Reproductive Toxicology 36 (2013) 40–52

Contents lists available at SciVerse ScienceDirect

Reproductive Toxicology

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

Organotins: A review of their reproductive toxicity, biochemistry, and environmental fate

Jones Bernardes Graceli[a,*], Gabriela Cavati Sena[a], Pedro Francisco Iguatemy Lopes[a], Gabriela Carvalho Zamprogno[b], Mércia Barcellos da Costa[b], Ana Flavia Locateli Godoi[c], Dayana Moscardi dos Santos[d], Mary Rosa Rodrigues de Marchi[e], Marcos Antonio dos Santos Fernandez[f]

[a] Departament of Morphology, UFES-Federal University of Espirito Santo, Espírito Santo, Brazil
[b] Departament of Biological Sciences, UFES, Brazil
[c] Environmental Engineering Department, UFPR – Federal University of Paraná, Curitiba, Brazil
[d] Institute of Oceanography, USP – University of São Paulo, São Paulo, Brazil
[e] Institute of Chemistry, UNESP – University Estadual Paulista, Araraquara, Brazil
[f] Oceanography Department, UERJ-Rio de Janeiro State University, Rio de Janeiro, Brazil

ARTICLE INFO

Article history:
Received 31 December 2011
Received in revised form 5 November 2012
Accepted 23 November 2012
Available online 8 December 2012

Keywords:
Organotins
Environmental fate
Biochemistry
Reproductive toxicity
Obesogens

ABSTRACT

The review purposes are to (1) evaluate the experimental evidence for adverse effects on reproduction and metabolism and (2) identify the current knowledge of analytical procedures, biochemistry and environmental aspects relating to organotins. Organotins are pollutants that are used as biocides in antifouling paints. They produce endocrine-disrupting effects in mollusks, such as imposex. In rodents, organotin exposure induces developmental and reproductive toxicity as well as alteration of metabolic homeostasis through its action as an obesogen. The adverse effects that appear in rodents have raised concerns about organotins' potential health risk to humans in relation to organotin exposure. At present, triorganotin, such as tributyltin, have been demonstrated to produce imposex, and mammalian reproductive and metabolic toxicity. For most mammals, triorganotin exposure predominantly occurs through the ingestion, and this compound can cross the placenta. With these risks in mind, it is important to improve our knowledge of organotins' effects on environmental health.

1. Introduction

Organotins (OTs) belong to an organometallic class of pollutants. They are composed of an atom of tin that is covalently bonded to one or more organic chains [1] and another functional group, such as chloride, oxide, or hydroxide, which are represented by methyl, butyl, octyl, and phenyltin groups. The existence of OTs has been known since 1853, but they did not become important for industrial use until the 1940s. Since then, they have come into extensive use in several industrial sectors, mainly as biocides in antifouling boat paints [2]. Antifouling paints are used to reduce encrustations by barnacles, algae, mussels, and other marine invertebrates [3]. Antifouling solutions are based on two main triorganotins, tributyltin (TBT) and triphenyltin (TPT), which are the most toxic OTs.

OTs commonly break down in the environment. For instance, TBT degrades to dibutyltin and monobutyltin, and TPT degrades to diphenyltin and monophenyltin. The final degradation product is inorganic tin (Sn^{4+}), which is stable. Because of their organic chains, OTs are hydrophobic; this feature depends on the alkyl/aryl bond of the tin atom (in other words, the number of groups and the length of the organic chain). These compounds have low solubility in water, and their solubility depends on their pH, ionic strength, and temperature. In aqueous solutions, they can appear as neutral, ionically paired complexes and cations [4]. There is a relationship between the chemical form of OTs and their transport properties, bioavailability, and toxicity in the environment [5]. These properties can also be influenced by the organic matter content of the environment or the specific tissue in question [6,7].

The toxicity of OTs is controversial; their level of toxicity may be related to their concentration, exposure time, bioavailability, and biota sensitivity as well as the presence of various compounds in the environment. OTs are a diverse group of widely distributed environmental pollutants [8] that have been implicated as endocrine disruptors [9]. The increase in OTs toxicity may be related to their insolubility in water because their hydrophobicity is the main chemical characteristic that is responsible for their

* Corresponding author at: Departamento de Morfologia/CCS, Universidade Federal do Espírito Santo, Av. Marechal Campos, 1468, Prédio do básico, sala 5, 290440-090 Vitória, ES, Brasil. Tel.: +55 27 3335 7540; fax: +55 27 3335 7358/7334/7330.
E-mail addresses: jbgraceli@gmail.com, jbgraceli@ccs.ufes.br (J.B. Graceli).

0890-6238/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.reprotox.2012.11.008

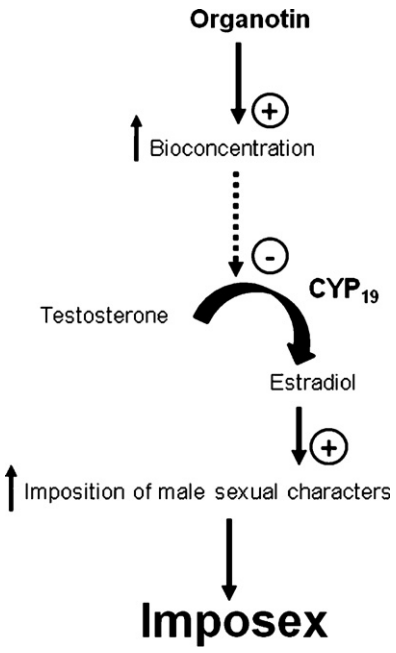

Fig. 1. Diagram illustrating the down-regulation of effective aromatase activity (CYP 19) mediated by organotin in mollusks, inducing imposex. The dashed arrow and the continuous arrows indicate an inhibitory (−) and a stimulatory (+) effect, respectively.

bioconcentration [10]. Usually, maximum toxicological activity is found when organisms are exposed to triorganotins, such as TBT [1].

OTs are markedly toxic to mollusks and can produce endocrine-disrupting effects. For instance, TBT and TPT can induce imposex, or the imposition of male sex characteristics in female snails [11,12]. The mechanism by which these OTs cause imposex is unclear, but OTs are known to induce the inhibition of one aromatase, a cytochrome P450 that converts testosterone into estradiol [12] (Fig. 1). This process occurs in a dose-dependent manner [13] making it useful as a biomarker for different contamination levels [14].

OTs are also suspected to cause endocrine-disrupting effects in mammals, humans [15] and rodents [16,17], in part as a consequence of the consumption of contaminated seafood. Human exposure may result from dietary sources, such as seafood, or through contaminated drinking water [18]. *In vitro* exposure to TBT or TPT in human choriocarcinoma cell lines decreases DNA and protein synthesis [19]. TPT inhibits human aromatase [20] and other steroidogenic enzymes, affecting sexual development in rodents [16,21,22]. Therefore, OTs have many complex effects on the endocrine systems of both genders that can induce morphological changes in the target organs.

TBT is also a potent agonistic ligand of vertebrate nuclear receptors, retinoid X receptors (RXR) and peroxisome proliferator-activated receptor-gamma (PPARy). The physiological consequences of receptor activation have been demonstrated in experimental models of adipogenesis [8]. Thus, TBT alters metabolic and lipid homeostasis parameters, induces the differentiation of adipocytes *in vitro* and increases adipose mass *in vivo* [8,23].

2. Analytical procedures and biochemistry

A variety of analytical techniques have been developed to study the speciation of OTs, mainly in sediments and biota [24]. The choice of a suitable solvent is the first step and is based on the solvent's ability to extract the various OTs that are in the matrix, which in turn depends on the nature of intermolecular forces, the geometric arrangement, and the balance between the polar and non-polar characteristics of the OTs to be extracted [5].

2.1. Extraction

Because OTs are bonded to the sediment surface, complete matrix dissolution is not required. More than half of the existing extraction procedures use a combination of an organic solvent of low to medium polarity with an acid [25]. Hexane, toluene, or dichloromethane are the solvents that are most often used in combination with acetic or hydrochloric acids. Liquid–liquid extraction and Soxhlet extraction are the classic methods, although they are used less often than the ultrasonic radiation technique that is currently in popular used for OTs extraction [26].

2.2. Derivatization

The technique most often used for derivatization is the Grignard reaction [5,27]. Ethylation and pentylation are usually employed because they allow for the determination of methyl, propyl, butyl, and phenyltin species [5]. Alkylation reactions with hydride generation reactions have been used to produce volatile derivatives. Sodium tetrahydroborate ($NaBH_4$) and sodium tetraethylborate are frequently used in this process [28]. Generally, the reduction is performed at a pH below the pK_a of the species of interest [29]. This method provides good sensitivity for aqueous samples. However, for complex samples (from sediments and biota), it presents a number of disadvantages, such as the limited number of compounds that can be determined and the instability of $NaBH_4$ [25].

2.3. Cleanup

A cleaning procedure is needed to eliminate matrix components and improve analysis reliability. OTs are particularly sensitive to interferents, and extract purity is a concern [5]. Sulfur (in anoxic sediments) is co-extracted and alkylated during Grignard reagent derivatization, yielding mono-, di-, and trisulfide dialkylated derivatives. If these derivatives are not removed, they can interfere with the chromatographic analysis of OTs as a result of their coincident retention time (co-elution). Silica gel, alumina, and florisil (these are preferred for biotic matrices) are the most common adsorbents used during cleanup [25].

2.4. Separation procedures

Most of the analytical methods that were developed to quantify OTs require hyphenated techniques, which are detection techniques with a specific detector that is suitable and a quantifying technique for a specific element. About two-thirds of the techniques used in OT analysis are based on gas chromatography (GC) [5]. One advantage of GC is the use of internal standards and surrogates to verify some of the analytical steps, such as quantification and recovery. The main disadvantage of GC is the requirement for volatile derivatives [25]. Mono-, di-, and triorganotin compounds are not sufficiently volatile, and a derivatization step is therefore needed. However, many techniques that are based on high performance liquid chromatography (HPLC) have been developed for OTs analysis [30–33], but interfacing HPLC with detection systems can be challenging, and the number of compounds that can be analyzed in a single run is limited in comparison to GC [34].

2.5. Detection

There are a number of available methods that use some form of GC. Flame ionization detectors, electron capture detectors, atomic