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Nanoparticular surface-bound PCBs, PCDDs, and PCDFs—a novel class of potentially higher toxic POPs

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Abstract In a previous study, Env Sci Poll Res:1-7, 2015 showed that polychlorinated biphenyls (PCBs), polychlorinated dibenzo dioxins (PCDDs), and polychlorinated dibenzo furanes (PCDFs) are found in commercially available (nano) particular titanium dioxide as a result of the fabrication. Here, we give a brief perspective and reason the toxicity of these new classes of persistent organic pollutants (POPs) by reviewing also their nanoparticular properties, such as surface-to-volume ratio, photocatalytic activity, polarity shifts, and stealth effect. These insights point towards a new class of POPs and toxicologic effects, which are related to the size but not a result of nanotechnology itself. We pave the way to the understanding of until now unresolved very complex phenomena, such as the indoor exposure, formation, and transformation of POP and sick-building syndrome. This is a fundamental message for nanotoxicology and kinetics and should be taken into account when determining the toxicity of nanomaterials and POPs separately and as a combination.

Keywords Polychlorinated biphenyls (PCBs) · Polychlorinated dibenzo dioxins (PCDDs) · Polychlorinated dibenzo furanes (PCDFs) · Titanium dioxide (TiO_2) nanoparticles (NPs) · Stealth effect · Radical oxidative stress (ROS) · Sick-building syndrome · Indoor exposure · Toxicokinetics · Nanotoxicology · Cosmetics · Food additives · Pigments · Hydroxylated-POPs

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Introduction

Nanotoxicological studies endeavor to determine whether and to what extent the exceptional properties of nanoparticles (NPs) pose a threat to humans or the environment (Ai et al. 2011). The nonlinear increase of NP surface-to-volume ratio with decreasing size causes differing physico-chemical properties to their bulk counterparts, such as polyradical properties due to dangling bonds, surface functionalization, and stealth effects. However, properties other than surface-to-volume ratio may influence potential toxicity of NPs, including their shape, size, surface structure, inner structure, surface charge, aggregation, agglomeration, solubility, and polarity (Nel et al. 2006; Bolis et al. 2012). For example, the chemical properties of nanomaterials are known to increase production of reactive oxygen species (ROS), including free radicals (Nel et al. 2006). ROS has been identified as a primary mechanism of NP toxicity, possibly leading to oxidative stress, inflammation, and consequent damage to proteins, membranes, and DNA (Nel et al. 2006). ROS occurs in a wide range of

nanomaterials including carbon fullerenes, carbon nanotubes, and NPs of metal oxides. The extent of NP applications and the range of NP features, make health risk assessments of NP exposure very complex.

As discussed in a previous article (Ctistis et al. 2015), we found that titanium dioxide (TiO_2) nanoparticles contain persistent organic pollutants (POPs)—potentially surface bound—e.g., polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins (PCDDs), and polychlorianted dibenzofurans (PCDFs). POPs are organic compounds resistant to environmental degradation through chemical, biological, and photolytic processes. The activity of POPs can thereby dramatically change in the presence of catalytic active NPs while being bound to their surface, e.g., the formation of hydroxylated POP analogues on the catalytic active NPs in the presence of ROS. The NPs with POP load (NP-POPs) add to the attributes of POPs, for example environmental persistence, long-range transportation capability, bioaccumulation in human and animal tissue, bioaccumulation in food chains, and significant impacts on human health and the environment (Robertson and Hansen 2015). We would like to highlight that the shift of polarity of lipophilic POPs by being adsorbed to hydrophilic NPs such as TiO_2 might completely change their known routes of uptake, tissue distribution, excretion, accumulation, and interference with, e.g., DNA, proteins, enzymes, and cell membranes. This in turn raises questions about the results of nanotoxicology studies on TiO_2, which have not taken impurities of POPs and their activation into account.

It is our hypothesis, based on literature and our recent findings, that nanoparticle surface-bound POPs, such as PCBs, PCDDs, and PCDFs, alter the physico-chemical and toxicological properties of POPs separately and in their combination. In this paper, we reason probable toxicity and toxicokinetic pathways of the surface-bound PCBs, PCDDs, and PCDFs on TiO_2. We support our hypothesis by looking at the physico-chemical properties, such as binding, surface-to-volume ratio, and photocatalysis of the nanoparticles and infer the properties of the surface-bound POPs from them.

Discussion

We assume that NP surface-bound POPs such as PCBs, PCDDs, and PCDFs change the results of nanotoxicological analysis negatively. This is due to the additional toxicity of POPs in general. We discuss a probable scenario showing a size dependence of the toxicological effect of POPs bound to the surface of NPs using as example TiO_2. Furthermore, we reason that the toxicokinetics including the route of exposure, uptake pathways, transport, distribution, and excretion of these POPs is altered by the binding to TiO_2 NPs.

Surface-to-volume ratio and consequences on binding POPs at the surface

It is generally accepted that with smaller particle size the toxicity of NPs increases. This was shown for TiO_2 NPs (Oberdörster et al. 2005). As biological endpoint, the percentage of neutrophils in lung lavage of rats and mice were determined as an indicator of inflammation. There is a clear correlation between inflammation and surface area. In this carefully conducted study (Oberdörster et al. 2005), the crystal structure was as well defined and kept the same. This is important due to the higher production of ROS of anatase in comparison to rutile structure of TiO_2. The comparison of the two crystal structures is necessary because the crystal structure of rutile and anatase (the two main structures of TiO_2 in commercially available powders) differs significantly and leads to different surface structure and termination. Therefore, the two (nanoparticular) structures have a significantly different influence on the catalytic activity of NP (Diebold 2003).

A direct consequence of the small particle size is that the number of surface atoms is very large compared to the number of volume atoms (Fig. 1a). Therefore, the particle surface exhibits a large amount of dangling bonds, which can interact with the environment resulting in a higher inflammation response. The toxicity of the particles is most likely higher due to their increased surface-to-volume ratio, which leads to the effect that the same mass equivalent exhibits a surface being orders of magnitudes larger than that of a bulk sample.

We want to add three additional aspects to this model. First, by focusing on the number of absorbed molecules per volume absorbed on the surface of a NP. Calculating the number of molecules per volume absorbed on the surface of the particle (Fig. 1b) results in a $1/r$ dependence, directly mirroring the ability to affect these adsorbates. Increased concentration of POPs adsorbed onto a surface of a nanoparticle like TiO_2 results as well in a higher toxicity of the sample. Secondly, looking more closely to the energetic properties, the small particle size leads to a large inner pressure and thus also a higher surface tension σ of the particle, which is an order of magnitude larger compared to bulk material, and which can be calculated by the Kelvin equation (Nanda et al. 2003; Rai et al. 2006).

Figure 1c shows a simplified numerical calculation for the surface free energy dependence on the nanoparticle radius being calculated via (Zhang et al. 2009):

$$\gamma = \frac{2}{r^2}\int_{r_0}^{r} frdr \quad \text{for } r_0 < r < r_1$$

$$\gamma = \frac{r_1^2\gamma_1}{r^2}\frac{2}{r^2}\int_{r_0}^{r} frdr \quad \text{for } r > r_1,$$

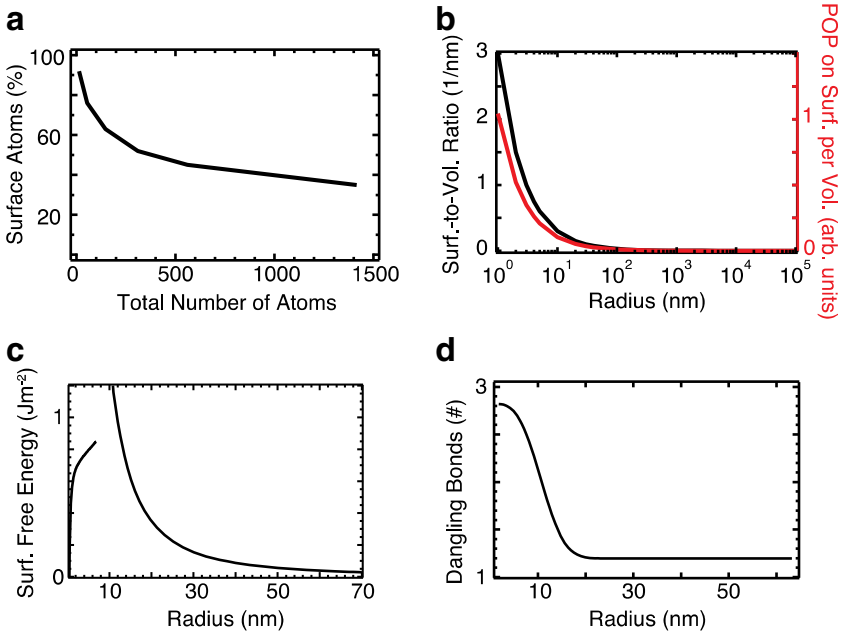

Fig. 1 **a** Surface atoms compared to the total number of atoms in a NP. **b** Surface-to-volume ratio versus nanoparticle radius (*black*). The area increases rapidly with decreasing radius. Number of adsorbed POPs shown on the example of PCDDs and PCDFs on the surface per unit volume against the particle radius (*red*). It is apparent that for small radii, the NPs effectively affect more the adsorbed particles. **c** Surface free energy versus TiO_2 NP radius. **d** Number of dangling bonds with respect to the radius of a NP

where γ_1 is the surface free energy at r_1, the experimental accessible minimal radius of the particle. It is visible that there is a maximum at a particle size of approximately 15 nm.

The surface tension increase comes along with an increase in the surface free energy and therefore with a higher reactivity of the particles, i.e., their ability to attract adsorbates such as PCDDs, PCDFs, and PCBs to lower the surface energy. This effect can even be amplified by the different crystal structures and resulting surface reconstructions when using either anatase or rutile. As a result, the chance that POPs are absorbed on the nanoparticle surface is higher resulting in a higher probability to find POPs in NPs of smaller size. The surface tension and the surface free energy increases and results in a higher catalytic reactivity of the particles, i.e., activating and metabolizing POPs is increased and by that the toxicity of the POPs in the sample. The toxicity of the nanoparticles is increased by these assumptions. If these toxic effects are either additive or synergistic has yet to be demonstrated in future studies going much more into detail and will be presented in this series in a later stage.

The remaining question is how the POPs bond to the surface of the NPs. We will focus on the rutile facet in agreement with the studies presented earlier (Ctistis et al. 2015). The binding of small organic molecules to rutile facets is of great interest and has been studied at molecular resolution, in particular to understand and unravel catalytic properties of different rutile crystal facets. For example, Lanzilotto et al. (2011) studied the growth of pentacene molecules on the surface of rutile TiO_2(110). By scanning tunneling microscopy (STM) and near-edge X-ray absorption fine structure (NEXAFS), they found that pentacene was physisorbed with its long molecular axis oriented parallel to the surface and aligned along the [001] direction. Interestingly, the molecules lie flat on the surface, revealing a tilt angle of approximately 25° with respect to the surface plane. In this manner, pentacene forms molecular lines oriented perpendicular to the rows of bridging oxygen atoms (Fig. 2a) (Godlewski and Szymonski 2013). In a study from Zheng et al. (2009), the adsorption of the ionic liquid (1-ethyl-3-methyl-imidazolium bromide) [Emim] to rutile (110) was of interest for a novel synthetic route for TiO_2 nanoparticles (Fig. 2b) (Zheng et al. 2009; Kumar and Rao 2014). Figure 2b gives a schematic projected view of $[Emim]^+$ cations anchored onto the rutile (110)-plane to form tight coverage layer via the original cell. The above examples provide a brief impression of how small organic molecules adsorb to rutile surfaces. However, to the best of our knowledge, examples of how PCBs, PCDDs, and PCDFs adsorb to rutile surfaces cannot be found in the literature. Due to the different substitution patterns found in these POPs and grades of substitution, the electron density varies accordingly in the aromatic rings influencing $\pi-\pi$ interactions for particle surface binding. Further, sigma bonds are influenced by the negative inductive effect of the chloro- substituents, too. Another fundamental difference of PAHs such as pentacene is the presence of lone pairs of chloro- substituents. These may also interact directly with the rutile surface as well as the aromatic rings.

In conclusion, this offers a broad variety of binding types, binding strengths, and pre-coordinative catalytic activation of PCBs, PCDDs, and PCDFs, which is the subject of ongoing work in our research group and a follow-up publication in this series.

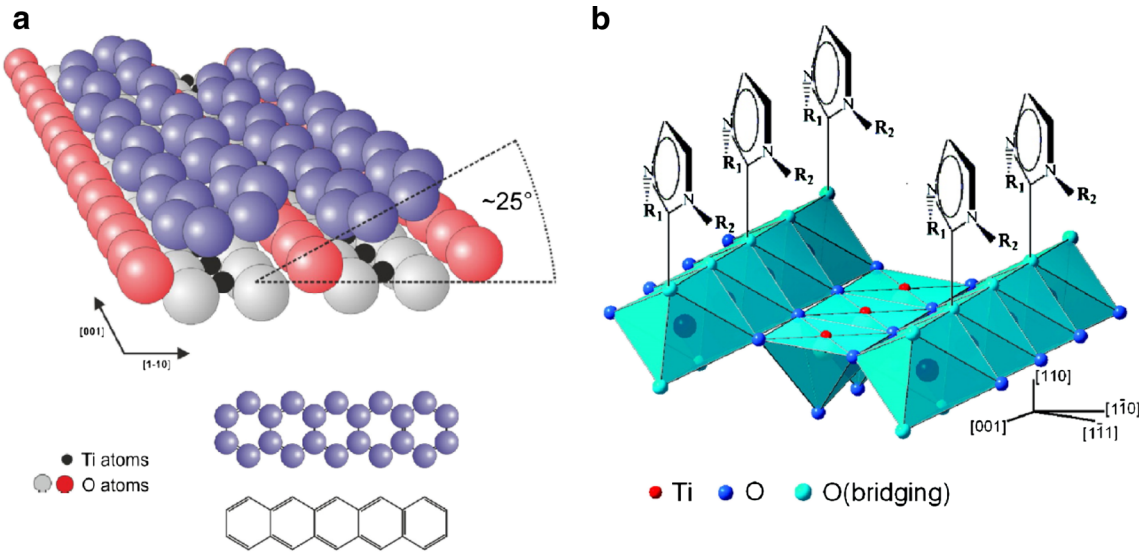

Fig. 2 Binding of small organic molecules to rutile (110) surfaces. **a** physiosorbed pentacene and **b** (1-ethyl-3-methyl-imidazolium bromide) (Emim) + cation anchoring to surface oxygen of rutile (Figure adapted from (Zheng et al. 2009; Godlewski and Szymonski 2013))

Photo- and thermo-catalytic degradation of POPs

Several studies report the catalytic degradation of PCBs in the presence of TiO_2 for example, in the remediation of PCB-contaminated soil by washing and subsequent TiO_2 photocatalytic degradation (Zheng et al. 2009), and in the thermal decomposition of PCBs (Tajik et al. 2013). A more influential and well-studied property of TiO_2 NPs is their use as photocatalysts. Being a wide bandgap semiconductor ($E_{gap} = 3 - 3.5$ eV), an irradiation with UV light is necessary to activate reactions. Figure 3c shows schematically the reaction path. Under UV excitation, an electron-hole-pair is created in the conduction and valance band, respectively. If the particle is small, as in the case of nanosized particles, then both electron and hole can travel to the surface of the particle during their specific lifetime. There are now three possible reaction chains open: (i) the photo-generated electron can react with an electron acceptor on the surface and thus reduce it, (ii) the photo-generated hole reacts with a donor and oxidizes it, or (iii) the electron-hole pair recombines under excitation of a photon, which might trigger further reactions. These main reaction chains lead to hydroxylation of water and more interestingly to the decomposition of PCBs in other congeners as described by Lu et al. (2011). Hereby, the Cl-atom is separated from the chloro-aromatic molecule, leaving two radicals to react further. A more indirect reaction mechanism that is also possible under UV excitation of TiO_2 is an energy transfer to an adsorbed molecule due to the existing surface charge and the subsequently changed surface potential. It can affect the binding strength of the $\pi - \pi$ bonds in aromatic ring systems such as PCBs, thereby exciting the PCBs and rendering further reactions possible.

In addition to the size of the TiO_2 NPs, the crystal structure is of crucial influence on the formation of radical oxidative stress (ROS). It is reported that anatase/rutile 80/20 % and 3—5 nm generates sixfold more ROS than rutile under UV irradiation (Sayes et al. 2006). TiO_2 NPs are normally a mixture of anatase and rutile crystal forms (Xue et al. 2010; Petković et al. 2011). The presence of POPs and the catalytic activity of TiO_2 under radiation might be an answer to the unknown sources of PCB mixtures and other POPs in home environments. This may also be a factor in the so-called sick-building syndrome (Abdul-Wahab and Jansz 2011), see Fig. 3a.

Stealth effect of the NPs in the presence of POPs

In nanomedicine, PEGylated NPs with poly(ethylene glycol) (PEG) are often referred as "stealth" NPs (Li and Huang 2010) because they escape the surveillance better. However, this stealth effect is not unique to PEGylated NPs. Due to the high surface tension of NPs and the dangling bonds (see Fig. 1c, d) on their surface with increasing size, the NPs tend to bind plasma proteins and other biomolecules on their surface—same as they bind to PEG. By that, the recognition of macrophages, such as the Kupffer cells in the liver, of these "ambient-stealth" NPs is much smaller then expected. The uptake and a prolonged circulation half-life is an important result of this effect. This has direct effect for the toxicity of the POPs like PCBs bound on the surface of TiO_2. We assume that remaining in the plasma is increased and thus their biological availability. This "ambient-stealth" effect results in special translocation effects of the NPs as well as of the bound POPs. It is known they cross the blood-air barrier of the lungs gaining access to the circulation and by that to the organs

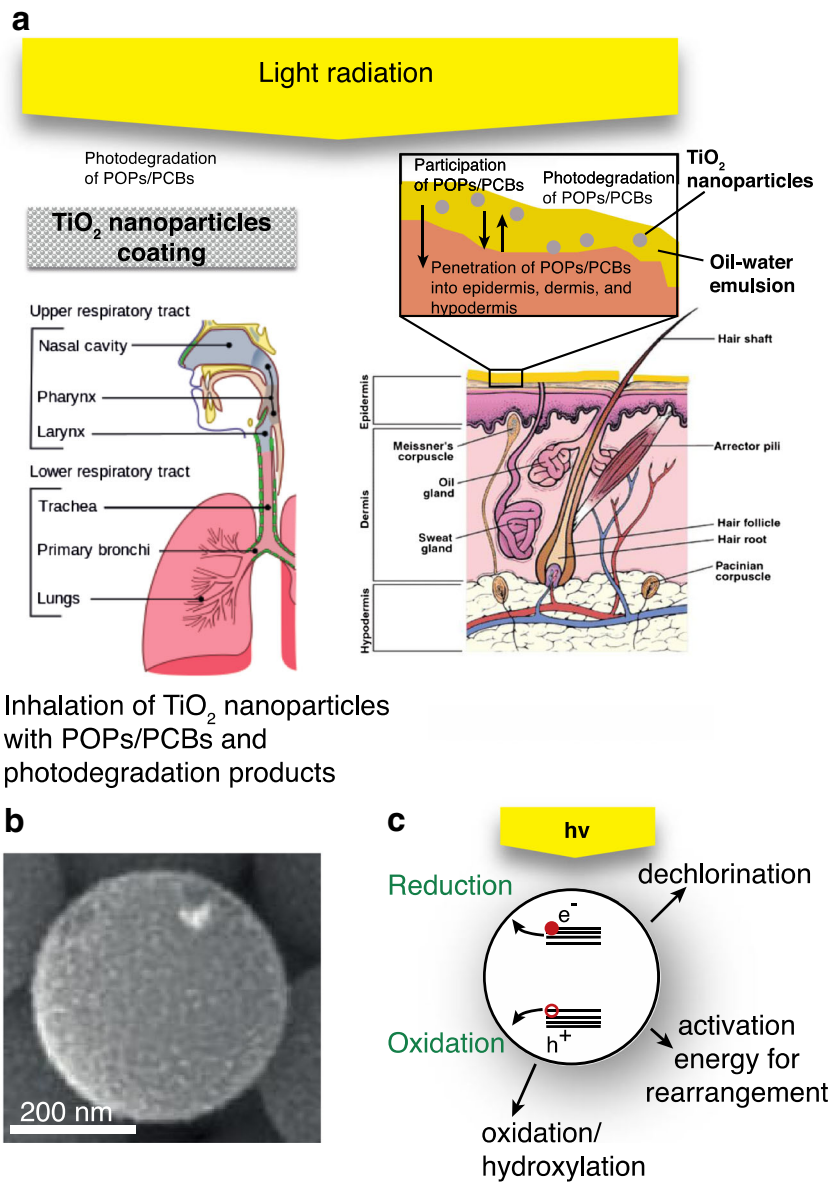

Fig. 3 **a** Schematics of where NPs can affect the human body. Due to their properties, they can be hydrophilic as well as lipophilic thus entering the body through the respiratory system as well as through the dermis. **b** Scanning electron micrograph (*SEM*) of a TiO_2 NP with a diameter of $d = 400$ nm. **c** Schematics of the processes during photocatalysis. The main part is the excitation of the electron-hole pair, which then can react at the surface with the adsorbed molecules rendering oxidation and reduction processes possible

(Mühlfeld et al. 2008). The entering mechanism into different cell types is a major focus of nanotoxicology. There is evidence that an uptake via the well-known pathways of endocytosis takes place (Kuhn et al. 2014). But although other mechanisms are observed but yet not fully understood, the translocation in the body plays a major role for the toxicokinetics.

Toxicokinetics of TiO_2-PCDDs and TiO_2-PCDFs

PCDDs/PCDFs are primarily taken up by dietary of fat. Of the total exposure of 119 pg/day of a North American citizen (Schecter et al. 2001), 38 pg/day are obtained by ingestion of beef, 24.1 pg/day from dairy, 17.6 pg/day from milk consumption, 12.9 pg/day from chickens, and 12.2 pg/day from pork ingestion. Consumption of fish results in 7.8 pg/day, eggs 4.1 pg/day, and only 2.2 pg/day by inhalation, 0.8 pg/day by soil ingestion and water is negligible. We suggest that, based on our findings that PCDDs/PCDFs are adsorbed on TiO_2, an additional route of exposure based on the toxicokinetics of TiO_2 is possible, which forms the major mass percentage of the TiO_2-PCDD and TiO_2-PCDFs. While PCDDs/PCDFs are lipophilic and are stored in fatty tissues, TiO_2 nanoparticles are not distributed to the fatty tissue, but through the blood stream to organs, see Fig. 4. We expect that the half-life time of TiO_2-PCDD and TiO_2-PCDFs is comparable to TiO_2 NPs and should be much shorter compared to estimated elimination half-life for highly chlorinated dioxins (4–8 chloro-substituents) in humans ranging from 4.9 to 13.1 years (Milbrath et al. 2009). However, while metabolism of PCDDs/PCDFs is very slow via cytochrome P450, we expect an increased metabolism on the NP bound PCBs due to the catalytic reactivity of the surface and the formation of ROS.

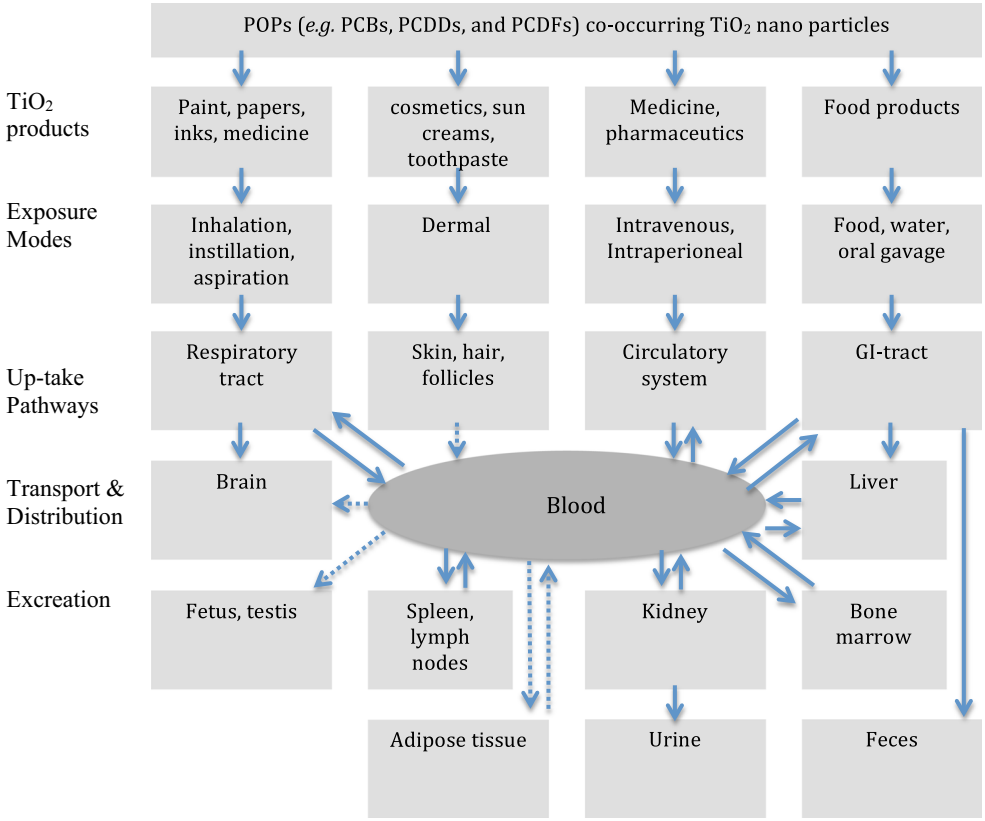

Fig. 4 Sources and potential routes of exposure of PCDDs/PCDFs co-occurring with TiO_2 nanoparticles, toxicokinetics, and accumulations sites. The hydrophilic surface of TiO_2 result in different uptake pathways, transport and distribution, and excretion and accumulation of co-occurring—potentially surface bound—POPs. The model for NP-POPs is based on findings and suggestions of TiO_2 nanoparticles as model NPs. The *arrows in dotted lines* represent uncertainties in the TiO_2 model

Inhalation, instillation, and aspiration

POPs from TiO_2 in paints, papers, and medication are inhaled, instilled, and aspirated via the respiratory tract. The size of the TiO_2 NPs as carrier of or vehicle for POPs leads to different uptakes. Rodent studies show that in the respiratory tract, most particles in the range of 1–5 nm are distributed throughout the nasopharyngeal, tracheobronchial, and alveolar regions; 50 % of the 20 nm particles are found in the alveolar region, while particles ≥500 nm remain in the epithelial tissue of the airways (Shi et al. 2013). Human data are currently not available (Kuempel et al. 2006). On WKY/NCrl BR rats, a fraction of the TiO_2 NPs (20 nm, 24 h) are translocated from the airway lumen to interstitial tissue and thus released into the systemic circulation (Mühlfeld et al. 2007). The same has been shown for intratracheal instillation (21 nm, 42 days) (Oberdorster et al. 1994; Sager et al. 2008). It has also been demonstrated that after 28 days, TiO_2 NPs (21 nm) reached the kidney and liver via the blood circulation (Li et al. 2010). Humans breathe primarily through the nose, termed nasal breathing. The nasal cavity has two segments, namely the respiratory segment and the olfactory segment. The respiratory segment is lined with ciliated pseudostratified columnar epithelium. It has a vascularized lamina propria allowing the venous plexuses to expand with blood. The olfactory segment is lined with the olfactory epithelium, which contains receptors for the sense of smell. Olfactory mucosal cell types include bipolar neurons, supporting (sustentacular) cells, basal cells, and the Bowman's glands. The olfactory nerve (cranial nerve I) is formed by axons of the bipolar neurons and enters the brain through the cribiform plate. Studies (Wang et al. 2008a; Wang et al. 2008b) on murine brains report that intra-nasally instilled TiO_2 NPs (80 nm rutile, 155 nm anatase; 500 μg/ml; 2, 10, 20, and 30 days) can be taken up by sensory nerves and translocated to the brain. By this mechanism, biological activated POPs can be translocated to the brain, see Fig. 4.

Dermal absorption

POPs bound to TiO_2 NPs in cosmetics, sun creams, and toothpaste could be absorbed dermally via the skin, hair, and follicles. However, this is generally unlikely in healthy skin, as only fatty compounds with a molecular weight <500 should penetrate the epidermis (Senzui et al. 2010). This penetration is of interest due to the direct contact of skin with consumer products, such as cosmetics and sunscreens. In the case of sunburned skin, micro-raptures should allow TiO_2 NPs to migrate. However, studies do not prove evidence of this pathway (Pflücker et al. 2001; Schulz et al. 2002; Gamer et al. 2006; Newman et al. 2009; Sadrieh et al. 2010). Similarly, NPs in vacant hair follicles do not show penetration of viable epidermis (Lademann et al. 1999). Contradictory studies with test

persons over a period of 2–6 weeks using tape stripping of the skin show increased values of TiO_2 NPs (10–50 nm) in the epidermis (Tan et al. 1996). Studies of hairy skin also show a penetration of 20 nm through hair follicles or pores (Xu et al. 2011; Sagawa et al. 2012). The close contact of POPs bound to TiO_2 NPs with the viable epidermis suggests the potential pathway of biological activated POPs by the properties of the nanovehicles through the skin to the blood stream, even when the NPs themselves do not enter. The POPs fulfill the criteria to penetrate. The combination of sun exposure, the photocatalytic properties of TiO_2 NPs, the proximity of POPs on the skin's surface, and the fatty environment (oil/water emulsions) suggests that a major route of exposure to POPs originates from sun creams and screens, and cosmetics, see Figs. 3 and 4.

Intravenous, subcutaneous, intraperitoneal

POPs bound to TiO_2 particles in intravenous and intraperitoneal pharmaceutics and medicine are uptaken via the circulatory system. In nanomedicine, intravenous or subcutaneous injections of TiO_2 NPs carriers is a unique delivery method (Zhao and Castranova 2011), useful in imaging and therapeutics, e.g., photosensitizers (Yuan et al. 2010). In addition, studies demonstrate that TiO_2 NPs show antibacterial properties under UV radiation (Yuan et al. 2010; Montazer et al. 2011) and that TiO_2 NPs (3 nm) can pass through the blood-brain barrier (Li et al. 2010), see Fig. 4.

Gastrointestinal absorption

POP bound to TiO_2 NPs in food products, water, and drugs are absorbed via oral gavage to the gastrointestinal tract. TiO_2 NP concentrations in water are generally low (Shi et al. 2013). A typical diet may contribute 300–400 μg/day. Highest concentrations are found in sweets, candies, and gums (<100 nm) (Lomer et al. 2002; Hagens et al. 2007). For medical purpose, TiO_2 NPs have been developed as efficient carriers to enhance oral uptake of drugs and vaccines (Hillyer and Albrecht 2001) and they translocate these drugs to other tissues (Jani et al. 1994). Uptake via Peyer's patches has been proposed, because of the elevated concentrations in lymph (Wang et al. 2007). Through this mechanism, the POPs bound to TiO_2 NPs can migrate to the liver and the blood stream and from there to all target organs. Before doing so, the catalytical nanosurface can activate and metabolize the POPs, thereby making them more water soluble. From there, the transport and distribution in the body via the blood stream takes place to the brain, liver, spleen, lymph nodes, kidney, bone marrow, and potential adipose tissue of released POPs and their metabolites, see Fig. 4.

Excretion

Excretion and accumulation of TiO_2 has been shown to take place in the fetus, testis, spleen, lymph nodes, kidney, and bone marrow (Liu et al. 2013). We suggest that the POPs and their metabolites bound to the TiO_2 NPs will be excreted and accumulated in the same way. While being dislocated and accumulated to these sites, the POPs will be in equilibrium according to their specific partition coefficient with their surrounding tissue. This can imply that the TiO_2 particles accumulate while the adsorbed POPs are released over time and redistributed. The accumulation patterns of the POPs may differ due to the TiO_2 vehicles strongly with freely POPs. However, the redistribution will also show an uptake in adipose tissue. TiO_2 particles can be excreted via urine and feces depending on the route of exposure, see Fig. 4.

Conclusions

We reason based on the findings in literature and our own experimental work (Ctistis et al. 2015) that POPs such as PCBs, PCDDs, and PCDFs change their physico-chemical properties while co-occuring with NPs. Nanoparticular POPs shift their polarity, e.g., lipophilic POPs become more water soluble. As a result of this, they change their routes of exposure, the tissue distribution, and the excretion are different to the corresponding parent POPs. The catalytic activity of NP surfaces in the presence of oxygen forming ROS might enhance the transformation into oxidized epoxides, oxiranes, and hydroxylated POP analogues. These oxidized POPs analogues show in studies toxicological metabolic and receptor activity, potentially membrane distortion, and adduct formation. These effects are strengthened by the increased number of molecules on the surface compared to increasing surface-to-volume ratio by decreasing size of the NP. In addition, the strength and activation of the bound POP increases with decreasing size and the toxicological effects might not be linear to their concentrations. POP patterns like the ones of PCBs that do not match Arcolor mixtures might be explained by their transformation in indoor and outdoor settings on the surface and co-occurrence on NPs in pigments such as wall papers exposed to light irradiation. The formation of higher PCDDs and PCDFs out of PCBs by thermal treatment and light exposure renders possible (Choudry and Hutzinger 1982), since TiO_2 can potentially function as catalyst, thus directly converting PCB to PCDF and PCDD. The latter reaction step is now in the focus of ongoing studies in our lab.

Our hypotheses are a novel pathway to the understanding of toxicokinetics of NP-POPs and have still to be tested by further research. A rigorous study of these effects is thus needed. We furthermore recommend an extraction or cleaning process for TiO_2 NPs after production, to reduce the quantity of

POPs and the potential human burden via this route in consumer goods.

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References

Abdul-Wahab SA, Jansz J (2011) Sick building syndrome: in public buildings and workplaces. Springer, Berlin; Heidelberg; New York

Ai J, Biazar E, Jafarpour M et al (2011) Nanotoxicology and nanoparticle safety in biomedical designs. Int J Nanomedicine 6:1117–1127

Bolis V, Busco C, Ciarletta M et al (2012) Hydrophilic/hydrophobic features of TiO 2 nanoparticles as a function of crystal phase, surface area and coating, in relation to their potential toxicity in peripheral nervous system. J Colloid Interface Sci 369:28–39

Choudry GC, Hutzinger O (1982) Photochemical formation and degradation of polychlorinated dibenzofurans and dibenzo-p-dioxins. Residue Rev 84:113–161. doi:10.1007/978-1-4612-5756-1_3

Ctistis G, Schön P, Bakker W, and Luthe G (2015) PCDDs, PCDFs, and PCBs co-occurrence in TiO_2 nanoparticles, Env Sci Poll Res pp1-7, doi:10.1007/s11356-015-5628-7

Diebold U (2003) The surface science of titanium dioxide. Surf Sci Rep 48:53–229. doi:10.1016/S0167-5729(02)00100-0

Gamer AO, Leibold E, Van Ravenzwaay B (2006) The in vitro absorption of microfine zinc oxide and titanium dioxide through porcine skin. Toxicol In Vitro 20:301–307. doi:10.1016/j.tiv.2005.08.008

Godlewski S, Szymonski M (2013) Adsorption and self-assembly of large polycyclic molecules on the surfaces of TiO2 single crystals. Int J Mol Sci 14:2946–2966. doi:10.3390/ijms14022946

Hagens WI, Oomen AG, de Jong WH et al (2007) What do we (need to) know about the kinetic properties of nanoparticles in the body? Regul Toxicol Pharmacol 49:217–229. doi:10.1016/j.yrtph.2007.07.006

Hillyer JF, Albrecht RM (2001) Gastrointestinal persorption and tissue distribution of differently sized colloidal gold nanoparticles. J Pharm Sci 90:1927–1936. doi:10.1002/jps.1143

Jani PU, McCarthy DE, Florence AT (1994) Titanium dioxide (rutile) particle uptake from the rat GI tract and translocation to systemic organs after oral administration. Int J Pharm 105:157–168. doi:10.1016/0378-5173(94)90461-8

Kuempel ED, Tran CL, Castranova V, Bailer AJ (2006) Lung dosimetry and risk assessment of nanoparticles: evaluating and extending current models in rats and humans. Inhal Toxicol 18:717–724. doi:10.1080/08958370600747887

Kuhn DA, Vanhecke D, Michen B, et al (2014) Different endocytotic uptake mechanisms for nanoparticles in epithelial cells and macrophages. Beilstein J Nanotechnol 1625–1636. doi: 10.3762/bjnano.5.174

Kumar SG, Rao KSRK (2014) Polymorphic phase transition among the titania crystal structures using a solution-based approach: from precursor chemistry to nucleation process. Nanoscale 6:11574–11632. doi:10.1039/c4nr01657b

Lademann J, Weigmann HJ, Rickmeyer C et al (1999) Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. Skin Pharmacol Appl Skin Physiol 12:247–256. doi:10.1159/000066249

Lanzilotto V, Sanchez-Sanchez C, Bavdek G et al (2011) Planar growth of pentacene on the dielectric TiO2(110) surface. J Phys Chem C 115:4664–4672. doi:10.1021/jp111011z

Li SD, Huang L (2010) Stealth nanoparticles: High density but sheddable PEG is a key for tumor targeting. J Controlled Release 145:178–181. doi:10.1016/j.jconrel.2010.03.016

Li Y, Li J, Yin J et al (2010) Systematic influence induced by 3 nm titanium dioxide following intratracheal instillation of mice. J Nanosci Nanotechnol 10:8544–8549. doi:10.1166/jnn.2010.2690

Liu K, Lin X, Zhao J (2013) Toxic effects of the interaction of titanium dioxide nanoparticles with chemicals or physical factors. Int J Nanomedicine 8:2509–2520

Lomer MCE, Thompson RPH, Powell JJ (2002) Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. Proc Nutr Soc 61:123–130. doi:10.1079/PNS2001134

Lu S-Y, Wu D, Wang Q-L et al (2011) Photocatalytic decomposition on nano-TiO2: destruction of chloroaromatic compounds. Chemosphere 82:1215–1224. doi:10.1016/j.chemosphere.2010.12.034

Milbrath MOG, Wenger Y, Chang CWCW et al (2009) Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. Environ Health Perspect 117:417–425. doi:10.1289/ehp.11781

Montazer M, Behzadnia A, Pakdel E et al (2011) Photo induced silver on nano titanium dioxide as an enhanced antimicrobial agent for wool. J Photochem Photobiol B 103:207–214. doi:10.1016/j.jphotobiol.2011.03.009

Mühlfeld C, Geiser M, Kapp N et al (2007) Re-evaluation of pulmonary titanium dioxide nanoparticle distribution using the "relative deposition index": evidence for clearance through microvasculature. Part Fibre Toxicol 4:7. doi:10.1186/1743-8977-4-7

Mühlfeld C, Gehr P, Rothen-Rutishauser B (2008) Translocation and cellular entering mechanisms of nanoparticles in the respiratory tract. Swiss Med Wkly 138:387–391, doi: 2008/27/smw-12153

Nanda KK, Maisels A, Kruis FE et al (2003) Higher surface energy of free nanoparticles. Phys Rev Lett 91:106102. doi:10.1103/PhysRevLett.91.106102

Nel A, Xia T, Mädler L, Li N (2006) Toxic potential of materials at the nanolevel. Science 311:622–627. doi:10.1126/science.1114397

Newman MD, Stotland M, Ellis JI (2009) The safety of nanosized particles in titanium dioxide- and zinc oxide-based sunscreens. J Am Acad Dermatol 61:685–692

Oberdorster G, Ferin J, Lehnert BE (1994) Correlation between particle size, in vivo particle persistence, and lung injury. In: Environmental health perspectives., pp 173–179

Oberdörster G, Oberdörster E, Oberdörster J (2005) Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 113:823–39

Petković J, Zegura B, Stevanović M et al (2011) DNA damage and alterations in expression of DNA damage responsive genes induced by TiO(2) nanoparticles in human hepatoma HepG2 cells. Nanotoxicology 5:341–353. doi:10.3109/17435390.2010.507316

Pflücker F, Wendel V, Hohenberg H et al (2001) The human stratum corneum layer: an effective barrier against dermal uptake of different forms of topically applied micronised titanium dioxide. Skin Pharmacol Appl Skin Physiol 14:92–97. doi:10.1159/000056396

Rai A, Park K, Zhou L, Zachariah MR (2006) Understanding the mechanism of aluminium nanoparticle oxidation. Combust Theory Model 10:843–859. doi:10.1080/13647830600800686

Robertson LW, Hansen LG (2015) PCBs: recent advances in environmental toxicology and health effects., University Press of Kentucky

Sadrieh N, Wokovich AM, Gopee NV et al (2010) Lack of significant dermal penetration of titanium dioxide from sunscreen formulations

containing nano- and submicron-size TiO2 particles. Toxicol Sci 115:156–166. doi:10.1093/toxsci/kfq041

Sagawa Y, Futakuchi M, Xu J et al (2012) Lack of promoting effect of titanium dioxide particles on chemically-induced skin carcinogenesis in rats and mice. J Toxicol Sci 37:317–327

Sager TM, Kommineni C, Castranova V (2008) Pulmonary response to intratracheal instillation of ultrafine versus fine titanium dioxide: role of particle surface area. Part Fibre Toxicol 5:17. doi:10.1186/1743-8977-5-17

Sayes CM, Wahi R, Kurian PA et al (2006) Correlating nanoscale titania structure with toxicity: a cytotoxicity and inflammatory response study with human dermal fibroblasts and human lung epithelial cells. Toxicol Sci 92:174–185. doi:10.1093/toxsci/kfj197

Schecter A, Cramer P, Boggess K et al (2001) Intake of dioxins and related compounds from food in the U.S. population. J Toxicol Environ Health A 63:1–18

Schulz J, Hohenberg H, Pflücker F et al (2002) Distribution of sunscreens on skin. Adv Drug Deliv Rev 54:S157–S163. doi:10.1016/S0169-409X(02)00120-5

Senzui M, Tamura T, Miura K et al (2010) Study on penetration of titanium dioxide (TiO(2)) nanoparticles into intact and damaged skin in vitro. J Toxicol Sci 35:107–113

Shi H, Magaye R, Castranova V, Zhao J (2013) Titanium dioxide nanoparticles: a review of current toxicological data. Part Fibre Toxicol 10:15. doi:10.1186/1743-8977-10-15

Tajik R, Asilian H, Khavanin A et al (2013) Degradation of transformer oil (PCB compounds) by microwave radiation, ethanol solvent, hydrogen peroxide and dioxide titanium for reducing environmental hazards. Iran J Toxicol 6:757–765

Tan MH, Commens CA, Burnett L, Snitch PJ (1996) A pilot study on the percutaneous absorption of microfine titanium dioxide from sunscreens. Australas J Dermatol 37:185–187. doi:10.1111/j.1440-0960.1996.tb01050.x

Wang J, Zhou G, Chen C et al (2007) Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration. Toxicol Lett 168:176–185. doi:10.1016/j.toxlet.2006.12.001

Wang J, Chen C, Liu Y et al (2008a) Potential neurological lesion after nasal instillation of TiO2 nanoparticles in the anatase and rutile crystal phases. Toxicol Lett 183:72–80. doi:10.1016/j.toxlet.2008.10.001

Wang J, Liu Y, Jiao F et al (2008b) Time-dependent translocation and potential impairment on central nervous system by intranasally instilled TiO2 nanoparticles. Toxicology 254:82–90. doi:10.1016/j.tox.2008.09.014

Xu J, Sagawa Y, Futakuchi M et al (2011) Lack of promoting effect of titanium dioxide particles on ultraviolet B-initiated skin carcinogenesis in rats. Food Chem Toxicol 49:1298–1302. doi:10.1016/j.fct.2011.03.011

Xue C, Wu J, Lan F et al (2010) Nano titanium dioxide induces the generation of ROS and potential damage in HaCaT cells under UVA irradiation. J Nanosci Nanotechnol 10:8500–8507. doi:10.1166/jnn.2010.2682

Yuan Y, Ding J, Xu J et al (2010) TiO2 nanoparticles co-doped with silver and nitrogen for antibacterial application. J Nanosci Nanotechnol 10:4868–4874. doi:10.1166/jnn.2010.2225

Zhang H, Chen B, Banfield JF (2009) The size dependence of the surface free energy of titania nanocrystals. Phys Chem Chem Phys 11:2553–2558

Zhao J, Castranova V (2011) Toxicology of nanomaterials used in nanomedicine. J Toxicol Environ Health B 14:593–632

Zheng W, Liu X, Yan Z, Zhu L (2009) Ionic liquid-assisted synthesis of large-scale TiO2 nanoparticles with controllable phase by hydrolysis of TiCl4. ACS Nano 3:115–122. doi:10.1021/nn800713w