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EDITORIAL

Nanotoxicology and oxidative stress control: cutting-edge topics in toxicology

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Every summer, the editors of the Archives of Toxicology analyse their most cited articles from the previous 2 years. Topping this year's list as the most cited original article is the pharmacokinetic and biodistribution study on silica nanoparticles (Xie et al. 2010). This study demonstrates that silica nanoparticles are retained for more than 30 days in various organs of mice (Table 1). The high interest and citation rates of this systematic biodistribution study illustrate the importance and relevance of nanoparticles to the field of toxicology today. The second most cited original article is the study by Drobná et al. (2010) on the metabolism and transport of inorganic arsenic. The high interest generated by the results of this study is not surprising. Arsenic poisoning, as a result of drinking water from contaminated wells, represents one of the largest man-made catastrophes in recent history (Golka et al. 2010). A study on the mechanism of action of silver nanoparticles ranks third in this citation analysis (Table 1).

In addition to original work, review articles were also included into our analysis. In the last 2 years, the most cited review, and coincidentally the most cited article, proposed a systems biology concept of an autocatalytic generation of oxidative stress, which is intensified by positive feedback loops and plays a central role in several degenerative diseases and toxic insults (Kell 2010). Following the review of Kell et al. is a comprehensive summary of the mechanisms of action and toxicological relevance of the mycotoxin, deoxynivalenol, also named 'vomitoxin' (Pestka 2010). The review of Adler et al. (2011) on in vitro systems ranks third, illustrating that the development of alternative methods currently represents a cutting-edge topic in toxicology.

The present citation analysis does not, by any means, represent a ranking of the scientific quality of our articles. However, it identifies the fields of research that attract the most attention and, therefore, may be a sensitive indicator of how our discipline could evolve in the future.

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Table 1 Key messages of the most cited articles in Arch Toxicol (2010–2011)

Key messages	References
Many degenerative diseases and toxicological insults converge on iron dysregulation. This review summarises several concepts of autocatalytic production of hydroxyl radicals—a process intensified by positive feedback loops. Systems biology approaches predict that interventions with, for example, iron chelators and antioxidants may prove most effective in diseases such as Parkinson's, Huntington's, Alzheimer's, prions as well as various forms of intoxications. The comprehensive review is the most cited article of the current evaluation period (2010–2011)	(1) Kell (2010)
The trichothecene mycotoxin deoxynivalenol (DON) is produced by the fungus Fusarium in wheat and corn. This review summarises the molecular mechanisms of DON, which include ribotoxic stress, disturbed protein synthesis, compromised cell signalling, differentiation and proliferation. Proinflammatory gene induction, disruption of the growth hormone axis and altered gut integrity finally lead to gastroenteritis (vomitoxin), anorexia, immunotoxicity and impaired reproduction in experimental animals. This review is the second most cited article of this evaluation period	(2) Pestka (2010)
This review summarises the state of the art of in vitro toxicity tests in five critical fields of toxicity: toxicokinetics, repeated-dose toxicity, carcinogenicity, skin sensitisation and reproductive toxicity. The background of this review stems from the prohibition of animal-tested cosmetics on the market in Europe after 2013. The status and perspectives of each field are carefully analysed. For example, for skin sensitisation, in vitro techniques may already be able to identify sensitisers ahead of 2017. However, in other fields, particularly carcinogenesis, repeated-dose toxicity and reproductive toxicity, a time frame for in vitro alternatives cannot yet be estimated. This comprehensive review ranked third in the current evaluation period	(3) Adler et al. (2011)
Silica nanoparticles (SiNPs) are widely developed for biomedical applications. This study quantitatively analysed the time-dependent tissue and subcellular distribution of SiNPs in mice, including radioactive counting, transmission electron microscopy and histology. SiNPs that accumulate in lungs, liver and spleen are retained for more than 30 days. These particles are endocytosed by macrophages and could cause liver toxicity. This is the most cited original article of the current evaluation period. It underlines the emergence of nanotoxicology as one of the most popular fields in toxicology	(4) Xie et al. (2010)
Metabolism of inorganic arsenic (iAs) is critical for its toxicity. This study analysed the relevance of arsenic transporters on human hepatocytes for the generation of methylated metabolites from iAs. A major finding is that MRP2 expression inversely correlates with cellular retention of iAs, as well as methylated metabolites in hepatocytes. This suggests that MRP2 plays an important role in the efflux of iAs and its metabolites. This study is the second most cited original article from the evaluation period	(5) Drobná et al. (2010)
The comprehensive review article gives an overview of mutagenicity and carcinogenicity studies on selenium, and discusses the molecular mechanisms involved. At low concentrations, selenium shows anticarcinogenic effects. However, at concentrations higher than needed for nutrition, selenium proves to be genotoxic and carcinogenic. This study may help regulate the use of selenium in nutrition	(6) Valdiglesias et al. (2010)
Silver nanoparticles (AgNPs) caused a concentration-dependent increase in reactive oxygen species (ROS), mitochondrial damage, DNA adducts and apoptosis in a human alveolar cell line. Pre-treatment with antioxidants reduced ROS as well as DNA adducts underlining the relevance of ROS in toxicity of AgNPs. This study ranks third among the most cited original articles	(7) Foldbjerg et al. (2011)
Metabolomics have successfully identified novel biomarkers of disease prognosis and drug efficacy as well as toxicity. This review summarises how novel biomarkers discovered by metabolomics should be verified and introduced into clinical practice	(8) Mamas et al. (2011)
This review focusses on the following aspects of selenium toxicity: (1) The majority of epidemiological studies suggest a cancer-preventing activity. (2) In cancer treatment, selenium acts as a pro-oxidant by inducing apoptosis. (3) The use of *Saccharomyces cerevisiae* is reviewed as a powerful tool to study the mode of action of selenium	(9) Brozmanová et al. (2010)
Ammonium perfluorooctanoate, used in the production of fluoropolymers, induces hepatocellular hypertrophy in rats by activation of the nuclear receptors, PPAR alpha and CAR/PXR	(10) Elcombe et al. (2010)
Formaldehyde causes nasal cancer and lymphohematopoietic malignancies (LHM) in laboratory animals. Nasal cancer seems to be associated with cytotoxicity-induced proliferation. LHM occurs at even higher doses than nasal cancer. This study discusses the guideline value of 0.08 ppm formaldehyde to prevent carcinogenic effects	(11) Nielsen and Wolkoff (2010)
(1,3)-Beta-D-glucan, which occurs on damp building materials, induces an inflammation-associated gene transcription profile in mouse lungs	(12) Rand et al. (2010)
This review discusses the future perspectives of organoselenium as pharmacological agents. It also focuses on epidemiological evidence that selenium overexposure leads to chronic degenerative diseases	(13) Nogueira and Rocha (2011)
This is a comprehensive review on the protective network controlled by the Keap1–Nrf2 axis, focussing on proliferation, angiogenesis and apoptosis	(14) Baird and Dinkova-Kostova (2011)

Table 1 continued

Key messages	References
This review on Nrf2 focusses on the relevance of Nrf2 disruption in colon, bladder, lung, stomach, breast, skin and liver cancers	(15) Slocum and Kensler (2011)
This review gives an overview on how arsenate and arsenite interfere with intracellular signal transduction networks	(16) Druwe and Vaillancourt (2010)
High brain concentrations of the organoselenium compound, diphenyl diselenide, are associated with shorter time to seizure episodes in rats	(17) Prigol et al. (2010)
The development of Parkinson's disease following exposure to welding fumes is an area of growing concern. This study demonstrates that repeated exposure of rats to manganese-containing welding fumes causes persistent alterations in dopaminergic targets	(18) Sriram et al. (2010)
Recent studies suggest that inhaled nanoparticles from diesel engine exhaust may also reach the brain. This study demonstrates that the inhalation of diesel engine exhaust by rats causes region-specific gene expression changes in the brain that is comparable to that observed in the lung	(19) van Berlo et al. (2010)
Phosphorylated butyrylcholinesterase and phosphorylated albumin were compared as biomarkers of organophosphorus exposure	(20) Read et al. (2010)
This review gives a comprehensive update of the micronucleus assay, including its toxicological relevance, protocols, application as a high-throughput assay and mechanisms of micronucleus formation	(21) Kirsch-Volders et al. (2011)
The comprehensive review gives an overview of the use of human pluripotent stem cells, embryonic stem cells and induced pluripotent stem cells in developmental, cardio- and hepato-toxicity testing	(22) Wobus and Löser (2011)
Furan is formed during thermal treatment of food and is consistently found in baby foods. It induces both hepatocellular and bile duct tumours in rodents. This review gives a thorough risk assessment of furan in human diet	(23) Bakhiya and Appel (2010)
The liver tumour promoter piperonyl butoxide generates reactive oxygen species which increase c-Myc- and E2F1-related pathways and thereby activate cell proliferation	(24) Kawai et al. (2010)
Oxidative stress alone is not sufficient to explain specific mechanisms induced by nanoparticles. This article addresses nanoparticle-induced activation of MAP kinase cascades, p38, JNK, NF-kappa B and Nrf2 signalling pathways	(25) Marano et al. (2011)
Flavonoids have been reported to provide neuroprotection. However, this article provides evidence of a more complex situation: Both quercetin and quercitrin protected the mitochondria of rat brain slices from MeHg-induced lipid peroxidation. In contrast, rutin was not protective. Ca^{2+} plays a central role in MeHg-induced toxicity	(26) Wagner et al. (2010)
Silica nanoparticles (SiO_2-NPs) were found in the endosomes and the cytosol of HeLa cells. No accumulation in mitochondria or nuclei was seen. In contrast, the larger 'submicron particles' (SiO2-SMPs) accumulated in lysosomes	(27) Al-Rawi et al. (2011)
A single-nucleotide polymorphism, rs710521[A], located near TP63, and recently discovered in genome-wide association studies, was associated with human bladder cancer risk in a case–control series of 1,425 cases and 1,740 controls	(28) Lehmann et al. (2010)
The pyrethroid insecticide, cypermethrin disrupts testosterone synthesis in testes of mice	(29) Wang et al. (2010)
The capping material of nanocrystal quantum dots, and not the material of the core, determines toxicity	(30) Hoshino et al. (2011)
The toxicokinetics of thiomersal is completely different from that of methylmercury. Therefore, toxicity data from methylmercury studies are not appropriate when assessing the risk from mercury released from the ethylmercury-releasing preservative, thiomersal	(31) Rodrigues et al. (2010)
Perfluorooctane (PFOS) is a bioaccumulative pollutant. In rat brain tissue, PFOS activates calcium signalling and c-Fos, as well as c-Jun	(32) Liu et al. (2010a, b)
This study applied a genotoxicity assay based on the detection of histone H2AX phosphorylation to compare bisphenol A and bisphenol F. Bisphenol A was not found to be genotoxic, whereas bisphenol F showed positive effects	(33) Audebert et al. (2011)
Sodium fluoride suppresses proliferation and induces apoptosis in cultivated osteoblasts. This effect was caused by decreased insulin-like growth factor-1 expression	(34) Wang et al. (2011)
The flavonoid quercetin protects against methylmercury-induced DNA damage and oxidative stress in rats	(35) Barcelos et al. (2011)

Table 1 continued

Key messages	References
This review discussed the current possibilities and perspectives of in vitro test systems for nanotoxicology	(36) Clift et al. (2011)
The aspect ratio (defined as the ratio length: diameter) of carbon nanotubes has no influence on genotoxicity	(37) Kim et al. (2011)
Inorganic arsenic induces apoptosis in the cerebrum of mice	(38) Yen et al. (2011)
Increasing age leads to alterations of hepatic cytochrome P450 isoforms in rats. CYP1A1, CYP1A2, CYP2B1 and CYP2E1 were maximally expressed at 3 weeks, and then later decreased	(39) Yun et al. (2010)
This review gives an update on the mechanisms of action and cellular targets of toxic metals, as well as the use of chelating agents for pharmaceutical treatment	(40) Sinicropi et al. (2010)
This review summarises epidemiological studies on maternal exposure to particulate matters and adverse pregnancy outcomes. Overall, there is no convincing evidence of an association	(41) Bosetti et al. (2010)
Transition metal ions induce lipid peroxidation in artificial phospholipid liposomes	(42) Repetto et al. (2010)
The antioxidants, isoquercitrin and melatonin reduce oxidative stress-mediated liver tumour promotion by the benzimidazole anthelmintic, oxfendazole in rats	(43) Nishimura et al. (2010)
Administration of silver nanoparticles to rats caused a dose-dependent accumulation of particles in the lamina propria of the small and large intestine, increased numbers of goblet cells and altered mucus composition	(44) Jeong et al. (2010)
The author critically discusses Hermann J. Muller's well-known Nobel lecture where a linear dose–response for radiation-induced germ cell mutations was presented. In contrast to this concept, Calabrese presents arguments speaking against the linear no-threshold model	(45) Calabrese (2011)
Zinc oxide nanoparticles induce the release of pro-inflammatory cytokines in mouse and human cell systems	(46) Heng et al. (2011)
A single intratracheal instillation of carbon nanotubes may induce early lung fibrosis	(47) Park et al. (2011)
Indole-3-carbinol and flutamide increased the expression of CYP1A1 and induced liver cell foci in rats	(48) Shimamoto et al. (2011)
Synephrine is added to dietary supplements for weight loss. The hydroxyl group in the p-position favours transporter-mediated uptake into cardiomyocytes. Moreover, isomerisation of synephrine influences its toxicological profile	(49) Rossato et al. (2011)
DNA strand breaks induced by platinum nanoparticles are mediated by platinum ions released from the nanoparticles	(50) Gehrke et al. (2011)
This review deals with the description and comparison of cyclotron-based irradiation techniques for the generation of radiolabelled nanoparticles applicable in nanotoxicity tracing approaches	(51) Gibson et al. (2011)
In urinary bladder cancer, all known validated individual SNPs are associated with only a moderate risk that is too low to justify preventive measures. The authors review this issue and propose that these so-called wimp SNPs may interact and, therefore, collectively result in much higher risk with preventive relevance	(52) Golka et al. (2011)
The genotoxic potential of dental composite components, such as bis-GMA, TEGDMA, HEMA and MMA, was studied in gingival fibroblasts. It was found that DNA strand breaks comparable to those induced by irradiation are only achieved with unrealistic concentrations	(53) Durner et al. (2011)
Elevated expression of Th2 cytokines and signal molecules during the inflammation response in silica-induced pulmonary fibrosis in mice is mediated by IL-6R alpha	(54) Tripathi et al. (2010)
This study shows that beta-carboline alkaloids, such as rutaecarpine, annomontine and xestomanzamine A, are stimulators of AhR and lead to AhR-targeted gene expression	(55) Haarmann-Stemmann et al. (2010)
Possible oestrogenic effects of cadmium were analysed in the rat intestine. Cadmium exposure was shown to modulate molecular and functional parameters of oestrogenicity, such as proliferation and expression of the oestrogen-regulated gene ER beta	(56) Höfer et al. (2010)
Exposure to the commercial formulation of the herbicide glyphosate during puberty disrupts the reproductive development of rats by altering testosterone level and testicular morphology	(57) Romano et al. (2010)

Table 1 continued

Key messages	References
Gene expression alterations in the brains of neonatal mice exposed to methylmercury and polychlorinated biphenyls, alone or in combination, reveal not only toxicity effects but also a protective detoxification response upon co-exposure	(58) Shimada et al. (2010)
Perinatal exposure to perfluorooctane sulphonate during the critical period of brain development may have neurotoxic effects on the CNS by altering the expression of calcium-dependent signalling pathway molecules	(59) Liu et al. (2010a, b)
An overview of the currently available metabolic databases is given, with the MetaCyc family being described in particular detail	(60) Karp and Caspi (2011)

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