Lucija Peterlin Mašič et al., J Clin Toxicol 2017, 7:3(Suppl)
DOI: 10.4172/2161-0495-C1-024

Bisphenol A analogs and new brominated flame retardants: Do their metabolites have endocrine activity?

Lucija Peterlin Mašič and **Darja Gramec**
University of Ljubljana, Slovenia

Statement of the Problem: Structural analogs of bisphenol A (BPF, BPAF, BPS) are commonly used as its alternatives in industrial and commercial applications. Nevertheless, the question arises whether the use of other bisphenols is justified as replacements for bisphenol A in mass production of plastic materials. Knowledge about the metabolic pathways and enzymes involved in metabolic bio-transformations is essential for understanding and predicting mechanisms of toxicity. The activities on different nuclear receptors of the new brominated flame retardants 2-ethylhexyl 2,3,4,5-tetrabromobenzoate (TBB) and bis(2-ethylhexyl) 2,3,4,5-tetrabromophthalate (TBPH), and their main carboxylic acid metabolites 2,3,4,5-tetrabromobenzoic acid (TBBA) and mono(2-ethylhexyl) tetrabromophthalate (TBMEPH) were also investigated.

Methodology & Theoretical Orientation: The bisphenols metabolism using pooled liver and intestine microsomes, as well as recombinant human cytochromes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4) was tested using LC-MS/MS. For nuclear receptor testing *in vitro* systems were used to evaluate the estrogenic, androgenic, glucocorticoid, thyroid, PXR and PPARs activities of parent chemicals and their metabolites.

Conclusion & Significance: Once enter the body; the bisphenols are subjected to both oxidative metabolism and mainly conjugation. However, conjugation, which is mainly with glucuronic acid, is the predominant metabolic pathway for bisphenols and this is therefore considered to be an important mechanism for bisphenols detoxification. However, comprehensive testing of BPAF-glucuronide on all nuclear receptors has been performed and will be presented. On the other hand, it has been detected that metabolites of bisphenols and flame retardants have enhanced endocrine activities. For example, the estrogenic activities of MBP and hydroxycumyl alcohol are significantly higher than that of BPA. Even the formation of small amounts of those metabolites can significantly affect estrogenic activity. This was observed also for the novel brominated flame retardants TBB and TBPH, which showed weak or no activity on estrogen and androgen receptors, while their metabolites showed significant anti-estrogenic and anti-androgenic effects. Although conjugation is an extremely important detoxification pathway for bisphenols, it cannot completely eliminate their toxic effects in the body. Environmental estrogens can elicit their responses not only through binding to ERs, but also through numerous alternative pathways, and very low concentrations are needed for measurable effects. Despite their rapid glucuronidation, small amounts of bisphenols remain in their free form. As these can be further metabolized to their biologically active metabolites, these represent the risk for human health.

Biography

Lucija Peterlin Mašič is an Associate Professor for Medicinal Chemistry and an Assistant Professor for Toxicological Chemistry. She has expertise in Medicinal Chemistry and Toxicology. She has studied the influence of metabolism on endocrine activities of hormone disrupting chemicals such as analogs of bisphenol A and novel brominated flame retardants with different *in vitro* assays. Her research interests are also *in vitro* studies of drug metabolism, testing compounds acting on nuclear receptors (estrogen, thyroid, androgen, glucocorticoid, PXR, FXR and PPARs), metabolism of xenobiotics and activity studies of their metabolites, bimolecular mechanism studies of toxicity, structure and ligand based drug design, etc.

Lucija.peterlin@ffa.uni-lj.si

Notes: