

**Editorial:**

**KEY MESSAGES OF RECENT PUBLICATIONS  
 IN THE FIELD OF TOXICOLOGY**

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In order to address the field of tension between toxicology as well as basic and clinical sciences, we closely cooperate with our partner journal Archives of Toxicology. To give our readers a rapid overview of recent developments we have summarized the key messages of the most cited publications. For better orientation we grouped the articles into the categories inorganic compounds (Table 1), toxicogenomics (Table 2), molecular toxicology (Table 3), organ toxicity and mechanisms (Table 4), reproductive toxicology (Table 5), genotoxicity and carcinogenicity (Table 6), as well as reviews and short communications (Table 7). We hope that our service facilitates the overview over recent achievements in toxicology and stimulates further reading.

**Table 1:** Inorganic compounds

Key message	Reference
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 <sup>2+</sup> plays a central role in MeHg-induced toxicity.	Wagner et al., 2010
Silicia nanoparticles (SiO <sub>2</sub> -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’ (SiO <sub>2</sub> -SMPs) accumulated in lysosomes.	Al-Rawi 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.	Rodrigues et al., 2010
The aspect ratio (defined as the ratio length: diameter) of carbon nanotubes has no influence on genotoxicity.	Kim et al., 2011a
Inorganic arsenic induces apoptosis in the cerebrum of mice.	Yen et al., 2011
Transition metal ions induce lipid peroxidation in artificial phospholipid liposomes.	Repetto et al., 2010
Zinc oxide nanoparticles induce the release of pro-inflammatory cytokines in mouse and human cell systems.	Heng et al., 2011
DNA strand breaks induced by platinum nanoparticles are mediated by platinum ions released from the nanoparticles.	Gehrke et al., 2011

**Table 1** (cont.): Inorganic compounds

Key message	Reference
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
Possible estrogenic effects of cadmium were analyzed 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
Only minor pulmonary irritation and inflammation potencies were found for TiO <sub>2</sub> 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
Studies on genetic susceptibility to carcinogenicity are fundamental for improving risk assessment strategies. This report shows that the polymorphic status at the locus of A35931C in XPD/ERCC2 might modulate the risk for arsenic-related skin lesions.	Lin et al., 2010
By assessing time-dependent pathological alterations in rats administered subtoxic or toxic MeHg doses for 3 weeks, the authors determine that MeHg at toxic doses causes selective functional alteration of choroid plexus before leading to pathological alterations in the brain.	Nakamura et al., 2011
This study shows that normal working conditions in a boric acid production plant present low risk of boron toxicity, as indicated by daily boron exposure levels lower than those associated with developmental and reproductive toxic effects in animals and absence of reproductive toxicity indicators in those workers.	Duydu et al., 2011
Welding fume is a complex aerosol of different metals. This study indicates that stainless steel welding fume induces more lung injury and inflammation compared with mild steel fume after a short-term inhalation exposure in rats.	Antonini et al., 2011
Sperm hyperactivity, needed for successful fertilization, is decreased when exposed to sodium fluoride in a dose dependent manner. Exposure to elevated fluoride levels decreased intracellular Ca <sup>2+</sup> and downstream Ca <sup>2+</sup> -dependent signalling pathways.	Sun et al., 2010
Silver nanoparticles (Ag NPs) have significant antimicrobial properties, and for the first time, the mechanism underlying their toxicity was investigated. Ag NPs caused death by inhibiting proliferation, upregulating pro apoptotic Bcl-2 members, and inhibiting PKC family members. PKC zeta was shown to be particularly important for Ag NP-mediated toxicity.	Lee et al., 2011a
Exposure to manganese chloride (MnCl) can lead to neurotoxicity with Parkinson-like symptoms. The increased oxidative damage induced by MnCl is accompanied by accumulation of NF-E2-related factor2 (Nrf2) in the cytoplasm and nucleus, which subsequently binds to the antioxidant response element (ARE) of antioxidant genes. The addition of an additional antioxidant, tert-butylhydroquinone (t-BHQ), prevents the cytotoxicity induced by MnCl.	Li et al., 2011a
The search for cancer-predictive biomarkers continues to be challenging as three potential biomarkers - SMRP, CA125 and CYFRA21-1 - proved to be highly specific, but not very sensitive, as predictors of lung cancer and malignant mesothelioma in a cohort of workers exposed to asbestos.	Gube et al., 2011

**Table 1** (cont.): Inorganic compounds

Key message	Reference
Parallel application of glutathione during inorganic arsenic treatment can promote arsenic metabolism by methylation and might facilitate excretion of arsenicals.	Wang et al., 2011a
Investigation of inorganic arsenite on four different rat derived cell lines gives hints that Nrf2 might be the reason for cardiac toxicity of arsenite.	Sumi et al., 2011
Upon exposure to high fluoride and low iodine, rat brain proteins related to cell signaling, energy metabolism, and protein metabolism were found to be deregulated.	Ge et al., 2011
Maternal injection of cisplatin to pregnant guinea pigs lead to hearing loss and cochlear hair cell apoptosis in pups.	Hao et al., 2011
The dispersion stability of carbon nanotubes (CNTs) used in toxicity tests was evaluated. During 16 weeks dispersion stability decreased in the following order: BSA, Tween 80, DPPC, and DMSO for the MWCNTs and BSA, DPPC, Tween 80, and DMSO for the SWCNTs.	Kim et al., 2011b
For the first time it was reported that two codominant alleles at a genetic locus are responsible for the susceptibility to Cd-induced testicular toxicity in inbred rat strains.	Shimada et al., 2011
Methylation of iAs has been implicated in arsenic toxicity, however, the mechanism of methylation is not fully understood. The study shows that AS3MT expression generates dimethylated arsenicals which enhanced the cytotoxic effect of arsenite.	Watanabe et al., 2011
Mercuric chloride induced urinary excretion of Oat5 in rats, suggesting that it might be an early indicator of mercury-induced nephropathy, which predicts the perturbation before the manifestation of histopathological damages.	Di Giusto et al., 2010

**Table 2:** Toxicogenomics

Key message	Reference
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
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
Using recombinant UGT2B15 enzymes (wild type and mutants) the authors establish that variants with D85Y substitution have a markedly reduced $V_{max}$ and $CL_{int}$ values, with no changes in $K_m$ .	Hanioka et al., 2011
Ethanol can induce severe toxic effects in developmental brain. By gene array analysis in a model of neural stem cell differentiation in vitro, the authors identify two main gene clusters influenced by ethanol: a Wnt-Fzd and a cluster of heat shock proteins genes and the heat shock transcription factor HSF5.	Choi et al., 2011a

**Table 2 (cont.): Toxicogenomics**

Key message	Reference
Second-generation antihistamine drugs overdose or reduced metabolism may increase ventricular arrhythmia. The present study identified gene signatures indicative of toxicity, namely cardiotoxicity, oxidative stress, heat shock proteins, hypoxia and inflammation, suggesting that these sets of these genes could serve as biomarkers for cardiotoxicity.	Lee et al., 2010
This paper describes an analysis of the mutation pattern by benzene in the TP53 gene using the 'Functional Analysis of Separated Allels in Yeast' technique.	Billet et al., 2010
The authors found a strong correlation between proteasomal induction and lipid elevations in a rat model for HIV protease inhibitor-induced hyperlipidemia. The identification of proteasome gene regulation allowed them to develop a rapid screen for identifying novel PIs that do not induce the proteasome.	Waring et al., 2010
This publication is the first comprehensive gene expression profiling study conducted for welding fume exposure in monkeys. The expressed genes are expected to be useful in helping to understand transcriptional changes in monkey lungs after welding fume exposure.	Heo et al., 2010
The study shows that a genetic polymorphism of the insulin-like growth factor (IGFBP-3) binding protein-3 gene may be involved in the etiology of bladder transitional cell carcinoma (TCC). Larger studies are needed for further confirmation.	Safarinejad et al., 2011
The combination of hepatic transcriptomics and proteomics was used to investigate the molecular dynamics of glutathione depletion induced by diethyl maleate (DEM) in rat. The genes Trib3, Srxn1, Myc, Asns, Igfbp1, Txnrd1, or Hmox1, were suggested as robust mRNA biomarkers for evaluating hepatic glutathione depletion. L-FABP, MAWDBP, aldo-keto reductase family 1 member A1, catalase and ATP synthase subunit beta were suggested as potential protein biomarkers.	Yamauchi et al., 2011

**Table 3: Molecular toxicology**

Key message	Reference
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 includes increase of CAT and GSH-Px activities as well as decrease in caspase-3 activation.	Romero et al., 2010
Based on its selective pro-apoptotic effect over the tumor cell line Hep G2 and not on the normal WRL68 liver cells, the novel <i>P. vulgaris</i> lectin has a potential therapeutic use on liver cancer.	Fang et al., 2011
This article describes detailed molecular mechanisms of ceramide induced apoptosis in stem cells, initiated by ROS and propagated by caspases.	Park et al., 2011a
Due to its antioxidant potential, diphenyl diselenide has been studied as a potential protective molecule. In this article, the authors present clear evidence on a cytotoxic potential of (PhSe) <sub>2</sub> in a neuronal cell line, mediated by the ERK1/2 pathway.	Posser et al., 2011

**Table 3** (cont.): Molecular toxicology

Key message	Reference
Methylation changes in mouse liver, in response to a methyl deficient diet with or without arsenic, were sex-dependent. This may account for the differences in susceptibility of males and females to various diseases that are dependent on epigenetic modifications.	Nohara et al., 2011
Inducing the drug transporter, p-glycoprotein (P-gp) with doxorubicin decreased paraquat-induced cytotoxicity; a protection reversed by inhibiting P-gp with a specific inhibitor. Caco-2 cells proved to be an efficient model to study the mechanisms of paraquat toxicity.	Silva et al., 2011
Lipopolysaccharide (LPS) can cause septic shock, a response regulated by alveolar type II epithelial cells. In this study, the authors showed that LPS induces a time and concentration dependent decrease in A549 cell viability, with a concurrent increase in reactive oxygen species (ROS) and apoptosis via the intrinsic mitochondria-dependent pathway. Pretreating the cells with the antioxidant, N-acetylcysteine attenuated LPS-induced ROS formation and cell death.	Chuang et al., 2011
Phosphate and tyrode buffer are suitable for inhibition and reactivation kinetics of human erythrocyte AChE, while TRIS and MOPS buffer markedly changed kinetics of AChE.	Wille et al., 2011
The shellfish toxins okadaic acid and dinophysin toxin 2 show different cell cycle arrests in HepG2 compared to clone9 cells; in addition different expressions of cyclins and cyclin dependent kinases had been observed.	Rubiolo et al., 2011
Entry pathway of tested nanoparticles shifted from direct penetration to endocytosis depending on size. 30 nm particles led to reduction in Zn <sup>2+</sup> and Mg <sup>2+</sup> content in nuclei and to increased p53 in the whole cell. While particles of 50 -100 nm localised in acidic vesicles and showed increased p53 in nuclei.	Zhang et al., 2011
Depleting regulatory T cells in mice aggravates 1,3-beta-glucan induced lung inflammation.	Liu et al., 2011a
Sub-chronic exposure of mice to perfluorooctanesulfonate altered the host's immune state towards a more T(H)2-like state with increased IL-4, IL-10, IgG, IgG1, and IgE, but decreased IL-2, IFN-gamma, and IgM levels.	Dong et al., 2011
A neurotoxin-like protein derived from Egyptian cobra venom was fractionated chromatographically. The venom fractions exerted various cytotoxic effects against different cancer cells.	El Hakim et al., 2011
(S)-dimethyl 2-(3-(phenyltellanyl) propanamido) succinate, a telluro-amino acid derivative showed glutathione peroxidase-like activity in rat brain homogenates, but genotoxic and mutagenic effects in adult male mice.	Meinerz et al., 2011
The authors developed a novel proteomic analysis platform which they named antigen-subtracted 2-DE/MS strategy. The article describes the new technique and includes a comparative proteomic analysis for 16HBE and 16HBE-C GO/G1 cell proteins. New proteins involved in carcinogenesis, oxidative stress and protein synthesis were identified and showed that this new technique improves resolution of protein samples.	Zhao et al., 2011a
The proteasome inhibitor MG132 reduces growth of As4.1 juxtaglomerular cells via caspase-independent apoptosis. The changes in ROS and GSH levels by MG132 and caspase inhibitors partially influenced the growth inhibition and death of As4.1 cells.	Han et al., 2010a

**Table 3** (cont.): Molecular toxicology

Key message	Reference
In their in vivo assessment of antiemetic drugs in Beagle dogs, the authors found evidence that predominantly Neurokinin-1 (NK(1)) and to a lesser extent 5-hydroxytryptamine 3 (5-HT(3)) receptors are involved in lycorine-induced emesis facilitating a target-orientated therapy.	Kretzing et al., 2011
This paper describes a biochemical and pharmacological characterization of BpirPLA(2)-I, the first acidic Asp49-PLA(2) isolated from Bothrops pirajai snake venom. The authors suggest a possible relationship between the basic or acid character of PLA(2) enzymes and the functionality of the Ca <sup>2+</sup> ion binding loop.	Teixeira et al., 2011
'Designer steroids' are misused for doping purposes in the bodybuilding scene. Results suggest that the MHC expression shift (MHC II/d/x upregulated, MHC II/b downregulated) induced by NOR, madol and TP could serve as a molecular marker to determine anabolic activity of anabolic steroids at least in skeletal muscle of orchi rats.	Frese et al., 2011
The study shows that amlodipine exerts a significant inhibition on adriamycin-induced toxicity in rat mesangial cells by affecting the expression of TGF-β/Smad signaling intermediates p-Smad2 and Smad4.	Song et al., 2011
The authors demonstrate that PAHs found in the Chattanooga Superfund site induce apoptosis in vitro via activation of group IVC PLA2, and this may be the mechanism for vascular damage in mice inhabiting the Superfund site.	Tithof et al., 2011
Acrolein significantly downregulated cellular NF-κB activity as well as LPS- induced NO production in human skin cells without altering cellular levels of the phosphorylated and nonphosphorylated forms of Iκ-Bα, implying that the effect of acrolein on cellular NF-κB activity is independent of Iκ-Bα.	Moon, 2011
The authors report potent proteolytic and neurotoxic but no hemorrhagic activities in crude toxins from salivary excretion (SE) of <i>H. angulatus</i> . In addition, the authors purify a cysteine-rich secretory protein called helicopsin from the SE that exhibited robust neurotoxic activity.	Estrella et al., 2011
The authors report two main effects of Brevetoxin toxicity in mast cells: an initial degranulation and increase in IL-6 expression independent of IgE receptor, followed by cellular toxicity within 24 h by LDH release and Annexin-V staining.	Hilderbrand et al., 2011

**Table 4:** Organ toxicity and mechanisms

Key message	Reference
The pyrethroid insecticide, cypermethrin disrupts testosterone synthesis in testes of mice.	Wang et al., 2010
Sodium fluoride suppresses proliferation and induces apoptosis in cultivated osteoblasts. This effect was caused by decreased insulin-like growth factor-1 expression.	Wang et al., 2011b
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., 2010a

**Table 4** (cont.): Organ toxicity and mechanisms

Key message	Reference
A single intratracheal instillation of carbon nanotubes may induce early lung fibrosis.	Park et al., 2011b
The genotoxic potential of dental composite components, such as BisGMA, 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 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
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., 2011b
A comparison of the effects of curcumin and resveratrol on aflatoxin B-1-induced liver injury in rats revealed that only curcumin has a hepatoprotective effect against damage by aflatoxin B-1.	El-Agamy, 2010
Pentachlorophenol (PCB) and its metabolites are very potent toxicants that are still in use worldwide. This article reveals detailed mechanisms of toxicity induced by these chemicals in human lymphocytes with implications on pathology and their use as a sensitive cell type for toxicity testing.	Michałowicz, 2010
Bisabololoxide A, a chamomile tea constituent, can induce apoptosis of thymocytes, rising important issues on herbal tea toxicity.	Ogata et al., 2010
Ziram is a widely used fungicide in agriculture and as an accelerating agent in latex production. The authors report a novel immunotoxicity effect of this compound namely induction of apoptosis/necrosis in U937 cells.	Li et al., 2011b
Neuropathy Target Esterase (NTE) is the primary target esterase of organophosphorus compound-induced delayed neuropathy. Some studies suggest it may perform a function in embryonic development. This study reports NTE expression in ESC and its variation during first stages of in vitro differentiation to embryonic bodies. The role of this activity and the meaning of the variations detected during differentiation requires further studies.	Pamies et al., 2010
Pentabromodiphenyl ether (PentaBDE) more dramatically altered the redox status in rat liver compared to the other commonly used flame retardant, decabromodiphenyl ether (DecaBDE), as seen by increased activity of reducing enzymes, fatty acid degeneration, liver mass, CYP activities and microsomal enzymes. These endpoints were significantly less or not detectable in rats treated with DecaBDE.	Bruchajzer et al., 2010
Kidney damage induced by adriamycin (ADR) is marked by increased levels of hydrogen sulfide (H <sub>2</sub> S), which leads to increased inflammation and oxidative stress. DL-propargylglycine (PAG) was shown to inhibit ADR-induced nephrotoxicity in rats treated with different concentrations of ADR up to 15 days.	Francescato et al., 2011
Known nanoparticles, fullerenes (also known as fullerols or fullerenols) [C-60(OH)(n)] cause cytotoxicity by disrupting mitochondrial function as determined by mitochondrial permeability transition. Disruption to the mitochondria results in mitochondrial depolarization, decreased ATP synthesis, oxidized GSH and proteins, and lipid peroxidation. An interesting finding is that the number of hydroxyl groups may influence toxicity.	Nakagawa et al., 2011

**Table 4** (cont.): Organ toxicity and mechanisms

Key message	Reference
Generation of hydroxyl radical ((OH)-O-aEuro cent) in the striatum due to carbon monoxide (CO) poisoning is independent of hypoxia, which is also generated after exposure to CO. There also appears to be a threshold concentration at which OH-O-aEuro cent is formed.	Hara et al., 2011
Instead of supporting the more expected hypothesis that metabolites of benzo-a-pyrene (BaP) lead to more oxidative stress, reduced vascular nitric acid bioactivity and increased blood pressure, the authors observed inflammation in the lung after 7-day intranasal exposure to BaP, and altered circadian rhythm of blood pressure.	Gentner and Weber, 2011
The timing and concentration of the carbamate, physostigime used to treat organophosphate (OP) poisoning should be re-visited due to the possibility of increased toxicity and even mortality observed in a guinea pig model after treatment with the OP, soman. Obidoxime, at low concentrations, was the most effective therapeutic agent, reversing many of the effects of soman-induced toxicity.	Joosen et al., 2011
This study is presenting a local lymph node assay to assign disperse dyes sensitising potency. With this assay the dyes can be arranged into four potency classes.	Ahuja et al., 2010a
There is a significant correlation between melamine intake and urolithiasis in infants.	Ke et al., 2010
3,3 '-diselenodipropionic acid can ameliorate the polarisation of Th1/Th2 immune balance towards Th2 during body irradiation. This might be the reason for the prevention of oxidative stress in small intestine.	Kunwar et al., 2011
Monocrotaline/lipopolysaccharide co-treatment caused renal toxicity in mice. Co-treatment with tissue factor (TF) antisense oligonucleotide partially prevented renal damage and improved animal survival.	Abdel-Bakky et al., 2011
Diindolylmethane, a natural compound derived from cruciferous vegetables, induced the phospholipase C-dependent release of intracellular Ca <sup>2+</sup> in HA59T human hepatoma cells and caused dose-dependent cell death.	Cheng et al., 2011
Acrylamide treatment similarly affected the nervous system of young and adult male rats but lead to more pronounced spermatid degeneration in younger animals.	Takahashi et al., 2011
In a model of human primary lung cells, DNA damage induced by H <sub>2</sub> O <sub>2</sub> treatment correlated well with PARP-1 activity.	Ahmad et al., 2011
The anthracycline antineoplastic drug daunorubicin does not cause cardiotoxicity by affecting the glutathione antioxidant system as seen in a rabbit model of intravenous injection, or treatment of H9c2 rat cardiac cells.	Vávrová et al., 2011
In mice, the intake of fluoride with drinking water induced histopathological lesions of liver and kidney that were correlated with synthesis of stress proteins.	Chattopadhyay et al., 2011
Cyclophosphamide injection in adult female rats reduced the expression of uroplakin, a mucosal barrier against toxic materials, in urinary bladder mucosa. The reduced expression of uroplakin was preserved by concomitant treatment with mesna.	Kyung et al., 2011
This study deals with the effects of Pyrogallol (PG) on As4.1 juxtaglomerular cells. MAPK inhibitors attenuated As4.1 cell growth inhibition and death mediated by PG treatment. The changes in O <sub>2</sub> <sup>•-</sup> and GSH levels by PG and/or MAPK inhibitors appeared to affect the growth and death of As4.1 cells.	Han et al., 2010b



**Table 4** (cont.): Organ toxicity and mechanisms

Key message	Reference
<p>The aim of our study was to assess irritative effects of SO<sub>2</sub> up to 2 ppm on the airways using non-invasive methods like exhaled breath condensate (EBC), nasal lavage fluid (NALF) and exhaled nitric oxide (FeNO). Acute low dose SO<sub>2</sub> exposure in not adapted subjects did not induce airway irritation or/and inflammation measured under the tested conditions.</p>	<p>Raulf-Heimsoth et al., 2010</p>
<p>This study describes the involvement of sensory nerves and TRPV1 receptors in the rat airway inflammatory response to two environment pollutants: diesel exhaust particles (DEP) and 1,2-naphthoquinone (1,2-NQ). The authors found that DEP-induced airways oedema is highly influenced by increased ambient levels of 1,2-NQ and takes place by neurogenic mechanisms involving upregulation of TRPV1 and tachykinin receptors.</p>	<p>Costa et al., 2010</p>
<p>In vivo cholinergic toxicity and lethality was studied in freely moving guinea pigs upon exposure to the organophosphorus nerve agents sarin (GB) and VX. Seizures generated from GB resulted in more rapid and severe cholinergic effects, elevation of ACh level and increased glutamate levels. Glutamate did not increase in the VX seizure group. The authors conclude that seizure activity per se contributes to the elevated levels of brain ACh observed after nerve agent exposure.</p>	<p>O'Donnell et al., 2011</p>
<p>Monolayer cultures of primary hepatocytes, isolated from freshly removed livers are as commonly used as in vitro tool. The present study elucidated two cell death peaks, shortly after cell seeding and in the final stages of the cultivation period. The authors explain the underlying molecular processes and give strategies for increasing cell survival in this in vitro system.</p>	<p>Vinken et al., 2011</p>
<p>Biodiesels contain biocides in order to inhibit and remove microbial growth. The toxicity of four candidate biocides were tested using the NR8383 cell line and freshly isolated rat alveolar macrophages, the latter being among the first cell type exposed to inhaled biodiesel aerosols. The study suggested the biocide CMIT to cause respiratory effects and the need for further investigations and further animal studies.</p>	<p>Poon et al., 2011</p>
<p>Isoline-induced oxidative stress injury to the livers of newly weaned and young mice is age-dependent and due to the different responses of the glutathione antioxidant system.</p>	<p>Liang et al., 2011</p>
<p>Cadmium nephrotoxicity was tested in combined enzymatic and <sup>13</sup>C-NMR measurements with a mathematical model of lactate metabolism. The authors showed that cadmium chloride highly diminishes the entire flux through the gluconeogenic pathway without altering the fluxes through enzymes of the tricarboxylic acid cycle.</p>	<p>Faiz et al., 2011</p>
<p>In order to characterize idiosyncratic liver injury the authors injected monocrotaline (MCT) in combination with modest inflammatory conditions induced by LPS in mice. Their experiments clearly showed that the expression of ox-LDL, CXCL16, and TF represents an early event in the onset of hepatotoxicity induced by MCT/LPS.</p>	<p>Hammad et al., 2011</p>
<p>The toxicokinetics and the biodistribution profile of the Shiga toxin type 2 (Stx2) was studied in rat. High accumulation was found in the lungs, kidneys, nasal turbinates and sometimes the eyes.</p>	<p>Liu et al., 2011b</p>
<p>The repeated administration of the flame retardant pentabromodiphenyl (PentaBDE) effected heme biosynthesis and leads to strongly enhanced porphyrin concentrations in the liver. Also the urinary excretion of total porphyrins was augmented.</p>	<p>Bruchajzer, 2011</p>

**Table 4** (cont.): Organ toxicity and mechanisms

Key message	Reference
This study identifies a novel mechanism of phthalate toxicity in reproductive organs, namely induction of PLD via pERK1/2 activation, leading to testicular Leydig cell damage.	Lee et al., 2011b
NaF and TCDD have potentiative, harmful effects on the formation of dental hard tissue formation, as evidenced by morphological changes in whole tooth photographs, histological tissue sections and impaired mineralization.	Salmela et al., 2011
The mechanism underlying DBAA toxicity is not fully understood. The study shows that DBAA in vivo induces downregulation of cytochrome p450c17a at mRNA and protein level, a key enzyme in the biosynthesis of androgens, revealing a potential mechanism for DBAA toxicity in spermatogenesis.	Carr et al., 2011
This study shows that species differences in FYX-051-induced nephropathy are produced by combined effects of purine metabolism, urinary xanthine solubility, and plasma concentrations of FYX-051.	Shimo et al., 2011
The idiosyncratic toxicity of Ticlopidine (TIC) is suspected to occur by reactive metabolites covalently binding to proteins. The authors demonstrate that GSH depletion in animals enhances TIC covalent binding to liver proteins which may be involved in hepatotoxicity induced by TIC.	Shimizu et al., 2011
Increasing number of adverse effect case reports suggests that KP transdermal formulation can cause photoallergic reactions. The authors demonstrated that KP transdermal patch with TiO <sub>2</sub> - included backing provide improved photostability and photosafety over conventional fabric KP patch.	Choi et al., 2011b
Mebendazole has been reported to cause liver injury with inflammatory responses. The authors report that MBZ and structurally similar drugs induce release of TNF $\alpha$ and IL-8 from human monocytes via activation of ERK1/2 MAPK pathway.	Mizuno et al., 2011
The phytochemicals zerumbone and auraptene effectively reduced TCDD and DTT toxicity, by protecting U937 macrophages from TCDD-induced apoptosis and blocking TCDD and DTT-induction of COX-2 and PDGF mRNA.	Sciullo et al., 2010
The study shows the in vivo effects of GLA on dopaminergic neurotransmission, namely GLA induced release of dopamine, probably mediated by an exocytotic, action potential-dependent mechanism, independent of dopamine transporter.	Nunes et al., 2010
Adverse effects of ortho-phthalaldehyde (OPA) have been reported in patients. Subcutaneous administration of OPA in mice induced a strong acute immune response, and additionally induced specific IgE and IgG in the sera, suggesting that OPA acts as an hapten.	Morinaga et al., 2010

**Table 5:** Reproductive toxicology

Key message	Reference
The study successfully used two validated in vitro tests, the rat whole embryo culture and the mouse embryonic stem cell test, to confirm the embryotoxicity of the immunosuppressive drug, mycophenolate mofetil. These results support what was observed in previous in vivo studies, and support the use of in vitro tests to measure teratogenic compounds.	Eckardt and Stahlmann, 2010

**Table 5** (cont.): Reproductive toxicology

Key message	Reference
Newborn rats with prenatal acrylamide intoxication show alterations in lipid metabolism and serum protein changes.	Allam et al., 2010
Fluoride exposure of male mice altered the expression of genes involved in several sperm biological processes. Furthermore, fluoride exposure seemed to trigger sperm apoptosis by oxidative stress thereby reducing male fertility.	Sun et al., 2011
Maternal exposure to acrylamide induced compensatory mechanisms in the fetal nervous system, probably as a correction of impaired neurogenesis and migration.	Ogawa et al., 2011
Injection of alkaline but not neutral or acidic solution into mouse embryos at embryonic day 15 caused a significant increase in the number of apoptotic cells in the trigeminal ganglia at embryonic day 16.	Mukai et al., 2011
Perinatal exposure to methylmercury (MeHg) and/or PCB153 affects cerebral dopamine D1- and D2-Rs in a gender-, time-, and brain area-dependent manner. Combined treatment does not exacerbate the neurochemical effects of the individual compounds.	Coccini et al., 2011
Moxifloxacin exerted clear embryotoxic effects in vitro using the murine limb bud culture, however, only at concentrations that are higher than plasma concentrations observed during therapy.	Bode et al., 2010

**Table 6:** Genotoxicity and carcinogenicity

Key message	Reference
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.	Lehmann et al., 2010
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
The flavonoid quercetin protects against methylmercury induced DNA damage and oxidative stress in rats.	Barcelos et al., 2011
The antioxidants isoquercitrin and melatonin reduce oxidative stress-mediated liver tumour promotion by the benzimidazole anthelmintic, oxfendasole in rats.	Nishimura et al., 2010
Indole-3-carbinol and flutamide increased expression of CYP1a1 and induced liver cell foci in rats.	Shimamoto 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
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
Using a two stage hepatocarcinogenesis model, this article describes early mechanisms in liver tumor progression, mainly via metal-related molecules, suggesting a role for lipid peroxidation and GST-P/Tfrc induction but not for Mt-1/2.	Mizukami et al., 2010

**Table 6** (cont.): Genotoxicity and carcinogenicity

Key message	Reference
The carcinogenic potential of Diuron, a widely used herbicide, remains controversial. This study indicates that Diuron is a promoting agent to the urinary bladder but not to the mammary gland.	de Moura et al., 2010
The precise mechanism of oxfendazole (OX)-induced hepatocarcinogenesis is still unclear. The authors report that OX not only altered xenobiotic and antioxidant functions but also promoted cell proliferation in neoplastic lesions, suggesting that dysregulation of cell proliferation and apoptosis play important roles in OX-induced hepatocarcinogenesis.	Dewa et al., 2011
Although 3-MCPD is known to be mutagenic, its carcinogenic potential remains controversial. The authors conclude that drinking water administration in rats of 3-MCPD for 104 weeks revealed no evidence of carcinogenic potential.	Jeong et al., 2010b
Gatifloxacin (GFX), a third generation fluoroquinolone (FQ) and component of a new antituberculosis drug, caused more genotoxic damage than earlier drugs when tested in human lymphocytes. Prolonged sampling time was needed to see the effects, and aberrations were observed with non-cytotoxic concentrations supporting the need to review the conventional setups of these studies.	Anupama et al., 2010
In human lymphocytes and a human acute lymphoblastic cell line, the monomer bisphenol A-glycidyl methacrylate (BisGMA), a component of dental fillings, caused broad spectrum DNA damage with severe DNA strand breaks. Such damage was shown to cause a delay in the S phase of the cell cycle, thus facilitating repair.	Drozd et al., 2011
Widely used fungicide and anthelmintic, thiabendazole, caused increased aneugenicity, as observed by an increase in micronucleus formation, in isolated human lymphocytes.	Santovito et al., 2011a
Wy-14,643 causes DNA damage in livers of rats which is repaired by DNA repair genes.	Suzuki et al., 2010
The short-chain chlorinated paraffin C500C causes a peroxisome proliferation and a downregulation of $\alpha 2u$ in male rat liver.	Warnasuriya et al., 2010
Enzymatically modified isoquercitrine suppresses the liver tumor-promoting activity of phenobarbital by inhibiting nuclear translocation of CAR, and not by suppression of oxidative stress.	Morita et al., 2011
The hepatocarcinogen aflatoxin B-1 produced dose-related DNA damage in fetal livers of turkey and chicken embryos after in ovo injection. Turkey embryos appeared to be slightly more susceptible to the treatment.	Williams et al., 2011a
Using the comet assay, differences between the genotoxicity of orally administered bisphenol A and octylphenol were evident only in rats that received higher doses of the substances.	Ulutaş et al., 2011
In ovo diethylnitrosamine injection induced hepatocellular transformation reflecting disruption of differentiation and proliferation as well as gallbladder agenesis in fetal turkeys.	Williams et al., 2011b
The concentration-dependent cytotoxic and antimutagenic effects of the natural antitumor quinone biflorin were tested on Salmonella, yeast and V79 mammalian cells. At lower concentrations, biflorin has significant antioxidant and protective effects against the cytotoxicity, genotoxicity, mutagenicity, and intracellular lipid peroxidation induced by $H_2O_2$ in yeast and mammalian cells, which can be attributed to its hydroxyl radical-scavenging property. However, at higher concentrations, biflorin is cytotoxic and genotoxic.	Vasconcellos et al., 2010

**Table 6** (cont.): Genotoxicity and carcinogenicity

Key message	Reference
The authors studied EP4 upregulation of Ras signaling and feedback regulation of Ras in human colon tissues and cancer. They suggest that Ras overexpression leads to cell proliferation through activating Ras/PI3K/GSK3 beta/EP4 PGE <sub>2</sub> receptor signals and caused a feedback regulation of Ras by EP4 in colorectal tumor progression.	Wu et al., 2010
The fibroblast growth factor 9 (FGF-9) has strong potential roles in benzo(a)pyrene-induced CL5 cell invasion and human lung adenocarcinoma metastasis. Benzo-(a)pyrene and motorcycle exhaust particulate (MEP) increased FGF-9 mRNA expression and induced invasive ability of CL5 cells. Immunohistochemistry detected FGF-9 protein in the adenocarcinoma cells but not in normal epithelium.	Ueng et al., 2010
The widely used antileishmanial drug Glucantime <sup>®</sup> had no genotoxic effect in vitro on human lymphocytes but induced DNA damage in vivo in mice. The authors conclude that Glucantime <sup>®</sup> is a pro-mutagenic compound that causes damage to DNA after reduction of pentavalent antimony (SbV) into the more toxic trivalent antimony (SbIII) in the antimonial drug meglumine antimoniate.	Lima et al., 2010
In this toxicogenomic analysis 68 deregulated hepatocarcinogen-specific genes were identified as promising candidate biomarkers of cancer in chemically induced hepatocarcinogenesis in rasH2 mice on days 7 and 91 after treatment. Biomarker filter analysis suggested that 28 signature genes are involved in early-stage hepatocarcinogenesis.	Park et al., 2011c
The cyanobacterial alkaloid cylindrospermopsin (CYN) is being increasingly identified in drinking water supplies worldwide. This thorough study describes the different aspects of genotoxicity of CYN in detail and recommends to consider it in human health risk assessment.	Straser et al., 2011
The DNA methylation status of the lysophosphatidic acid 3 (LPA3) gene was disturbed in established HCC's and rats fed on choline-deficient L-amino acid-deficient (CDAA) diet. LPA1 and LPA2 receptor genes were unmethylated in rats fed normal diet, but methylation increased time-dependently in rats fed with CDAA diet. Thus LPA receptor genes might be involved during hepatocarcinogenesis induced by the CDDA diet.	Okabe et al., 2011
The authors developed a model to determine the genotoxic potential of formaldehyde (FA) in occupationally exposed individuals. In FA exposed and control subjects the frequency of chromosomal aberrations (CAs) in peripheral blood lymphocytes and two metabolic gene polymorphisms were correlated. FA induces CAs even to low levels of daily exposure, indicating an increased risk of genetic damage for workers to this air pollutant.	Santovito et al., 2011b
The inhibition of Cyt-P450-linked mixed function oxidases and benzene-induced genotoxicity in bone marrow and lung cells by polyphenolic acetates are mediated by the action of calreticulin transacetylase.	Kumar et al., 2011
Although fenofibrate caused transient DNA damage in rat liver, it also induced expression of DNA repair genes (e.g. Apex1, Ogg1 and Mlh1). This compensatory DNA repair response might account for the lack of permanent genotoxic damage.	Tawfeeq et al., 2011
RasH2 transgenic mice receiving 1 % DIDP developed a higher number of hepatocellular adenomas compared to wild type and rasH2 control mice, an effect not observed in previous rodent studies, indicating that this model is suitable for short term carcinogenicity testing.	Cho et al., 2011

**Table 6** (cont.): Genotoxicity and carcinogenicity

Key message	Reference
<p>Concentration and time dependent experiments with carcinogenic genotoxins showed a simultaneous increase in both superoxide anions and Ty1 retrotransposition rates, which were blocked by addition of the scavenger N-acetylcysteine. Thus, the carcinogen-induced high level of reactive oxygen species plays a key role in the response of Ty1 test to carcinogenic genotoxins.</p>	<p>Dimitrov et al., 2011</p>

**Table 7:** Reviews and short communications

Key message	Reference
<p>Many degenerative diseases and toxicological insults converge on iron dysregulation. This review summarises several concepts of auto-catalytic 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).</p>	<p>Kell, 2010</p>
<p>The trichothecene mycotoxin deoxynivalanol (DON) is produced by the fungus, <i>Fusarium</i> 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.</p>	<p>Pestka, 2010</p>
<p>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.</p>	<p>Adler et al., 2011</p>
<p>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.</p>	<p>Drobná et al., 2010</p>

**Table 7** (cont.): Reviews and short communications

Key message	Reference
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 anti-carcinogenic 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.	Valdiglesias et al., 2010
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.	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 pro-oxidant by inducing apoptosis. (iii) The use of <i>Saccharomyces cerevisiae</i> is reviewed as a powerful tool to study the mode of action of selenium.	Brozmanová 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.	Nielsen and Wolkoff, 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 on the protective network controlled by the Keap 1-Nrf2 axis, focussing on proliferation, angiogenesis and apoptosis.	Baird and Dinkova-Kostova, 2011
This review on Nrf2 focusses on the relevance of Nrf2-disruption in colon, bladder, lung, stomach, breast, skin and liver cancers.	Slocum and Kensler, 2011
This review gives an overview on how arsenate and arsenite interfere with intracellular signal transduction networks.	Druwe and Vaillancourt, 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.	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 hepatotoxicity testing.	Wobus and Löser, 2011
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
The capping material of nanocrystal quantum dots, and not the material of the core, determines toxicity.	Hoshino et al., 2011
This review discussed the current possibilities and perspectives of in vitro test systems for nanotoxicology.	Clift et al., 2011
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.	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

**Table 7** (cont.): Reviews and short communications

Key message	Reference
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
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
An overview of currently available metabolic databases is given with the MetaCyc family being described in particular detail.	Karp and Caspi, 2011
Mimicking a high fat diet by treating wild type mice with the bile acid, deoxycholic acid (DOC) at high physiologic levels, induced colonic tumours in 17 of 18 treated mice. The dietary antioxidant, chlorogenic acid, reduced tumour formation.	Bernstein et al., 2011
This review article summarises the protective effect of the antioxidant and mucolytic agent, N-acetylcysteine on contrast-induced acute kidney injury.	Briguori et al., 2011
This review expresses the need of alternative testing systems and herein the expectations on stem cells.	Seiler et al., 2011
This paper provides an up-to-date review of the progress made in the field of development of in vivo animal models for testing the allergic potential of novel proteins which resemble existing allergens. Finding and validating a strain of an animal species that is prone for allergic disorders equivalent to human individuals with a predisposed background is very desirable.	Ahuja et al., 2010b
This review provides a compendium of the results of genotoxicity and carcinogenicity assays performed on 70 marketed antihistamines.	Brambilla et al., 2011
Toxic effects on the Caco-2 cell line induced by Microcystin-LR, a toxin produced by toxic cyanobacteria, were higher at 48 h compared to those observed at 24 h. Differentiated Caco-2 cells were slightly more sensitive than undifferentiated cells. The most sensitive endpoint for the cell line was the reduction of total protein content.	Puerto et al., 2010

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