Organotin Exposure and Vertebrate Reproduction: A Review

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Organotin (OTs) compounds are organometallic compounds that are widely used in industry, such as in the manufacture of plastics, pesticides, paints, and others. OTs are released into the environment by anthropogenic actions, leading to contact with aquatic and terrestrial organisms that occur in animal feeding. Although OTs are degraded environmentally, reports have shown the effects of this contamination over the years because it can affect organisms of different trophic levels. OTs act as endocrine-disrupting chemicals (EDCs), which can lead to several abnormalities in organisms. In male animals, OTs decrease the weights of the testis and epididymis and reduce the spermatid count, among other dysfunctions. In female animals, OTs alter the weights of the ovaries and uteri and induce damage to the ovaries. In addition, OTs prevent fetal implantation and reduce mammalian pregnancy rates. OTs cross the placental barrier and accumulate in the placental and fetal tissues. Exposure to OTs in utero leads to the accumulation of lipid droplets in the Sertoli cells and gonocytes of male offspring in addition to inducing early puberty in females. In both genders, this damage is associated with the imbalance of sex hormones and the modulation of the hypothalamic–pituitary–gonadal axis. Here, we report that OTs act as reproductive disruptors in vertebrate studies; among the compounds are tetrabutyltin, tributyltin chloride, tributyltin acetate, triphenyltin chloride, triphenyltin hydroxide, dibutyltin chloride, dibutylin dichloride, diphenyltin dichloride, monobutyltin, and azocyclotin.

Keywords: organotin compounds, reproduction, vertebrates, endocrinology, environmental pollutants

INTRODUCTION

Organotins (OTs) are organometallic compounds that are widely used in industry, such as in the manufacture of plastics, pesticides, paints, and others (1, 2). Despite being easily degraded in the environment, several studies have shown the toxicological effects in different trophic levels of the food chain (3, 4). In 2008, the World Health Organization decreed a ban on the use of OTs in paints on vessels. However, many countries did not adopt this ban. OTs are classified as endocrine-disrupting chemicals (EDCs), leading to inappropriate endocrine system functioning in various species (5, 6). Thus, their exposure can cause damage, sometimes irreversibly, such as the process of imposex in which female gastropods develop male sex organs (3). For humans and other vertebrates, the major route of OTs exposure is by the intake of contaminated seafood, and studies evaluating their toxicological risks are limited (7–11). OTs impair reproductive functioning, and the damage is associated with the imbalance of sex hormones and with improper modulation of the hypothalamic–pituitary–gonadal axis function of rodents (12–14). Here, we report that OTs act as reproductive disruptors in vertebrate
studies (Table 1); among them are tetrabutyltin (TeBT), tributyltin chloride (TBTCl), tributyltin acetate (TBTAc), triphenyltin chloride (TPTCl), triphenyltin hydroxide (TPTOH), dibutyltin chloride (DBTCl), dibutyltin dichloride (DBTCl2), diphenyltin dichloride (DPTCl2), monobutyltin (MBT), and azocyclotin.

REPRODUCTIVE TOXICOLOGY

Male Reproductive Function
Several studies have evaluated OT exposure in male vertebrates, highlighting the dose-dependent impairment by OTs in different experimental models (15–19). Male mice at postnatal day (PND) 21 exposed to TBTCl at concentrations of 0.5, 5, and 50 µg/kg for 3 days presented a reduction in testis weight (20). There was also a decrease in testis weight in Swiss Webster mice on PND 15 exposed to a dose of 15 mg/kg/30 days of TPTCl as well as a reduction in epididymis, prostate, and seminal vesicle weight (21). Mitra et al. (22) reported that TBTCl exposure for 3 days at doses of 10–30 mg/kg caused an accumulation of tin in rat testes. Thus, the OTs were able to accumulate in the male reproductive tract, leading to morpho-functional abnormalities.

| Animal models/dose/OTs | Fish | Frog | Rodents | Monkey |
|------------------------|------|------|---------|--------|
| (0.01–25 µg/kg) | (0.5 µg to 0.5 g/L) | (100 ng to 125 mg/kg) | (2.5–3.8 mg/kg) |
| TriOTs | Azocyclotin | Azocyclotin | TriOTs | DiOTs | DiOTs |
| Adult male | | | | |
| Organ weights (g/bw) | | | | |
| Testes, epididymis | NR | NR | NR | ↓ | NR | NR | (20, 21) |
| Prostate, seminal vesicle | NR | NR | NR | ↓ | NR | NR | (21) |
| Sn accumulation | NR | NR | NR | ↑ | NR | NR | (22) |
| Histopathology | | | | |
| Spermatocytes/spermatids | NR | ↑ | NR | ↓ | NR | NR | (20, 24) |
| Seminiferous tubules | NR | ↓ | NR | ↓ | NR | NR | (20, 23, 24) |
| Testes | Fibrosis | NR | NR | ↑ | Edema | NR | NR | (15, 22) |
| Leidig cells (number) | NR | NR | NR | ↓ | NR | NR | (22) |
| Sex hormones | ↓ | FSH | NR | ↑ | T | ↑ | LH, ↑ T | NR | NR | (13, 15, 24, 26, 27) |
| In utero effect | | | | |
| Cryptorchidism | NA | NA | NA | ↔ | NR | NR | (12) |
| Preputial separation | NA | NA | NA | ↔ | NR | NR | (54) |
| Testes, epididymis and prostate weight | NA | NA | NA | ↑/↔ | NR | NR | (12, 54) |
| Gonocytes, Sertoli cells (number) | NA | NA | NA | ↓ | NR | NR | (55) |
| Spermatid and sperm (number) | NA | NA | NA | ↓/↔ | NR | NR | (12, 54) |
| Sex hormones | NA | NA | NA | ↑ | T, ↑ LH, ↓ E2 | NR | NR | (12, 55, 54) |
| Adult female | | | | |
| Estrous cyclicity | NR | NR | NR | Impaired | NR | NR | (14, 31) |
| Ovary weight (g/bw) | NR | ↑ | ↓ | ↑ | NR | NR | (21, 24, 27, 29, 32) |
| Sn accumulation | NR | NR | NR | ↑ | NR | NR | (14) |
| Histopathology | Ovarian follicles | NR | NR | NR | ↑ Apoptosis, ↑ Atretic | NR | NR | (14, 31, 34) |
| Folliculogenesis | NR | Impaired | NR | ↓ Mature follicles | NR | NR | (14, 24, 31, 37) |
| Sex hormones | NR | ↑ T, ↓ E2 | NR | ↑ E2, ↑ T | NR | NR | (14, 24, 29, 31) |
| In utero effect | | | | |
| Vaginal opening | NA | NA | NA | ↑/↓ | NR | NR | (26, 56) |
| Estrous cyclicity | NA | NA | NA | Impaired | NR | NR | (26, 56) |
| Ovary morphology | NA | NA | NA | Impaired | NR | NR | (55) |
| Fertility | | | | |
| Loss pre- and postimplantation | NR | NR | NR | ↑ | ↑ | ↑ | (40–43) |
| Number of live fetuses | ↓ | NR | NR | ↑ | NR | NR | (41, 45) |
| Sex ratio (female/male) | ↔/↑ | NR | NR | ↔ | NR | ↔ | (19, 23, 41, 43–45) |
| Litter size | NR | NR | NR | ↑/↔ | NR | NR | (39, 41) |
| Hatchability/egg viability | ↔/↑ | NR | NR | NR | NR | (19, 44) |

OTs, organotins; TriOTs, triorganotins (tributyltin chloride, tributyltin acetate, triphenyltin chloride, triphenyltin hydroxide); DiOTs, diorganotins (dibutyltin chloride, dibutyltin dichloride, diphenyltin dichloride); Sn, tin; ↑, increased; ↓, decreased; ↔, unchanged or similar to control; NR, not reported; NA, not applicable; bw, body weight; LH, luteinizing hormone; T, testosterone; FSH, follicle-stimulating hormone; E2, estrogen; Fish, zebrafish (Danio rerio), rockfish (Sebastiscus marmoratus), and Oryzias latipes; frog, Xenopus laevis, Rodents, rats and mice; monkey, Macaca fascicularis.
Studies have reported a consensus that OTs are very harmful to vertebrate reproduction and the quality of spermatozoa (20, 23, 24). A reduction in the numbers of spermatocytes and spermatids as well as sperm viability and an increase in abnormal gametes were observed in male rats after exposure to TBTCl in a dose-dependent manner (20). Similar data were observed in zebra fish (Danio rerio); when exposed to different doses of TBTCl from the first day of incubation of the eggs to PND 70, they exhibited effects such as reduced or completely lost sperm motility, absence of flagella, and the presence of only abnormal spermatozoa in semen (23). Similarly, zebra fish exposed to 0.09 and 0.45 µg/L of azocyclotin presented a reduction of 21.4 and 58.1% in the number of spermatogenesis (24). However, there was an increase in spermatocytes with exposure to azocyclotin at levels of 0.09 (17.5%) and 0.45 µg/L (63.8%) in these fish at 5–6 months of age (24). Several histological studies have reported that OTs dramatically affect the reproductive apparatus cells in vertebrates (15, 21, 22, 25). Exposure to doses of TBTCl (10, 20, 30 mg/kg) for 1,100–1,300 h affected spermatogenesis, increased the lumen size of the seminiferous tubules, and caused testicular interstitial edema along with evident Leydig cell loss in male rats (22). The seminiferous tubule in male mice that received doses of TPTCl ≥3.75 mg/kg body weight (bw)/day presented a smaller tubule diameter and germinal epithelial reduction, suggesting that TPTCl exposure impaired spermatogenesis (21). Severe interstitial fibrosis was also observed in the interlobular septum of the testis with exposure to 10 ng/L TPTCl in rockfish (Sebastes marmoratus), and there was testicular vacuolization at 48 days of exposure (15).

The hormones associated with reproductive control are also affected by the presence of OTs (13, 15, 26, 27). S. marmoratus exposed to 10 ng/L TPTCl exhibited a decrease in follicle-stimulating hormone (FSH) mRNA expression (15). In rats, exposure to 6 mg of TPTCl/kg resulted in increased levels of luteinizing hormone (LH) (13). However, mice exposed for 3 days at 0.05 and 0.5 mg/kg TBTCl exhibited a reduction in serum LH levels of approximately 50% on PND 84 (26). In other studies, rats and hamsters exposed to TBTCl at 15 mg/kg/30 days and 100–150 ppm/kg/65 days, respectively, presented a reduction in testosterone levels (13, 24). By contrast, testosterone levels increased in the treatment of frogs (Xenopus laevis) with 0.5 µg/L of azocyclotin (27). In addition, studies have shown a reduction in serum estrogen levels and/or testes weight upon exposure to various OTs (TBTCl, TPTCl, or azocyclotin) in different rodent, toad, and fish species (15, 20, 26, 27).

**Female Reproductive Function**

Organotins can also affect the female reproductive function in different animal models (12, 16, 19, 28–30). Rats exposed to 100 ng/kg of TBTCI have abnormalities in the estrous cycle and present increased ovary and serum tin levels (14, 31). In addition, OTs led to a decrease in the weight of the reproductive organs of rodents in a dose-dependent manner (21, 32–35). By contrast, Grote et al. (29) found an increase in rat ovarian weight when exposed to doses of 2–6 mg/kg/day of TPTCl for 30 days. Ma et al. (24), when exposing zebra fish to 0.09 and 0.45 µg/L of azocyclotin for 21 days, reported a reduction in the gonadosomatic index. Li et al. (27) demonstrated that adult frogs exposed to 0.05 and 0.5 g/L azocyclotin for 28 days also presented a reduction in the gonadosomatic index. The study also reported an increase in the number of hermaphroditic frogs after exposure to azocyclotin (27).

Furthermore, it has been reported that exposure to OTs causes impairment of the release and production of sex hormones (14, 24, 27, 29, 33). Grote et al. (29) demonstrated that rats treated with 6 mg/kg of TPTCl had increased serum estrogen levels. By contrast, other studies have shown a reduction in the serum estrogen levels and increased testosterone in TBTCI-treated rats (14, 27, 31, 36). Ma et al. (24) demonstrated that azocyclotin treatment caused an increase in testosterone levels and a decrease in estrogen levels in the ovaries of female zebra fish. It is also known that these xenobiotics cause abnormalities in uterine and ovarian morphology, impairing ovarian follicular development and increasing the number of atretic ovarian follicles in rodents (14, 31). Lee et al. (34) treated rats with 1–10 mg/kg bw of TBTAc for 7 days and observed an increase in ovarian follicular apoptosis. Shen et al. (37), by administering TPTCl in vivo (female mice: 5 or 10 mg/kg/day by oral gavage for 10 days) and in vitro (germin al vesicle oocytes: 100 mg/mL/1), found impairment in oocyte development in vitro and a reduction in the number of secondary and mature ovarian follicles in vivo. In zebra fish treated with azocyclotin, the development of the oocyte was also impaired (24). Thus, OT exposure impairs ovarian function in vertebrates, possibly leading to a loss of fertility.

**FERTILITY**

Exposure to OTs in vertebrates negatively affects fertility, impairing major reproductive indicators such as pre- and postimplantation, the number of live pups, litter size, and so on (14, 38, 39). Studies have shown that female rats exposed to 7.6 and 15.2 mg/kg TBTCl presented greater pre- and postimplantation loss and a reduction in bw and the number of live fetuses in the treated groups (40). In addition, female rats exposed to 20 mg/kg TBTCl at gestational days (GDs) 0–19 showed a significant increase in postimplantation loss (41). In the same model, female rats exposed to 15.2 and 30.4 mg/kg DBTCl for 3 days showed an increase in pre- and postimplantation embryo loss (42). This embryonic/fetal loss was also observed in cynomolgus monkeys (Macaca fascicularis) exposed in utero to 2.5 and 3.8 mg/kg of DBTCl by the organogenesis period but with no effects on morphological development (43). Monkeys exposed to 2.5 and 3.8 mg/kg DBTCl for 30 days did not show any differences in the sex ratio (43). In female rats, exposure to 20 mg/kg TBTCl reduced the litter size and increased fetal numbers. However, the sex ratio did not show significant differences in utero exposure (41). Data show that the exposure of Swiss mice to 1.875, 3.75, or 7.5 mg/kg TPTCl did not result in changes to the litter size (39). Studies with the Oryza latipes fish model showed that, when exposed to a diet of 5 and 25 µg/g TBTCl for 3 weeks, the fish produced eggs with a reduced hatch
capacity. However, no differences were observed in the sex ratio (44). In another study, using the same fish species but with exposure to TPTCl at different levels, reductions in the female birth rate and the number of eggs were observed for each female. In addition, the incubation capacity decreased, and many embryos died before hatching due to developmental defects (45). However, zebra fish exposed to TBT at 1 µg/g of diet showed no difference in hatchability and egg viability; however, a decrease in fecundity was observed, and the proportion of females was significantly higher (19). By contrast, zebra fish kept in tanks with a continuous flow of TBT of 0.1 ng/L from the post-hatch days 0–70 had a higher proportion of males (23).

PLACENTAL ASSESSMENT

Several studies have shown that placental functions are also affected by the toxicological actions of OTs (Table 2) (46–49). In a human placental tissue collected between 1997 and 2001 from Finland (Turku) and Denmark (Copenhagen), relatively infrequent detection of MBT (percentage of samples > limit of quantification (LOQ) ranging from 10 to 11%) and more frequent detection of TBTCl and TPTCl (percentage of samples > LOQ ranging from 31 to 99%) were reported. The levels of di- and triorganotins in the placental samples collected from Finland were higher than in the placental samples collected from Denmark, especially for TBTCl (99 versus 37%, respectively) (48, 49). Cooke et al. (50) found 650 ng/g TBTCl in the placenta of female rats exposed to 10 mg/kg bw/day and on GD 20, and the TBTCl levels in the placenta were approximately 5-fold higher than the levels in maternal blood and 10-fold higher than in the milk on PND 6.

Heidrich et al. (46) suggest that OTs alter the enzymes of the placental steroidogenic pathway. TBTCl was found to be a partial competitive inhibitor of human placenta cytochrome P450 aromatase activity with an IC₅₀ value of 6.2 µM. The residual activity of TBTCl-saturated aromatase was 37%. DBTCl acted as a partial but less potent inhibitor of activity (65% residual activity), whereas TeBT and MBT had no effect. By contrast, human 3β-HSD (3β-hydroxysteroid dehydrogenase) type 1 activity was only moderately inhibited by TBTCl (80% residual activity) (46).

In the human choriocarcinoma cell line (JAR cells) used as a placental experimental model, the findings on aromatase were contrary to those by Heidrich et al. (46). TBTCl and TPTCl at a nontoxic level of 10⁻⁷ M for 48 h caused, through a cAMP-independent pathway, a dose-related increase in human chorionic gonadotrophin (hCG) secretion and an increase in aromatase activity; furthermore, this augmentation in enzymatic activity occurred concurrently with increases in mRNA expression and estrogen biosynthesis from androstenedione (28). Otherwise, neither of the mono-alkyltin compounds altered hCG production or aromatase activity (47). DBTCl stimulated aromatase activity at 30 nM but failed to induce hCG production. By contrast, DPTCl stimulated hCG production at 30 nM but not aromatase activity (47). Moreover, the changes in hCG and aromatase mRNA expression were nearly parallel to those in hCG secretion and aromatase activity (47).

These placental factors are both induced by specific ligands of retinoid X receptors (RXRs) (47). The treatment of an RXRα-transfected human choriocarcinoma cell line (JEG-3 cells) with 1–100 nM TBTCl for 24 or 48 h stimulated luciferase (LUC) expression from 1.5- to 9-fold, and exposing the cells to the same concentrations of TPTOH induced LUC expression from 1.8- to 19-fold, suggesting that low doses of these OTs activate RXR (47). The peroxisome proliferator-activated receptor gamma (PPAR-γ) ligand failed to increase the mRNA expression of aromatase in JAR cells, suggesting that PPAR–RXR is not involved in OTs-induced aromatase expression in the human placenta and that the RXR homodimer may be required for OTs-induced aromatase expression (47). By contrast, PPAR agonists, in addition to RXR agonists, stimulate mRNA expression of hCG, indicating that OTs-induced hCG expression might involve either PPAR–RXR heterodimers or RXR homodimers (47).

Exposure for 48 h to 100 nM of each OTs (TBTCl, TPTOH, and TPTCl) caused an increase in 17β-HSD I activity in JAR cells. TBTCl and TPTCl metabolites also altered 17β-HSD I activity, but the level of activation decreased in proportion to the dealkylation

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**TABLE 2 | Summary of placental changes induced by OTs.**

| Animal models/dose/OTs | Rodents (100 ng to 125 mg/kg) | Human (0.25–20 mg/kg or 6.2 µM) | JAR and JEG-3 cells (1–100 nM) |
|------------------------|-----------------------------|---------------------------------|-------------------------------|
|                        | TriOTs | DiOTs | TriOTs | DiOTs | TeBT | MBT | TriOTs | DiOTs | MBT |
| Placenta               |         |       |        |       |      |     |        |       |     |
| Sn accumulation        | ↑       | NR    | ↑       | NR    | NR   | ↑   | NR     | NR     | NR   |
| Aromatase activity     | NR      | NR    | ↓       | ↓     | ↔    | ↔   | ↑       | t/#   | NR   |
| 3β-HSD activity        | NR      | NR    | ↓       | ↔     | ↔    | ↔   | ↑       | t/#   | NR   |
| hCG secretion          | NR      | NR    | NR      | NR    | NR   | NR  | ↑       | ↑     | NR   |
| RXR activation         | NR      | NR    | NR      | NR    | NR   | NR  | ↑       | ↑     | NR   |
| 17β-HSD I activity     | NR      | NR    | NR      | NR    | NR   | NR  | ↑       | ↑     | ↑    |
| Progesterone           | NR      | NR    | NR      | NR    | NR   | NR  | ↑       | ↑     | ↑    |

OTs, organotins; TriOTs, triorganotins (tributyltin chloride, trihexyltin chloride, triphenyltin hydroxide); DiOTs, diorganotins (dibutyltin chloride, dibutyltin dichloride, diphenyltin dichloride); TeBT, tetra- butyltin; MBT, monobutyltin; Sn, tin; ↑, increased; ↓, decreased; ↔, unchanged or similar to control; NR, not reported; Rodents, rats and mice; Human, placenta samples were obtained as reported in Ref. [46, 48, 49]; JAR and JEG-3 cells, human choriocarcinoma cell lines.
or dearylation (mono- < di- < tri-) in JAr cells. The OTs that enhanced the catalytic activity of 17β-HSD I also increased its mRNA expression. However, the mRNA effects were much more pronounced than the changes in catalytic activity (51). Exposure at the same levels and time to TBTCI and TPTCl enhanced progesterone production in JAr cells (52). TBTCI and TPTCl metabolites also altered progesterone production. However, TeBT failed to stimulate this placental function at doses of <100 nM (52). Taken together, placental OT levels and hormonal changes should reflect the abnormal placental function, and these irregularities could be associated with the abnormal development and fetal exposure levels.

**GENERATIONAL EFFECTS**

Intrauterine exposure to TBTCI at different doses and routes did not alter the male:female ratio of pups in rats (50, 53). However, the exposure of zebra fish to 1 µg of TBTCI/g via the diet increased the proportion of females (19). Furthermore, in rats, gestational exposure to 125 ppm TBTCI did not alter the process of the descent of the male testis (12); nevertheless, in humans in Denmark, a positive correlation of the levels of DBTCI in the placenta with the occurrence of cryptorchidism in newborns was found (48). Furthermore, preputial separation in mice was not altered when exposed to 1, 10, and 100 µg/kg of TBTCI in utero (54).

Exposure to TBTCI by the diet with 5, 25, and 125 ppm of TBTCI/g of chow in the gestational period (GP) of rats induced a reduction in the epididymis, prostate, and testis weights in a dose-dependent manner (12). However, no significant changes in the weight of the male mouse sex organs were observed after exposure to 1, 10, and 100 µg/kg TBTCI (54), demonstrating different susceptibility/sensitivity to OTs according to the exposure model.

Studies have shown that testes can be a target organ for OTs action, as can be observed in the histological irregularities (12, 54, 55). Rat fetal testes exposed to 20 mg/kg TBTCI showed reduced numbers of gonocytes, Sertoli cells, and Leydig cells. In addition, there are differences in the expression of connexin 43 in Leydig cells, which may be reduced or completely absent (55). Moreover, seminiferous epithelial vacuolization, the retention of spermatids in the epithelium, and the retardation of spermatid maturation were observed in adult rats (12), while in mice, the sloughing of germ cells was observed in the seminiferous tubules (54); both were exposed to TBTCI in the GP.

In the parameters for sperm, OT–GP exposure has dose-dependent toxicological effects that vary according to the model of exposure used. In rats exposed to TBTCI via the diet, the spermatid and sperm counts were reduced, but no morphological changes or reduction in sperm motility were observed (12). In mice exposed to TBTCI in the GP until weaning, a dose-dependent reduction in sperm count was observed on both PND 49 and PND 152. A dose-dependent reduction in sperm motility at doses of 10 and 100 µg of TBTCI/kg bw (54) was also observed.

Rats exposed to TBTCI showed a dose-dependent increase in serum testosterone and LH levels as well as a reduction in the serum estrogen levels only in animals exposed to 125 ppm of TBTCI (12). In addition, mice exposed to a TBTCI dose of 10 mg Sn/kg in GD 15 showed increased expression of the LH β-subunit mRNA (53). Meanwhile, mice exposed to TBTCI from the GP until weaning showed a reduction in intratesticular estrogen levels only on PND 49 (54). The most disturbing effects were observed in humans, where the LH levels in 4-month-old boys had a negative correlation while the inhibin B levels correlated positively with the levels of TBTCI in the placenta of women from Finland (48).

The effects of GP on OTs in the reproductive system of mammalian females have been underestimated until the present. Ogata et al. (56) reports that F1 and F2 generations of rats with a whole-life dietary concentration of 125 ppm of TBTCI showed a delay of approximately 6 days for vaginal opening and an impaired estrous cycle. In mice exposed to 10 or 100 µg of TBTCI/kg bw/day from GD 6 of pregnancy through the period of lactation, female offspring showed early vaginal opening and first day in estrus, thus presenting early puberty (26). In the same study, the animals showed no alteration in the weight of the female sex organs or hormonal levels. However, the animals showed a prolongation of the estrus and diestrus phases and irregularities in the estrous cycle (26). Intrauterine exposure to TBTCI at doses of 10 and 20 mg/kg bw altered the fetal ovarian morphology of rats with reduced germ cell numbers and increased apoptotic cells (55).

**CONCLUSION**

Organotins induce endocrine-disrupting effects in vertebrates, including humans, mainly by the exposure to OT-contaminated seafood intake. The effects of OTs have been associated with gender-specific changes in the morphological functioning of reproductive organs, including gonadal cell dysfunction and weight variation in the sex organs. Moreover, OTs are capable of crossing the placental barrier and thus accumulate in the placenta and in fetal tissues, generating congenital abnormalities. The toxicity level of OTs in various species may be related to their concentration and the timing or period of life of exposure. Thus, toxicological and bioavailability studies are needed for regulatory agencies to make informed decisions about the safety of OTs in food and for the environment in general.

**AUTHOR CONTRIBUTIONS**

The topics of the article were divided among the authors JA, PP, EM, IS, CC, ON, RF, LL, JG, who contributed with research and writing. In addition, JA and PP oversaw, assemble, and review the article. JA and PP contributed equally to the study.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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