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In-vitro estimation of bioaccessibility of chlorinated organophosphate flame retardants in indoor dust by fasting and fed physiologically relevant extraction tests

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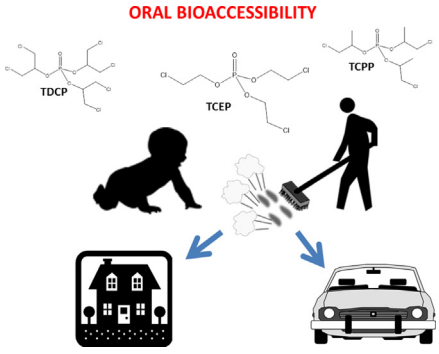
HIGHLIGHTS

- FOREhST for bioaccessibility of emerging flame retardants in indoor dust under fed conditions
- UBM for bioaccessibility of emerging flame retardants in indoor dust under fasting conditions
- Determination of chlorinated alkyl phosphates in household and automobile cabin dust
- Reliable determination in gastric and gastrointestinal extracts by LC-MS/MS
- Exposure assessment model for toddlers

GRAPHICAL ABSTRACT



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ABSTRACT

This paper reports the evaluation of in-vitro physiologically relevant extraction tests for ascertainment of the bioaccessible fractions of emerging flame retardants from indoor dust in the gastric and gastrointestinal compartments. Standardized bioaccessibility tests under both fasting (UBM-like test) and fed (FOREhST test) conditions simulating the macronutrient composition of an average child diet were harnessed for investigation of the oral bioaccessibility of chlorinated organophosphate esters, *namely*, tris(2-chloroethyl) phosphate (TCEP), tris(1-chloro-2-propyl) phosphate (TCPP) and tris(1,3-dichloro-2-propyl) phosphate (TDCP), in household and automobile cabin dust samples with varying concentration levels of contaminants. Minimal processing of the biomimetic extracts (only protein precipitation using acetonitrile) was proven feasible by analysis with liquid chromatography-mass spectrometric detection (LC-MS/MS). An inversely proportional relationship was identified between log K_{ow} and oral bioaccessibility concentrations for TCEP, TCPP and TDCP in both dust samples with maximum bioaccessibility fractions for TCEP within the range of 50–103%. Non-bioaccessible fractions were determined by matrix-solid phase dispersion. Limits of quantification of LC-MS/MS in surrogate digestive fluids ranging from 0.4–0.8 ng/mL suffice for determination of freely dissolved fractions of the two less hydrophobic species. Our results indicate that lipophilic food commodities used under fed-state gastrointestinal extraction conditions do not increase availability of TCEP, TCPP and TDCP in body fluids, and therefore conservative conditions in human health risk explorations for the target moderately polar flame retardants might be obtained with simplified tests under fasting conditions. This also holds true for the UBM/FOREhST bioaccessibility data for SRM

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2585 (organic contaminants in house dust). Estimated average daily intake doses for toddlers incorporating oral bioaccessibility data afforded body burdens for the three chlorinated alkyl phosphates of ca. 3000 to 700 times below reference dose values, which indicate that long-term exposure to chlorinated organophosphate esters via accidental ingestion of indoor dust does not pose health risks to toddlers.

1. Introduction

Human exposure assessment of legacy and emerging persistent organic pollutants in environmental solids usually capitalizes upon exhaustive extraction procedures based on accelerated solvent extraction or, alternatively, on microwave or ultrasound assisted extractions with non-polar or moderately non-polar solvents aimed at quantifying the total concentration of target species within the solid matrix (Xu et al., 2013; Subedi et al., 2015; Poole et al., 2016). This conservative model aligns well with the precautionary principle adopted by many environmental agencies (e.g., US-Environmental Protection Agency, European Environment Agency, and Spanish Ministry of Agriculture, Food and Environment) (United States Environmental Protection Agency, 2016; United States Agency for Toxic Substances and Disease Registry (ATSDR), 1995; European Environment Agency, 2016; Spanish Ministry of Agriculture, Food and Environment, 2016). Over the past decade, independent researchers (Fedotov and Miró, 2008; Bacon and Davidson, 2008; Koch and Reimer, 2012; Rostami and Juhasz, 2011) and newly endorsed international regulations (e.g., ISO/TS 17402:2008, ISO/TS 17924:2007) (ISO/TS 17402:2008, 2008; ISO/TS 17924:2007, 2007) have, however, identified that the actual hazardous effects of potentially contaminated environmental solid substrates might be likened to bioaccessible and bioavailable contaminant fractions. In-vitro bioaccessibility testing signalling potentially available concentrations to biota is usually preferred over in-vivo testing inasmuch as animal models are thus overcome (Koch and Reimer, 2012). Bioaccessible pools are measured as the fraction of dissolved contaminants entering the food web under environmental or physiological relevant scenarios using chemical extractants as a proxy of biotic processes (e.g., bioaccumulation, mineralization or gastrointestinal digestion) (Bacon and Davidson, 2008; Rosende and Miró, 2013; Dean and Ma, 2007). A great deal of effort has been devoted to harnessing bioaccessibility tests in order to get insight into the partitioning and mobility of trace elements (Fedotov and Miró, 2008; Bacon and Davidson, 2008; Rosende and Miró, 2013). Notwithstanding this fact the role of chemical bioaccessibility to predict bioaccumulation and microbial mineralization of organic xenobiotics is a subject matter of increasing interest though refereed mostly to legacy contaminants, usually polycyclic aromatic hydrocarbons (PAH) (Fedotov et al., 2012; Cachada et al., 2014; Cui et al., 2013; Lal et al., 2015), using cyclodextrin derivatives, *n*-butanol or Tenax-based partial extractions or measurements of freely dissolved concentrations by passive samplers (Ortega-Calvo et al., 2015).

Human exposure to persistent organic pollutants may occur via a number of pathways including consumption of contaminated food and incidental soil, toy or jewellery ingestion, especially for infants and toddlers by hand to mouth activity, and dermal absorption (Koch and Reimer, 2012; Rostami and Juhasz, 2011; Guney and Zagury, 2012; Collins et al., 2015; Beriro et al., 2016). However, a predominant exposure route and contamination source is via accidental ingestion of contaminated household, office and car dust (Collins et al., 2015; Roosens et al., 2009; Fang and Stapleton, 2014; Johnson et al., 2010) in as much as urban populations might spend up to 90% of their time in indoor environments (Brasche and Bischof, 2005). This is particularly relevant for flame retardants used as additives to avoid fire ignition in every-day consumer products, such as personal computers, electronic household equipment and foams in automobile cabins (Collins et al., 2015; Roosens et al., 2009; Johnson et al., 2010). Hence, a number of physiologically based extraction tests (PBET) using surrogate body fluids have been reported in the literature with varying gastrointestinal tract compartments (Koch and Reimer, 2012; Rostami and Juhasz, 2011; Dean and Ma, 2007; Fedotov et al., 2012). As for organic compound-laden solid materials, the colon-extended PBET (Tilston et al., 2011) is the in-vitro bioaccessibility test of common choice (Collins et al., 2015; Fang and Stapleton, 2014). Importantly, oral bioaccessibility tests are operationally defined whereby their relevance in a risk assessment/exposure scenario is conditioned to proper validation by in-vivo animal models (Cachada et al., 2014). Based on these premises, the Bioaccessibility Research Group in Europe (BARGE) (BARGE-Bioaccessibility Research Group of Europe, 2016) undertook a joint decision to validate a PBET for risk assessment of metal and metalloid contamination in soils against juvenile swine as a human digestion model (Wragg et al., 2009; Denys et al., 2012) due to similarities between the GIT tract of immature swine and toddlers (Lal et al., 2015; Denys et al., 2012). BARGE launched the fasted Unified BARGE Method (UBM) (Wragg et al., 2009) in 2009, in which the human GIT is simulated through three different compartments (mouth, stomach and upper intestine), with the secretion of saliva, gastric acid, bile and pancreatic fluids (along with transit times) mimicked by synthetic body fluids resembling the GIT biochemical environment. For persistent hydrophobic organic pollutants, a standardized oral bioaccessibility test based on UBM, but in the fed state, was specifically designed for PAH-laden contaminated soils, referred to as Fed Organic Estimation Human Simulation Test (FOREhST) (Cave et al., 2010). The assumption for hydrophobic species is that the addition of food components containing fat might foster the leaching of target species into the GIT solution and thus might simulate conservative worst-case scenarios for risk assessment investigations (Cave et al., 2010; Lorenzi et al., 2012). Bile salts working as surfactants might also lead to increased solubilisation by formation of micelles with the organic compounds (Oomen et al., 2000).

To the best of our knowledge the FOREhST method has not been applied to any other environmental organic contaminant and solid matrix other than PAH, DDT-class pesticides and soil. The aim of this work is thus to explore the potential applicability of FOREhST and fasting bioaccessibility tests in assessing in-vitro oral bioaccessible concentrations of emerging contaminants (*namely*, organophosphate esters, OPEs) in household and automobile cabin dust. The production and usage of OPEs as additive flame retardants is increasing in members of the UNEP Stockholm Convention and several US states to cope with strict fire-safety regulations in response to the phase out of brominated flame retardants, and the restriction in the reuse of products that might contain banned polybrominated diphenyl ethers (Reemtsma et al., 2008; Brandsma et al., 2013; Dodson et al., 2012; Stapleton et al., 2012). We have selected three chlorinated OPEs, viz., tris(2-chloroethyl) phosphate (TCEP), tris(1-chloro-2-propyl) phosphate (TCPP) and tris(1,3-dichloro-2-propyl) phosphate (TDCP), inasmuch as previous reports indicate that they occur along with tri (2-butoxyethyl) phosphate in the highest concentrations in indoor dust, as a consequence of their usage in furniture, toys and car upholstery composed of polyurethane foam, and predominated the OPE congener profile in a variety of microenvironments (Fang and Stapleton, 2014; Reemtsma et al., 2008; Abdallah and Covaci, 2014; Brommer et al., 2012). These flame retardants might become potential hazardous compounds for infants and toddlers due to their crawling activities and their hand-to-mouth habit. In fact, the European Economic Community

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