TOXICOLOGY AND FORENSIC MEDICINE

Openventio PUBLISHERS

ISSN 2474-8978 Open Journal http://dx.doi.org/10.17140/TFMOJ-1-e004

Editorial

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Volume 1 : Issue 1
Article Ref. #: 1000TFMOJ1e004

Article History
Received: June 8th, 2016
Accepted: June 9th, 2016
Published: June 9th, 2016

Citation
Buha A, Matović V. Toxicology of mixtures - Cd +PCBs experimental model. *Toxicol Forensic Med Open J*. 2016; 1(1): e9-e11. doi: 10.17140/TFMOJ-1-e004

Toxicology of Mixtures - Cd +PCBs Experimental Model

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Humans are exposed to hundreds of thousands of chemicals from very different sources and the presence of more than 200 xenobiotics has been so far determined in human blood or urine.[1] Hence, exposure assessment and toxicological evaluation should be focused on mixtures rather than on single chemicals. The importance of "cocktail effects" evaluation is summarized in European Commission statement that highlighted that even low level exposure to a complex cocktail of pollutants over decades can have significant effect on the health status of European citizens.[2] Although, toxicity studies and risk assessments are focused on single chemicals, research on the toxicology of mixtures have emerged decades ago. Actually, more than thirty years ago United States Environmental Protection Agency (EPA) published Guidelines for the Health Risk Assessment (HRA) of Chemical Mixtures[3] and after a few years Technical Support Documents and Guidance Manuals[4,5] followed by the efforts of Agency for Toxic Substances and Disease Registry (ATSDR)[6] and Organisation for Economic Cooperation and Development (OECD).[7] However, although a certain progress has been made, the toxicology of mixtures remains a matter of great concern and challenge for the scientific community.

Indeed, to study and assess the potential health risks of "cocktails of pollutants" properly, it is of paramount importance to understand the basic concepts of joint action and interactions of chemicals. Components of a mixture can act independently in the body leading to the addition of doses or responses, or their actions can combine thus leading to stronger - synergistic or weaker - antagonistic response.[6,8,9] These combined actions of mixture compounds resulting in response different than expected by additivity are defined as interactions and can be of toxicokinetic or toxicodynamic type. Furthermore, the investigations on the toxicity of chemical mixtures provide evidence that both chemicals with similar or dissimilar modes of action may produce combined effects at doses below their No Observed Effect Level/No Observed Effect Concentration (NOEL/NOEC), suggesting that a mixture can produce a toxic effect not observed for any component of the mixture.[10]

One of the biggest challenges that toxicology of mixtures is facing today, is to define adequate model for the mixture toxicity evaluation. The choice of the study design for chemical mixture toxicity assessment is influenced by the number of chemicals in the mixture, dose-response relationship for single chemicals and their mechanisms of toxicity i.e. ability to interact. Risk of chemical mixtures can be assessed by using whole mixture approach in which mixtures are evaluated as single entities or by using component-based approach such as dose addition, response addition or approach in which interactions between components are also considered. The concept of dose addition is used for chemicals with similar mode of action while response addition is used for dissimilarly acting chemicals. Up-to-date several types of models have been proposed for specific-interaction studies: isobolographic model, multifactorial analyses, fractionated factorial designs, effect/response-surface analysis, physiologically-based pharmacokinetics modeling, etc.[9,11-13] However, all these methodologies have certain limitations, are commonly extremely costly *in vivo* studies and are sometimes difficult to interpret.

Cadmium (Cd) and Polychlorinated biphenyls (PCBs) are widely spread persistent environmental pollutants that enter food chain and pose risk to human health. Therefore we investigated the effects of single exposure to different doses Cd or PCBs and the effects of co-

ISSN 2474-8978 Open Journal http://dx.doi.org/10.17140/TFMOJ-1-e004

exposure to these chemicals. During the experiment the effects on body weight gain, hematological parameters, liver and kidney function, as well as their thyroid disrupting effects were investigated in rats. Animals were treated orally for 28 days with six different doses of Cd or PCBs ranging from 0.3 to 10 mg /kg b.w./day or 0.5 to 16 mg /kg b.w./day, respectively. In order to investigate combined effects of Cd and PCBs, nine groups of animals were exposed to different dose combinations of Cd and PCBs (1.25, 2.5 or 5 mg Cd/kg b.w./day and 2,4 or 8 mg PCBs/kg b.w./day). Detailed data on the experiment, statistical methods and concept used for interaction assessment are given in our previously published paper.[14]

The study demonstrated significant effects on body weight gain suggesting possible developmental toxicity, and also confirmed hematotoxic, hepatotoxic and nephrotoxic effects of these toxic agents. The obtained results also gave the evidence of thyroid disrupting effects: cadmium mainly caused decrease in T3 hormone levels suggesting predominant disruption of extrathyroid processes, while PCBs showed more profound effect on T4 hormone levels presumably as the result of PCBs direct effect on thyroid gland.

Investigation on the effect of co-exposure to Cd and PCBs implicates different toxicological profile of mixtures if compared to single chemicals. Thus, regarding the effects on hematological parameters, the mixture produced decrease in red blood cells count and hemoglobin content, the effects that were not observed during single chemical treatment, while the effects on white blood cells count and platelets were shown to be additive. Mixture exerted more profound decrease in body weight gain i.e. additive effect of Cd and PCBs. Additive effects of these chemicals were also observed for investigated parameters of liver function indicating no toxicodynamic interactions between these chemicals in liver. On the other hand, synergistic interactions between Cd and PCBs were proved for the parameters of kidney function. As reported in our previous study,[14] alterations in thyroid function, i.e. levels of thyroid hormones in serum can be attributed to the synergism between these two chemicals.

Based on these results, it could be concluded that single agent toxicity studies cannot fully predict the toxicity of mixtures. Our findings implicate that toxicity of mixture can be more profound than the toxicity of its components, and furthermore that mixture of chemicals can produce toxicity although the same dose regime of single components induces no toxic response. This study contributes to better understanding of mixture toxicity and gives one more piece of evidence that exposure assessment and safety evaluation should focus on chemical mixtures rather than on single chemicals.

CONFLICTS OF INTEREST: None.

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