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(Nano)-Titanium dioxide (Part II): health hazard potential

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Summary

Nano-titanium dioxide (nano-TiO_2) is the nanomaterial produced in the largest amounts and is already contained in numerous products, both in the regular and in nano-scale size. It is therefore also the best investigated nanoparticle. Many in-vivo and in-vitro studies have been conducted to test for potential health hazards, although the epidemiological studies have not demonstrated any TiO_2-specific effects. Currently, however, no nano-TiO_2-specific epidemiological studies and no data are available on potential exposure. Nonetheless, various international bodies have classified the material as "possibly carcinogenic in humans" based on animal experiments and have pointed to the risks. There is no specific regulation for nano-TiO_2 and therefore the regulation for (ultra-)fine particulate emission isapplied.

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Introduction

Titanium dioxide (TiO_2) has been produced industrially for more than 100 years[1]; this explains why nano-titanium dioxide (nano-TiO_2) is the best-investigated nanomaterial. The question of health risks of TiO_2 both in its regular and nano-form is therefore highly relevant. Numerous epidemiological as well as in-vivo and in-vitro studies have been conducted in order to determine the risks. This dossier provides a brief overview. Details and compilations of studies along with more comprehensive risk assessments are available from international bodies (EU, IARC, OECD, FDA, CDC).

Uptake of TiO_2: Exposureroutes

Nanomaterials and nanoparticles (NP) can be incorporated directly into the body through inhalation or by swallowing[1]. One topic of discussion is that the skin is a natural barrier against NPs, but that these substances can enter via the pores. For the general public, the two relevant routes are exposure of the skin – by using TiO_2-NP-containing sunscreens – and swallowing of nano-containing TiO_2 in the form of a food additive. For those persons in the NP-production industry, the main route into the body is inhalation and swallowing.

Epidemiological studies

No epidemiological studies explicitly designed to examine nano-scale titanium dioxide particles are available. Nonetheless, numerous studies have been conducted on the effects of the TiO_2 particles released during industrial production and processing on employees. All such epidemiological studies concluded that there is no evidence of an increased risk of lung cancer or other types of cancer[2-4]. Nonetheless, one should be careful because the absence of a clear evidence of a cancer risk is not a definitive conclusion to the potential carcinogenic capacity of nano-TiO_2. In a statement in 2010, the German Federal Institute of Risk Assessment (Bundesinstitut für Risikobewertung, BfR) it is explicitly stated: "Conclusions about a cancer risk associated with exposure to nano-TiO_2 cannot be drawn based on the available epidemiological investigations"[5].

Tests on animals: in-vivo studies

Uptake via the lungs: inhalation

Numerous studies on animals have investigated damage to the respiratory organs by nano-TiO_2. The effects are heterogeneous and depend on the experimental animals, with considerable differences between rats, mice and hamsters. Nonetheless, these studies uniformly show that inhaled TiO_2-NPs are deposited in the lungs. There, they can trigger inflammatory reactions; these, however, are temporary as long as the exposure is not chronic[6; 7]. After administration of high doses of TiO_2-NP (5 days, 50 mg/m^3), the inhaled particles are deposited in the lung as agglomerates; they were found inside the lymph nodes associated with the lungs (in the ma-

crophages). No NPs were detected in other organs after short-term exposure[8]. In contrast, TiO_2-NPs in low doses were further transported to the liver and kidneys, whereby the lungs remained unaffected and the other organs showed temporarily altered metabolite rates. The authors concluded that highly dosed TiO_2-NPs agglomerate in the lungs and induce strong inflammatory reactions, but that no further transport to the liver and kidneys takes place. The reason is that the lungs are overloaded: the macrophages can no longer phagocytize, and no further transport of the NPs is possible. At low doses, some of the NPs are further transported to other organs, whereby no health impacts were demonstrable[9; 10]. Subchronic exposures led to similar results[11; 12].

Chronic exposure of the lungs to nano-TiO_2 can also lead to inflammatory changes such as oxidative stress and fibroses – depending on the dose inhaled. This can lead to lung cancer[13]. The underlying mechanism of action is thought to involve so-called secondary genotoxicity, that is chronic inflammation processes and damage to the DNA and other macromolecules through oxidative stress[14; 15; 16]. Note that the photocatalytic effect of nano-TiO_2 is not relevant in the lungs because no UV radiation penetrates there.

Another topic of debate is whether nano-TiO_2 can enter the brain. The question whether NPs can reach the brain via the lungs or along the olfactory nerve is currently under investigations. The few studies conducted to date are controversial. We do know, however, that only few particles reach the brain, so that a short-term dose is insufficient to induce damage. Long-term effects have not been demonstrated yet[17; 18].

In summary, the in-vivo studies on inhalation/installation have shown that nano-TiO_2 can trigger dose-dependent effects in the lungs. In rats, changes in lung clearance and an increase in particle retention due to overload were observed at very high doses. These can trigger inflammatory reactions, oxidative stress, fibroses and even lung cancer. It remains unclear whether the studies involving highly dosed NPs are relevant. Studies on mice showed lung impairment and inflammation but not fibroses or cancer; hamsters showed the least impairment. That particles and dust can cause lung disease is a well-known phenomenon which is not related to nano-TiO_2 as such.

Uptake via the gastrointestinal tract: ingestion

Regular TiO_2 is acertified food additive (E171). The addition of TiO_2-NPs to foods or food packaging in not uniformly regulated EU wide. In Germany, however, it is not permitted. One study shows that – based on the production process – that more than one third of the E171 in foods contains nanoparticles (diameter < 100 nm)[19]. TiO_2-NPs can therefore enter the gastrointestinal tract. The authors calculated the daily intake of adults to be ca. 1 mg TiO_2/kg body weight. Accordingly, 1/3 of this (ca. 300 µg/kg) could potentially be present in nano-size. Moreover, small amounts of TiO_2 from the lung can enter the gastrointestinal tract through re-swallowing. Unfortunately, only few studies are available on the uptake of nano-TiO_2 via the gastrointestinal tract[11; 20]. It is known, however, that TiO_2 can be reabsorbed into the human body from the gastrointestinal tract. In a study TiO_2 (diameter 160 and 380 nm, 3 and 46 mg) in gelatine capsules was administered for test persons, after which a size-dependent resorption into the blood was detected. The smaller the particles, the quicker the resorption[21]. In another study, female rats were orally administered 12.5 mg rutile TiO_2/kg (500 nm) for 10 days. The authors found small amounts of translocated TiO_2-NP in the liver, spleen, lung and peritoneum, but not in the heart and kidneys[22]. The assumption is that most of the particles taken up were excreted with the feces.

Another study investigated the genotoxic effect in pregnant mice that consumed nano-TiO_2 with their drinking water in a (very high) dose of between 60 and 600 µg over a period of five days. These mice took up nano-TiO_2 in the second half of their pregnancy, and their offspring showed special DNA damage, oxidative stress and/or inflammatory reactions attributable to secondary effects[23].

Uptake through the skin: dermal

The use of TiO_2-NPs as components of sunscreens is one of the key applications. More than one half of the synthetically produced nanoparticles of this type are used inthis sector. In sunscreens, TiO_2-NPs function as physical filters. This approach is gradually replacing chemical filters because the latter can cause skin irritation or allergies (see[1]). A range of calculations are available on the amount of nano-TiO_2 used in sunscreens. In the case of a suntan lotion containing 5 % nano-TiO_2, the assumption is that 0.5 to 2.3 g/application/person (for adults) and 0.17 to 0.76 g/application/child (3-year-old) is applied to the skin[24; 25].

The primary question, however, is whether the NPs reach living skin cells, where they can potentially cause damage. It is commonly accepted that TiO_2-NPs remain on the surface of the skin and in the region of the dead upper layers (stratum corneum, see[26]). The EU-research project "Nanoderm" also came to the conclusion that no negative health effects are to be expected when sunscreens containing nanoparticles are applied to healthy skin. Note that these particles are coated – first to prevent photocatalytic activity, i.e. the formation of free radicals, and second to prevent agglomeration[27]. A frequent topic of discussion is the "aging" of NPs in sunscreens and the loss of the NP coating. Nonetheless, studies show that the remaining coating continues to provide protection against the formation of free radicals[28; 29].

Recent studies have also determined that nano-TiO_2 does not penetrate into the body through the skin[6]: the skin with its many layers serves as a good barrier. One topic of discussion is whether NPs can penetrate into deeper layers via the hair follicles. In a study on test persons, coated nano-TiO_2 (UV-Titan M 160 in an oil-water suspension) was applied to 160 cm^2 of human skin (2 mg sunscreen/cm^2, 5 times per day for three days, once on day 4). No particles were detected in the deeper layers of the stratum corneum. In isolated skin regions, however, TiO_2-NPs were detected in individual hair follicles[30]. No long-term studies on the potential accumulation of such particles in the follicles are available; the health hazard is considered as unlikely. It is unclear, however, what happens when the barrier function of the skin is compromised, such as in the case of injuries, sunburn and various skin diseases. Currently, only one study is available, where it is shown that skin of pigs subjected to UVB radiation (sunburn) is not permeable to nano-TiO_2, but that the particles remain in the upper layers of the epidermis[31]. Another study was devoted to more closely examining the penetration of NPs into the skin. Sunscreen with nano-TiO_2 was applied to the skin of mini-pigs for 4 weeks (2 mg cream/cm^2 skin (4-times per day, 5 days per week, 4 weeks) and small (not significant) amounts of NPs were also found in the deeper skin layers and in several lymph nodes[32].

The EU expert group "Scientific Committee on Consumer Products" (SCCP), in a position paper on "safety aspects of nanomaterials in cosmetics", points out that "it is currently hardly possible to detect small amounts

Table 1: Categorization of substances that can be carcinogenic in humans (after IARC/WHO41)

Group 1	Carcinogenic in humans	107 agents
Group 2A	Probably carcinogenic in humans	63 agents
Group 2B	Possibly carcinogenic in humans	271 agents
Group 3	Not classifiable as to its carcinogenicity to humans	509 agents
Group 4	Probably not carcinogenic to humans	1 agents

of nanoparticles that potentially reach deeper skin layers and possibly also the bloodstream. Nonetheless, when the applied dose of nanoparticles is very high, small amounts could accumulate and trigger adverse health effects …"[33]. This mechanism is conceivable, but there is currently no scientific evidence or verification to support this statement.

Investigations on cells – in vitro

In-vitro studies are typically used to investigate mechanistic questions. The tested parameters include so-called biological endpoints such as survival rate, cell death, formation of free radicals etc. in order to determine potential mechanisms of action leading to cell damage. The choice of cells is important because, depending on the organ from which they stem, cell-type-specific effects can occur. Typically, in-vitro studies can only reveal acute effects. The development of (multi-)cell models that closely approach in-vivo conditions is a promising approach that is currently undergoing research.

In order to successfully expose cells to TiO_2-NPs, the NPs must undergo complex treatment because they show a strong tendency to agglomerate. This also means that the number of free NPs is rather low. Very high doses of nano-TiO_2 (> 50 $\mu g/cm^2$) are known to cause cell damage in vitro and to affect almost all biological endpoints. Nonetheless, cells react differently to different doses. Such high doses, however, never occur in everyday life or when regulations are adhered to in the case of occupational exposure[34; 35].

TiO_2 belongs to the class of substances known as granular bio-persistent dusts. This means they are not degraded in the body but either remain there or are excreted. In high concentrations, inhaling such dusts can cause inflammatory or fibrotic changes as well as lung tumors in rats. The tumor formation develops indirectly due to the inflammation in the lung region. This, in turn, reflects the increased uptake of particles by macrophages and other immune-relevant cells, whereby increased amounts of free oxygen radicals are formed. These can damage adjoining cells and the DNA (see[36]), which can ultimately end in inflammation or even malignancy. Numerous studies have been conducted with various lung, blood and epithelial cells to investigate this mechanism. In all cases, only high doses of TiO_2-NPs showed toxic effect. Although high doses in vitro also cause genotoxic effects, these are attributed to the secondary genotoxicity due to the persistent inflammation[37; 38].

In-vitro studies using human intestine cells show similar results, albeit only few studies are available. Applying high doses (20 and 80 $\mu g/cm^2$) of TiO_2-NPs triggered significant membrane damage and vitality losses, but no relevant genotoxic effects were detected[39].

Skin cells are also an object of research. Numerous studies have been conducted in an attempt to determine potential gene-damaging or other effects, with contradictory results. One clear conclusion is that, that the dose, the size, shape, as well as the physical and chemical properties of the NPs are relevant when particles enter the interior of the cell (see overview[40]).

Expert assessments of the risks

A number of expert groups are involved with estimating the human health risks of substances. Often, the focus is on the carcinogenic effects. These assessments use evidence-based results of scientific investigations with predetermined criteria to enable comparability between the studies.

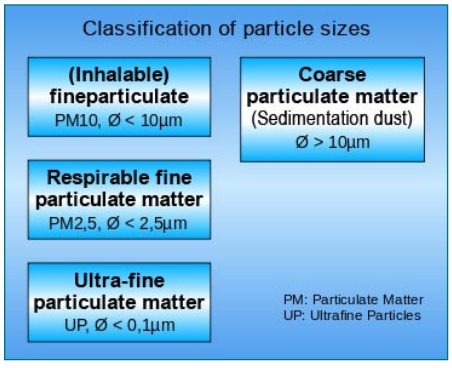
The World Health Organization's International Agency for Research on Cancer (IARC/WHO) has assessed TiO_2 – without consideration of size – as "possibly carcinogenic in humans"[41]. This classification into the risk category 2B is based on what is seen as "sufficient" evidence of increased rates of lung tumors in rats that have inhaled TiO_2-NP over lengthier periods (see Table 1).

The CDC/NIOSH (USA) came also to the assessment that ultrafine TiO_2 particles represent a potential occupational carcinogen at the workplace[13]. This is because these particles, similar to other only poorly soluble ultrafine particles with low toxicity (PSLT), consistently triggered dose-dependent lung damage and lung tumors in rats.

The so-called "MAK-Kommission" (commission dealing with maximum allowable concentrations at the workplace) of the Senate Commission, German Science Fund (DFG-Senatskommission) now groups the inhalable dust fraction (see Fig. 1 and below) of TiO_2 dusts in category 3A, representing "demonstrated carcinogenic substances in animals". In this case as well, ultrafine (nano-scale) particles were *not* considered in the assessment[15].

All three organizations based their categorizations on the results of experiments with animals because no data and no cases are known that point to tumor development in humans due to nano-TiO_2.

Figure 1: Classification of particle sizes. In some cases, particles are considered to be fine particulate matter only at a diameter < 2.5 µm. Accordingly, particles with a diameter > 2.5 µm are already considered to be coarse particulate matter (after[51])



On the regulation of nano-titanium dioxide

The question whether TiO_2 dusts originating during the production process entail health risks has long been a topic of epidemiological research. Numerous measurements have been conducted at workplaces and the overall exposure been calculated for days, years and the entire working life. The measured dust concentrations – the so-called inhalable fraction – amounted to 6.1 mg/m^3 air in the period 1976-1980. This value dropped to ca. 1.0 mg/m^3 between 1996 and 2000[3]. The alveolar/respirable (smaller particle size) fraction was calculated to lie between 0.1 and 0.7 mg/m^3 air, with peak exposures of up to 8.0 mg/m^3 air[15; 42]. The epidemiological studies[2-4] found no evidence of an elevated lung cancer risk. Animal experiments, however, have shown that inhaling TiO_2 – as well as other granular and bio-persistent dusts without known specific toxicity – can trigger dose-dependent inflammatory lung damage and even lung tumors. This mechanism is valid for all granular bio-persistent dusts, not only for TiO_2. Current regulations or recommendationson legally binding workplace concentrations do not consider the specific risks of small (ultrafine and nano-scale dusts (see Fig.1). Equally, no agreement exists on the potentially carcinogenic effects of granular bio-persistent dusts. Accordingly, lower limit values are currently under discussion.

Regulations for ultrafine and nano-scale titanium dioxide particulate matter at the workplace

The term (inhalable) particulate matter generally refers to particulate matter with a particle size smaller than 10 μm (PM10); (alveolar) ultrafine particles, in contrast, are smaller than 0.1 μm (see Fig. 1). In Austria the limit value for TiO_2 is 6 mg/m^3 regardless of size. The internationally valid guide values for the permissible concentrations of TiO_2-containing particulate matter at the workplace range between 3 mg/m^3 in Switzerland and Germany, and 10 mg/m^3 in numerous other countries[41]. In most cases these values refer to average exposure values over an 8-hour workday (TWA, time weighted average).

In Germany the "Allgemeine Staubgrenzwert" (general airborne dust limit) is valid; it is directed at avoiding "unspecific effects of dusts on the respiratory organs of employees". Up until 1997, this pertained only to the smaller particle fraction, the alveolar/respirable fraction. Since then, however, the potential effects of the components deposited in the bronchial tubes, the inhalable components, have been assessed based on a separate limit value (see Table 2). An expert group (Senate Commission) of the German Science Fund (DFG) has been tasked with developing reasoned proposals for the limit values. The recommended limit values will become legally binding only after the official assessment by the Committee on Hazardous Substances ("Ausschuss für Gefahrstoffe", AGS) and the publication as a "technical rule for hazardous substances" ("Technische Regel für Gefahrstoffe", TRGS). The TRGS rules explicitly state that the general dust limit value is not applicable for ultrafine particle fractions[43].

Beyond the "general airborne dust limit", which is equivalent to the "maximum allowable concentration at the workplace" (MAK), a second value is often defined, namely the "workplace limit value" ("Arbeitsplatzgrenzwert", AGW): it is derived from the former two and is the average of the concentrations measured in regular intervals during a work shift (shift average). For TiO_2 the TRGS has assumed "no specific effects" on respiratory organs. Therefore, adhering to the AGW provides adequate health protection. In contrast, the DFG has classified TiO_2 as a "demonstrated carcinogenic substance in animals" (category 3A). For TiO_2 dust the DFG has therefore recommended a drastic reduction in the limit value for the alveolar component from 1.5 to 0.3 mg/m^3.

In the USA the limit value for dust exposure involving TiO_2 is 15 mg/m^3 air. In 1988 the US National Institute for Occupational Safety and Health (NIOSH) classified TiO_2 as a potentially carcinogenic substance and recommended keeping the exposure to the lowest level possible. The revised TiO_2 assessment recommends stricter limit values of maximally 2.4 mg/m^3 for fine particulate matter and maximally 0.3 mg/m^3 for ultrafine and nano-scale particulate matter for a 10-hour workday[13].

TiO_2 in consumer products, cosmetics, foods etc.

Principally, the handling of titanium dioxide – like all chemicals in the EU – has been regulated since 2007 by the REACH regulation and the CLP regulation (for the classification, labeling and packaging of substances)[44-46]. The determining property – both in REACH and in CLP – has been chemical structure, not shape or size. Nonetheless, in the nano-regulation sector, things are apparently changing.

- Commission Regulation (987/2008) already rescinded the exemptions for several substances that were previously classified as "non-hazardous" in REACH Appendix IV. Higher risks can be involved due to "inherent substance properties", requiring a special risk analysis for nano-scale forms of carbon and graphite (carbon nanotubes and C_{60}).
- In 2010, changes were made to the REACH regulation (453/2010). In relation to the publication of the"safety data sheets", they specify for the first time that nanomaterial-relevant information isalso required, e.g. grain size distribution, surface chemistry and physico-chemical properties that govern reactivity.

In the future, stricter regulations will be in place for market approval of cosmetics, foods and biocides as well as for electronic wastes. This will include mandatory classification with the label "nano" and clear regulations on safety assessments.

In the USA the use of TiO_2 is regulated by the Food and Drug Administration (FDA) without consideration of size. Regarding its use in the food additive E 171, the FDA has since 1966 specified a maximum proportion of 1 %

Limit value or suggested limit value	Expert group (and year)
Particulate matter (MAC value) Alveolar component (A): ..... 1.5 mg/m^3 inhalable component (E): ..... 4 mg/m^3	DFG (1997)[48]
Shift average (AGW-TRGS 900) Alveolar component (A): ..... 3 mg/m^3 inhalable component (E): ..... 10 mg/m^3	AGS (2001)[49]
Recommended new MAC value for GBS-dusts Alveolar component (A): ..... 0.3 mg/m^3 (except ultrafine particles)	DFG (2011)[50]

Table 2: Limit values or suggested limit values for fine particulate matter containing TiO_2, but not for ultrafine or nanoparticles

on a per weight basis; TiO_2 is also included in the list of permitted color additivesin medications, cosmetics and contact lenses[47]. With the new FDA regulations that came into force in June 2012, the testing specifications and classificationof sunscreens are newly regulated, yet without restrictions for nano-scale particles consisting of TiO_2.

Conclusions *see Dossier 035en*

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