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Scientific update on nanoparticles in dentistry*

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Nanoparticles having a size from 1 to 100 nm are present in nature and are successfully used in many products of daily life. In dental materials, nanoparticles are typically embedded but they may also exist as by-products from milling processes. Possible adverse effects of nanoparticles have gained increased interest, with the lungs being the main target organ. Exposure to nanoparticles in the dental laboratory is addressed by legal regulations. In dental practice, nanoparticles are mainly produced by intra-oral grinding/polishing and removal of materials, by wear of restorations or release from dental implants. Based on worst-case mass-based calculations, the additional risk as a result of exposure to nanoparticles is considered to be low. However, more research is needed, especially on vulnerable groups (patients with asthma or chronic obstructive pulmonary disease). An assessment of risks for the environment is not possible because of lack of data. Exposure-reduction measures mainly include avoidance of abrasive processes (for example, by proper sculpturing), cooling by the use of water spray and sufficient ventilation of treatment areas.

Key words: *Nanoparticles, composites, titan, organs, risk assessment*

INTRODUCTION†

Nanomedicine is the controlled use of nanotechnologies/nanoparticles in healthcare, leading to new pathways for the diagnosis and treatment of human diseases[1]. Nanoparticles are present in nature and are used in daily life; for example, in cosmetic products, such as sun screens [in which titanium dioxide (TiO_2) or zinc oxide (ZnO) particles are added as ultraviolet (UV) light filters], or in toothpastes, in dietary supplements and in sprays used for coating, cleaning and impregnation[2]. Silicon dioxide (SiO_2), magnesium oxide (MgO) and TiO_2 are tested and licensed food additives in some countries[3]. Altogether, use of nanotechnology has great potential for improving daily life.

In dentistry, nanoparticles are intentionally embedded into products to improve material properties[4]. Dental materials that intentionally release nanoparticles are rare; such materials include scanning sprays for computer-aided design/computer-aided manufacturing (CAD/CAM)[5] or occlusion indicator foils. On the other hand, nanoparticles can be non-intentional by-products from milling processes for fillers. It has been estimated that nanoparticles are present in about 3,500 dental materials. The aim of this brief survey is to provide some basic information for the dental community on nanoparticles. The original text for this review has been published recently elsewhere[6]; here, we provide a shortened version.

DEFINITIONS

According to the European Union (EU), nanoparticles have one or more external dimensions in the size range from 1 to 100 nm[7]. More detailed definitions are provided by the International Organization for Standardization (ISO)[8,9]. Nano-sized single particles may, however, arise readily to form clusters, namely aggregates (strongly bonded) and agglomerates (weakly bonded)[8]. The definition of a nanomaterial (e.g. by the EU[7]) is presently under discussion and

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†In this review literal citations e.g. from ISO, EU and other documents are used without quotation marks in each case for better readability; respective references are provided.

may be changed; therefore, in this review only the term nanoparticle (see above) is used.

The dose for nanoparticle exposure is often the number of particles[10] or the total surface of applied nanoparticles. There is also a tradition of mass being used for risk assessment (e.g. for dust exposure[11]). Furthermore, the only presently available limit values (e.g. for fine dust exposure) are given as mass values and this is why the present risk analysis used mass.

BIOLOGICAL RELEVANCE OF NANOPARTICLES - WHY CARE?

Compared with bulk materials, the surface area/volume ratio [volume-specific surface area (VSSA)] of nanoparticles is greatly increased and therefore they are much more reactive compared with larger particles with the same composition. The elution/release of potentially toxic substances may also be enhanced. It is also possible for the passage/translocation of nanoparticles through the intestines into the lymphatic system[12]. As a consequence of cellular uptake of nanoparticles, upregulation of reactive oxygen species, DNA damage and impaired DNA repair have been reported[13]. Contamination of the surface of nanoparticles, for example with endotoxin, is possible[14].

Fibres play a role, especially in regard to inhalation[10]. Multiwalled carbon nanotubes are carcinogenic to rat lungs[15]. However, the International Agency for Research on Cancer (IARC)[16] did not consider the evidence to be strong enough to alter its evaluations (possibly carcinogenic to humans – Group 2B). Furthermore, chronic inflammation, especially in patients with asthma or chronic obstructive pulmonary disease (COPD)[17], has been reported. There seems to be a significant association between air concentration of the fine dust fraction and increased risk of lung cancer[18], cardiovascular diseases[19] and allergic reactions in atopic patients[20]. The relevance of these findings in dentistry is unknown.

NANOPARTICLES IN/FROM DENTAL MATERIALS

Resin-based composites contain anorganic filler particles of different sizes, ranging from supra-micron, to sub-micron and nano-sized[21]. Today, mainly radio-opaque glass-fillers containing, for example, barium, zirconium, strontium or ytterbium with a size between 400 nm and 1 μm, or even larger, are used together with nano-sized particles such as pyrogenic silica (SiO_2) or zirconium dioxide (ZrO_2)-SiO_2. The filler particles are embedded in the resin matrix and chemically attached to it through silane coupling.

Zinc phosphate cements contain ZnO or MgO particles in the powder, glass ionomer cements contain finely ground glass particles and some products may contain pyrogenic silica as nanofillers. Hydraulic calcium silicate cements contain different calcium silicates and aluminates[22] and impression materials contain a variety of fillers (e.g. ZnO or TiO_2). Filler size is normally in the micrometre range, but nanoparticles can be non-intentional by-products of the milling process.

The above-mentioned materials are delivered as premixed pastes which are cured by light activation within 1 minute or as paste/paste or powder/liquid systems, which have to be mixed and which set in <5 minutes. Nanoparticles on implants are strongly bound ('fixed') to the surface of the implant[10] to prevent infection (e.g. silver nanoparticles) or to improve biocompatibility [e.g. apatite or titanium (Ti) particles[23]]. Furthermore, pigments in the form of nanoparticles are used. When grinding resin materials, nanoparticles containing substances of unknown composition derived from the resinous matrix through heat generation[24] may be produced.

NANOPARTICLES IN/FROM DENTAL MATERIALS – RELEASE AND EXPOSURE

Occupational exposure

Nanoparticles are released as dust in the dental laboratory. Special legal regulations for occupational safety are available for different countries (e.g. Occupational Safety and Health Administration[25]).

In the dental office, premixed pastes (e.g. resin-based composite pastes) are used and nanoparticles in these pastes are described as 'free' with a high potential for systemic exposure[10]. However, the movement of particles in dental pastes is limited by 'capillary transverse pressure'[26,27]. This keeps wetted particles away from the surface of a paste-like material and thus nanoparticles in dental pastes are normally not available on the surface (K. Dermann, personal communication). The mixing of powder/liquid materials may lead to short-term exposure to particles for the dental personnel, but not for the patient. Actual data on release of nanoparticles from unset dental materials are, however, missing.

For set materials, peak concentrations of respirable dust could be observed when the dentist was finishing/polishing composite restorations in the front teeth without water coolant[28] and the airborne fraction was mainly nano-sized[29] with concentrations of above 10^6 particles/cm^3 in the breathing zone of both patient and dentist. Nanoparticles may also be produced by grinding resin materials, which per se do not contain nanoparticles[24].

The risk assessment presented in this review is based on 57 million fillings placed in Germany (in

2015)[30] and 71,425 practicing dentists (in 2015), representing, on average, three fillings per dentist each day with about 80% of fillings being of composite material. As dentists were included who normally do not place fillings, it can be estimated that three to six fillings are placed each day by every dentist who performs such procedures. Taking possible variations into account, for a risk assessment, 10 composite fillings per dentist per day are considered here to represent the worst-case scenario.

Exposure of patients

No release of nanoparticles from unset restorative materials is expected. For set materials, risk assessment is based on the above-mentioned figures from Germany for 82,175,684 inhabitants (at 31 December 2015). Thus, 0.67 fillings per inhabitant were placed in 2015. As this calculation also covers patients without teeth, an average exposure of one to two fillings per patient per year can be assumed. Taking possible variations into account, for a risk assessment, five fillings per year are assumed in a worst-case scenario.

Nanoparticles from dental-restorative materials may be generated by wear and swallowed. For resin-based composites, a mean annual occlusal wear of up 100 μm was reported in 2006[31]. In more recent studies, after 3 or 5 years *in situ*[32] annual wear rates of up to 30–40 μm were measured. For amalgam an annual wear rate of 60 μm was reported[31]. Wear rates are lower for ceramic materials than for composites[31]. For glass ionomer cements or combinations of resin materials with cements, data on wear are sparse. Generally, the wear for these materials is regarded to be greater than for composites. However, these materials are only recommended for Class I and Class V cavities with reduced wear[33].

In summary, for all dental-restorative materials a general loss of up to 50 μm per year seems a reasonable assumption. However, taking possible variations into account, for a risk assessment, beside 50 μm also 100 μm per year, and based on a recent study[34], 250 μm per 3 years, are taken as the worst-case scenario.

Titanium particles could be observed in peri-implant tissues and in newly formed bone[35] and were probably detached during insertion of the implant[36] or were released after insertion[37]. In a postmortem study[38] the highest Ti content detected in human mandibular bone was found to be 37,700 μg/kg of bone weight at a distance of 556–1,587 μm from the implants, and the intensity increased with decreasing distance from implants. Particles with sizes of 0.5–40 μm were found in human jawbone marrow tissues at distances of 60–700 μm from dental implants[38].

Silver nanoparticles (AgNPs) have been applied in different dental materials, but release data are rare. However, materials containing silver ion-implanted fillers had antibacterial effects[39] and metallic implant coatings released 550 μg/l of AgNPs after 168 hours[40].

Environment/Waste generation

Nanoparticles created during the removal of dental restorations may end up in the effluent of the dental office and thus in the environment; separators are only available for amalgam waste[41]. Bisphenol A (BPA) and several resin monomers are eluted from resin-based composites (bulk samples) over a long period of time[42]. From composite dust, up to 970 $\mu g/m^3$ of triethyleneglycol dimethacrylate (TEGDMA), 360 $\mu g/m^3$ of urethane dimethacrylate (UDMA), 180 $\mu g/m^3$ of bisphenol A glycidylmethacrylate (Bis-GMA) and 1.28 $\mu g/m^3$ of BPA were eluted into ethanol[43].

NANOPARTICLES IN/FROM DENTAL MATERIALS – RISK ASSESSMENT

This risk assessment concentrates on the additional effects of nanoparticles from dental materials. Material-related (mainly chemically induced) biocompatibility effects, such as allergic responses, are not covered here in detail.

Inhalation/Dust

Dust <5 μm and >0.01 μm can penetrate deep into the alveolar region of the lungs[44]. Particles released from composites are in the nanoscale size and thus able to reach the lungs of patients and dental personnel[29]. In spite of efficient macrophage phagocytosis[45], an overload may lead to an excessive production of inflammatory mediators and sustain inflammation and fibrotic changes. However, *in vitro* exposure of bronchial epithelial cells to up to 3.3 mg/ml of resin-based composite dust did not result in membrane damage or in the release of interleukin-1beta (IL-1β)[46]. Metabolic activity of the cells decreased at concentrations of dust particles of >660 μg/ml. In a similar study, alveolar macrophages were exposed to the respirable fraction (i.e. dust particles of size <5 μm)[45]. They were able to phagocytize the composite dust particles. As they tolerated a comparatively high cell burden (60 pg of dust particles per cell), the cytotoxic potential of respirable composite dust seemed to be low.

To estimate exposure to nanoparticles, the size distribution by number of particles is used, as published by van Landuyt *et al.*[28]. Thus, the nano-fraction corresponds to a concentration of 0.0004–0.0013% (w/

w) of the total dust. This order of magnitude is confirmed by data from Bradna *et al.*[47].

For the 10 restorations placed per dentist per year (see above), with five fillings in premolars (surface 75 mm^2) and five fillings in molars (surface 150 mm^2), this sums to a total surface of 225 mm^2. Assuming a vertical removal of 1 mm, this would result in an exposure of 450,000 μg of dust. The nano-fraction of this dust (taking the highest calculated w/w concentration) would be 18 μg per day. If about one-third of the 10 restorations are made in anterior teeth (surface 100 mm^2), then dentists are being exposed to approximately 20 μg of dust per day.

The German Agency for Occupational Safety[48] proposed 110–190 $\mu g/m^3$ as the maximum acceptable nanodust concentration over a working day of 8 hours. For air uptake of 10 m^3 during an 8-hour working day (ISO 10993-17[49]), the daily acceptable intake of nanodust would be 1,100–1,900 μg. Background exposure is estimated to be 400 μg of nanoparticles without apparent harm[50].

Although the present calculations are based on estimates, assumptions for exposure were very conservative and the calculated margins of safety are >20 to >100. This low exposure, together with the low cytotoxicity, indicates that no significant risk for dental personnel is expected. The same is true for patient exposure (of five fillings per year), being around 25 ng of nanodust per day.

It can be concluded that the uptake of nanoparticles after grinding/polishing of composites (and other restorative materials) and the health risks for the dental personnel and patients is low to negligible. However, no data are available for special vulnerable patient groups, like those with severe asthma or COPD.

Ingestion of nanoparticles

Nanoparticles from wear are swallowed with the prime target organ being the intestines. The following calculations are based on 20 restorations (12 in molars and eight in premolars) with a total surface of 480 mm^2. Taking 50, 100 or 83 μm as annual vertical loss, this equates to exposure to about 133, 266 or 221 μg of particles per day, per patient. Taking the nano-fraction as outlined above [0.0004–0.0013% (w/w)], it can be assumed that only 0.2–0.4 μg are nanoparticles. The normal daily (total) uptake of nanoparticles is about 400 μg per day[50]. Therefore, the uptake of nanoparticles abraded from restorations is likely to be low and the health risk in patients is considered to be acceptable.

Ingestion of nanoparticles is also assumed to be the major route of exposure during restoration removal. Assuming removal of five restorations per patient per year, less than 2 μg of nanoparticles per day are ingested. This calculation does not take into account the removal of particles through the high-vacuum suction, together with water cooling. Again, the expected exposure is very low, as is the additional particle-associated risk.

Ti nanoparticles from dental implants

Titanium is one of the most biocompatible metallic materials as a result of its ability to form a stable and insoluble protective oxide layer (TiO_2) on its surface[51]. Ti is preferentially used for endosseous dental implants[51] and the properties of Ti implants can be improved by using nanostructured Ti-containing particles or Ti nanoparticles (Ti-NPs)[52]. However, a recent *in vitro* study[53] demonstrated a size-dependent cytotoxicity and DNA damage of Ti particles. Genotoxic effects of Ti particles have also been detected, such as induction of apoptosis in mesenchymal stem cells[54]. It was claimed that peri-implantitis can arise by exposure to TiO_2, even in the absence of bacteria[55]. Furthermore, a previous postmortem study investigating metal particles released from implants showed bone marrow fibrosis[38]. In a clinical study, 0.6% of 1,500 patients were found to exhibit allergic reactions to Ti[56].

The highest Ti content detected in human mandibular bone was 37,700 μg/kg of bone[38]. Assuming that all Ti in the bone is Ti nanoparticles and that 1 kg bone equals 1 l of fluid, a Ti nanoparticles concentration of 37 μg/ml can be calculated. The half-maximal effective concentration (EC_{50}) for Ti nanoparticles in human cells is 2,800 μg/ml[53]. Therefore, it is assumed that Ti nanoparticles released from dental implants might have no toxicologically clinical effects.

Silver nanoparticles

Heinlaan *et al.*[57] described that AgNPs were very toxic to *Daphnia magna* (OECD202) (48-hour EC_{50}: 1–5.5 μg of Ag/l), as well as to *Danio rerio* (OECD236) (96-hour EC_{50}: 8.8–61 μg of Ag/l), embryos. These EC_{50} values are 10–100 times lower than the Ag(nano)particle concentrations measured after release from metallic implant coatings. There are also clinical problems associated with AgNPs, such as colour change[58] or impairment of the polymerization process of resin-based materials, which then leads to increased release of substances (e.g. monomers)[59]. The actual risk of the inclusion of AgNPs into resin-based composites is presently difficult to estimate. However, the potential of adverse biological effects of resin-based composites when adding AgNPs seems to be increased.

Risk for the environment

It can be assumed that particles from resin-based composites reach the environment and that included residual monomers will be released. However, in the 2014 EU report [Scientific Committee on Health and Environmental Risks (SCHER)][60] it is stated that the information available on the mercury (Hg)-free alternatives to amalgam does not allow a sound risk assessment for the environment to be performed.

CONCLUSIONS/RECOMMENDATIONS

Available data on possible adverse reactions derived from nanoparticles in dental materials or by processing dental materials dealing with additional particle-related risks are sparse and more research is necessary[10].

In the dental laboratory, technicians are exposed to nanoparticles as dust, and must follow available relevant national/international safety regulations. In dental practice, virtually no exposure to nanoparticles occurs when handling unset materials. Dental personnel are mainly exposed to nanoparticle dust produced by grinding/polishing set dental materials, irrespective of the presence of nanoparticles in the material. The lungs are the prime target organ. Actual risk assessment has shown that for the materials used at present, the additional particle-associated health risk for dental personnel after inhalation of nanoparticles as dust is likely to be low. Although no data on the long-term exposure of dental personnel to (dental) nanoparticles are available, such personnel have been exposed to nanoparticles for many decades already and there are so far no indications for an increased rate of non-allergic lung diseases.

Patients are exposed to nanoparticle dust or debris, but to a much lesser extent than dental personnel. Actual risk assessment has shown that the particle-associated health risk of materials used at present, for patients for both inhalation of nanoparticles and ingestion from wear, is likely to be low. Available information is limited, especially concerning the influence of dental material nanoparticles on special vulnerable patient groups, such as those with asthma or COPD. A risk assessment for the environment is presently not possible because of lack of data.

In any case, the amount of dust generated should be kept to a minimum by properly sculpturing the restoration. Cooling with water spray and effective suction whenever possible, when grinding and polishing intra-orally, are recommended. Effective local ventilation at treatment areas is also recommended, as is the use of encapsulated powder/liquid systems. Protective measures, such as wearing a mask, may limit exposure of dental personnel to small particles.

Addition of AgNPs may increase toxicity of the materials. For patients with Ti implants, the general risk of Ti nanoparticles is likely to be low[53]. Possible micromovements between implant and abutment should be avoided by ensuring a tight connection.

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Conflict of interest

The authors declare no conflict of interest.

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