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Biomarkers of human exposure to organophosphate flame retardants

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While the demand for flame retardants, such as organophosphate esters (PFRs), has increased following the banning of several brominated flame retardants, there are still major uncertainties regarding the human exposure to these compounds. Biomonitoring is considered the best approach to monitor internal exposure, yet little is known regarding the metabolic processes PFRs undergo in the human body and the identity of biomarkers of exposure. In the present study, we aim at presenting recommendations on the selection of the target biomarkers to be used when assessing the human exposure to PFRs through biomonitoring. These recommendations are largely based on our recently published *in vivo* and *in vitro* data completed with *in vivo* literature data. More precisely, we evaluate the usefulness of oxidative metabolites specific for one parent PFR as compared to non-specific or infrequently detected diesters formed by hydrolytic processes. Exposure biomonitoring studies for rapidly cleared chemicals require identification of stable (and specific) major metabolites for parent chemicals of interest.

We have reported the *in vitro* metabolism of several PFRs, including tris(1-chloro-2-propyl) phosphate (TCIPP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), tris(2-butoxyethyl) phosphate (TBOEP), ethylhexyl diphenyl phosphate (EHDPHP), triphenyl phosphate (TPHP), resorcinoldiphenyl phosphate (RDP) and V6, by human liver enzymes. Several metabolites, such as diesters and oxidative metabolites, have been suggested as potential useful for biomonitoring in urine. For the selection of biomarkers for PFR exposure, we have based our conclusions on findings from biomonitoring (*in vivo*) studies in urine and on the identification of PFR metabolites in *in vitro* liver preparations.

Together with the corresponding diesters (BDCIPP, BDCIPP, BBOEP, and DPHP), specific metabolites formed by oxidative metabolism, such as bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate (BCIPHIPP), bis(2-butoxyethyl) 3'-hydroxy-2-butoxyethyl phosphate (HO-TBOEP), bis(2-butoxyethyl) 2-hydroxyethyl phosphate, and (hydroxyphenyl diphenyl phosphate (HO-TPHP), are suggested to be used in biomonitoring studies. The *in vivo* formation of some PFR metabolites has not been confirmed, and as a result, their suitability for human biomonitoring is still unknown.