

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

Peter Schön^{1,2} · Georgios Ctistis^{1,3} · Wouter Bakker¹ · Gregor Luthe^{4,5,6}

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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

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- ¹ NanoBioInterface Research Group, School of Life Science, Engineering, and Design, Saxion University of Applied Sciences, M.H. Tromplaan 28, P.O. Box 70.000, 7500 KB Enschede, The Netherlands
- ² Materials Science and Technology of Polymers, MESA+ Institute for Nanotechnology, University of Twente, PO Box 217, 7500 AE Enschede, The Netherlands
- ³ Complex Photonic Systems (COPS), MESA+ Institute for Nanotechnology, University of Twente, PO Box 217, 7500 AE Enschede, The Netherlands
- ⁴ Department of Occupational and Environmental Health, The University of Iowa, 100 Oakdale Campus, Iowa City, IA 52242, USA
- ⁵ Interdisciplinary Graduate Program in Human Toxicology, The University of Iowa, 100 Oakdale Campus, Iowa City, IA 52242, USA
- ⁶ Luthe Pharma, Fabrikstrasse 2, 48599 Gronau, Germany

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 (TiO₂) nanoparticles (NPs) · Stealth effect · Radical oxidative stress (ROS) · Sick-building syndrome · Indoor exposure · Toxicokinetics · Nanotoxicology · Cosmetics · Food additives · Pigments · Hydroxylated-POPs

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

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Gregor Luthe g.luthe@saxion.nl

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 (TiO₂) 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 TiO₂ 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 TiO₂, 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 TiO₂. 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 surfacebound 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 TiO₂. 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 TiO₂ 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 TiO₂ 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 TiO₂. The comparison of the two crystal structures is necessary because the crystal structure of rutile and anatase (the two main structures of TiO₂ 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 TiO₂ 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):

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

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 TiO₂ 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 TiO₂(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 TiO₂ 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 TiO₂ for example, in the remediation of PCBcontaminated soil by washing and subsequent TiO₂ 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 TiO₂ NPs is their use as photocatalysts. Being a wide bandgap semiconductor $(E_{gap}=3-3.5 \text{ eV})$, 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 TiO₂ 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 TiO₂ 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). TiO₂ 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 TiO₂ 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 TiO₂. 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 TiO₂ 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 TiO₂-PCDDs and TiO₂-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 TiO₂, an additional route of exposure based on the toxicokinetics of TiO_2 is possible, which forms the major mass percentage of the TiO₂-PCDD and TiO₂-PCDFs. While PCDDs/PCDFs are lipophilic and are stored in fatty tissues, TiO₂ 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 TiO₂-PCDD and TiO₂-PCDFs is comparable to TiO₂ 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 TiO₂ nanoparticles, toxicokinetics, and accumulations sites. The hydrophilic surface of TiO2 result in different uptake pathways, transport and distribution, and excretion and accumulation of cooccurring-potentially surface bound-POPs. The model for NP-POPs is based on findings and suggestions of TiO2 nanoparticles as model NPs. The arrows in dotted lines represent uncertainties in the TiO₂ model



Inhalation, instillation, and aspiration

POPs from TiO₂ in paints, papers, and medication are inhaled, instilled, and aspirated via the respiratory tract. The size of the TiO₂ 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 \geq 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 TiO₂ 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, TiO₂ 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 TiO₂ NPs (80 nm rutile, 155 nm anatase; 500 μ g/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 TiO₂ 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 TiO₂ 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 TiO₂ 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 TiO₂ NPs in food products, water, and drugs are absorbed via oral gavage to the gastrointestinal tract. TiO₂ 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, TiO₂ 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 TiO₂ 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 TiO₂ 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 TiO₂ 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 TiO₂ particles accumulate while the adsorbed POPs are released over time and redistributed. The accumulation patterns of the POPs may differ due to the TiO₂ vehicles strongly with freely POPs. However, the redistribution will also show an uptake in adipose tissue. TiO₂ 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 surfaceto-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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