Chemosphere 153 (2016) 78–90

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Review

Review of OPFRs in animals and humans: Absorption, bioaccumulation, metabolism, and internal exposure research

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HIGHLIGHTS

- The absorption, bioaccumulation, metabolism and internal exposure of OPFRs are reviewed.
- Inhalation, ingestion and dermal contact are the main OPFRs absorptionpathways for humans.
- General *in vivo* and in vitro metabolic pathways of three different types of OPFRs are proposed.
- DAPs and MAPs are considered as putative biomarkers for the assessment of internal exposure of OPFRs in humans.

ARTICLE INFO

Article history:
Received 7 January 2016
Received in revised form
1 March 2016
Accepted 2 March 2016
Available online 21 March 2016

Handling Editor: J. de Boer

Keywords:
Organophosphorus flame retardants (OPFRs)
Absorption
Bioaccumulation
Metabolism
Internal exposure

ABSTRACT

Due to their widespread use, organophosphate flame retardants (OPFRs) are commonly detected in various environmental matrices and have been identified as emerging contaminants. Considering the adverse effects of OPFRs, many researchers have paid their attention on the absorption, bioaccumulation, metabolism and internal exposure processes of OPFRs in animals and humans. In this article, we first review the diverse absorption routes of OPFRs by animals and humans (e.g., inhalation, ingestion, dermal absorption and gill absorption). Bioaccumulation and biomagnification potentials of OPFRs in different types of organisms and food webs are also summarized, based on quite limited available data and results. For metabolism, we review the Phase-I and Phase-II metabolic processes for each type of OPFRs (chlorinated OPFRs, alkyl-OPFRs and aryl-OPFRs) in the animals and humans, as well as toxicokinetic information and putative exposure biomarkers on OPFRs. Finally, we highlight gaps in our knowledge and critical directions for future internal exposure studies of OPFRs in animals and humans.

Contents

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http://dx.doi.org/10.1016/j.chemosphere.2016.03.003
0045-6535/

1. Introduction

Organophosphorus flame retardants (OPFRs), which extensively used in furniture, textiles, mattresses, electronics and other processing chemicals, constitute one of the most frequently used flame retardants (EPA, 2005). OPFRs are being increasingly consumed since the restriction published on the use of penta- and octa-polybrominated diphenyl ethers (PBDEs) (Marklund et al., 2005b; Van der Veen and de Boer, 2012). According to statistical data, the consumption of OPFRs in Europe had reached to 85,000 tonnes in 2005 (EFRA, 2007). China produced more than 70,000 tons of OPFRs in 2007 (Wang et al., 2010). The global consumption of OPFRs was 500,000 tonnes in 2011 and was expected to 680,000 tonnes in 2015 (Van der Veen and de Boer, 2012; Wang et al., 2015a).

OPFRs basically exist in end-products by physical addition, which is responsible for their leakage from products during service time through volatilization, abrasion and leaching (Sundkvist et al., 2010). After emission, there are several ways in which OPFRs can reach remote areas, such as deposition, washout, infiltration, etc. (Andresen et al., 2004; Bacaloni et al., 2008; Schreder and La Guardia, 2014; Takimoto et al., 1999). Atmospheric washout by precipitation and industrial discharge from factories and wastewater treatment plants (WWTPs) have been identified as the most significant entry modes of OPFRs into aquatic and terrestrial systems (Cristale et al., 2013; Meyer and Bester, 2004; Wei et al., 2015). As a result, OPFRs are globally distributed and ubiquitously present in various environmental mediums, such as dust, indoor air, atmosphere, surface water, sediment and soil (Cequier et al., 2014b; Chung and Ding, 2009; Gao et al., 2014; Kim et al., 2011; Staaf and Ostman, 2005). A number of studies have found that indoor environments have significantly higher levels of OPFRs than brominated flame retardants (BFRs) (Ali et al., 2012; Brommer et al., 2012; He et al., 2015). Over the past decade, almost all of the OPFRs produced have been detected in marine and fresh water animal, avian, insect and human samples (SI Table S1).

OPFRs are synthetic phosphoric acid derivatives, whose structures vary depending on different ester linkages and can be roughly divided into three types: chlorinated OPFRs, alkyl-OPFRs and aryl-OPFRs (Table 1, where the abbreviations of the OPFRs in this review are provided). OPFRs have a wide range of physiological properties in the environment. For example, their solubility, log K_{OW} values, persistence, vapor pressure, bioconcentration factors (BCFs) are quite different (Table 1). These properties are important factors in assessing the behavior of OPFRs in the environment and for assessing their influence on organisms (Van der Veen and de Boer, 2012). Volatile OPFRs with higher vapor pressures, such as TBP, TEP and TCEP, tend to be more likely to emit into air and settled onto dust than heavier OPFRs (Wei et al., 2015). Aryl and alkyl-OPFRs with higher molecular mass are more hydrophobic, have similar BCFs and have an affinity for sediment and soil (Van der Veen and de Boer, 2012; Wei et al., 2015). Chlorinated OPFRs have been shown to be more water soluble and are considered to be persistent threats to aquatic animals (Reemtsma et al., 2008; Van der Veen and de Boer, 2012).

Considering the occurrence of OPFRs in organisms and in organisms' surroundings, increasing attention has been devoted to their adverse effects to organisms. Toxicological studies have shown that OPFRs have the potential to cause adverse reproductive, endocrine and systemic effects in animals as a result of long term exposure to animals (Dishaw et al., 2011; Liu et al., 2012; Porter et al., 2014; Van der Veen and de Boer, 2012). Aryl-OPFRs have been shown to contribute to heart toxicity by disturbing the expression of transcriptional regulators in zebrafish (Du et al., 2015). Chlorinated OPFRs, such as TCEP, TCIPP and TDCIPP, have been proven to be neurotoxic and carcinogenic (Ni et al., 2007; WHO, 1998, 2000). TDCIPP can easily enter the blood stream and induce tumors in the liver, kidney and testis (OEHHA, 2011). TDCIPP levels in house dust were found to be correlated with reduced concentrations of thyroid hormones (THs) levels and increased prolactin levels in males (Meeker and Stapleton, 2010). TDCIPP and TCEP are prohibited in Washington State, USA, according to the “Toxic Free Kids Act” (Washington Toxics Coalition, 2011). EU Directive 2014/81/EU also introduced specific limits (5 mg kg^{-1}) for TCEP, TCIPP and TDCIPP in certain toys (European Union Commision Directive, 2014).

Studies of the bioaccumulation, metabolism and toxicokinetics of OPFRs date back to the 1970s (Gold et al., 1978; MacFarland and Punte, 1966; Muir et al., 1980; St. John et al., 1976). Fewer studies had been conducted until concerns were raised regarding the reemergence of OPFRs due to their increasing usage and high environmental concentrations (Carlsson et al., 2000). To date, the behaviors of OPFRs in animals and humans have become hot-button issues. However, these long-term studies still have not been fully summarized. Studies of the absorption, bioaccumulation and metabolic processes will facilitate comprehension of the fates and the mechanisms of toxicity of OPFRs. Thus, a review of the available studies in a systematic framework is urgently needed to better understand the behaviors and fates of OPFRs in organisms. In this article, we organized recent studies on the absorption, bioaccumulation, biomagnification and the metabolic processes of OPFRs in animals and humans (Fig. 1), rather than simply listing the occurrences of OPFRs in biota, which has often been conducted in previous reviews (Alves et al., 2014; Reemtsma et al., 2008; Van der Veen and de Boer, 2012; Wei et al., 2015). In addition, we also propose a perspective on research into the internal exposure of OPFRs to animals and humans.

2. Absorption

The migration of OPFRs in the environment leads to their exposure to organisms (Abdallah and Covaci, 2014; Alves et al., 2014). There are diverse pathways for organisms to uptake or