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# Developmental toxicity of organotin compounds in animals

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Organotin compounds (OTs) have been used as biocides in antifouling paints and agriculture. The IMO introduced a global ban on the use of OTs in antifouling systems in 2001 due to their high toxicity. However, OTs have still been detected in the environment and pose a threat to the ecosystem. Several research groups have summarized the analytical methods, environmental fate, biochemistry, reproductive toxicity and mechanisms of actions of OTs. Here, we reviewed the developmental toxicity of OTs in various organisms such as sea urchin, ascidian, mussel, and fish. The differences in sensitivity to OT exposure exist not only in different species but also at different stages in the same species. Though some hypotheses have been proposed to explain the developmental toxicity of OTs, the solid evidences are greatly in need.

**Keywords: organotin, developmental toxicity, stage sensitivity, embryo, RXR**

## INTRODUCTION

Organotin compounds (OTs) have been widely used as biocides in antifouling paints and agriculture since the 1960s. Tributyltin (TBT) and triphenyltin (TPT) are most important OTs. TBT is considered the most toxic man-made and deliberately substances introduced into the environment. It can cause the imposex in gastropods—a condition in which male sex organs develop in females (Gibbs et al., 1987; Shi et al., 2005). Therefore, the International Maritime Organization (IMO) calls for a global treaty that bans the application of OTs as biocides (IMO, 2001). The unique story of TBT and imposex not only is one of the best examples of endocrine disruption in wildlife but also show us a typical story of the integration between the fields of scientific research and regulation (Sousa et al., 2013).

Despite this success, the story of OTs is far from its end. OTs are still widely used rather than in antifouling paints. OTs have been still detected in various environments in recent years (Yi et al., 2012; Ho and Leung, 2014). Thus, OTs inputs will continue, and the hazard of OTs will still exist. In recent years, several research groups have reviewed the analytical methods (Dubalska et al., 2013), environmental fate (Dubalska et al., 2013; Graceli et al., 2013; Sousa et al., 2013), reproductive toxicity (Graceli et al., 2013), and the mechanisms of actions of OTs (Pagliarani et al., 2013). The early developmental stages of organisms are highly sensitive to chemical exposure. Therefore, we reviewed the current study of developmental toxicity of OTs in the present paper.

## EFFECTS OF OTs ON DIFFERENT SPECIES AT EARLY DEVELOPMENTAL STAGES

Many studies have shown that OTs have high toxicity to embryos of various organisms at environmentally relevant concentrations (**Table 1**).

### SEA URCHIN

TBT significantly reduces the growth of sea urchin *Paracentrotus lividus* from post-fertilization to the pluteus stage at 0.01 μg/L (Marin et al., 2000). The length of the *P. lividus* pluteus somatic rods is significantly reduced by 1.5 μg/L TPT at 48 h post-fertilization. Progressive increases in skeletal anomalies are also detected. Embryos never reach the pluteus stage at 5 μg/L, and the development is blocked at the gastrula stage at 10 μg/L (Moschino and Marin, 2002).

### ASCIDIAN

TBT blocks *Styela plicat* embryo development to the larval stage from 1 μM. Exposure to 10 μM TPT soon after fertilization hinders embryonic cleavage and at the two-cell to four-cell stage blocks further development (Cima et al., 1996). Incubation of *Ciona intestinalis* neurula larvae in 0.1–10 μM TBT solutions for 1–2 h provokes serious anomalies thus causes an irreversible block of embryonic cleavage (Dolcemascolo et al., 2005).

### BIVALVES

TBT increases the mortality of *Crassostrea gigas* embryos at 0.36 μg/L at 24 h (Tsunemasa et al., 2011), and induces

**Table 1 | Comparison of developmental toxicity of organotin compounds in animals.**

| Species | Time | $LC_{50}$ | $EC_{50}$ | References |
|---|---|---|---|---|
| ***CRASSOSTREA GIGAS*** | | | | |
| Tributyltin | 2 h | 16 μg/L | – | Tsunemasa et al., 2011 |
| | 24 h | 3.9 μg/L | – | Tsunemasa et al., 2011 |
| Triphenytin | 2 h | 14 μg/L | – | Tsunemasa et al., 2011 |
| | 24 h | 2.7 μg/L | – | Tsunemasa et al., 2011 |
| ***MYTILUS GALLOPROVINCIALIS*** | | | | |
| Tributyltin | 48 h | – | 377 ng/L | Beiras and Bellas, 2008 |
| ***GILTHEAD SEABREAM*** | | | | |
| Tributyltin chloride | 24 h | 28.3 μg/L | – | Dimitriou et al., 2003 |
| Triphenytin chloride | 24 h | 34.2 μg/L | – | Dimitriou et al., 2003 |
| ***DANIO RERIO*** | | | | |
| Trimethyltin | 96 h | 8.2 μM | 2.8 μM | Chen et al., 2012 |
| Triphenyltin acetate | 96 h | 40 μg/L | – | Strmac and Braunbeck, 1999 |
| ***XENOPUS TROPICALIS*** | | | | |
| Triphenytin | 72 h | 5.25 μg·Sn/L | 0.96 μg·Sn/L | Yu et al., 2011 |

malformations of *Mytilus galloprovincialis* embryos at 0.161 μg/L (Beiras and Bellas, 2008). TBT also induces cytogenetic damage (sister chromatid exchanges and chromosomal aberrations) in *Mytilus edulis* embryo (Jha et al., 2000).

### FISH

TPT increases the mortality of European minnows *Phoxinus phoxinus* embryos at 3.9 μg/L and causes bent tails, opaque eyes and impaired swimming behavior in *P. phoxinus* larvae after 3 days exposure (Fent and Meier, 1994). TPT also induced skeletal and ocular deformations in other fishes at environmentally relevant concentration (Strmac and Braunbeck, 1999; Hu et al., 2009). TBT reduces the hatchability and causes dorsal curvature, severely twisted tails and pericardial edema in *Sebastiscus marmoratus* embryo at no less than 10 ngSn/L levels (Zhang et al., 2011).

### AMPHIBIAN

TBT and TPT induce multiple malformations in *Xenopus tropicalis* embryos at environmentally relevantly concentrations (Guo et al., 2010; Yu et al., 2011). The dominant phenotypes of malformation include abnormal eyes, enlarged proctodaeum, and narrow fins (Yu et al., 2011). TPT also significantly affects survival, growth, and days to metamorphosis in *Lithobates sylvaticus* larvae at 0.1 μg/L (Higley et al., 2013).

### MAMMAL

DBTCl (dibutyltin chloride) leads to a significantly decrease of survival rate of fetuses at terminal cesarean sectioning in cynomolgus monkeys after 2.5 mg/kg exposure. TPT induces postimplantation embryonic loss in pregnant rats, but no results indicate teratogenic responses. The study of mammals may suggest that OTs possesses no teratogenic effect in mammals (Ema et al., 2007).

## STAGE-SPECIFIC SENSITIVITY OF ANIMALS TO ORGANOTIN EXPOSURE

Toxicity of xenobiotics to embryos is dependent not only on type, level, and duration of exposure but also on developmental stages of exposure. In sea urchin, organotins strongly affect all stages (soon after fertilization, two to four cells, gastrula, and neurula) of *Styela plicata* embryo, but the most sensitive and critical stage is gastrula (Cima et al., 1996). Same sensitive stage has been reported in the *Ciona intestinalis* embryo (Vittoriaa et al., 2009). Gastrula is also the most sensitive stage when *Lytechinus variegatus* embryos is treated with TBT (Perina et al., 2011). The most susceptible developmental stage to trimethyltin (TMT) exposure is between 48 and 72 hpf in zebrafish embryo (Chen et al., 2012). The most sensitive stage is stage39/40 to stage41, followed by stage41 to stage43 in amphibian (*Xenopus tropicalis*) embryos after exposure to TPT (Yuan et al., 2011).

## MECHANISMS OF ACTION OF OTs IN ANIMALS

Several mechanisms of actions of OTs have been reported both *in vitro* and *in vivo* studies (Grün and Blumberg, 2006). However, the mechanism of OTs in the developmental stages is still not clear.

### NUCLEAR RECEPTOR

TBT and TPT have been proved to induce imposex in snails by binding to retinoid X receptor (RXR), as the natural ligand of RXR, *9-cis* retinoic acid (*9c*-RA) acts (**Figures 1A–C**) (Nishikawa et al., 2004; Nakanishi, 2008). Many studies have suggested that TBT or TPT disturb fish and frog embryos development through RXR (Yu et al., 2011; Zhang et al., 2011; Higley et al., 2013). Since the natural ligand of RXR (i.e., *9c*-RA) is a well-known teratogen by disrupting retinoic acid (RA) signal in vertebrate embryos (Minucci et al., 1996), it is reasonable to deduce that OTs induce malformations through RA signaling pathway (Hu et al., 2009). However, TPT and *9c*-RA induce totally different phenotypes of malformations and have different sensitive exposure windows in frog embryos (**Figures 1D–F**) (Yu et al., 2011; Yuan et al., 2011). These findings suggest that RA signal is not involved in OTs-induced teratogenicity.

### APOPTOSIS

In zebrafish (*Danio rerio*) embryo, 5 μM TMT exposure significantly promots apoptosis in the tail, this enhanced apoptosis in the tail may partly explain the attenuated tail touch response in the TMT treated embryo (Chen et al., 2011). Similar localized apoptosis in the tail is caused by TBT in *Sebastiscus marmoratus* embryo, which may be the reason of TBT induced twisted tails abnormality (Zhang et al., 2011). TMT actives the caspase 8/caspase 3 pathway for nuclear translocation of DNases in the primary cultured cortical neurons from embryonic mice, suggesting that TMT neurotoxicity is initially caused by activating this apoptosis pathway (Kuramoto et al., 2011).

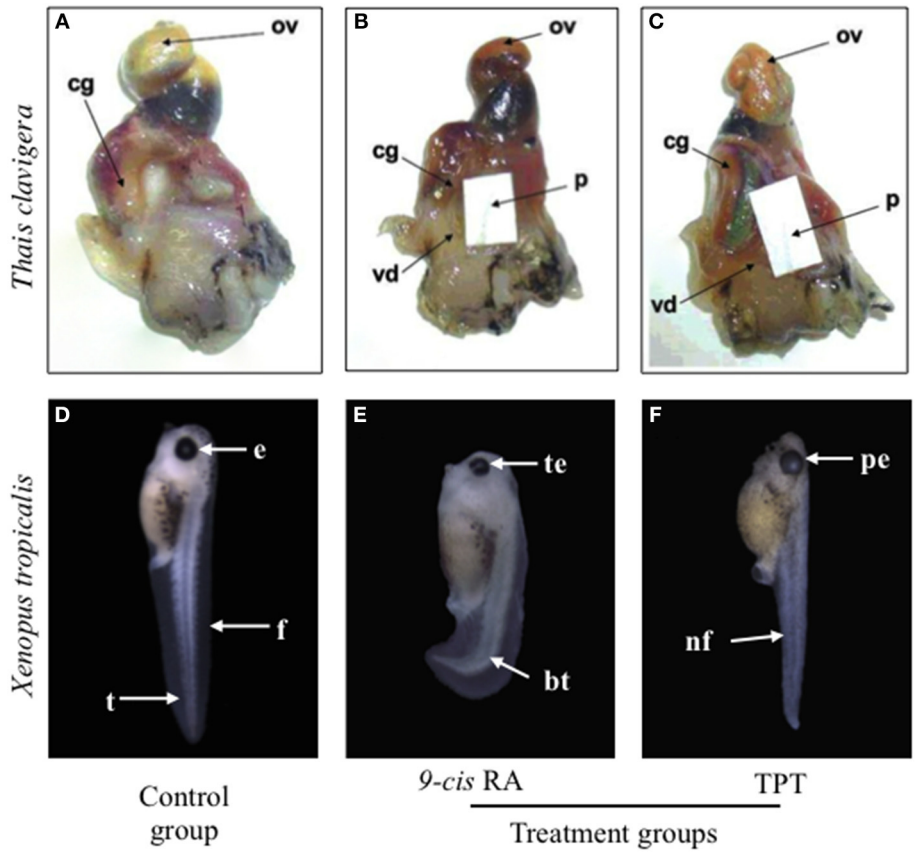


**FIGURE 1 | Comparison of toxic effects of triphenyltin (TPT) and *9-cis* retinoic acid (*9c*-RA) on snail (*Thais clavigera*) (A–C) and frog (*Xenopus tropicalis*) (D–F).** Photographs of **(A–C)** were cited from Nishikawa et al. (2004) with permission. cg, capsule gland; ov, ovary; p, penis; vd, vas deferens; e, eye; f, fin; bt, bent tail; te, turbid lens of eyes; nf, narrow fin; pe, protruding eye.

### INTRACELLULAR $Ca^{2+}$ HOMEOSTASIS

Calcium ion is a key signaling molecule in many developmental processes and plays a critical role in chemical-induced toxic cell killing and apoptosis. In the eggs of the sea urchin *Paracentrotus lividus*, TBT inhibits intracellular sequestration of $Ca^{2+}$ into the reticular compartment at low concentrations and inhibits the ion flow during skeletal deposition (Moschino and Marin, 2002).

### OTHER POTENTIAL MECHANISMS

TBT exposure results in a significant decrease of Na+/K+-ATPase activity in S. marmoratus brains and induces changes in the total pattern of phosphotyrosine and in the phosphorylation levels of ERK 1/2 in Ciona intestinali embryos (Zhang et al., 2008; Damiani et al., 2009). Another subfamily of MAPKs, c-Jun N-terminal kinase (JNK), is reported to be involved in part of the neuronal degeneration induced by TMT in cortical neurons of mice (Shuto et al., 2009).

## CONCLUSION AND FUTURE PERSPECTIVE

A lot of researchers have suggested that OTs show a high toxicity to many species, especially at their early life stages. The differences in sensitivity to OT exposure exist not only in different species but also at different stages in the same species. Though some hypotheses have been proposed to explain the developmental toxicity of OTs, the solid evidences are greatly in need. Further studies may help to fill gaps and to improve knowledge of developmental toxicity of OTs.

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