The nanotoxicology revolution

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It is well known that nanotechnology offers enormous potential for technological advancement (Ariga et al. 2012a, b; Tong et al. 2012; Dreaden et al. 2012; Wang et al. 2012; Marchan 2012; Tozak et al. 2013; Stewart and Marchan 2012; Piacham et al. 2013). Therefore, it is highly fortuitous that from the very beginning, toxicological research kept pace with the developments in the field of nanotechnology (Oberdorster et al. 2005, 2007; Nel et al. 2006; Lewinski et al. 2008; Hardman 2006; Singh et al. 2006; Xia et al. 2008; Smart et al. 2006; Donaldson et al. 2004; Linse et al. 2007). Each year, we the editors at the Archives of Toxicology review all the articles that were published the previous years in our journal, paying particular attention to those in research areas that are currently most relevant and exciting, and which contribute to the further development of toxicological sciences. It was not surprising that a significant fraction of articles matching these criteria were on nanotoxicology. A systematic analysis, however, produced some surprising results—nanotoxicology actually dominates the field of toxicology to a much higher degree than originally expected—six of the ten most cited articles focus on some aspect of nanotoxicology (Table 1). This ratio is almost similar to the fraction of submitted nanotoxicology articles. Therefore, we believe that our current title is justified in claiming a

nanotoxicology revolution, and as a result, necessary to summarize what we have learned in the past years and which questions still remain open.

No evidence for nano-specific toxicity

Although it has been suggested that nanoparticles should ‘be tested individually’ (Krug and Wick 2011), we see no evidence that nano-specific toxic mechanisms exist (review: Donaldson and Poland 2013a). For example, conventional particles induce toxicity via general mechanisms, such as oxidative stress and inflammation. So far, no convincing example has been published that particles below 100 nm exhibit a qualitative change with regard to mechanism of toxicity. Of course, a larger surface area, which is characteristic for smaller particles, may intensify interactions between particles and biological systems (Fubini et al. 2010; Donaldson et al. 2013b). However, this is not indicative of a qualitative step, but rather a ‘gradual magnification of the intrinsic hazard’ (Donaldson and Poland 2013a). Therefore, it does not seem to be justified to label all material or objects containing nanoparticles as hazardous.

Induction of oxidative stress and release of inflammatory cytokines

Numerous studies have meanwhile shown that some nanoparticles can induce oxidative stress and lead to the release of inflammatory cytokines. Of course, these are mechanisms that are also common for larger particles and numerous soluble compounds. Therefore, there is no benefit to publish further articles confirming these mechanisms in

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Table 1 Most cited articles in the archives of toxicology in 2011 and 2012

Key message	Reference	Times cited
Silver nanoparticles-induced cytotoxicity is associated with generation of reactive oxygen species and DNA adducts	Foldbjerg et al. (2011)	65
SiO ₂ nanoparticles (70 nm) and SiO ₂ submicron particles were compared for subcellular localization in HeLa cells. Both accumulated in endosomes. SiO ₂ nanoparticles, but not submicron particles, were preferentially localized to the lysosomes	Al-Rawi et al. (2011)	27
Zinc oxide nanoparticles increase levels of reactive oxygen species and stimulate the release of pro-inflammatory cytokines in mouse and human cell lines, as well as primary cells	Heng et al. (2011)	23
Inorganic arsenic causes p38 signaling and apoptosis in the mouse cerebrum	Yen et al. (2011)	18
The aspect ratio (length/diameter) can be used to predict toxicity of fibers. For multi-wall carbon nanotubes, the aspect ratio was not associated with genotoxicity but with cytotoxicity	Kim et al. (2011a)	16
A genotoxicity assay based on the detection of histone H2AX phosphorylation was used to study bisphenol A and bisphenol F in various cell lines. While bisphenol A was clearly negative, bisphenol F was genotoxic in HepG2 cells	Audebert et al. (2011)	15
Quercetin protects against methylmercury-induced oxidative stress and DNA damage in rats	Barcelos et al. (2011)	15
Single intratracheal instillation of single-walled nanotubes may induce lung fibrosis in mice	Park et al. (2011)	15
DNA strand breaks formed after incubation of cells with platinum nanoparticles are caused by platinum ions released from the particles	Gehrke et al. (2011)	14
The flavonoid fisetin induces apoptosis in HeLa cells by ERK1/2 signaling	Ying et al. (2012)	12
Silver nanoparticle-induced apoptosis in A459 lung cells is mediated by PKC zeta signaling	Lee et al. (2011)	12
Sodium fluoride decreases insulin-like growth factor-1 in mouse osteoblasts resulting in decreased proliferation and increased apoptosis	Wang et al. (2011)	12
Lead sulfide nanoparticles functionalized with either sodium 3-mercaptopropanesulfonate (MT) or sodium 2,3-dimercaptopropanesulfonate (DT) were compared. MT-functionalized nanoparticles released a higher amount of soluble lead ions and caused higher mortality in zebrafish	Truong et al. (2011)	12
DNA strand breaks caused by 0.25 mM bisphenol-A-glycidyl dimethacrylate correspond to the damage caused by 4 Gy of ionizing radiation	Durner et al. (2011)	12
Fullerenes target mitochondria resulting in mitochondrial depolarization, inhibition of ATP synthesis and oxidation of glutathione	Nakagawa et al. (2011)	11
Human intestinal cells hydrolyze the food contaminant 3-chloro-1,2-propanediol-1-monoesters thereby increasing the burden of 3-MSPD	Buhrke et al. (2011)	10
Indole-3-carbinol and flutamide promote hepatocellular tumors and massively induce CYP1A1	Shimamoto et al. (2011)	10
Levels of boron that cause reproductive toxicity in animals are not reached in humans under normal occupational conditions	Duydu et al. (2011)	10
A PBPK modeling approach was established to predict compound concentrations in the portal vein, hepatic vein and the vena cava after oral administration. Prediction analyses were performed for 29 compounds tested in 2-year bioassays and a 14-day short-term study	Mielke et al. (2011)	10
Arsenic influences global DNA methylation in the mouse liver	Nohara et al. (2011)	10
The anticancer agent, polyphyllin D causes apoptosis in human erythrocytes through membrane permeabilization and increased Ca ²⁺	Gao et al. (2012)	9
A new lectin isolated from <i>Phaseolus vulgaris</i> causes selective toxicity in HepG2 cells and may be a candidate for further development as an anticancer agent	Fang et al. (2011)	9
Polymorphic alleles of UGT2B15 are closely associated with variations in the metabolism of bisphenol A	Hanioka et al. (2011)	9
Workers in pathology wards exposed to formaldehyde have increased frequencies of chromosomal aberrations	Santovito et al. (2011)	9
Fenvalerate causes germ cell apoptosis via Fas signaling	Zhao et al. (2011)	9
TiO ₂ nanoparticles were tested in mice for a possible induction of pulmonary irritation. However, irritation and inflammation potencies were low	Leppänen et al. (2011)	9
A novel, simple and quick method for whole-liver de-cellularization was established	De Kock et al. (2011)	9
Lipopolysaccharide induces apoptosis in human alveolar epithelial cells by increasing reactive oxygen species and release of cytochrome c	Chuang et al. (2011)	9
Novel biomarkers were tested in a cohort of 629 subjects to predict malignant mesothelioma	Gube et al. (2011)	9
Nrf2 protects PC12 cells against MnCl ₂ neurotoxicity	Li et al. (2011)	8

Table 1 continued

Key message	Reference	Times cited
The biopersistent organic compound, perfluorooctane, increases hepatic expression of the carriers OAPT2 and MRP2 in rats	Yu et al. (2011)	8
Mn and Cr were cleared from the lungs of rats more quickly than Fe. This may lead to a more efficient translocation from the lung to other organs	Antonini et al. (2011)	8
Ethanol upregulates the small heat shock proteins HspB2 and HspB7 during the differentiation of mouse neural stem cells	Choi et al. (2011)	8
Human Caco-2-cells can be used to study P-glycoprotein induction as a toxic stress response	Silva et al. (2011)	8
Arsenic causes apoptosis in myoblasts by mito-toxicity	Yen et al. (2012)	7
The phytochemical, 4-methylsulfanyl-3-butenyl isothiocyanate strongly induces rat liver phase II metabolizing enzymes.	AbdullRazis et al. (2012)	7
The eIF2 alpha inhibitor, salubrinal protects HK-2 renal proximal tubular cells from CdCl ₂ -induced apoptosis	Komoike et al. (2012)	7
Propargylglycine, an inhibitor of endogenous H ₂ S formation, protects from nephrotoxicity induced by adriamycin	Francescato et al. (2011)	7
Agglomeration complicates the interpretation of nanoparticle toxicity test results. The present study evaluates the use of appropriate biocompatible dispersants	Kim et al. (2011b)	7
The cyanobacterial alkaloid, cylindrospermopsin, has been identified in drinking water. The present study demonstrates that cylindrospermopsin is genotoxic	Straser et al. (2011)	7

vitro. However, more useful questions still not sufficiently answered include ‘Which exposure scenarios would lead to sufficiently high concentrations to activate oxidative stress and cytokine release in vivo? What is the margin of safety compared to doses that would cause adverse effects?’

Biodistribution, toxicokinetics and accumulation

Relatively little data especially with respect to long-term exposures are available concerning biodistribution and toxicokinetics (Aggarwal et al. 2009; Estevanato et al. 2012; Menjoge et al. 2010; Garza-Ocanas et al. 2010; Katsnelson et al. 2011). Meanwhile, some general principles have been convincingly demonstrated. After intravenous application, gold nanoparticles are mostly found in the reticuloendothelial system in the liver, spleen, lymph nodes and bone marrow (Almeida et al. 2011). Larger gold nanoparticles are efficiently taken up by the liver, whereas smaller nanoparticles may target other organs (Almeida et al. 2011). The size of nanoparticles also influences their route of excretion. Furthermore, protein adsorption to the surface of nanoparticles, in addition to the surface charge and shape of nanoparticles, has been shown to influence pharmacokinetics. Nevertheless, relatively little is known about the biodistribution of nanoparticles in humans in vivo. The central question of interest is whether nanoparticles accumulate in organs or specific cell types to a degree that induce adverse effects. To answer this question, long-term studies are needed.

Role of immune cells

It has been convincingly shown that some nanoparticles can accumulate in immune cells, such as macrophages (Buono et al. 2009; Arnida et al. 2011; Lunov et al. 2011; Fedeli et al. 2013; Gasparotto et al. 2013). However, the degree of accumulation that occurs in humans after NP exposure is unknown. Other open questions include whether the accumulation of nanoparticles in immune cells results in immunotoxicity and how large is margin of safety.

Grouping of nanoparticles for risk evaluation

A final highly relevant question is whether we can group nanomaterials according to their mode of action. Such a grouping will substantially facilitate the risk evaluation process. The coming years will show whether a consensus on a mechanism or mode of action-based classification system can be achieved.

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