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Editorial

Environmental contaminants and target organ toxicities – new insights into old problems

Environmental contaminants comprise an extremely diverse group of natural and synthetic substances present in soil, air and water that can cause harmful effects in human populations or biological ecosystems. They may be introduced into the environment as a consequence of human activities such as agriculture, industrial production, burning of fossil fuels or wastewater discharge. Natural sources include release of air pollutants from volcanoes, biological decay and forest fires as well as metal contamination of ground water. The possible effects on human health or ecosystems from environmental contaminants are as diverse as the substances themselves, and the ever-increasing number of scientific studies on this subject is perhaps only matched by the increasing level of public concern. Making sense of an avalanche of often conflicting data requires going back to the first principle of toxicology: the dose makes the poison. In the case of environmental contaminants this requires an understanding of the toxicity or hazardous properties of the substance or mixture as well as an assessment of its environmental persistence and potential to bioaccumulate.

The current issue contains a series of 17 research articles and 11 reviews that aim to dissect the various aspects of biological effects encountered during exposure to environmental contaminants. The articles focus on the assessment of potentially hazardous substances and their impact on the development of adverse outcomes and diseases. In addition, evidence from in *in vivo* and *in vitro* models presenting the molecular mechanisms that lead to the development of toxicity and disease from exposure to environmental contaminants is presented. Emphasis is given to specific endpoints and biomarkers which can be used to assess the potential risk and toxicity caused by environmental contaminants *in vivo*. Human epidemiological studies which aim to clarify the associations between exposure to environmental contaminants and specific health effects are also included.

Pesticides are one of the most widely studied groups of environmental contaminants. They differ from other chemicals in that their purpose is to display biological activity (similar to pharmaceuticals), hence they would be expected to have (side)-effects on non-target organisms. As a consequence, they have a rich toxicological and ecotoxicological database because their authorization for use requires a formal risk assessment. Nevertheless, there is concern over potential human and environmental effects of pesticides, particularly upon long-term exposure to low levels, which may not be picked up in standard regulatory hazard testing schemes. One such example is the possible link between pesticides and neurodegenerative diseases (Baltazar et al., 2014). Although there is both experimental and epidemiological evidence for a link, so far no specific substance has been unequivocally shown to be causing a specific neurodegenerative outcome at typical environmental concentrations. Organophosphate chemicals are specific neurotoxins and concern has therefore been expressed over possible effects on the developing human brain. González-Alzaga et al. (2013) systematically reviewed the epidemiological literature on this subject and concluded that there is some evidence that prenatal exposure, in particular, may contribute to neurodevelopmental and behavioural deficits in children. However, due to the large variability in study design and methodologies, no firm conclusions could be drawn, prompting the authors to call for more standardized methodologies for future studies. The *in vitro* study by Campanha et al. (2014) provides some evidence that organophosphates can interfere with acetylcholinesterase trophic function during critical periods of strong cell adhesion and differentiation, while Benabent et al. (2014) found a previously unrecognized effect of organophosphates on additional esterases in soluble chicken brain fractions.

Apart from their known neurotoxic effects, organophosphates and other insecticides are suspected of other non-target effects which are of concern for human health. Michalakis et al. (2013) found high concentrations of dialkyl phosphate metabolites as well as organochlorine pesticides in hair samples of children with hypospadias and their parents compared to the general population and even to occupationally exposed workers. Pesticide effects on the male reproductive system were also the subject of the review by Mehrpour et al. (2014) who found highly variable results with regard to sperm quality, calling once again for well-designed long-term studies which take into account the potential multifactorial origins of male infertility. With regard to cancer risk, Parrón et al. (2013) using an ecological study design, found that the prevalence rates of cancer at most organ sites were significantly higher in Andalusian districts with high pesticide use. Costa et al. (2014) compared biomarkers of exposure, early effects and susceptibility in groups of conventional and organic farmers, and found that those farmers using pesticides had an increase in micronuclei and chromosomal aberrations, indicating a higher risk of genotoxicity. Both these studies are hypothesis-forming and the results need to be confirmed in other research studies.

The elucidation of mechanisms of neurotoxic damage by pesticides and biocides are the subject of two *in vitro* studies. Chantong et al. (2014) used a mouse BV-2 cell model to highlight

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the potential role of oxidative stress and pro-inflammatory cytokine markers in microglia cells in the development of dibutyltin-induced CNS damage. Neuroinflammation was also the subject of the investigation by Sandström von Tobel et al. (2014) who showed in a three-dimensional whole rat brain cell culture model that neurons partially recovered from early paraquat exposure whereas astrogliosis persisted, accompanied by delayed microglial activation which may induce further neurodegeneration. Neurotoxicity is also a feature of acute selenium intoxication, but possible nervous system effects of chronic exposure are much less well characterized. Vinceti et al. (2013) concluded from their review of experimental and epidemiological studies that there is a plausible mechanistic basis for neurotoxicity from long-term exposure and that the relatively few human studies looking at neurotoxicity endpoints have demonstrated non-specific symptoms such as lethargy, dizziness, paraesthesia and an excess incidence of amyotrophic lateral sclerosis. However, the evidence is limited due to methodological problems, so again, more well-controlled specific human studies are necessary.

Potential wildlife effects of persistent organic pollutants were investigated in carp by Karaca et al. (2014) and in waterbirds by Kocagöz et al. (2014) CYP1A and antioxidant activities in carp liver were substantially higher in areas with higher organochlorine pollution. In waterbirds, activities of antioxidant enzymes were correlated with liver concentrations of several organochlorines.

The presence of polyhalogenated chemicals in the environment has long been of concern due to their activity in biological systems, their persistence and ability to bioaccumulate. While many of the chlorinated chemicals such as PCBs and several polychlorinated pesticides have been banned or phased out, others such as the dioxins will continue to enter the environment as by-products of industrial activities or through natural processes such as forest fires. Sorg (2013) has reviewed the evidence for AhR activation as the main source of the toxicological properties of dioxins. Using the induction of chloracne as an example, he points out that certain AhR agonists found in vegetables do not cause this condition, whereas other chemicals and therapeutic agents may induce a chloracne-like syndrome without activating AhR. Jeanneret et al. (2013) analysed urine samples from a cohort of workers who were industrially exposed to high doses of dioxin in the 1960s. They focused on steroid metabolites and bile acids as potential biomarkers of long-term dioxin effects using an untargeted metabolomics approach. The analysis was guided by comparison with the urinary metabolic patterns related to the extreme phenotype represented by the dioxin poisoning of the former Ukrainian president Victor Yushchenko.

In recent years, other groups of halogenated compounds have become the focus of attention, in particular perfluorinated chemicals (PFCs) and polybrominated diphenyl ethers (PBDEs). One of the important knowledge gaps relates to the tissue burden of these chemicals. Fàbrega et al. (2014) tested a PBPK model for predicting PFOS and PFOA levels in blood and human tissue samples. While the model predicted blood levels well, this was not the case for tissue levels, showing the need for further and more detailed biological monitoring of these compounds. Endocrine disruption and immunotoxicity are among the possible adverse effects ascribed to PFCs. In a rat model, Pereiro et al. (2014) found that PFOS induced an inhibition of the hypothalamic-pituitary-adrenal axis activity at different levels, thereby altering corticosterone secretion. In addition, some morphological changes were seen in adrenal zona fasciculata cells. With regard to immunotoxicity, Corsini et al. (2014) reviewed recent experimental and epidemiological evidence and found that effects were seen in animal studies at dose levels comparable to those reported in highly exposed human populations and wildlife. Given that there is potential for bioaccumulation and exposure to multiple PFCs, they concluded that there was a risk of immunosuppressive effects in humans, particularly in the case of prenatal exposure.

Two reviews focus on the potential neurodevelopmental and neurobehavioural effects of PFCs and PBDEs. Roth and Wilks (2014) carried out a systematic review of recent epidemiological studies using a checklist-type quality assessment scheme. Methodological discrepancies were frequent, and associations with adverse neurodevelopmental and neurobehavioural outcomes were highly variable. Collectively, the data did not support a strong causal link with PBDE and PFC exposure, but they raise questions which should be explored in hypothesis-driven studies using harmonized methodologies and detailed exposure assessments. The mechanistic basis for possible neurodevelopmental effects of PBDEs is the subject of the review by Costa et al. (2013); they highlighted in particular two possible non-mutually exclusive modes of action. One could be the interaction with thyroid hormone homeostasis at different levels with an indirect effect on the developing brain. Alternatively or additionally, PBDEs may directly affect nerve cells through oxidative damage and interference with signal transduction and neurotransmitters.

Benzo[a]pyrene (BaP) is a ubiquitous environmental contaminant and known human carcinogen found in, amongst others, cigarette smoke, diesel exhaust, coal tar and grilled foods. BaP was used in the study by Androutsopoulos and Tsatsakis (2013) to induce CYP1 enzymes in an *in vitro* system. This led to an enhanced cytostatic effect caused by the flavonoid eupatorin-5-methyl (E5M) upon MCF7 breast cancer cells which offers a novel mechanism of action of CYP1 enzymes involving enhancement of the antitumor properties of E5M in cells exposed to CYP1 inducers. Two studies looked at the effects of prenatally administered BaP, one on adiposity in mice, and one on hyperoxic lung injury in rats. Ortiz et al. (2013) found that prenatal exposure to BaP increased visceral adiposity and caused hepatic steatosis in wild type female mice whereas GSH-deficient mice were resistant to these effects; this resistance was associated with hepatic downregulation of several genes involved in lipid biosynthesis and upregulation of antioxidant genes. Thakur et al. (2014) found an increased susceptibility of newborn rats to oxygen-mediated lung injury and alveolar simplification following maternal exposure to BaP, suggesting that modulation of CYP1A/1B1 enzymes, increases in oxidative stress, and BaP–DNA adducts contributed to this adverse outcome.

Bolognesi and Moretto (2013) reviewed exposure and biomonitoring data from studies carried out in the rubber manufacturing industry and concluded that a genotoxic hazard existed in certain plants, but the data are inadequate to estimate the genotoxic risk associated with the exposure in different manufacturing processes. They called for further studies addressing the genotoxicity of the exposure mixtures in the different production phases and processes of rubber manufacturing industries in order to refine exposure control and preventive measures.

There is an increasing need to develop reliable and cost-effective alternatives to the present battery of regulatory toxicity tests. Sogorb et al. (2014) have developed a step-wise approach to embryotoxicity and developmental toxicity testing. The first level would focus on short-term cellular assays to detect effects in early differentiation stages. The second level would involve longer-term cellular embryotoxicity tests to identify embryotoxicants that have an effect on late differentiation stages. The third stage would consider tests with whole zebrafish embryos because they allow the determination of hazards based on molecular and morphological alterations.

The selected papers in this issue emphasize the major impact that environmental contaminants may have on human and ecosystem health and highlight the increasing need for effective and integrated