodorant	0.4	0.01	0.1
Shave cream	1 (g/household/day)	0.01	0.1
Shower gel	10.1	0.1	1
Soap bar	2.5	0.1	1