EXCLI Journal 2012;11:692-702 – ISSN 1611-2156
Received: October 30, 2012, published: October 31, 2012

Editorial:

CURRENT DEVELOPMENTS IN TOXICOLOGY

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As already previously reported the EXCLI Journal closely cooperates with the Archives of Toxicology as a partner for articles focussing on basic and clinical research (Bolt, 2011; Bolt and Stewart, 2011). To give our readers an overview over current cutting-edge topics in toxicology we publish a compilation of brief 'key messages' from the most cited articles (Table 1). The citation ranking illustrates that research on nanoparticles has evolved to the currently most studied field in toxicology (Xie et al., 2010; Foldbjerg et al., 2011). As in the previous years oxidative stress research remains a cutting-edge topic (Kell, 2010). Clearly, alternative methods of toxicity testing represent an emerging field of research. This development was further intensified by the 7th amendment to the EU Cosmetics Directive that prohibits to put animal-tested cosmetics on the market after 2013 (Adler et al., 2011). Although this directive has been controversely discussed it has nevertheless initiated intensive research activities to establish novel in vitro tests. The review of Adler and colleagues gives a comprehensive analysis of the current status of alternative methods and of the time necessary to achieve full replacement of animal testing.

Table 1: Key messages of the most cited articles in Archives of Toxicology (2010-2011) (from: Bolt et al., 2012)

Key message	Reference
Many degenerative diseases and toxicological insults converge on iron dysregulation. This review summarises concepts of autocatalytic production of hydroxyl radicals a process which is intensified by positive feedback loops. Systems biology approaches predict that interventions, such as iron chelators and antioxidants may prove most effective in diseases such as Parkinson's, Huntington's, Alzheimer's, prions as well as any intoxications. The comprehensive review is the most cited article of the current evaluation period (2010, 2011).	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 are 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.	Pestka, 2010

Table 1 (cont.): Key messages of the most cited articles in Archives of Toxicology (2010-2011) (from: Bolt et al., 2012)

Key message	Reference
This review summarises the state of the art of in vitro toxicity tests in five critical fields of toxicity: toxicokinetics, repeated close toxicity, carcinogenicity, skin sensitisation, and reproductive toxicity. The background of this review is the prohibition to put 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 horizon cannot yet be estimated. This comprehensive review ranked third in the current evaluation period.	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 accumulate in lungs, liver and spleen, are retained for more than 30 days, are endozytosed by macrophages and could cause liver toxicity. This is the most cited original article of the current evaluation period. It underlines that nanotoxicology emerged as one of the most popular fields in toxicology.	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 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.	Drobná et al., 2010
The comprehensive review article gives an overview over the mutagenicity and carcinogenicity studies on selenium and discusses its molecular mechanisms. At low concentrations selenium shows anticarcinogenic effects. However, at concentrations higher than needed for nutrition it can be genotoxic and carcinogenic. This study may help to regulate the use of selenium in nutrition.	Valdiglesias et al., 2010
Silver nanoparticles (AgNPs) concentration dependently induced reactive oxygen species (ROS), mitochondrial damage DNA adducts and apoptosis in a human alveolar cell line. Pretreatment 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.	Foldbjerg et al., 2011
Metabolomics have successfully identified novel biomarkers of disease prognosis and drug efficacy as well as toxicity. This review recommends how novel biomarkers discovered by metabolomics should be verified and introduced into clinical practice.	Mamas et al., 2011
This review focusses on the following aspects of selenium toxicity: (i) The majority of epidemiological studies suggest a cancer-preventing activity. (ii) In cancer treatment selenium acts as a prooxidant inducing apoptosis. (iii) The use of saccharomyces cerivisiae is reviewed as a powerful tool for the study of the mode of action of selenium.	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.	Elcombe et al., 2010

Table 1 (cont.): Key messages of the most cited articles in Archives of Toxicology (2010-2011) (from: Bolt et al., 2012)

Key message	Reference
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 as preventive of carcinogenic effects.	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.	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.	Nogueira and Rocha, 2011
This is a comprehensive review about the protective network controlled by the Keap 1-Nrf2 axis, focussing on proliferation, angiogenesis and apoptosis.	Baird and Dinkova-Kostava, 2011
This review about Nrf2 focusses on the relevance of Nrf2-disruption in colon, bladder, lung, stomach, breast, skin and liver cancer.	Slocum and Kensler, 2011
This review gives an overview how arsenate and arsenite interfere with intracellular signal transduction networks.	Druwe and Vaillancourt, 2010
High brain concentrations of the organoselenium compound diphenyl diselenide are associated with shorter time to seizure episodes in rats.	Prigol et al., 2010
The development of Parkinson's disease following exposure to welding fumes is an area of emerging concern. This study demonstrates that repeated exposure of rats manganese containing welding fumes causes persistent alterations in dopaminergic targets.	Sriram et al., 2010
Recent studies suggest that inhaled nanoparticles from diesel engine exhaust may also reach the brain. This study demonstrates that inhalation of diesel engine exhaust by rats causes region specific gene expression changes in brain to a comparable extent to that observed in the lung.	van Berlo et al., 2010
Phosphorylated butyrylcholinesterase and phosphorylated albumin were compared as biomarkers of organophosphorus exposure.	Read et al., 2010
This review gives a comprehensive update of the micronucleus assay: toxicological relevance, protocols, application as high-throughput and mechanisms of micronucleus formation.	Kirsch-Volders et al., 2011
The comprehensive review gives an overview over the use of human pluripotent stem cells, embryonic stem cells and induced pluripotent stem cells in developmental, cardio and hepatotoxicity testing.	Wobus and Löser, 2011
Furan is formed during thermal treatment of food and is consistently found in baby foods. It induces hepatocellular and bile duct tumors in rodents. This review gives a thorough risk assessment of furane in human dict.	Bakhiya and Appel, 2010
The liver tumor promoter piperonyl butoxide generates reactive oxygen species which increase c-Myc- and E2F1-related pathways and thereby activate cell proliferation.	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 Nrf-2 signalling pathways.	Marano et al., 2011

Table 1 (cont.): Key messages of the most cited articles in Archives of Toxicology (2010-2011) (from: Bolt et al., 2012)

Key message	Reference
Flavonoids have been reported to provide neuroprotection. However, this article gives evidence of a more complex situation: Quercetin and quercitrin protected mitochondria of rat brain slices from MeHg induced lipid peroxidation. In contrast, rutin did not show a protective effect. Ca 2+ plays a central role in MeHg induced toxicity.	Wagner et al., 2010
Silica nanoparticles (SiO2-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.	Al-Rawi et al., 2011
A single nucleotide polymorphism, rs710521[A] located near TP63, 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.	Lehmann et al., 2010
The pyrethroid insecticide cypermethrin disrupts testosterone synthesis in testes of mice.	Wang et al., 2010
The capping material of nanocrystal quantum dots and not the material of the care determines toxicity.	Hoshino et al., 2011
The toxicokinetics of thiomersal is completely different from that of methylmercury. Therefore, toxicity data of methylmercury are not an appropriate reference for assessing the risk from mercury released from the ethylmercury releasing preservative thiomersal.	Rodrigues et al., 2010
Perfluorooctane (PFOS) is a bio-accumulative pollutant. In rat brain tissue PFOS activates calcium signalling and c-fos as well as c-jun.	Liu et al., 2010a
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.	Audebert et al., 2011
Sodium fluoride suppresses proliferation and induces apoptosis in cultivated osteoblasts. This effect was caused by decreased insulin-like growth factor-I expression.	Wang et al., 2011
The flavonoid quercetin protects against methylmercury induced DNA damage and oxidative stress in rats.	Barcelos et al., 2011
This review discussed the current possibilities and perspectives of in vitro test systems for nanotoxicology.	Clift et al., 2011
The aspect ratio (defined as the ratio length: diameter) of carbon nanotubes has no influence on genotoxicity.	Kim et al., 2011
Inorganic arsenic induces apoptosis in the cerebrum of mice.	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 three weeks and decreased late.	Yun et al., 2010
This review gives an update about the mechanisms of action and cellular targets of toxic metals as well as the use of chelating agents for pharmaceutical treatment.	Sinicropi et al., 2010
This review summarises epidemiologic studies on maternal exposure to particulate matters and adverse pregnancy outcomes. Overall, there is no convincing evidence of an association.	Bosetti et al., 2010
Transition metal ions induce lipid peroxidation in artificial phospholipid liposomes.	Repetto et al., 2010
The antioxidants isoquercitrin and melatonin reduce oxidative stress mediated liver tumor promotion by the benzimidasole anthelmic oxfendasole in rats.	Nishimura et al., 2010

Table 1 (cont.): Key messages of the most cited articles in Archives of Toxicology (2010-2011) (from: Bolt et al., 2012)

Key message	Reference
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.	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.	Calabrese, 2011
Zinc oxide nanoparticles induce the release of pro-inflammatory cytokines in mouse and human cell systems.	Heng et al., 2011
A single intratracheal instillation of carbon nanotubes may induce early lung fibrosis.	Park et al., 2011
Indole-3-carbinol and flutamide increased expression of CYP1A1 and induced liver cell foci in rats.	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.	Rossato et al., 2011
DNA strand breaks induced by platinum nanoparticles are mediated by platinum ions released from the nanoparticles.	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.	Gibson et al., 2011
In urinary bladder cancer all known validated individual SNPs are associated with only 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.	Golka et al., 2011
The genotoxic potential of dental composite components, such as BisGMA, TEGDMA, HEMA and MMA, was studied in gingivial fibroblasts. It was found that DNA strand breaks comparable to those induced by irradiation are only achieved with concentrations that are unrealistic.	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.	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-target gene expression.	Haarmann-Stemmann et al., 2010
Possible estrogenic effects of cadmium were analysed in the rat intestine. Cadmium exposure was shown to modulate molecular and functional parameters of estrogenicity such as proliferation and expression of the estrogen-regulated gene ER beta.	Höfer et al., 2010
Exposure to the commercial formulation of the herbicide glyphosate during the puberty period disrupts the reproductive development of rats by altering testosterone level and testicular morphology.	Romano et al., 2010
Gene expression alterations in the brains of neonate mice exposed to methylmercury and polychlorinated biphenyls, alone or in combination, reveal not only toxicity effects but also a protective, detoxication response upon co-exposure.	Shimada et al., 2010

Table 1 (cont.): Key messages of the most cited articles in Archives of Toxicology (2010-2011) (from: Bolt et al., 2012)

Key message	Reference
Perinatal exposure to perfluorooctane sulfonate during the critical period of brain development may have neurotoxic effects on the CNS by altering the expression of calcium-dependent signaling pathway molecules.	Liu et al., 2010b
An overview of currently available metabolic databases is given with the MetaCyc family being described in particular detail.	Karp and Caspi, 2011
The mechanism by which fenvalerate negatively affects male reproduction and spermatogenesis was investigated. The results show that fenvalerate induces germ cell apoptosis in testes by upregulating expression of Fas and FasL.	Zhao et al., 2011
Only minor pulmonary irritation and inflammation potencies were found for TiO2 nanoparticles in standardised mouse bioassays.	Leppänen et al., 2011
The importance of nanoparticle surface functionalization could be shown in an in vivo model of embryonic zebrafish, whereby two lead sulfide nanoparticles with identical core size but different surface functionality led to drastic differences in embryo mortality.	Truong et al., 2011
This work uncovers a cell density-related resistance to cytotoxicity induced by zinc oxide nanoparticles in monolayer cultures of different cell lines and emphasizes the importance of standardization of cell culture protocols for toxicology screening.	Heng et al., 2011
Prediction of relevant concentrations for in vitro studies of cytotoxicity can be successfully achieved by applying BPTK modelling.	Mielke et al., 2011
The mechanism underlying perfluorooctane (PFOS)-mediated decrease in circulating thyroid hormone levels was studied. It was shown that PFOS increased hepatic expression of OATP2 and MRP2 leading to enhanced hepatic uptake and metabolism of T4.	Yu et al., 2011
The carotenoid lutein protects against cisplatin-induced DNA damage and chromosome instability in peripheral blood cells by improving antioxidant defense.	Serpeloni et al., 2010
Standardisation of the cell response to sodium nitroprusside (SNP) revealed that long-term culturing-associated resistance to SNP-induced cell toxicity was accompanied by higher levels of the stress protein Hsp70. Suggested mechanism of action of Hsp70 include increase of CAT and GSH-Px activities as well as decrease in caspase-3 activation.	Romero et al., 2010
The genotoxicity potential of beauvericin (BEA) and ochratoxin A (OTA) was evaluated in PK15 cells and human leukocytes using the alkaline comet assay. It was found that BEA is more toxic than OTA and that the combined genotoxic action is additive or both synergistic and additive depending on the cell line.	Klarić et al., 2010
A comparison of the effects of curcumin and resveratrol on aflatoxin B-1-induced liver injury in rats revealed that only curcumin has an hepatoprotective effect against damage by aflatoxin B-1.	El-Agamy, 2010

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