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Editorial overview: Mechanistic toxicology

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Edited by **Stephen Safe** and **Martin van den Berg**

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Stephen Safe Professor Safe is a faculty member in the Department of Veterinary Physiology and Pharmacology and the Department of Biochemistry and Biophysics at Texas A&M University. His research is focused on the development of mechanism-based anticancer drugs that target specificity proteins, the orphan nuclear receptor 4A1 (NR4A1), NR4A2, the Ah receptor, and the role of the Ah receptor ligand in microbiome–gut interactions He has received awards from Texas A&M University and the Society of Toxicology (Burroughs Wellcome Toxicology Scholar, Distinguished Toxicology Scholar Award, and Merit Award). He was awarded honorary doctorate of science degrees from the University of Guelph and Queen's University in Canada. He has more than 790 refereed publications and an h-index of 124.

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Martin van den Berg Prof. Dr. Martin van den Berg is an emeritus professor in toxicology at Utrecht University in the Netherlands. He is also appointed as an honorary professor in environmental toxicology at the University of Queensland (Brisbane) and a visiting professor at the Royal Chulabhorn Research Institute and Graduate School in Bangkok. In autumn 2006, he received an honorary

Current Opinion in Toxicology is a journal that focuses on the broad field of toxicology and invites authors to share their opinions and viewpoints, and this issue of the journal is focused on toxicological mechanisms. Most of the articles in this issue deal with environmental and lifestyle toxicants and provide recent updates in these important fields.

Chromium is a widely dispersed environmental contaminant that induces both toxic and genotoxic responses which are dependent, in part, on the oxidation state of the metal. Des Marias and Costa outline the complexities of chromium toxicology and conclude that chromate-induced carcinogenesis, especially that of chromium VI, is complex and due to multiple pathways. The authors also discuss the relevance of chromium III as a food supplement.

Arsenic is another metal toxicant, and unlike chromium, arsenic exposure and toxicity has primarily been through drinking water. Cohen et al outline exposure and mechanistic scenarios, the latter pointing toward a nongenotoxic mechanism of action, and the authors argue that for risk assessment, a threshold-based mechanism should be used. It is concluded that inorganic arsenic levels of <150 mg/L represent a threshold for protection from cancer.

Organophosphate intoxication is primarily through occupational routes and potential exposure to chemical warfare agents. Reddy not only has reviewed the neurotoxic mechanisms but also highlights the need for development of new mechanism-based antibodies that target specific neurotoxic pathways. These so-called neurosteroids may also be effective in treating long-term neuropsychiatric effects of these compounds.

Cave et al have focused their review on the potential role of polychlorinated biphenyls in nonalcoholic fatty liver disease and the role of the gut liver axis in mediating this response. This is a complex field that has to interpret results induced by mixtures, which have both aryl hydrocarbon receptor components and biologically active compounds that act through diverse pathways.

Two highly topical reviews on aspects of cigarette and alcohol-induced toxicities are also included in this issue. Miranda et al outlined the

doctorate from the Umea University in Sweden. His research areas include a broad range of toxicological topics such as effects of mixtures of organic persistent pollutants, interactions of endocrine chemicals on steroidogenesis, and the development of *in vitro* assays for toxicological testing. He (co)authored more than 350 articles and has an h-index of 61 (2019).

extensive neurotoxicity of prenatal alcohol exposure, which induces widespread damage in the fetus with the cerebral cortical region being particularly sensitive. The functional neurotoxic effects of prenatal alcohol exposure in offspring are well documented. However, underlying mechanisms are complex and involve multiple factors including extracellular vesicles and microRNAs. Orzabal and Ramadoss have reviewed the toxicities of e-cigarette exposure during pregnancy and early life of the offspring. Some interesting observations are provided that will give future guidance in terms of assessing adverse effects of e-cigarettes in humans. Overall, it is concluded that the use of e-cigarettes should be avoided during pregnancy.

Carcinogenic effects of smoking have been well established at multiple sites in the body. Van den Berg and van Duursen reviewed the effects of cigarette smoking and endometrial cancer. This is one of the few diseases where there is evidence that smoking is protective, but the reason(s) for this is still poorly understood. The mechanisms of toxicant-induced damage involve many possible pathways in which the Ah receptor may play a central role.

Bedi and Golding have discussed the potential role of epigenetic pathways such as DNA methylation and related changes in gene expression as contributing factors. They conclude that cell context is an extremely important factor in mediating the role of environmental chemical-induced epigenetic effects. This review also addresses the importance of lifestyle and environmental factors, and attention is given to some specific chemicals.

Conflict of Interest

The authors declare no conflict of interest.