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Review

Toxicity of Organotin Compounds Present in the Environment to Mammals

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Organotin compounds are synthetic organometallic compounds with high lipophilicity, persistence, and slow degradation rates in the environment, which promote bioaccumulation and biomagnification through the food chain. Tributyltin (TBT) is widely used in antifouling paints, wood preservatives, and pesticides. It persists in sediments and enters the human diet via seafood. Exposure has been detected in breast milk and umbilical cord blood. In mammals, organotin compounds demonstrate efficient gastrointestinal absorption, are distributed in lipid-rich organs, that is, the liver, adipose tissue, adrenal glands, and brain, and are primarily excreted via bile and feces. Regarding its mechanism of action, TBT disrupts endocrine and cellular homeostasis through multiple pathways. It disturbs steroid production, acting as an agonist for RXR/PPARγ to promote lipogenesis, impairs mitochondrial function, increases reactive oxygen species, disrupts Ca^{2+} balance, and induces intrinsic apoptosis. Immunotoxicity and developmental toxicity are issues of concern. The neurotoxic effects include increased blood–brain barrier permeability, localized brain accumulation, glutamate-mediated excitotoxicity, and sustained downregulation of the AMPA subunit GluA2 via NRF-1. This renders neurons Ca^{2+} permeable and vulnerable to stress. Although TBT is the most studied species, comparative findings for its metabolites, dibutyltin and monobutyltin, remain fragmentary, and chronic and life-stage-specific risks have not been fully elucidated. In this review, I have synthesized the current knowledge on environmental sources, fate, and mammalian toxicity and outlined priority areas for risk assessment.

Key words organotin compounds, tributyltin, endocrine disruption, neurotoxicity, bioaccumulation

INTRODUCTION

Organotin compounds are synthetic compounds in which organic groups are covalently bonded to a tin atom. Tributyltin (TBT) was widely used worldwide during the latter half of the 20th century as a marine antifouling paint, wood preservative, pesticide, and industrial catalyst.[1,2] It has rapidly gained popularity as a means to improve fuel efficiency in commercial and fishing vessels owing to its high anti-algal and anti-fouling activity. However, it has become clear that its bioaccumulation in aquatic ecosystems and toxicity to non-target organisms cause serious environmental problems. The phenomenon of imposex in marine gastropods was shown to occur even with trace TBT exposure, alerting the world to organotin compounds as potent endocrine disruptors.[3] Against this backdrop of environmental impacts, the use of TBT-containing antifouling paints has been banned. However, TBT remains persistent in marine sediments. Hotspots with high TBT concentrations persist, maintaining chronic exposure risks for marine organisms and higher-tier consumers, including humans.[4] There have been reports from multiple countries, including Japan, that have detected TBT and its metabolite, dibutyltin (DBT), in commercially available seafood, breast milk, and umbilical cord blood. This has raised concerns that exposure pathways from the environment to humans pose a realistic health risk.[5] Organotin compounds have extremely high lipophilicity and environmental persistence because of their chemical structure, potentially causing long-term and irreversible biological effects through accumulation in fatty tissues. In recent years, the range of organisms affected by organotin compounds has expanded from aquatic invertebrates to mammals and higher animals, including humans. The multifaceted biological and toxicological effects of TBT, such as endocrine disruption, mitochondrial toxicity, immunosuppression, and neurological dysfunction, have been reported both *in vitro* and *in vivo*. TBT's function as an agonist for the retinoid X receptor (RXR) and peroxisome proliferator-activated receptor gamma (PPARγ) suggests links to human chronic diseases such as metabolic disorders, obesity tendencies, and developmental disorders. This necessitates toxicity assessment based on the new paradigm of environmental obesogens.[6] Organotin compounds have biological activity that can interfere with diverse physiological functions even at extremely low concentrations. They also degrade slowly in the environment, making them a group of substances that continue to raise concerns regarding their impact on living organisms. Therefore, a pre-

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cise understanding of their toxicity mechanisms at the molecular and cellular levels and the reconstruction of risk assessments for mammals, especially humans, is essential for future chemical management policies.

To date, studies on the toxicity of organotin compounds have primarily focused on acute toxicity assessments in aquatic invertebrates and fish. A full understanding of their effects on mammals, particularly higher vertebrates, including humans, remains elusive. Many existing studies are heavily biased toward TBT, and toxicity information on other organotin compounds such as DBT, monobutyltin (MBT), and triphenyltin (TPT) remains fragmentary. Therefore, there are still limitations in predicting toxicity based on chemical structure and in achieving an integrated understanding of structure-activity relationships (SAR). Many existing toxicity tests rely on animal model studies based on high-concentration, short-term exposure, which are insufficient for evaluating the chronic effects under low-dose, long-term exposure conditions occurring in the environment. Highly lipophilic organotin compounds readily accumulate in adipose tissue,[7] and minimal exposure may cause long-term irreversible effects. Despite the potential for such exposures to cause long-term effects on the homeostasis of the endocrine, nervous, and immune systems during sensitive life stages such as the fetal and developmental periods, risk assessment for these effects remains inadequate. This review aims to organize the status and challenges toward an understanding of the toxicity mechanisms in mammals, focusing on TBT and comparing it with other organotin compounds.

CLASSIFICATION AND CHEMICAL STRUCTURE OF ORGANOTIN COMPOUNDS

Organotin compounds are organometallic compounds with a structure in which one to four organic groups (primarily alkyl or aryl) are bonded to a tin atom. They are classified based on the number of bonds as MBT, DBT, TBT, and tetraalkyltin. Compounds containing aryl groups such as TPT are classified as triaryltins. From an environmental toxicological perspective, TBT and its metabolite, DBT, are of particular concern. TBT contains three butyl groups, which exhibit high lipid solubility and biological membrane permeability. It exerts diverse toxic biological effects, including endocrine disruption. TBT undergoes stepwise hydrolysis in the environment, metabolizing to DBT and MBT,[8] which exhibit toxicity in mammals.[9] In contrast, tetraalkyltins have relatively little biological activity or toxicity. In contrast, TPT is an aromatic organotin with three phenyl groups and has partly different toxicity profile than TBT. TPT is particularly toxic to the liver, hematopoietic system, and nervous system. Although highly lipophilic, they have different characteristics from TBT in terms of metabolic degradability and membrane permeability.[10] These organotin compounds are analyzed from the perspective of SAR, where the type (butyl group vs. phenyl group) and number of organic groups likely directly influence the toxicity intensity and mechanisms of action. Therefore, organotin compounds can be classified based on their chemical structures. Their toxicity profiles and environmental behaviors depend strongly on their molecular structures. To understand the biological toxicity of organotins, classification based on their chemical structure and the associated organization of physicochemical properties is essential.

USES, SOURCES, AND RELEASE PATHWAYS

Organotin compounds have been used in diverse industrial applications since the mid-20th century owing to their antibacterial, antifouling, and preservative properties. TBT has been widely introduced in ports worldwide since the 1950s as the primary component of commercial ship-bottom coatings, namely, antifouling paint. Although TBT effectively suppressed the growth of fouling organisms, contributing to the maintenance of navigation efficiency and improving fuel economy, its high biological toxicity has severe impacts on non-target organisms. Therefore, it became subject to regulations in many countries from the 1990s onward. Beyond hull coatings, organotin compounds have diverse applications such as wood preservatives (TBT and DBT) for anti-fouling and insect prevention, pesticides (fungicides and insecticides) for fruit trees and crops (TPT and TBT), thermal stabilizers for polyvinyl chloride (MBT and DBT), and industrial catalysts/polymerization aids used in organic synthesis (DBT and MBT). Through these applications, organotin compounds can be released into the environment via diverse pathways. The major release pathways are as follows: 1. direct marine release from paint abrasion and peeling; 2. runoff from farmlands and forests; 3. discharge via urban drainage systems from industrial effluents and sewage treatment plants; and 4. leaching from degraded plastic products.[11] TBT and TPT persist long-term in sediments and coastal deposits around ports and shipyards.[12] Given the broad applications of organotin compounds and their mobility and transformation in the environment, they represent a substantial exposure source to humans and ecosystems through diverse pathways. Therefore, understanding their actual emissions and dynamics is critical as a foundation for toxicity assessments and regulatory strategies.

ENVIRONMENTAL FATE (TRANSPORT, DEGRADATION, ACCUMULATION)

Owing to their chemical and biological properties, organotin compounds exhibit complex migration, degradation, and accumulation behaviors in water bodies, sediments, and living organisms. Understanding the dynamics of each environmental component is essential for assessing toxicity. In aquatic environments, organotin compounds are primarily adsorbed onto particulate matter, settle, and often persist long-term in bottom sediments. TBT and TPT are highly hydrophobic and have extremely low water solubility. This causes them to bind to particles relatively quickly in water and migrate to sediment. TBT in these sediments is resistant to hydrolysis under anaerobic conditions, with half-lives extending to several years.[13] Conversely, in aerobic environments where oxygen is present, microbial hydrolysis proceeds, leading to the stepwise degradation of TBT, DBT, and MBT. However, the rate of this degradation is highly dependent on environmental conditions, that is, temperature, pH, and organic matter content.[14] In the soil, organotin compounds readily bind to clay minerals and organic matter, limiting their mobility and resulting in low degradability. Organotin compounds originating from agricultural and industrial activities persist in surface soils and groundwater systems, raising concerns as localized sources of soil contamination have been reported.[15] Therefore, the mobility, degradability, and bioaccumulation of organotin compounds in the environment vary depending on the environmental conditions.

Environmental monitoring and exposure assessments require the development of environmental fate models that consider interactions between the characteristics of each compound and the local environment.

EXPOSURE VIA BIOACCUMULATION AND FOOD CHAINS

Organotin compounds are highly lipophilic and do not degrade readily in the environment. Therefore, they tend to accumulate over time in organisms after being taken up by the environment. TBT and TPT have high bioconcentrations and bioaccumulation factors,[16] raising concerns about the exposure pathways through the food chain, from aquatic organisms to terrestrial predators, and ultimately to humans. In aquatic ecosystems, TBT first accumulates in plankton and benthic invertebrates, and then becomes concentrated in fish, seabirds, and mammals. Studies have detected high concentrations of TBT in the liver, kidneys, and muscles of fish, observing trophic magnification, where concentrations increase with predatory levels.[17] TBT has been detected in the livers of marine mammals, such as dolphins and seals, indicating that exposure is progressing, including in organisms higher up the food chain.[18] Human exposure is primarily thought to occur through the consumption of seafood. TBT and DBT have been detected in seafood products distributed in the markets of various countries, including Japan, and chronic dietary intake of TBT is possible.[5,19] TBT can be detected in breast milk, umbilical cord blood, and the placenta.[20] Organotin compounds move and accumulate throughout the food chain in the environment, accumulating in top predators, including humans. Consequently, they should be recognized not only as local pollutants but also as chemicals posing exposure risks on a global scale. Unlike acute toxicity, the effects of chronic low-dose exposure to food sources are less visible and difficult to assess, making coordination with environmental monitoring and food safety policies essential.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION (ADME)

Organotin compounds are primarily taken up by mammals via oral exposure. Highly lipophilic compounds, such as TBT and TPT, readily pass through the cell membranes of intestinal epithelial cells, resulting in relatively high absorption rates from the small intestine.[21] Animal studies indicate that approximately 30–80% of orally administered TBT is absorbed, depending on the compound's lipophilicity, dose, and solvent conditions.[22] In addition to oral routes, dermal absorption and inhalation exposure have been reported.[23] However, their contribution is generally lower than that of oral exposure. In human worker exposure models, the dermal absorption of TBT is considered limited.[24] However, absorption cannot be ruled out under conditions of prolonged contact or the presence of wounds. Exposure studies in laboratory animals have also reported their uptake via inhalation. Nevertheless, the low volatility of TBT and TPT suggests that respiratory exposure in daily environments is likely to have a limited impact. Placental transfer is of particular concern regarding absorption during pregnancy. Studies in rats and mice have reported that orally administered TBT is transferred to the fetus, affecting body weight, and neurodevelopment.[25,26] Consequently, the importance of the gastrointestinal absorption pathway has been emphasized from the perspective of fetal exposure.

The absorbed organotin compounds are transported via the bloodstream to tissues throughout the body. Animal studies using rats and mice have shown that TBT and TPT, which are particularly lipophilic, are preferentially distributed to high-fat organs such as the adipose tissue, liver, adrenal glands, kidneys, and testes.[27] In the liver and kidneys, these compounds come into contact with enzyme systems involved in metabolism and excretion, making these organs potential targets for toxicity. The liver is the central organ where the accumulation and metabolism of organotins occur. In TBT exposure experiments in mice, liver concentrations significantly exceed blood concentrations, suggesting a high concentration and accumulation potential.[27] Distribution to the central nervous system (CNS) has been observed, with TBT migrating into lipid-rich brain tissue and the spinal cord.[28] This finding is critically important for investigating the potential links to neurotoxicity and developmental toxicity. TBT crosses the placental barrier and is transferred to the fetal liver, brain, gonads, and other tissues.[26] When pregnant mice were orally administered TBT, fetal TBT concentrations were equivalent to or higher than maternal levels, suggesting potential direct effects on developing tissues.[29] Furthermore, lactational exposure of infants via breast milk has been noted. TBT transfer into milk, which has a high fat content, may pose a long-term toxicity risk to newborns.[30] Therefore, organotin compounds are distributed widely throughout the body and selectively accumulate in developing and highly sensitive organs. Understanding their distribution is crucial to elucidating their toxicity mechanisms.

Organotin compounds taken up by mammals undergo enzymatic metabolic reactions primarily in the liver. TBT undergoes stepwise debutylation, converting it into DBT and MBT. This process is likely mediated by cytochrome P450 enzymes,[31,32] but the detailed underlying mechanism remains unclear. This metabolic pathway does not necessarily signify detoxification. Rather, intermediate metabolites like DBT exhibit adipogenic and immunosuppressive effects, raising concerns about secondary toxicity from metabolites.[33] The metabolic rate of TBT and the accumulation of intermediates are significantly influenced by species differences, sex differences, age, and individual variations in enzyme activity. Relatively rapid metabolism has been reported in rats, whereas the debutylation reaction in the human liver may be limited.[34] During pregnancy and development, the detoxification enzyme systems are less well developed, leading to substantially reduced metabolic capacity in fetuses and newborns. This poses the risk of TBT being retained in the body for extended periods. In contrast, TPT is thought to follow different metabolic pathways than TBT, with the stability of its aromatic structure contributing to a slower metabolism. TPT exhibits a slower metabolism in both humans and experimental animals, potentially leading to long-term accumulation in the body. This differs from TBT's toxicity characteristics and warrants attention.[34] Future research should focus on identifying the metabolic enzymes for each compound, assessing metabolic rates, and evaluating the biological activities of the metabolites.

The primary excretion pathway for organotin compounds is fecal excretion via bile and feces. Lipid-soluble organotins such as TBT and TPT are metabolized in the liver and excreted into bile, being eliminated from the body through the

digestive tract.[23] This pathway aligns with typical excretion patterns observed for highly lipid-soluble organometallic compounds. In contrast, urinary excretion is relatively low.[23] This is thought to be due to low-polarity compounds, such as TBT and TPT, which have low filtration efficiency by the renal glomerulus and low excretion efficiency in the renal tubules. However, not highly lipophilic tins, such as MBT and inorganic tin, exhibit a relatively higher urinary excretion rate. The time required for excretion, that is, the biological half-life, varies substantially depending on the compound type, animal species, tissue, and exposure conditions. In animal studies, the half-life of TBT in the liver ranges from 2 to 10 d, whereas in the adipose tissue, it can extend to several weeks or more.[35] TPT persists in the body for even longer periods, making delayed excretion a critical factor for assessing its chronic effects.

Although there are no direct reports on organotin compounds, it is possible that organotin compounds undergo enterohepatic circulation. In this pathway, chemicals secreted into bile are reabsorbed in the small intestine and returned to the liver, prolonging their residence time in the body. This circulation is characteristic of lipophilic compounds and is a factor contributing to the long-term persistence of chemicals in the body. Excretion capacity is also influenced by physiological factors such as age, sex, enzyme activity, and nutritional status. Concern exists for pregnant or lactating individuals and neonates, where underdeveloped bile secretion and renal function may reduce excretion efficiency and increase the accumulation risk. Therefore, the slow excretion of organotin compounds is a key factor contributing to their long-term persistence in the body. Exposure assessment must consider acute toxicity, accumulation potential, and chronic toxicity.

The ADME characteristics of organotin compounds vary substantially among animal species and individuals, making them critical factors for toxicity and risk assessments. While the absorption and metabolism of TBT are relatively rapid in laboratory animals, humans have a lower metabolic capacity, posing a risk of retention. In fish and amphibians, absorption occurs primarily through the skin and gills, resulting in toxicity profiles distinct from those of mammals. Differences in metabolic enzyme expression and detoxification capacity exist based on sex, age, and developmental stage, with fetuses and juveniles being particularly susceptible. Genetic background, nutritional status, and liver disease also influence ADME and increase the accumulation risk. Therefore, health impact assessments require the use of individualized models and IVIVE rather than simple extrapolation from animal test data.

ENDOCRINE DISRUPTING EFFECTS

Organotin compounds, particularly TBT, have diverse and severe effects on the mammalian endocrine system. Their mechanism of action primarily involves two axes: inhibition of steroid hormone synthase activity and potent agonistic effects on nuclear receptors. Regarding effects on steroid hormone synthesis, TBT and DBT suppress the expression and activity of cytochrome P450 enzymes in Leydig cells and adrenal cortical cells.[36] This leads to a substantial reduction in testosterone and estradiol production. Male rats exposed to high-dose TBT exhibit reduced testicular weight, impaired spermatogenesis, and a marked decrease in blood testosterone levels.[37] In vitro reporter assays have shown that TBT exhibits agonist-like activity toward nuclear receptors, particularly the retinoid X receptor (RXR) and peroxisome proliferator-activated receptor gamma (PPARγ).[38,39] RXR and PPARγ are responsible for transcriptional control in diverse physiological processes such as lipid metabolism, glucose metabolism, sexual differentiation, and development. Excessive activation by TBT is likely involved in disrupting endocrine homeostasis and promoting adipocyte differentiation, that is, the obesogen hypothesis, and fetal developmental abnormalities.[39,40] TBT-induced RXR activation possibly causes widespread transcriptional abnormalities across multiple hormonal systems because of the functional characteristics of RXR-forming heterodimers with other nuclear receptors, such as the vitamin D receptor and thyroid hormone receptor. This implies that TBT's effects extend beyond a single endocrine axis, affecting multiple systems, including the hypothalamic–pituitary–gonadal (HPG) axis and hypothalamic–pituitary–adrenal (HPA) axis.

Female rats exposed to TBT during pregnancy exhibited altered expression of sex hormone receptors, demonstrating that TBT interferes with developmental endocrine control networks. These effects have also been linked to reduced reproductive function and metabolic abnormalities in adulthood, making long-term impact assessment of developmental exposure a critical future research priority. Therefore, the endocrine-disrupting effects of organotin compounds, particularly TBT, affect multi-stage physiological functions spanning reproduction, development, and metabolism through a dual mechanism involving enzyme activity inhibition and nuclear receptor activation. Because the endocrine system responds sensitively to even minor molecular changes, chronic exposure to organotins carries a risk of causing biological dysfunction than acute toxicity.

OXIDATIVE STRESS AND APOPTOSIS

Organotin compounds exert broad toxicity on mammalian cells both through endocrine disruption and by inducing oxidative stress and activation of apoptosis (cell death). TBT has been shown in multiple studies involving neurons, immune cells, and endocrine cells to cause excessive production of reactive oxygen species (ROS) via mitochondrial dysfunction.[41-43] TBT induces a decrease in mitochondrial membrane potential, leading to inhibition of ATP production and disruption of calcium homeostasis. Therefore, mitochondria become a primary source of ROS while becoming highly vulnerable to oxidative damage. TBT exposure suppresses the activity of antioxidant enzymes, including SOD, catalase, and glutathione peroxidase, leading to a substantial disruption of the intracellular redox balance.[41,44] Oxidative stress causes oxidative damage to DNA, proteins, and lipids essential for maintaining cellular homeostasis and also functions as an inducer of apoptosis via the mitochondrial pathway. TBT promotes the release of cytochrome c from mitochondria, leading to apoptosome formation in the cytoplasm and the activation of caspase-3.[41-43,45]

TBT interferes with the expression of Bcl-2 family proteins involved in apoptosis regulation, inducing a decrease in the expression of the anti-apoptotic protein (Bcl-2) and an increase in the expression of the pro-apoptotic protein (Bax), elevating the Bax/Bcl-2 ratio. This change is a central mechanism determining the progression of apoptosis by enhancing mitochondrial membrane permeability.[46] TBT affects signaling pathways such as the MAPK, that is, ERK, JNK, and p38

pathway and the NF-κB pathway, potentially disrupting the control at the crossroads of cell survival, inflammation, and death in a multi-layered manner. The TBT-induced activation of JNK and p38 MAPK contributes to the transcription and translation of apoptosis-promoting factors. Activation of these pathways by TBT may control the precise timing and location of cell death following oxidative stress.[46,47] Therefore, organotin compounds act not only as toxicants at the receptor level, but also as multifaceted toxicants that simultaneously disrupt fundamental cellular mechanisms such as intracellular energy metabolism, antioxidant defense, and apoptosis control. Consequently, the biological response to organotin exposure should be understood not only as a specific receptor response, but rather as a breakdown of the stress response governing the overall cell fate.

IMMUNOTOXICITY AND DEVELOPMENTAL TOXICITY

Organotin compounds are chemicals that cause serious effects on the endocrine and metabolic systems, the immune system, and developmental processes. TBT have been reported to be toxic in numerous *in vivo* and *in vitro* studies, causing immune cell dysfunction and fetal developmental abnormalities. TBT and DBT suppress the functions of a wide range of immune cells, including T cells, B cells, natural killer cells, and macrophages. Studies using human peripheral blood mononuclear cells have shown that TBT strongly weakens cellular immune responses by suppressing IL-2 production, inhibiting T-cell proliferation, and inducing apoptosis.[48] Inhibitory effects on NK cell activity and macrophage phagocytic capacity have also been reported.[47] TBT exhibits toxicity toward bone marrow hematopoietic stem cells,[49] causing functional impairment and differentiation abnormalities in the precursors of immune cells. This is particularly pronounced in growing and developing individuals, potentially leading to immune system dysregulation such as reduced infection defense capacity and enhanced allergy-like responses.

The teratogenicity of organotin compounds primarily manifests as fetal endocrine disruption, neurodevelopmental disorders. Studies involving the administration of high-dose TBT to pregnant mice have shown that TBT exposure causes pregnancy abnormalities such as reduced fetal weight, increased embryo resorption, and impaired placental development. In mice administered with TBT during early pregnancy, reduced fetal weight, placental weight, and area were observed. Decreased expression of molecules involved in placental development, suppressed cell proliferation, increased apoptosis (cell death), and increased oxidative stress were observed. These changes likely contribute to fetal developmental disorders and pregnancy abnormalities.[50] Experiments administering TBT to pregnant mice and rats have reported reduced fetal weight, increased embryonic and fetal mortality, and skeletal abnormalities, such as cleft palate and rib abnormalities. These results suggest that exposure to TBT and its related compounds during pregnancy adversely affects fetal development, skeletal formation, and placental function, increasing the risk of congenital abnormalities.[51] TBT changes in reproductive organ weight, and reductions in testosterone and luteinizing hormone levels in male rats, affecting sexual development during puberty.[52] This is closely related to the aforementioned endocrine disrupting effects, suggesting that developmental toxicity may not be limited to morphological abnormalities but also includes functional impacts extending to behavior and metabolic function. Thus, organotin compounds exert multilayered toxicity, targeting the core defense and regeneration systems of living organisms, including the immune system and developmental processes.

NEUROTOXICITY

Trimethyltin (TMT) is a volatile organotin with potent neurotoxic effects. Although it was once a substance of concern for industrial hygiene exposure,[53] it is now unlikely to be encountered in environmental exposure scenarios and has therefore not been discussed here. Among the organotin compounds present in the environment, TBT and TPT exhibit neurotoxicity that causes structural and functional impairments in the mammalian CNS. In animal studies, TBT administration has been confirmed to increase blood–brain barrier permeability and tin accumulation in the brain. Accumulation has been observed in multiple brain regions, including the striatum, hippocampus, hypothalamus, and cerebellum. The striatum exhibits higher susceptibility to oxidative damage than other regions.[54]

We investigated the mechanisms underlying TBT-induced cell death in primary cultured rat cortical neurons. The results showed that 500 nM TBT rapidly increases the extracellular glutamate (Glu) concentration, and the excessive release of Glu stimulates its receptors, inducing neuronal cell death, the so-called Glu neurotoxicity.[55-57] Although Glu neurotoxicity is one of the fundamental phenomena underlying neuronal death in cerebral ischemia and certain neurodegenerative diseases, this is the first report to demonstrate that environmental chemicals induce Glu neurotoxicity at a lower concentration than micromolar. Next, we further reduced the TBT concentration and established experimental conditions in which primary cultured cortical neurons were exposed to TBT for 9 d. They attempted to identify the marker genes and proteins that detect neuronal abnormalities induced during the early stages preceding neuronal death. The results showed that 20 nM TBT specifically and persistently reduced GluA2 mRNA and protein levels.[60] GluA2 (previously known as GluR2) is a subunit of the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor and normally functions to block calcium influx into the cell. AMPA receptors containing the GluA2 subunit have low calcium permeability, and a reduction in GluA2 levels increases the calcium permeability of AMPA receptors. Measurement of the intracellular calcium concentration showed a significant increase in the group continuously exposed to 20 nM TBT. This leads to the neuronal cell death induced by Glu stimulation at concentrations that do not normally induce neuronal cell death. Although reduced GluA2 expression alone did not cause cell death, sustained reduction in GluA2 expression increased the number of calcium-permeable AMPA receptors lacking the GluA2 subunit. This renders neurons vulnerable, making them more susceptible to cell death from weak stimuli.[58] An investigation of the mechanism by which TBT reduces GluA2 showed that it decreases the activity of a transcription factor called nuclear respiratory factor-1 (NRF-1).[59] The TBT concentration required to reduce NRF-1 activity is 20 nM, which is close to the concentration detected in the brain and represents the lowest concentration among previously reported toxic effects. These findings have important toxicological implications.

TBT is also an organotin compound implicated in learning and memory impairments. Animal studies have indicated that TBT exposure causes reduced estrogen receptor alpha expression and increased oxidative stress in the prefrontal cortex and hippocampus, contributing to memory deficits.[60] TBT causes various behavioral abnormalities in rodents. Administration of TBT during the fetal period in rats resulted in hyperactivity in adulthood, along with delayed learning in spatial tasks (radial arm maze) and enhanced amphetamine-induced hyperactivity.[61] Acute TBT exposure has been confirmed to cause a dose-dependent decrease in spontaneous motor activity and inhibition of conditioned avoidance response acquisition, suggesting that TBT significantly impacts behavior.[62] In a study where TBT was administered intracerebrally to juvenile rats, an increase in spontaneous motor activity during the dark phase was observed at 4–5 weeks of age.[63] Therefore, TBT causes abnormalities in rodent behavior and neurodevelopment.

EPIGENETIC AND TRANSGENERATIONAL EFFECTS

Organotin compounds, particularly TBT, are gaining attention both as acute toxicants and as epigenetically mediated developmental toxins that exert long-term and transgenerational effects on biological functions and phenotypes. These effects are crucial for understanding non-genetic inheritance and delayed effects that cannot be fully explained using conventional toxicological frameworks. TBT activates the PPARγ pathway, increasing the expression of genes associated with adipocyte differentiation. It also promotes adipocyte differentiation by upregulating miR-223 expression. TBT exposure causes PPARγ to bind to the miR-223 promoter region, inducing its expression.[64] Chamorro-García *et al*. (2013) demonstrated that fetal exposure to TBT in mice caused increased adipose tissue, enlarged and increased adipocyte numbers, reprogramming of mesenchymal stem cells (MSCs) into the adipocyte lineage, and lipid accumulation in the liver, that is, a non-alcoholic fatty liver disease-like phenotype, with these effects being transmitted to the F3 generation.[35] TBT exposure promotes differentiation into adipocytes and suppresses osteogenesis through epigenetic memory in MSCs. The expression of genes involved in lipid storage, transport, synthesis, and breakdown was elevated in the liver. These effects are connected to multi-domain toxicological phenotypes, such as developmental toxicity, endocrine disruption, metabolic abnormalities, and neurodevelopmental disorders, and are closely related to the Developmental Origins of Health and Disease (DOHaD) hypothesis, a central issue in modern toxicology.

CONCLUSION

This review fully summarizes the current knowledge on the structural characteristics, environmental fate, and ADME properties in mammals, as well as the multi-layered toxicity mechanisms of organotin compounds, including endocrine disruption, neurotoxicity, immunotoxicity, and developmental toxicity. Organotin compounds, particularly TBT, profoundly interfere with fundamental physiological processes such as cell differentiation, proliferation, and apoptosis through abnormal agonist actions on nuclear receptors, such as RXR, PPARγ, mitochondrial dysfunction, and disruption of intracellular Ca^{2+} homeostasis. TBT may induce transgenerational phenotypic changes, such as predisposition to obesity and developmental abnormalities, via epigenetic modifications. Therefore, it should be understood not only as an acute toxicant but also as an environmental factor possessing programming toxicity. However, many aspects of organotin toxicity assessments remain inadequate. For instance, knowledge regarding compounds other than TBT (e.g., DBT and TPT) is limited, and systematic toxicity comparisons based on SAR represent a critical future challenge. There is a strong need to establish next-generation toxicity assessment methods that combine chronic/low-dose exposure models, in silico predictions, transgenerational evaluations, and omics analyses.

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