ORGANOTINS: SOURCES AND IMPACTS ON HEALTH AND ENVIRONMENT

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GLOSSARY

Endocrine Disrupting Chemicals: According to the Endocrine Society, an Endocrine Disrupting Chemical (EDC) is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.

Imposex: the superimposition of male sexual characters onto females of gonochoristic gastropods. The superimposed sexual characters include the development of a penis and/or a *vas deferens*. The length/size of the penis and VD is proportional to the concentration of TBT and this phenomenon is regarded as a highly specific biomarker in TBT monitoring.

Obesogens: chemicals that inappropriately alter lipid homeostasis to promote adipogenesis and lipid accumulation. These chemicals have the ability to inappropriately activate the master nuclear receptor of adipogenesis (PPARγ) and therefore to influence the onset of obesity.

OSPAR: OSPAR Commission. This commission deals with the protection and conservation of the marine environment of the North-East Atlantic.

PARCOM: PARIS COMMISSION. This commission was constituted by a group of experts who advised North Sea countries on environmental policy and legislation. The Paris Convention of 1974 was unified with the Oslo Convention from 1972, and it was updated and extended by the OSPAR Convention in 1992.

Rotterdam Convention: Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade. This Convention regulates the import of several hazardous chemicals in which TBT is included (see complete list at www.pic.int/Default.aspx?tabid=1132)

Nomenclature

AFS: Antifouling systems

AFS Convention: International Convention on the Control of Harmful Antifouling Systems on Ships

EC: European Commission

DBT: Dibutyltin

IFNγ: interferon gamma

IMO: International Maritime Organization

MEPC: Marine Environment Protection Committee of the IMO

NK Cells: human natural killer

OTs: Organotin compounds

PVC: Polyvinyl chloride

REACH: Registration, Evaluation, Authorization and Restriction of Chemicals (European Union Regulation)

TBT: Tributyltin

TNFα: tumor necrosis factor alpha

TPT: Triphenyltin

VDSI: Vas deferens sequence index

Keywords

Antifouling paints, biocides, cardiotoxicity, endocrine disruptors, immunotoxicity, imposex, neurotoxicity, obesogens, organotins, tributyltin,

Abstract

Organotin compounds are used as biocides, plastic stabilizers and catalysts for the production of polyurethanes and silicones. Their notoriety is due to tributyltin (TBT), a potent biocide extensively used in antifouling paints until the beginning of the XXI century. As a consequence of its widespread use, TBT was responsible for the contamination of the marine environment at a global scale, causing several deleterious effects towards non-target organisms, including imposex in gastropods which is still considered the best example of endocrine disruption in wildlife. In mammals, including humans, organotins' negative effects comprise cardiotoxicity, neurotoxicity, immunotoxicity, and endocrine/metabolic dysfunction, including obesity.

1. Introduction

The presence of organotin compounds (OTs) in the environment is largely a consequence of human activities. In fact, except for a specific group that can also be synthetized by bacteria (methyltins), all organotin compounds are of anthropogenic origin. Organotins became a matter of concern due to one specific compound - tributyltin (TBT). This organotin was used as the active ingredient in antifouling systems (AFS) to combat marine biofouling since the early 1960s until the beginning of the XXI century. It was, therefore, introduced in the marine environment at an unprecedented scale for a man-made chemical. The global scale of contamination (encompassing all the world oceans and coastal areas) alongside with the bizarre deleterious effects towards non target organisms (including anomalies in shell calcification in oysters and the masculinization of female gastropods - imposex), attracted the attention of the scientific community and put TBT in the forefront of scientific research. In 1998 Imposex was considered the best example of endocrine disruption in wildlife (Matthiessen and Gibbs, 1998) and it

remains so. This highly sensitive biomarker provides information on the effects of TBT both at the individual and at the community levels since severely affected females are unable to reproduce, causing population decline. Furthermore, the unequivocal relationship between exposure and negative effects imposed the need to implement restrictions on TBT, with the added advantage that imposex could be used as a tool to evaluate legislative effectiveness. In fact, a significant part of the prolific scientific literature on organotins, and in particular TBT, deals with monitoring in the aquatic environment using imposex as a tool to evaluate the effectiveness of successive measures introduced all over the word to restrict the use of TBT in AFS. In 2008 this culminated with the global ban on organotin compounds in antifouling systems (when the 2001 'International Convention on the Control of Harmful Anti-Fouling Systems on Ships' of the International Maritime Organisation came into force).

As already stated, although responsible for OTs notoriety, imposex in gastropods is not the only negative effect of organotins; several reports using in vitro and in vivo experiments with different organisms, including mammals, as well as some epidemiological surveys, indicate that OTs are potent endocrine disruptors. Some recent evidence also suggests that TBT is a potent obesogen.

However, one should be aware that of all OTs produced worldwide, only a relatively small fraction (less than 20%) was used in the biocides industry; the majority was used in the manufacture of PVC (polyvinyl chloride) (mainly dibutyltins, dioctyltins and mono substituted organotins), polyurethane foams, and silicones. Given the ubiquity of such products and the potential impact towards ecosystem and human health, the toxicity of other OT compounds has also been assessed. Experimental data suggest that OTs are immunotoxic, genotoxic, cardiotoxic and neurotoxic.

Given all the evidence of organotin toxicity and widespread environmental dissemination, their use has been increasingly regulated/banned, at first as biocides in AFS and as pesticides in agriculture and later as stabilizers in plastics and catalysts in the production of polyurethanes and silicones. Despite these restrictions and bans, the widespread contamination of the maritime environment and their ubiquitous occurrence in consumer products, ensure that organotins have a constant presence in humans' everyday life, creating exposure scenarios on a regular basis. Hence, the scientific community is now focused on the characterization of human exposure pathways so that exposure sources can be identified and preventive measures can be adopted, while trying to understand the molecular mechanisms responsible for OTs toxicity.

2. Chemical structure, production and applications

Organotin compounds are characterized by a tin (Sn) atom that is covalently bound to one or several organic substituents and to an inorganic or organic ligand (e.g. chloride, fluoride, oxide, hydroxide, carboxylate, or thiolate). The organic substituents include for example methyl, ethyl, butyl, propyl, phenyl or octyl groups. The type of ligand and the degree of substitution are responsible for the compounds' physical and chemical characteristics. It is however the number and nature of the organic substituents that mostly influence their toxicity, with inorganic tin being virtually nontoxic, whilst trisubstituted compounds exhibit the maximum toxicological activity (WHO, 1980).

Organotin compounds are generally grouped according to the number of organic groups, namely: tetra-, tri-, di- and mono-organotins. They are further classified according to the type of organic substituents, i.e., methyl, ethyl, butyl, propyl, phenyl, octyl. Generally, the most common alkyl chains are butyl and octyl and the most common aromatic ring is phenyl.

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2.1. Production and applications

Organotin compounds are an extremely versatile group of anthropogenic organometals with more than 800 different available compounds (Hoch, 2001). They are used as stabilizers of PVC, catalysts for the production of polyurethanes and silicones and they were used in the past as biocides in antifouling paints and agriculture (Sousa et al., 2013).

Tetraorganotins (R_4Sn), triorganotins (R_3Sn_X), diorganotins (R_2SnX_2), and monoorganotins ($RSnX_3$) in which the R groups include methyl, butyl, octyl, cyclohexyl, phenyl, or neophyl are commercially important (ASTDR, 2005). Generally, tetraorganotins are used as intermediates in the production of tri-, di-, and monoorganotin compounds and may also be used as oil stabilizers. Triorganotin compounds exhibit excellent biological activities and they were used, for example, as disinfectant products in cooling systems of a variety of industries (e.g. power plants, breweries, tanneries, textiles mills), as pesticides in agriculture, as biocides in consumer products (e.g. allergic pillows, shoes, sportswear, textiles). However, their main application was as biocides in AFS formulations, mainly tributyltin (TBT) and to a lesser extent triphenyltin (TPT). Diorganotin compounds are used as polyvinyl chloride (PVC) stabilizers and as catalysts in the production of polyurethane foams and in room-temperature vulcanization of silicones. They are also used in glass treatment processes, and as dewormers in poultry farming, water-proofing agents for cellulosic materials (e.g. cotton textiles, paper and wood), printer toners, stabilizers of press ink, flame retardants for wool fabrics and binders in water-based varnishes. Monoorganotin compounds are used as stabilizers in PVC films and in glass treatment (WHO, 1980, ASTDR, 2005, WHO, 1990).

3. Historical aspects and trends of organotin compounds in the environment

The first organic tin compounds were synthetized in the mid XIX century. The British chemist Edward Frankland synthetized diethyltin diiodide in 1853 and 6 years later tetraethyltin. However, for almost 100 years these compounds remained confined to the laboratory with no commercial or industrial application. Only after the discovery of diorganotins capacity to stabilize polyvinyl chloride (PVC) did the industrial production of these compounds start. When exposed to high temperatures and UV light, PVC polymers undergo dehydrochlorination compromising their stability. Organotins act as polymer stabilizers preventing degradation. OTs were used as stabilizers in the plastics industry since the 1940s in the USA, and the 1950s in Europe and Japan (Hoch, 2001, de Carvalho Oliveira and Santelli, 2010). At about the same time that OTs usage in the plastics industry gathered momentum, researchers from The Netherlands discovered (in 1954) the biocidal properties of triorganotin derivatives. At first, TBT was used in African countries as a molluscicide to kill the freshwater snails that acted as the intermediate hosts of the trematode parasite responsible for the schistosomiasis disease. After its successful use to prevent the spread of this disease, TBT was registered as a wood preservative and later as biocide in antifouling systems (WHO, 1990).

3.1. TBT and antifouling paints

When a structure is submerged into water, it is rapidly colonized by organisms from different trophic levels, such as algae, crustaceans and mollusks, among others. This phenomenon is known as biofouling and it poses several problems to the naval industry. According to the International Maritime Organization (IMO) a ship at sea can gather as much as 150kg m^{-2} during a period of 6 months. Due to the increased drag, fuel consumption will be added by 40% to maintain cruise speed (IMO, 1999). The application of AFS is thus of great importance and in the beginning of the XXI century the antifouling market reached an estimated annual value of 3 billion euros (Dafforn et al., 2011). Much of this success was due to the use of TBT as biocide. In its “golden period”, the TBT global market varied between 2,000 to 3,000 metric tons per year (Matthiessen, 2013). The use of TBT started in the early 1960s, being intensified in the 1970s when self-polishing paints were developed. In fact, according to the IMO, at that time most of the sea vessels used TBT paints. This widespread use was motivated not only by the excellent biocidal properties that allowed a ship to continuously operate for more than 60 months before returning to dry-dock, but also by the belief that TBT was degraded to nontoxic inorganic tin

once release into the water column (Sousa et al., 2013). However, this proved to be a wrong assumption.

3.2. Deleterious effects of TBT

The first deleterious effects of TBT were detected in Arcachon Bay (France), a location famous for its oyster farms and recreational marinas. Originally, a decline in the population of the gastropod *Ocenebra erinacea* was noted, but because this species was an oyster predator and considered a pest, this early warning sign was ignored. It was only in the 1970s and early 1980s when shell calcification anomalies in the oysters started to appear, followed by complete reproduction failure that the authorities started to investigate. Following the research work conducted by Alzieu and co-workers it was possible to establish a connection between those deleterious effects in the oysters and the presence of TBT in the bay (Alzieu, 2000).

On the other side of the Atlantic, in the American state of Connecticut, a bizarre phenomenon in gastropod females was described in the early 1970's. The phenomenon, coined by Smith (1971) as imposex, was characterized by the development of a penis behind the right tentacle of *Nassarius obsoletus* females. In the 1980s, following a series of lab and field studies conducted along the Connecticut coast, an association between imposex development and TBT was established. This relationship was then confirmed in the UK, by the work of Bryan and Gibbs (1991) through a series of lab and field experiments with the gastropod *Nucella lapillus*. The results from field work allowed the authors to conclude that TBT was responsible for the local extinction of the gastropods' populations. The same authors proposed the use of imposex as a biomarker to evaluate TBT pollution and developed the *vas deferens* sequence index (VDSI) to evaluate the degree of female masculinization. Imposex has now been described in more than 200 gastropod species worldwide and is used as a specific biomarker of TBT pollution. Its robustness was validated by the OSPAR Commission (an organization including 15 European Governments as well as the EU constituted to protect the marine environment of the North-East Atlantic), and recommended to monitor TBT pollution levels across Europe.

Despite the fact that mollusks are particularly sensitive to TBT pollution, other organisms are also deeply affected by this pollutant. The deleterious effects of TBT are widespread across different taxonomic groups (see Sousa et al., 2013 for a list of references). In bacteria TBT inhibits growth, solute transport, reproduction and macromolecule biosynthesis, affects respiration, and decreases productivity. In phytoplankton, it reduces respiration, photosynthetic activity, and primary productivity, alters photosynthetic pigment content, induces drastic changes in biochemical composition, and changes in the community structure. In crustaceans it

also induces changes in the community structure, it reduces reproductive performance and neonate survival, inhibits larval developmental ratio and decreases juvenile growth rates. In plants, it impairs the development of motile spores, reduces photosynthetic activity, growth and transpiration rates, and it bioaccumulates in plants used for human consumption. In fish, TBT inhibits growth, is lipotoxic, genotoxic and neurotoxic. It also induces masculinization and sperm abnormalities, reduces fecundity, inhibits ovarian development, is responsible for embryo abnormalities, larval malformations, liver vacuolation, hematopoietic tissue hyperplasia and it inhibits Cytochrome P450.

In mammals, TBT exposure is associated with reproductive anomalies, including reduced spermatogenesis and embryo malformations. It is responsible for neurobehavioral alterations and immunological disorders. TBT is also considered to be cardiotoxic towards mammals and more recently it was demonstrated that it suppresses osteoclastogenesis and induces adipose tissue differentiation and obesity, being thus considered to be environmental obesogen.

3.3. Environmental distribution - Unexpected locations

The extensive use of TBT and, to a lesser extent TPT, as biocides in AFS lead to an unprecedented contamination of the marine environment at a global scale. This contamination is easily understood if we consider that during a time period of 3 days a commercial ship can release the equivalent of 600 ng L^{-1} of tin into the water column. Once released into the water column TBT rapidly adsorbs to suspended organic matter that will deposit into the underlying sediments where it will keep the compound sequestered for several decades. Hence, sediments may be regarded as the ultimate sink for TBT and thus may secondarily act as reservoirs that can release TBT when disturbed.

The presence of TBT in the coastal areas of the 5 continents is well documented. Furthermore, TBT can also be found in remote locations such as in the deep sea, in the Arctic and in Antarctica. Such global distribution alongside the reported deleterious effects towards non target organisms makes it a source of global concern that requires transnational concerted remediation strategies.

4. Key relevant regulations or legislation

4.1. Regulations on the use of TBT as biocide in AF paints

The economic and environmental impact of TBT pollution led to the introduction of successive legislative measures. The first regulations were implemented in those countries where the TBT deleterious effects were more evident, i.e., France and England. In 1982, shortly after the collapse of the oyster industry in Arcachon Bay (SW France), the French government banned the

use of TBT-based AFS in small boats (<25m). This prohibition was founded in the belief that the small fishing boats and yachts anchored in the marinas of the bay were the culprits of TBT contamination in the area. In 1986, TBT use was also regulated in the United Kingdom. UK restrictions were applied not only to small boats but also to aquaculture structures, and were motivated by the severe ecological impacts caused by TBT in South West England, where local gastropod populations were extinct. The ban of TBT-based AFS in small boats was further extended to the Northeast Atlantic in the same year through the PARCOM recommendation (87/1) (enacted under the OSPAR convention mentioned previously). Similar restrictions were adopted in the USA and New Zealand in 1988; in Australia, Norway and Canada one year later; and in Japan in 1990. Following the implementation of the ban for small boats it was possible to observe a recovery of the ecosystems at specific coastal locations in Europe and Australia. Nevertheless, at the same time several reports documented the widespread occurrence of imposex-affected females in offshore and remote areas including Antarctica (see Sousa et al., 2013 for a list of references). Such facts corroborated the belief that TBT pollution was not restricted to coastal areas where ports and marinas were located but was widespread around the globe. Such global distribution could only be explained by the release of TBT from large vessels. This belief was validated in 1994 by a report that demonstrated that imposex and TBT pollution in offshore locations was associated with major shipping lanes (Hallers-Tjabbes et al., 1994). Given all the evidence, the Marine Environment Protection Committee of the IMO (MEPC) started to work on a legal document that would control the use of TBT-based AFS on ships. In October 2001, the MEPC adopted the 'International Convention on the Control of Harmful Antifouling Systems on Ships' (AFS Convention). This convention intended not only to ban the use of OT-based AFS but also to develop mechanisms to protect the introduction of hazardous substances as alternatives to OT-based paints. The effective date for the prohibition of application and re-application was set to be January 1st, 2003 and the interdiction on the use and circulation set for January 1st, 2008. However, those dates were not met because the Convention could only enter into force one year after being ratified by 25 countries whose combined fleets corresponded to not less than 25% of the world's merchant shipping tonnage. This only came to happen in September 2007, when Panama became the 25th state ratifying the Convention. Therefore, on September 1st, 2008, the AFS convention entered into force. However, the production and application of organotins in AFS is still ongoing in some developing countries, which are not members of the International Maritime Organization.

4.2. Other regulations on TBT and organotins

Tributyltin compounds are listed in Annex III of the Rotterdam Convention, and therefore subjected to the Prior Informed Consent (PIC) Procedure. At present, most of the Parties to the Convention have already reported the final decision of "No consent to import" or "Consent to import only subject to specified conditions".

The use of organotin compounds in toys was restricted in Europe by the European Toy Safety Directive (2009/48/EC). This directive establishes tin migration limits from toys or components of toys, that cannot be exceeded (e.g. 0.9 mg/kg of organic tin in dry, brittle, powder-like or pliable toy material). The use of organotins in other consumer products was regulated in European Union through Decision 2009/425/EC and afterwards by Regulation Nº276/2010 that amended Annex XVII of the REACH Regulation (EC) No. 1907/2006. According to these restrictions, the majority of organotin compounds (tributyltin, triphenyltin and dioctyltin) had their effective ban in 2012, whilst DBT's effective ban only entered into force on January 1st, 2015. Therefore, since those dates, in Europe, all articles and mixtures on stock, not meeting the imposed threshold limits may not be sold or used. Organotins in materials used in the production of food containers are an exception to these restrictions and, in Europe, are regulated by Reg. No. 1935/2004 (Sousa et al., 2013). With respect to potable water pipes, and according to the European Council of Vinyl Manufacturers, tin stabilizers were already phased out by the industry, and in Europe their use was restricted to France and Belgium in contrast to the US, where they were widely used in water supply infrastructures.

In the USA, organotin stabilizers in vinyl chloride plastics containers, films or panels that are in contact with food are regulated under the Code of Federal Regulations (Reg. 21CFR178.2650). Accordingly, OTs can only be used at levels not exceeding three parts per hundreds of resin and under specific temperature conditions.

5. Human exposure to organotins

OTs can be found in a wide variety of manufactured products including household items (e.g., wallpaper, textiles, pillows); kitchenware (e.g., silicone molds, silicon-coated baking paper); consumer products (e.g., footwear, clothes, toys, diapers, sanitary pads); medical devices (e.g., breast implants, silicone valves, tubes and bags). They are also present in food items (e.g., seafood; vegetables, cereals and fruits as a result of their use as biocides in AF paints and as pesticides in crops) and beverages (e.g. drinking water, milk, juices, wines and spirits due to their contact with pipes and reservoirs that have OTs in their composition) (for a complete list of references see Sousa et al., 2013).

With such widespread occurrence, humans are bound to be exposed to OTs on a daily basis through ingestion of contaminated food and dust or direct contact with contaminated products.

Traditionally, ingestion of seafood contaminated with TBT was considered to be the main exposure route to humans. However, recent reports disclosed that house dust ingestion may also contribute to the OTs total daily intake (Kannan et al., 2010, Sousa et al., 2017). Furthermore, there is concern of exposure to OTs trough medical devices made of silicone. Specific groups of the population are particularly vulnerable, such as patients in intensive care units and/or individuals in close, continued contact with silicone devices, such as breast implants, silicone valves, tubes and bags (SCHER, 2006).

5.1. Possible health effects

Due to the limited number of epidemiological studies, the evidence of deleterious effects towards human health emanates essentially from *in vitro*, *ex vivo* and *in vivo* studies with mammals, mainly rodents.

Experimental data obtained from these models demonstrate that TBT negatively affects the male reproductive system either by structural damages in testicular cells or by the disruption of the biochemical mechanism responsible for the maintenance of glucose homeostasis (see Cardoso et al., 2016 and references therein). However, and contrary to what happens with other endocrine disruptors, no studies relating OTs levels and infertility are available. The cardiotoxicity of TBT was assessed using rodents and the results demonstrated that TBT alters endothelial cell integrity and impairs the coronary vascular reactivity response to estradiol, produces endothelial denudation in isolated rat hearts and decreases the expression of smooth muscle actin protein in aortic rings (Mala, 2008). There are few studies dealing with the neurotoxic potential of OTs. The available studies (once again in rats) suggest that TBT can disrupt the blood brain barrier, and induces oxidative stress, causing cell death and consequently initiates neurodegeneration in the brain (Mitra et al., 2013). However, further studies with lower levels of TBT and longer exposure times are necessary in order to better understand the role of OTs in neurodegeneration.

The endocrine and metabolic dysfunction potential of OTs has received increasing attention in the last few years. Studies with *in vitro* models revealed that TBT promotes adipogenesis trough RXR and PPAR activation. *In vivo* experiments confirmed these findings, and further demonstrated that prenatal exposure to TBT in mice is associated with adiposity later in life and that these effects might be heritable (Heindel et al., in press). TBT was the first obesogen compound described and is, until today, considered the model obesogen despite the fact that, up until now, there is no epidemiological evidence supporting the role of organotins in the obesity epidemic.

The immunotoxicity of OTs towards humans has been studied for almost 20 years. Data obtained from experimental models clearly demonstrate that both TBT and DBT interfere with the response of human natural killer (NK) cells and alters the secretion of the pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) as well as interferon gamma (IFNγ) from human immune cells *in vitro* (Lawrence et al., 2013). DBT is further considered a potent immunotoxicant capable of interfering with the natural ability of cells to control important immune responses and inflammation (Gumy et al., 2008). Such findings about DBT toxicity, together with the fact that TBT is metabolized in the human liver into DBT, suggest that at least some of the effects allocated to TBT may be, in fact, caused by this metabolite. Hence, when evaluating OTs levels, it is of crucial importance to simultaneously evaluate TBT metabolites' concentrations.

There are few surveys reporting OTs levels in humans and even less associating the measured concentrations with health outcomes (Sousa et al., 2013). In fact, of the 24 studies that reported OTs levels in human samples, only seven analyzed OTs levels in large data sets (>30). Of those, only two addressed health issues. These two surveys studied the levels of OTs in placenta samples from Finland and Denmark and their possible association with congenital cryptorchidism (Rantakokko et al., 2013), and with the ponderal index (PI) and growth during the first 18 months of life in Finnish boys (Rantakokko et al., 2014). Overall, the results disclosed relatively low levels of OTs in placental samples, with most compounds bellow the detection limit of the analytical technique in use. However, in placental samples from Finland, TBT was detected in 99% of the samples. Despite the limited number of samples and the conflicting results between both countries with respect to OTS concentrations and cryptorchidism, a positive association between placenta TBT and increased weight gain during the first 3 months was found. Such results might suggest a possible obesogenic effect. However, given the limited number of samples and follow up time, it is not possible to draw any robust conclusion of any TBT obesogenic effect in humans, and therefore, more research is urgently needed.

6. Lessons learned and Future Perspectives

The history behind organotin compounds provides an excellent illustration for the Earth's most recent geological period – the Anthropocene. A group of chemicals (almost entirely) of anthropogenic origin are released into the environment in large quantities, and end up yielding unwanted, sometimes unexpected, dire consequences to the ecosystems health. History shows that, in the case of TBT, a total worldwide ban was necessary, since the costs largely outweighed the benefits. However, fifteen years after this ban, aquatic biota keeps on suffering TBT's deleterious effects. There are lessons to be learned from this story. In the Anthropocene, an incredible amount of contaminants was released in the environment, sometimes at an

unprecedented scale for the history of mankind. These contaminants will at some point cause deleterious effects in the ecosystems and human health. Those effects may be as trivial as the extinction of a plague or as bizarre and complex as the masculinization of invertebrates or the obesity in mammals. Either way, never again in the future should it take as long to implement legislation to protect the ecosystems' and human health as it did with the story of TBT.

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List of relevant websites

European Union Legislation: http://eur-lex.europa.eu/

International Convention on the Control of Harmful Anti-fouling Systems on Ships: http://www.imo.org/en/About/Conventions/ListOfConventions

Rotterdam Convention: http://www.pic.int/

United States Food and Drug Administration Code of Regulations: www.ecfr.gov

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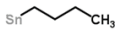
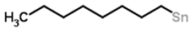
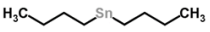
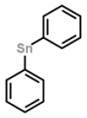
Table 1. Summary of selected organotin compounds, organized by number and nature of the organic substituents, with main applications, formula, and chemical structure. Chemical structures adapted from Royal Society of chemistry's Chemspider©.

Organotin classes	General formula	Applications	Chemical Structures	Selected references
Monosubstituted	**$RSnX_3$**	Stabilizers in PVC films Glass treatment (Limited applications when compared to other OTs)	 **Monobutyltin** (MBT) C_4H_9Sn  **Monophenyltin** (MPT) C_6H_7Sn  **Monooctyltin** (MOT) $C_8H_{20}Sn$	WHO (1990); ATSDR (2005)
Disubstituted	**R_2SnX_2**	Stabilizers in plastics industry (particularly PVC) Catalysts in the production of polyurethane foams and in room-temperature vulcanization of silicones Glass treatment processes as precursors for SnO2 film Dewormers in poultry farming Water-proofing agents for cellulosic materials (e.g. cotton textiles, paper and wood) Flame retardants for wool fabrics Binder in water-based varnishes	 **Dibutyltin** (DBT) $C_8H_{18}Sn$  **Diphenyltin** (DPT) $C_{12}H_{10}Sn$  **Dioctyltin** (DOT) $C_{16}H_{34}Sn$	WHO (1990); Hoch (2001); de Carvalho Oliveira and Santelli (2010); Antizar-Ladislao (2008)
Trisubstituted	**R_3SnX**	Biocides in antifouling paint formulations Fungicides, insecticides, miticides, and antifeedants in agrochemical industry Pesticides for ornamental plants Miticides in citrus fruits Acaricides in vineyards Insecticide and fungicide in wood preservation Biocide in construction materials Disinfectants and biocides for cooling systems in power stations, pulp and paper mills, textile mills, breweries, tanneries Insecticides and antifeedants in textiles Biocides in allergic pillows Biocides in insoles for shoes Biocides in cycling shorts padding Biocides in sprays for athlete's foot treatment		WHO (1990); Hoch (2001); RPA (2005)
Tetrasubstituted	**R_4Sn**	Intermediates in the preparation of other organotin compounds Oil stabilizers		WHO (1990); de Carvalho Oliveira and Santelli (2010)