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Triclosan and Methylparaben-Induced Neurotoxicity and Cardiotoxicity in Zebrafish: Mechanistic Insights into Endocrine Disruption

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Abstract

Endocrine-disrupting chemicals are a class of chemicals that attenuate or disrupt the endocrine system. These chemicals have structures similar to endogenous hormones and thereby interfere with the body's natural hormone functioning, hampering normal homeostasis, reproduction, development, and/or behaviour. Currently, about 45 chemical substances have been identified in this category. Apart from causing endocrine disruption, these chemicals also cause disturbances in other bodily systems, including the nervous and cardiovascular systems. While the mechanisms behind endocrine disruption by these chemicals are well studied, other toxic effects, such as cardiotoxicity and neurotoxicity, are poorly studied. Zebrafish models have recently been used to study these effects owing to the developmental similarities of the neural and cardiac systems when compared to humans. These studies identify and bring out the mechanism of action of specific endocrine-disrupting chemicals on different systems of the body, using various endpoints. Our review article aims to comprehensively summarise the association of these chemicals with neural and cardiovascular dysfunction in zebrafish models, with a special focus on the effects of Triclosan (TCS) and Methyl Paraben (MP).

Keywords: Cardiotoxicity, Methyl Paraben, Neuroendocrine, Neurotoxicity, Triclosan, Zebrafish

1. Introduction

The rapid growth of population and the technological advancements have resulted in innumerable pollutants and newly synthesised compounds containing Endocrine-Disrupting Chemicals (EDCs). EDCs are exogenous chemical agents that have chemical structures similar to endogenous hormones and thereby interfere with the natural hormone functioning in the body and hamper normal homeostasis, reproduction, development, and/or behaviour in the body[1]. Several studies have examined the toxicity of EDCs on the reproductive system, thyroid, and corticoid function[2]. Recently, the association of EDCs with neural and cardiovascular dysfunction has garnered increased attention, with multiple studies performed on zebrafish (*Danio rerio*) models reporting the detrimental effects of EDCs in the neural and cardiovascular systems in both developmental and adult stages. It was reported that TCS, an EDC, used as an anti-microbial agent, delayed the development of secondary motor neurons and caused malformations of the heart at concentrations between 2 to 2.8 μM [3]. Further, parabens also exert similar effects on the neural and cardiac systems[4]. These studies are considered highly reliable due to their use of well-established *in vivo* zebrafish models, which are recognised for their small size, defined genetic background, high reproductive capacity and most importantly, the close resemblance of their molecular pathways and physiological processes to those of humans[5]. Further, the similarity in the development of the blood-brain barrier when compared to humans and the technological development that allows non-invasive imaging in *in vivo* analyses of cardiovascular phenotypes are additional features that validate the use of zebrafish models in studying cardiovascular and neural diseases,

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respectively[6,7]. Our review article aims to comprehensively report the association of EDCs with neural and cardiovascular dysfunction in zebrafish models, with a special focus on the effects of triclosan and methylparaben.

2. Effects of EDCs on Neural Functioning

The nervous and endocrine systems work together in a process known as neuroendocrine integration to control the body's physiological processes. Harmful chemicals like EDCs disrupt the normal functioning of the endocrine system and thus lead to dysfunction of the nervous system, resulting in neurodevelopmental or behavioural disorders. EDCs have the potential to interfere with the production, transportation and release of numerous neurotransmitters—including serotonin, dopamine, glutamate, and norepinephrine—critical for regulating memory, learning, cognition, and behaviour[8]. Moreover, neurons often have steroid hormone receptors simultaneously at different stages of development, making them susceptible targets for EDCs[9,10]. EDCs that affect steroid-sensitive pathways in the brain can influence cognition, learning, memory, and other behaviours not related to reproduction, such as metabolism, along with reproductive neuroendocrine systems. Various types of EDCs employ different modes of action to induce neurotoxicity during different developmental stages, which are again dose dependent.

2.1 Neurotoxic Effect of Triclosan

Triclosan (TCS), a frequently used EDC in personal care products, causes nervous system disorders. In a study, zebrafish embryos exposed to TCS concentrations (control, 62.5, 125, and 250µg/L) led to increased vacuoles in the midbrain glia after 7 days[11]. At 96 h post-fertilisation (pf), treated zebra fish exhibited significant reductions in body length, head size, forebrain size, and eye size compared to the control[12]. In the 48-h post-fertilisation (hpf) larvae, spine bending increased with higher TCS-exposure concentrations. Behavioural analysis during the light-dark stimulation test revealed reduced daytime swimming activity and nighttime anxious behaviour in TCS-exposed larvae, indicating disruption of crucial neural activities, such as circadian rhythm[11]. Moreover, exposing larvae to sub-lethal concentrations of TCS for 4 days led to a reduced Touch-Evoked Escape Response (TEEK), indicating potential motor dysfunction. Fish exposed to TCS exhibited decreased acetylcholinesterase (AChE) activity and downregulation of AChE and synapsin IIa (syn2a) genes. The downregulation of the ache gene and AChE inhibition may disrupt cholinergic transmission, affecting acetylcholine receptors, while downregulation of the syn2a gene may interfere with vesicle trafficking at presynaptic terminals. These findings suggest that abnormal neuronal signalling may contribute to the observed reduction in the escape response, highlighting the need for further investigation into the molecular mechanisms behind TCS-induced neurotoxicity and behavioural dysfunction[13] (Figure 1).

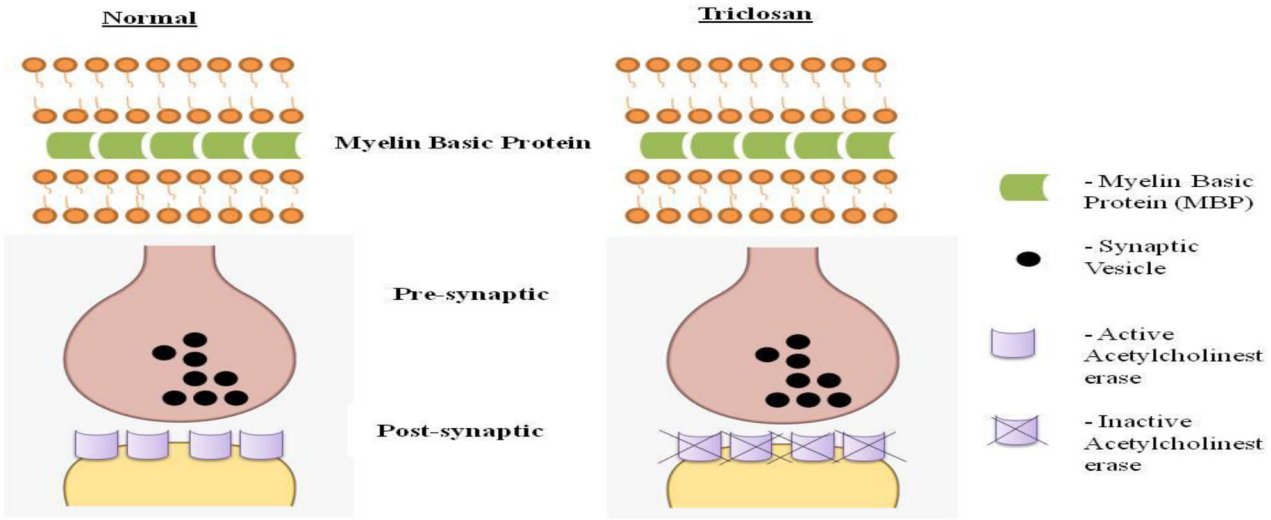


Figure 1. Mechanism of Triclosan-induced neurotoxicity.
Inhibition of acetylcholinesterase caused by triclosan results in dysfunctional cholinergic transmission, which leads to uncoordinated movement and other behavioural changes.

2.2 Molecular Mechanisms of Methylparaben-Induced Toxicity

Methylparaben (MeP) induces molecular and physiological alterations in zebrafish, primarily through the disruption of endocrine functions and modification of gene expression. Exposure to MeP results in significant developmental deformities, increased cell death and alterations in metabolic pathways, collectively impacting growth and behaviour in zebrafish models. MeP activates the zebrafish estrogen receptor (zfERβ2), disrupting steroid hormone production and metabolism, as evidenced by elevated levels of vitellogenin and estradiol[14]. Prolonged exposure affects neuroendocrine factors, influencing serotonin levels and acetylcholinesterase activity, both crucial for neurodevelopment and behaviour[15]. MeP exposure alters the expression of genes linked to cell cycle regulation (ccnd1) and cancer development (myca), suggesting potential long-term effects on cellular processes[16]. Changes in gene expression related to metabolic pathways, such as tyrosine and arachidonate metabolism, imply a broader impact on the physiological functions[14]. Zebrafish exposed to MeP exhibit increased anxiety-like behaviours and altered locomotor activity, particularly in females, indicating sex-specific responses to endocrine disruptors[15]. Research on developmental toxicity shows that MeP leads to higher rates of malformations and impaired heart functions, highlighting its detrimental effects on embryonic development[17]. Conversely, while MeP is recognised for its endocrine-disrupting effects, some studies suggest its acute toxicity may not be as pronounced compared to other parabens, emphasising the need for further research on chronic exposure effects and potential recovery mechanisms in zebrafish[16,18].

2.3 Neurotoxic Effects of MeP

Parabens are another common class of EDCs used as preservatives in cosmetic and personal care products. Among these, Methylparaben (MeP) is one of the widely used sub-classes, owing to its anti-fungal activity. Exposure to MeP has been shown to cause several neurodevelopmental defects in zebrafish models, with notochord curvature being the fundamental one. Notochord deformity is viewed as a fundamental neurodevelopmental defect, as it is an important structure in the neuroectoderm, and it functions to signal the formation of the floor plate and motor neurons. Further, the notochord is also involved in the patterning of other tissues such as sympathoadrenal progenitors and the left-right asymmetry of the heart tube[19]. Recent studies have reported that the zebrafish embryos exposed to 10 mg/L of MP showed notochord curvature at 72 h pf, while the hatched larvae treated with 30 mg/L of MeP at 72 h pf showed notochord curvature and tremor behaviour with head, pectoral fins, and spine tremors compared with the negative control group[20]. This behavioural phenotype is identical to tremor behaviour evoked by neurotoxic drugs such as pentylenetetrazole and Domoic Acid (DA), which act on GABA-A receptors and glutamate receptors, respectively[21]. Further, MP-treated larvae have also shown an increase in anxiety-like behaviour and decreased exploratory behaviour in novel tank diving tests, highlighting the role of methylparaben as an anxiogenic agent causing neuronal dysfunction. These changes in behaviour are associated with increased cortisol levels and decreased acetylcholinesterase (AChE) activity[22]. AChE is the principal enzyme that degrades Acetylcholine (Ach) in the brain and limits the concentrations of Ach in the neuronal synapse. Reduced activity of AChE, as observed in MP exposure, leads to increased Ach activity, which is proven to be positively correlated with increased anxiety and depression, explaining the observed anxiety-like behaviour in the zebrafish[23]. Further studies are required to understand the mechanistic role of methylparaben in altering AChE activity and cortisol levels in parallel with neurobehavioural and neurodevelopmental activities.

3. Effects of EDCs on Cardiac Functioning

Hormones play a crucial role in cardiac development, and exposure to EDCs during embryogenesis can have lasting effects, potentially impacting the organism's overall fitness. Disruption of endocrine pathways at sensitive life stages can lead to significant changes in cardiac development, resulting in both lethal and sub-lethal effects that may only become apparent in later life stages. Studies on zebrafish models, chosen for their similarity in early cardiac development to mammals, have been conducted to explore the effects of various EDCs on cardiac functioning. Additionally, the advantage of zebrafish models lies in their independence from a functional cardiovascular system during the first 5 days of development, allowing for phenotypic analysis following genetic alterations or chemical exposure[24].

3.1 Cardio-Toxic Effects of TCS

Studies using zebrafish models exposed to varying TCS concentrations revealed notable heart-related phenotypic defects in 72-h Post-Fertilisation (hpf) larvae, with a dose-response relationship. Treatment with 0.28 mg/L of TCS led to a slight Pericardial Cyst (PC), while 0.56 mg/L resulted in severe yolk retention, PC, and Sinus Venous (SV) bleeding. Models treated with 0.84 mg/L exhibited prominent dysplasia, including severe PC, SV bleeding, closure of swim sac (SS), ear capsule, and otolith differentiation defects. Moreover, Superoxide Dismutase (SOD) levels were significantly higher in the 0.14 and 0.28 mg/L treatment groups but lower in the 0.56 mg/L treatment group[25]. Changes in this antioxidant enzymatic activity indicate damage to cardiomyocytes, implying the presence of myocarditis—a common feature in various heart diseases[26]. The same study revealed that TCS exposure significantly reduced the expression of the cardiac progenitor cell marker nkx2.5, disrupting cardiac progenitor cell differentiation and initiating abnormal myocardial growth, leading to ventricular morphology destruction. Furthermore, the Ventricular Myosin Heavy Chain (vmhc) gene, essential for ventricular development, and the Atrial Myosin Heavy Chain (amhc) gene, involved in atrial muscle contraction, were both down-regulated following TCS exposure. This indicates structural and functional damage to both the atria and ventricles. Various signalling pathways, including adrenergic signalling in cardiomyocytes, the cyclic AMP (cAMP) signalling pathway, and pentose-glucuronate interconversions, were implicated in the cardiotoxicity. These effects were directly linked to dysregulated transcription levels of cardiac development-related genes such as ugdh, sox9b, ppp2r3a, and camk2a as shown in Figure 2 [25] (Figure 2).

3.2 Cardio-Toxic Effect of MeP

Phenotypic defects observed in zebrafish due to TCS exposure were also evident with MeP exposure. Cardiac developmental defects, particularly decreased heart rate and a cascade of other phenotypic defects, were observed in zebrafish models exposed to MeP. The reduction in heart rate can be noticed early in zebrafish development, starting at 22 hpf with the beating of the heart tube, and culminating in a fully functional cardiovascular system by 48 hpf[27]. It is demonstrated that even at low concentrations of 100 µg/L MP exposure, there is a decrease in heart rate and blood flow at 48 hpf[22]. The decreased heart rate is attributed to abnormal contraction of cardiomyocytes, as reflected in the significant reduction of molecular expression in ATPase-related genes, calcium channel-related genes, and

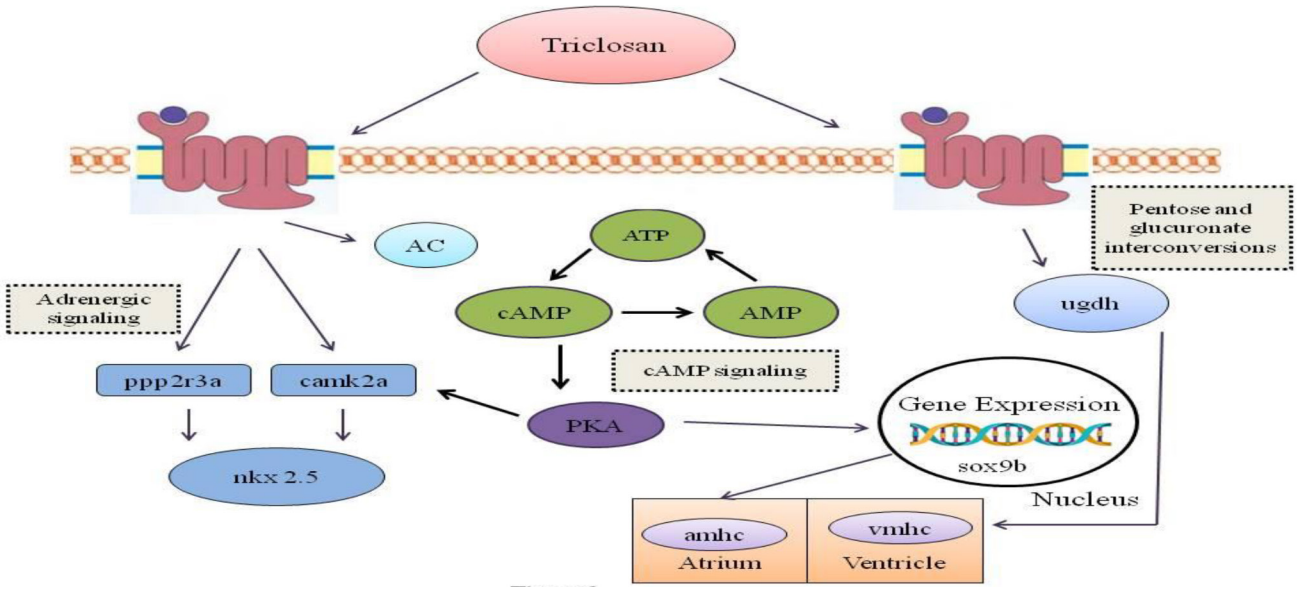


Figure 2. Mechanism of triclosan-induced cardiotoxicity.
Triclosan interferes with multiple pathways, including adrenergic signalling, cAMP signalling, and pentose/glucuronate interconversions, leading to abnormal expression of several significant genes such as nkx2.5, vmhc, and amhc genes. This abnormal signalling and impaired gene expression result in defects during heart formation. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; vmhc, Ventricular myosin heavy chain; amhc, arterial myosin heavy chain.

regulatory genes for cardiac troponin C after zebrafish exposure to MP[28,29]. Additionally, the reduction in the heart rate can be associated with reduced nitric oxide because of MP exposure, as reported by several studies[16,30]. Nitric oxide, being a vasoactive substance that regulates vascular tone in zebrafish embryos, may play a major role in MP-associated cardiotoxicity in zebrafish. Additionally, the notochord curvature as a result of MP exposure may also have a key effect on cardiac dysfunction, as notochord is responsible for the patterning of left-right asymmetry in the heart tube. Further, reduced heart rate and decreased blood flow amplify cardiac dysfunction as the flow of blood through the heart is essential for the formation of heart shape and cardiac contractility, forming a circularity of cardiac malformation[19] (Figure 3).

3.3 Role of Hormonal Pathways in Neurodevelopment and Cardiac Function

Hormones such as androgens, estrogens, and thyroid hormones play a pivotal role in the regulation of neurodevelopment and cardiac function, especially in vertebrate models like zebrafish (*Danio rerio*). Zebrafish are widely used for toxicological studies due to their conserved genetic pathways and rapid development, making them ideal for evaluating the effects of Endocrine-Disrupting Chemicals (EDCs). Among these, Methylparaben (MP) and Triclosan (TCS) have emerged as key environmental contaminants that adversely affect endocrine signalling and downstream developmental processes.

3.3.1 MeP and Hormonal Disruption in Zebrafish

MeP exposure in zebrafish has been correlated with significant disruptions in both cardiac and neurological development. Studies have demonstrated that MeP alters the levels of neuroendocrine markers such as AChE and serotonin, which are crucial for synaptic function and neural integrity[15]. Furthermore, MeP modifies the expression of genes involved in cardiac hypoxia responses and neuronal differentiation, including the upregulation of *myca* and *ccnd1*, suggesting a disruption in cellular proliferation and stress adaptation mechanisms.

3.3.2 Triclosan Effects on Thyroid Hormone and Estrogen Signalling

Triclosan primarily targets the thyroid hormone axis, leading to hyperplasia and functional inactivation of thyroid tissues. Given the critical role of thyroid hormones in metabolic regulation and neurogenesis, this interference has profound implications for cardiac and neural development[31]. TCS has also been shown to impair skeletal muscle development and calcium ion (Ca^{2+}) signalling—processes essential for cardiac contractility and muscle function[29]. These effects reflect a broader

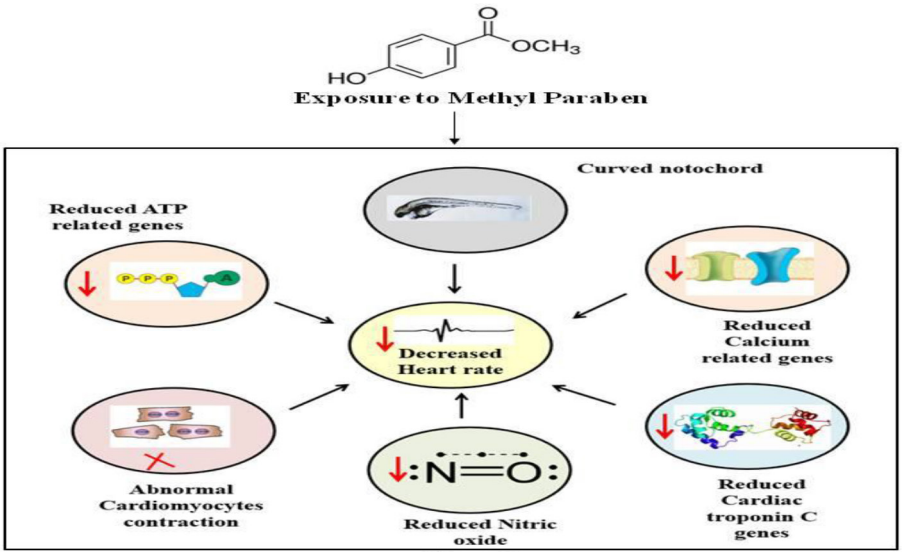


Figure 3. Potential mechanisms of methylparaben-induced cardiotoxicity.
Methylparaben induces cardiotoxicity in the form of reduced heart rate through these mechanisms: reduction in ATP-related genes; calcium-related genes, cardiac troponin C genes, nitric oxide, abnormal cardiomyocyte contraction, and curved notochord formation.

systemic toxicity extending beyond the thyroid gland. Although less prominently, TCS also influences estrogenic signalling. It has been reported to modulate estrogen-responsive gene expression in zebrafish embryos[32], suggesting potential crosstalk between thyroid and sex hormone pathways. Since estrogens and androgens play regulatory roles in both cardiovascular physiology and neurodevelopment, such disruptions may exacerbate the developmental toxicity caused by EDC exposure.

4. Conclusion

The endocrine system, vital for regulating metabolism, development, heart rate, and blood pressure, relies on hormones like androgen, estrogen, and thyroid. These hormones signal to specific receptors and interact with other pathways, contributing to the complexity of induced signalling cascades. As a result, the impact of Endocrine-Disrupting Chemicals (EDCs) on the endocrine system is evident in interconnected pathways. Examining the molecular impacts of EDCs on organisms, especially during development, is challenging due to the complexity of endocrine-regulated pathways and intricate cellular processes. The assessment of toxicity during these complex stages presents additional difficulties. Despite various studies demonstrating hormonal effects on development, the specific molecular pathways underlying these phenotypic effects remain unclear. Utilising the zebrafish as a model organism helps bridge research gaps. This species is widely used for developmental and toxicological studies, contributing significantly to our understanding of the neurotoxic and cardiotoxic effects of EDCs like triclosan and methylparaben. Both substances exhibit not only endocrine-disrupting effects but also neurotoxic and cardiotoxic effects. However, pinpointing the specific pathway affected by these toxicants is particularly challenging due to substantial crosstalk between endocrine pathways.

Future research is needed to match the molecular events of toxicity to a specific time point in the very complex timeline of development. Zebrafish models, along with other *in vitro* models, can effectively aid in this process. A comprehensive mechanistic understanding of how EDCs induce neurotoxic and cardiotoxic effects in zebrafish will enhance our ability to assess the impact of environmental contaminants on human health, contributing to human well-being.

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6. Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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