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Thyroid, neurodevelopmental, and kidney toxicities of common organic UV filters in embryo-larval zebrafish (*Danio rerio*), and their potential links

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ABSTRACT

Organic UV filters (OUVFs) have been commonly used in sunscreen and many consumer products. Following dermal application, these compounds can enter circulation and may cause systemic effects in humans. In the present study, we chose four OUVFs frequently detected in the environment, i.e., avobenzone (AVB), benzophenone-3 (BP-3), octocrylene (OC), and octyl methoxycinnamate (OMC), and evaluated their thyroid, neurodevelopmental, and kidney toxicities. For this purpose, zebrafish embryos (<4 h post fertilization, hpf) were exposed to sublethal concentrations of AVB, BP-3, OC, or OMC until 120 hpf. Exposure to all OUVFs decreased thyroid hormone (TH) levels, probably by enhanced metabolism and excretion of THs (*ugt1ab* and/or *sult1 st5*) in the larval fish. Exposure to the OUVFs also induced hypoactivities and/or anxiety-like behaviors: Regulatory changes of *mbp*, *gfap*, *c-fos*, *syn2a*, *sty1a*, and *stxbp1b* genes, support the changes in normal neurobehavior of the larval fish. Moreover, the OUVFs exposure caused increased proteinuria in the fish, along with transcriptional changes of *wt1*, *nephrin*, *podocin*, and *cdh17* genes, which could explain the observed reduction in kidney functions. Principal component analysis (PCA) implied the potential interplay of THs with neurogenesis, or podocyte differentiation of the larval fish. Toxicological consequences of altered TH homeostasis, neurobehavior, and kidney function at the early life stage warrant further investigations not only in humans but also in aquatic ecosystems.

1. Introduction

Due to growing public awareness of the harmful effects of ultraviolet (UV) irradiation, sunscreen products have been increasingly used over the past decades (Geoffrey et al., 2019). These products contain a variety of chemicals collectively called UV filters, which absorb or reflect UVA and UVB radiations (Sánchez-Quiles and Tovar-Sánchez, 2015). Avobenzone (AVB), benzophenone-3 (BP-3), octocrylene (OC), and octyl methoxycinnamate (OMC) are among the major organic UV filters (OUVFs) that have been widely used in numerous consumer products (Karthikraj and Kannan, 2018; Kwon and Choi, 2021; O'Malley et al., 2021).

Following consumer applications, UV filters can reach the aquatic environment through multiple pathways, including recreational activities and domestic wastewater inputs (Kwon and Choi, 2021; O'Malley et al., 2021). Consequently, AVB, BP-3, OC, and OMC have been detected in ambient water, e.g., marine and freshwater, at average concentrations ranging up to 0.2, 20.5, 172.0, and 7.6 μg/L, respectively (Bratkovics et al., 2015; Cadena-Aizaga et al., 2022; Sousa et al., 2019). Serious adverse effects have been reported for several OUVFs in aquatic ecosystem, which include coral bleaching and mortality (Paredes et al., 2013; Watkins and Sallach, 2021), growth retardation (Tao et al., 2023),

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and reproduction damages (de Paula et al., 2022; Li et al., 2023) in marine and freshwater organisms. Moreover, in humans, following dermal application, OUVFs can penetrate the skin and easily reach the bloodstream at levels that warrant caution (Matta et al., 2020). BP-3, OC, and OMC have been reported in the urine of general populations at levels up to 180.3, 74.3, and 0.58 μg/g creatinine, respectively (Bury et al., 2023; Chen et al., 2024; Markogiannaki et al., 2014). While AVB has rarely been assessed in the general human population, urinary concentration of AVB has been detected up to 11 μg/g creatinine following dermal applications under a real-life exposure scenario using a commercial sunscreen in an experimental study employing human volunteers (Hiller et al., 2019).

Increasing epidemiological evidence suggests that some OUVFs could affect the endocrine system, and possibly normal behavior and kidney functions (Kang et al., 2019; Oral et al., 2020; Wnuk and Kajta, 2021). However, most epidemiological, and experimental observations are limited to BP-3, and the available information is scattered over different experimental models, with a focus on specific toxicological outcomes and with little emphasis on underlying mechanisms. Moreover, knowledge on endocrine disruption is mostly related to sex hormones and reproduction (Ghazipura et al., 2017; Krause et al., 2012). Thyroid hormones (THs) are essential for the proper development and physiological functions of vertebrates (McAninch and Bianco, 2014), and hence the thyroid system is tightly regulated by the hypothalamic-pituitary-thyroid (HPT) axis (Fekete and Lechan, 2014). Adverse effects on thyroid system associated with OUVFs have mostly been studied with BP-3. Urinary BP-3 concentration was significantly associated with decreased serum TH levels in the general adult population in the U.S. National Health and Nutrition Examination Survey (NHANES) 2007–2008 (Kim et al., 2017), and a small cohort of pregnant women in Puerto Rico (Aker et al., 2016). The thyroid disrupting effects of BP-3 have been demonstrated in several experimental models, such as a pituitary gland cell (GH3) and larval fish (Lee et al., 2018).

There is a growing body of evidence that suggests the association of thyroid dysfunction with other noncommunicable diseases, such as neurobehavior impairment and chronic kidney disease (CKD), but experimental evidence that supports such links is rare. THs are considered essential for normal brain development. Among children with congenital hypothyroidism, compromised hippocampal size and memory weakness have been reported, compared to the control group (Wheeler et al., 2011; Wheeler et al., 2015). Similar human observations were reported in a prospective birth cohort of the Netherlands: The maternal TH levels measured at early pregnancy were associated with brain size, such as grey matter and cortical volume, and intelligence quotient (IQ) of the children at 6 to 10 years of age (Jansen et al., 2019; Korevaar et al., 2016). Thyroid hormones are also considered to interact with kidney structures and functions (Mansourian, 2012). For example, in a general human population who participated in the Korea National Health and Nutrition Examination Surveys (2013–2015), serum thyroid stimulating hormone (TSH) was negatively associated with estimated glomerular filtration rate (eGFR), supporting a potential link between THs and kidney function (Kim et al., 2020). Disruption in TH signaling could induce structural changes in podocytes in both diabetic rats and in human podocytes (Benedetti et al., 2019).

Indeed, a few laboratory studies have reported neuronal and kidney toxicities of BP-3 and OMC. For example, impairment of spatial memory and apoptosis of brain cells following exposure to BP-3 have been demonstrated in rodent studies (Pomierny et al., 2019; Skórkowska et al., 2020). Transcriptional changes in genes related to nephrogenesis (*wt1a*, *podocin*, and *nephrin*) and kidney injury (*kim-1*) were observed in larval zebrafish following a 120 h exposure to OMC (Chu et al., 2021). However, experimental studies investigating thyroid disruption along with neurobehavioral and kidney toxicities at the same time, along with transcriptional changes of related genes, have scarcely been conducted.

Zebrafish (*Danio rerio*) are teleost fish widely used as a model animal for investigating toxicological mechanisms of chemicals (Löhr and Hammerschmidt, 2011). They are known for their similarity to mammals, including humans, in terms of characteristics of thyroid, nervous, and renal systems (de Esch et al., 2012; Marelli and Persani, 2017; Lim et al., 2022). In the larval zebrafish, thyroid, neurological, and kidney systems are reported to become functional as early as 96, 24, and 48 h post fertilization (hpf), respectively. Moreover, larval zebrafish are small and easy to manipulate, making them an ideal model for fast and high-throughput screening of chemical toxicity (Marelli and Persani, 2017; Nguyen et al., 2023; Zindler et al., 2019).

The present study was conducted to understand potential health consequences of common organic OUVFs in the early stages of life, using embryo-larval zebrafish (Supporting Information Fig. S1). Four of the most commonly used OUVFs, AVB, BP-3, OC, and OMC, were chosen, and their effects on thyroid function, along with neurobehavioral and kidney-related outcomes were evaluated. The observations made in this study will help fill major knowledge gaps regarding the thyroid, neurodevelopmental, and kidney toxicities of OUVFs and their potential links during early developmental stages.

2. Materials and Methods

2.1. Test chemicals

AVB (also known as butyl methoxydibenzoylmethane), BP-3 (also known as 2-hydroxy-4-methoxybenzophenone) OC, and OMC (also known as ethyl hexyl methoxycinnamate or EHMC) were purchased from Sigma–Aldrich (St. Louis, MO, USA) (Supporting Information Table S1). Dimethyl sulfoxide (DMSO) was used as the solvent for the preparation of fish test solutions and was purchased from Junsei Chemical Co. (99.8 %, Tokyo, Japan). The solvent concentration was set at 0.01 % for AVB, OC, and OMC and 0.005 % for BP-3 by following OECD test guideline 23 (OECD TG 23) (OECD, 2018). The test media for fish exposure (control, middle, and maximum levels) were collected before and after the media renewal, and each sample was measured for OVUFs using a Nexera X2 ultra high-performance liquid chromatography (Shimadzu, Kyoto, Japan) coupled with a Triple Quad 4500 mass spectrometry system (SCIEX, Framingham, MA, USA) (Table S1-S4). Limits of detection (LOD) for OUVFs were 3.30, 0.17, 2.59, and 1.09 μg/L for AVB, BP-3, OC, and OMC, respectively. Nominal and measured concentrations of OUVFs are present in Table S5. Throughout the study, nominal concentrations were used for simplicity.

2.2. Zebrafish maintenance and spawning

Wild-type adult zebrafish (*Danio rerio*) were maintained at 26 ± 2 °C with a 16:8h light/dark photoperiod and fed with mosquito larvae and *Artemia* (Green Fish, Seoul, Korea) twice daily. Fertilized embryos were collected early on the morning of the day of exposure. Detailed information for obtaining zebrafish embryos is provided in Supporting Materials and Methods.

2.3. Zebrafish experimental design

Embryo-larval exposure was conducted between ~ 4 and 120 hpf, following OECD test guideline 236 (OECD, 2013) with minor modifications. Each treatment or control included four replicates: In each treatment, 1,200 embryos were randomly chosen and distributed into four glass beakers (1 L) filled with 500 mL exposure media, with 300 embryos in each beaker. The test concentrations of each OUVF were selected at sublethal levels for both embryo and larval zebrafish (for mortality see Fig. S2) and based on previous reports of their known endocrine disrupting effects (Chu et al., 2021; Ka and Ji, 2022; Kwon and Choi, 2021; Lee et al., 2018; NASEM, 2022). These concentrations were 1, 3, 10, and 30 μM for AVB; 0.04, 0.14, 0.44, and 1.40 μM for BP-3; 1, 3, 10, and 30 μM for OC; and 1, 3, 10, and 30 μM for OMC. The exposure solution was renewed every day, and water chemistry was checked before and after water renewal (Table S6-S9). During the exposure, embryo and larval survival, hatching rate, time to hatch, and body weight (wet weight of 220 larvae) were recorded (Fig. S2). This study was conducted with the approval of the Institutional Animal Care and Use Committee of Seoul National University, Seoul, Korea (IACUC/SNU-190114–5-1, SNU-210505–1).

2.4. *Extraction and measurement of thyroid hormones*

TSH (TSH, Cat No. CSB-EQ027261FI, Cusabio), total thyroxine (TT4, Cat No. TF E-2400, LDN), total triiodothyronine (TT3, Cat No. TF E-2300, LDN), free T4 (fT4, Cat No. TF E-2200, LDN), and free T3 (fT3, Cat No. TF E-2100, LDN) were measured from each replicate, i.e., a pooled 220 larval fish randomly chosen from each beaker, using enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's recommendations. For detailed protocols, refer to Supporting Materials and Methods.

2.5. *Activity and behavior analysis*

Following exposure, three larvae from each replicate (i.e., n = 12 per concentration) were randomly selected and deposited in pre-warmed 96-well plates (6.8 mm diameter and 300 µL volume in well size, at 26.5 °C) for behavioral observations. For this purpose, Daniovision® equipped with a live video tracking instrument (Ethovision, Noldus, Netherlands) was used. The larval fish were first acclimated for 10 min under light condition, followed by light (Light 1), dark (Dark 1), and light (Light 2) conditions of 20 min each. Mean velocity (mm/sec), total distance traveled (mm), and thigmotaxis ('wall-hugging behavior') under different lighting conditions were evaluated. Thigmotaxis was assessed by comparing the ratio of frequency to enter and time spent either in the inner or outer zones of the wells. The 'latency to first enter center' was defined as the time required (s) for the larval fish to enter the center zone for the first time.

2.6. *Proteinuria measurement*

Proteinuria was measured following a previous study (Wang et al., 2016). Briefly, following exposure, zebrafish were transferred to and maintained in fresh culture media for an additional 24 h. Then, water samples were collected, precipitated with trichloroacetic acid, washed with acetone, and reconstituted with Nanopure water, before being quantified for protein contents using the micro-BCA method by the manufacturer's recommendation. Detailed protocol can be found in Supporting Materials and Methods.

2.7. *Gene transcription*

Transcriptional alterations were measured for several genes related to the HPT-axis, TH metabolism and elimination, neuronal, and kidney toxicities (Table S10) using Applied Biosystems QuantStudio 3 (Foster City, CA, USA). For mRNA quantification, the threshold cycle (Ct) values for each gene of interest were normalized to a reference gene (*rp8*) (Fig. S3), using the $2^{-\Delta\Delta Ct}$ method (Livak and Schmittgen, 2001). Normalized values were expressed as the "fold difference." Detailed method for real-time qPCR analysis is provided in Supporting Materials and Methods.

2.8. *Statistical analysis*

Differences in response between the control and exposure groups were investigated using independent *t*-test or one-way variance (ANOVA) with Dunnett's test. Concentration-response relationship and correlation between thyroid dysfunction and developmental neurotoxicity, or kidney dysfunction were determined by Spearman correlation analysis, using SPSS® version 22.0 (Chicago, IL, USA). The *p*-value less than 0.05 was considered statistically significant. Principal component analysis (PCA) was performed to identify transcripts that were most responsible for the changes in thyroid, behavioral, or kidney outcomes. Data was log-transformed and scaled before conducting PCA analysis. To examine possible inter-relationships amongst gene transcripts following exposure to all OUVFs, we estimated partial correlation coefficients of the genes of interest by employing Gaussian model using 'inet' and 'glmnet' package in R (Version 2024.04.0 + 735).

3. Results

3.1. *Thyroid hormone level changes*

Regardless of the type of OUVFs, the exposure led to decreased TH levels in the whole-body homogenate of larval fish (Fig. 1). AVB (Fig. 1A-1E) and OC (Fig. 1K-1O) exposure significantly reduced whole-body levels of TSH, TT4, TT3, FT4, and FT3. BP-3 and OMC exhibited a similar trend of TH levels but with varying degrees of significance.

3.2. *Behavioral changes*

Regardless of lighting condition, exposure to the OUVFs caused hypoactivity, demonstrated by decreases in total distance moved (mm) and mean velocity (mm/s) in both light and dark conditions (Fig. 2 and Fig. S4). Thigmotaxis behavior differed by chemical (Fig. 2). Entries into the center area, or in-zone frequency, were significantly decreased following AVB (Fig. 2I) and OMC (Fig. 2L) exposure.

3.3. *Proteinuria level changes*

Exposure to AVB, BP-3, or OMC resulted in concentration-dependent increases of proteinuria (Fig. 3). The slope of the increase was more pronounced in the larval fish exposed to AVB and OMC.

3.4. *Genes related to thyroid, behavior, and kidney observations*

The mRNA expression of several HPT-axis genes was changed following exposure to each OUVF (Fig. 4 and Fig. S5-S8). After exposure to AVB, the mRNA expressions of *trhr*, *tshb*, *nis*, and *dio2* were significantly decreased, while those of *dio1*, *ugt1ab*, and *ttr* genes were significantly increased. In relation to BP-3, *trh*, *nis*, and *dio1* genes were significantly down-regulated, while *tshb*, *ugt1ab*, and *sult1 st5* genes were significantly up-regulated. For OC, *trhr* gene was significantly down-regulated, and *tshb*, *sult1 st5*, and *ttr* genes were up-regulated. After exposure to OMC, *trh*, *trhr*, *dio3*, *ugt1ab*, *sut1 st5*, and *ttr* genes were significantly up-regulated, while *dio1* gene was significantly down-regulated.

Several genes related to neurodevelopmental outcomes and neurotoxicity showed regulatory changes following OUVF exposure (Fig. S5-S8). Exposure to AVB significantly down-regulated *mbp*, *gfap*, *syn2a*, *sty1a*, and *stxbp1b* genes, and up-regulated *c-fos* gene. For BP-3, down-regulation of *mbp* and *c-fos* genes, and slight up-regulation of *gfap* was observed. In relation to OC, mRNA expressions of *mbp*, *gfap*, *gap43*, *c-fos*, *syn1a*, *sty1a*, and *stxbp1b* were significantly down-regulated. Following exposure to OMC, down-regulation of *stxbp1b* gene, and up-regulation of *c-fos* were observed. The genes associated with nephrogenesis, or kidney injury exhibited transcriptional changes following OUVF exposure (Table S11 and Fig. S5-S8). Exposure to AVB significantly down-regulated *wt1a*, *nephrin*, *sim1a*, and *cdh17* genes. Upon BP-3 exposure, *sim1a* and *cdh17* genes were significantly down-regulated, and *kim-1* gene was significantly up-regulated. OC exposure led to significant down-regulation of *wt1a* and *sim1a* genes. Following OMC exposure, *sim1a* and *cdh17* genes were significantly down-regulated.

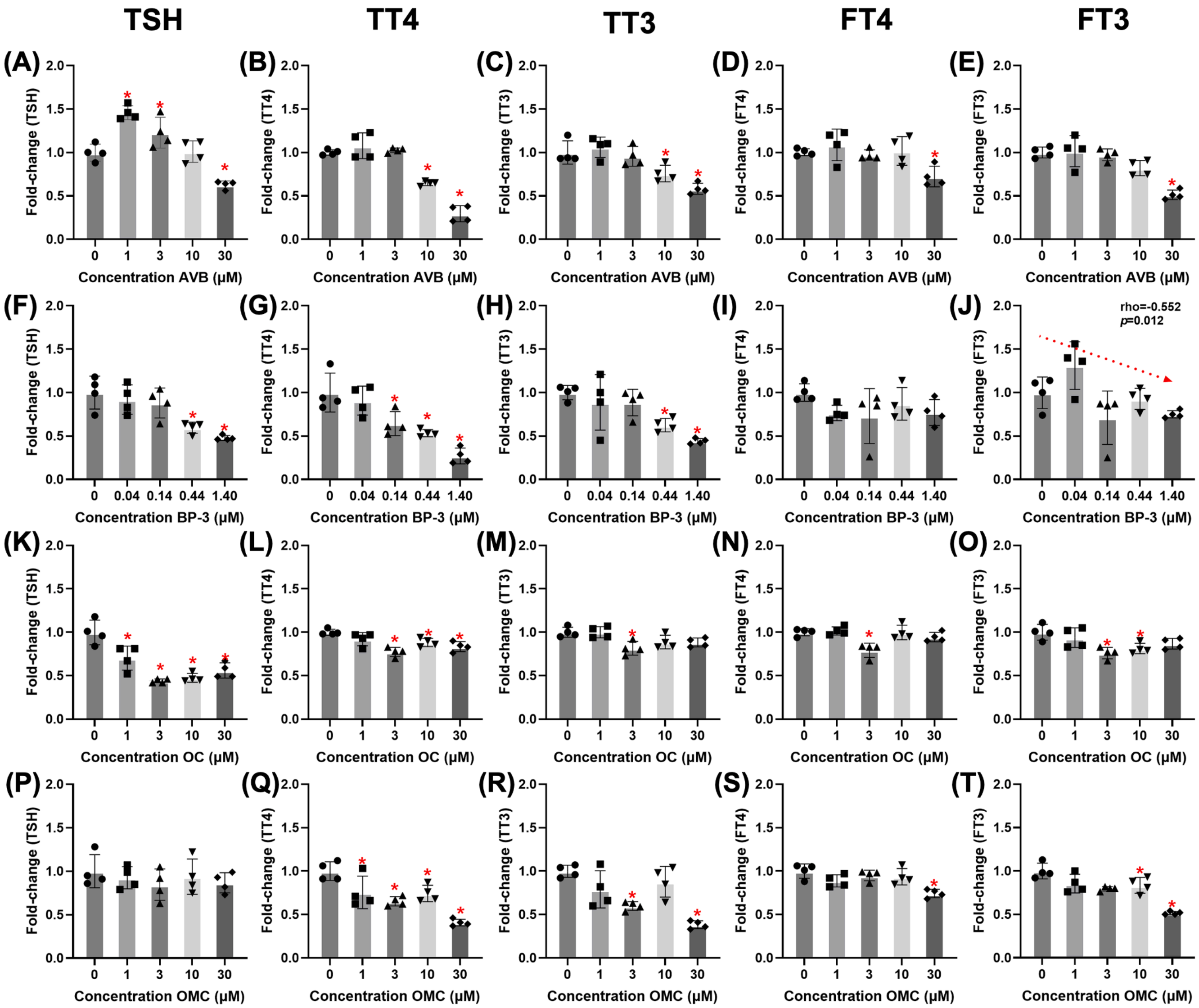

Fig. 1. Thyroid hormone levels in whole-body homogenates of larval zebrafish (120 hpf) following exposure to UV filters, (A-E) AVB, (F-J) BP-3, (K-O) OC, (P-T) OMC. The results are shown as mean ± SD of four replicates. Asterisk (*$p < 0.05$) indicates significant differences from the control, e.g., 0.01 % DMSO.

3.5. Association of THs with genes related to behavior and kidney functions

Transcriptional changes of thyroid-related genes showed significant correlations with those related to neurogenesis or kidney development in the zebrafish larvae (Table S12-S19). In larval fish exposed to AVB and BP-3, TH levels were positively correlated with locomotor activity, and negatively associated with proteinuria level of the larval fish ($p < 0.05$). After exposure to OMC in zebrafish larvae, significant positive correlations between TH levels and neurodevelopmental genes, such as *mbp*, *gap43*, *gfap*, *syn2a*, *syt1a*, and *stxbp1b*, were observed. In addition, similar negative correlations between THs and proteinuria levels were observed. For OC, a significant positive correlation was observed between TH levels and neurodevelopmental genes, such as *mbp*, *gap43*, *syn2a*, *syt1a*, and *stxbp1b*, and between TH levels and nephrogenesis genes, such as *sim1a*, *wt1a*, and *nephrin*. PCA of gene transcription profiles following exposure to OUVFs showed that the first two components (PC1 and PC2) were heavily loaded with the genes related to TH levels and behavioral changes or kidney function (Fig. S9).

4. Discussion

4.1. Thyroid disruption of UV filters

Significant decreases of THs following exposure to AVB, BP-3, OC, or OMC, observed in larval fish (Fig. 1), clearly indicate thyroid disrupting effects of these OUVFs during the early stages of life. With significant TH level changes observed as low as 0.14 μM, BP-3 has shown the most potent TH disrupting effect (Fig. 1). While thyroid disruption by OC has not yet been reported elsewhere, similar decreases of THs were reported in larval zebrafish by AVB (Ka and Ji, 2022) and BP-3 (Lee et al., 2018), and in both larval zebrafish and juvenile *O. latipes* by OMC (Chu et al., 2021; Lee et al., 2019). Up-regulation of both *ugt1ab* and *sult1 st5* genes could explain the current observations of decreased THs following exposure to each test OUVF (Fig. 4 and Fig. S5-S8). The Ugt1ab and Sult1 st5 play roles in the hepatic elimination of not only exogenous compounds but also endogenous molecules such as THs (Jugan et al., 2010; Kurogi et al., 2013). Similar up-regulation of both *ugt1ab* and *sult1 st5* genes have been reported in experimental models of hypothyroidism (lowered T4 and/or T3 levels) after exposure to various environmental chemicals in zebrafish of different life stages and rats (Barter and Klaassen, 1992; Chu et al., 2021; Lee et al., 2018). Significant up-

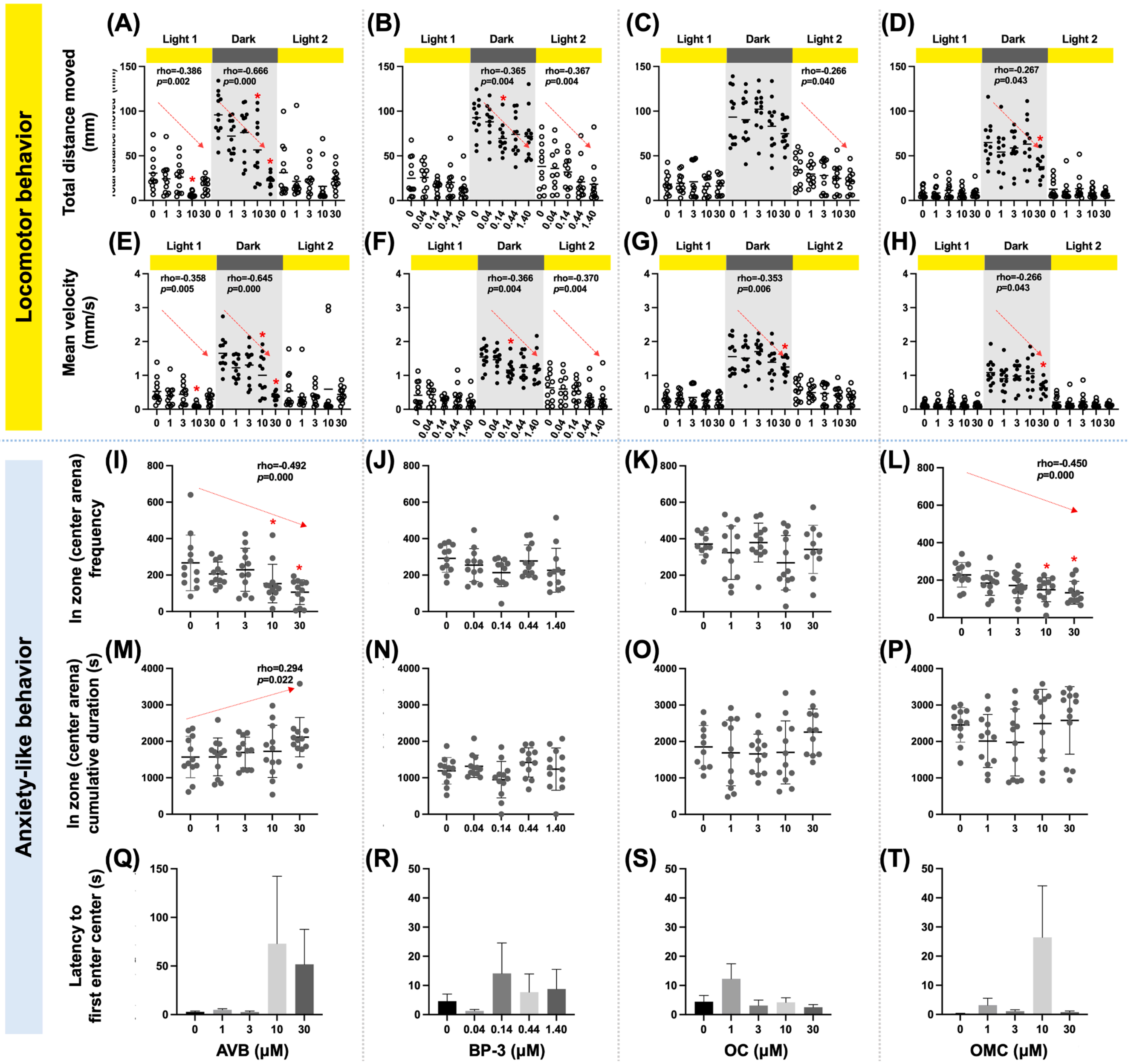

Fig. 2. Locomotor (A-H) and anxiety-like behavior (I-T) changes of larval zebrafish after exposure to OUVFs (AVB, BP-3, OC, OMC). The results are shown as mean ± SD of twelve replicates. Asterisk (*$p < 0.05$) indicates significant differences from the control, e.g., 0.01 % DMSO.

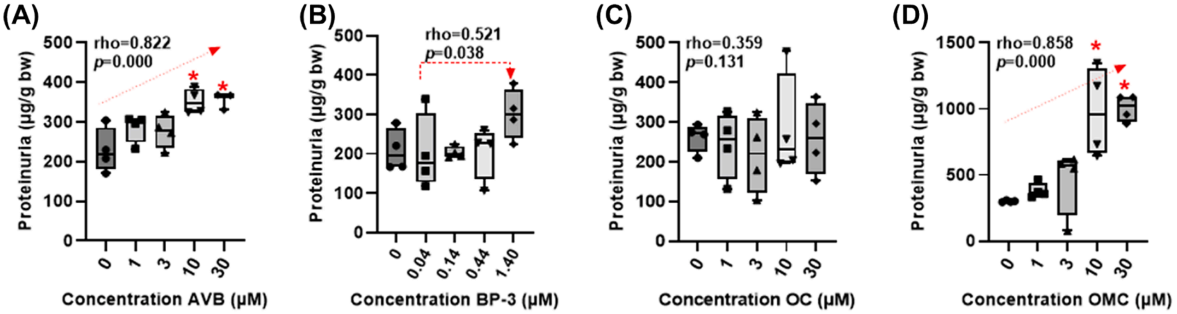

Fig. 3. Changes of proteinuria level in larval zebrafish (120 hpf) after exposure to UV filters, (A) AVB, (B) BP-3, (C) OC, (D) OMC. The results are shown as mean ± SD of four replicates. Asterisk (*$p < 0.05$) indicates significant differences from the control, e.g., 0.01 % DMSO.

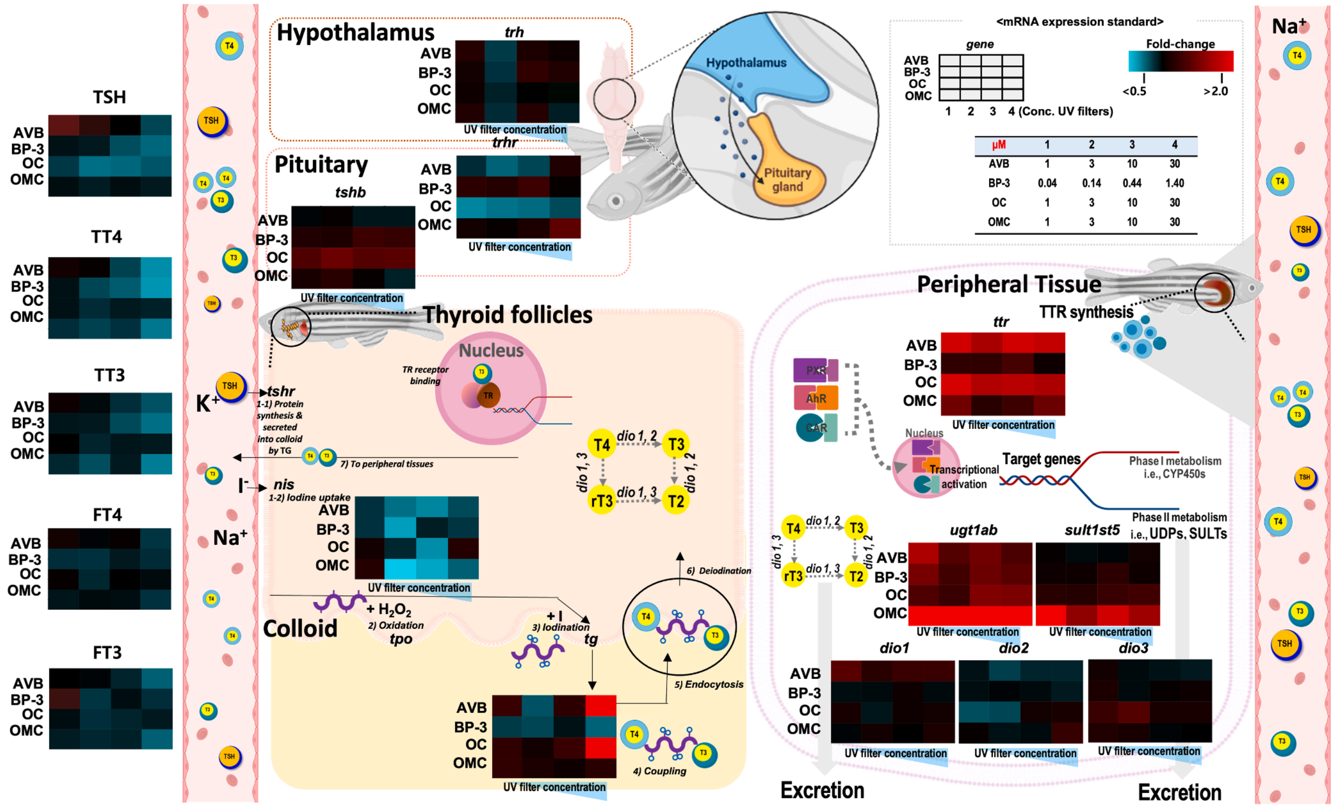

Fig. 4. Overview of TH regulations and mRNA expression changes of HPT-axis in larval zebrafish (120 hpf) after exposure to UV filters. (More information on the data shown in the heatmap can be found in Fig. S5-S8.

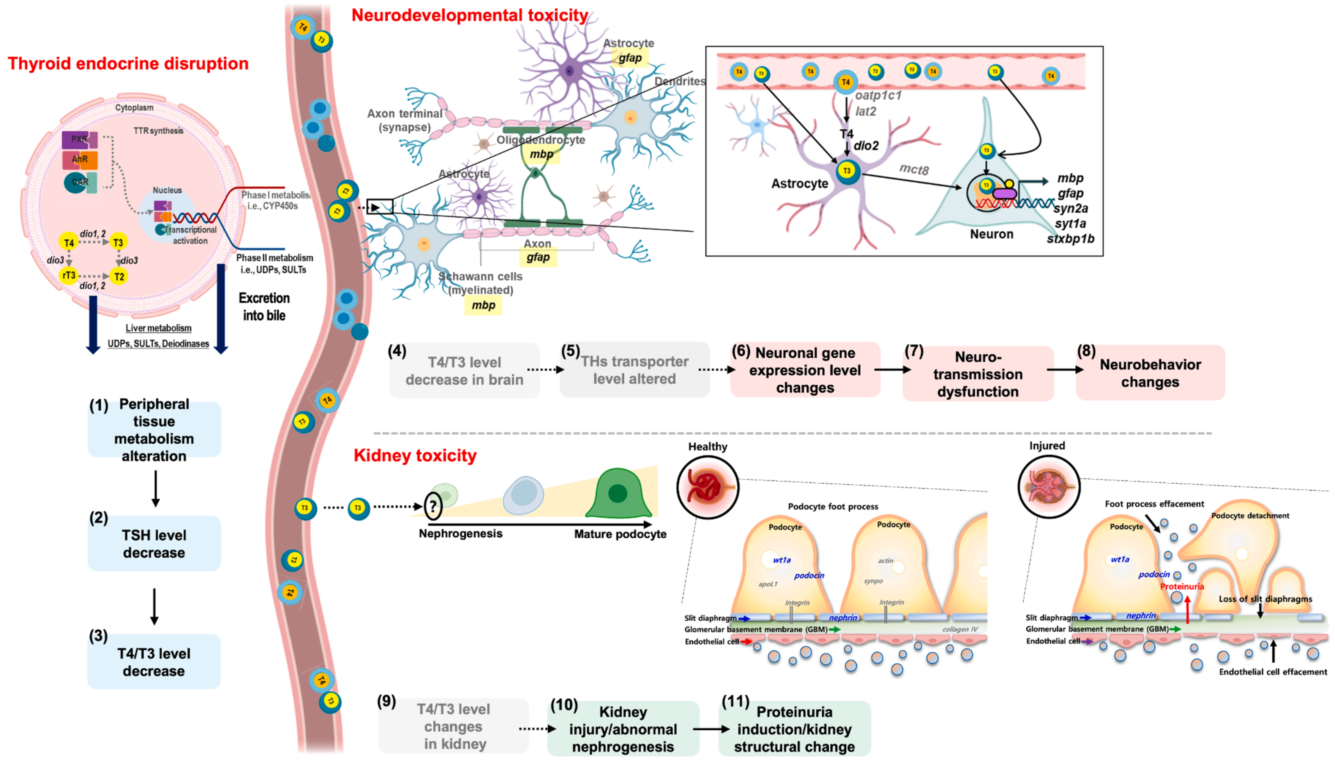

Fig. 5. Suggested mechanisms linking thyroid hormone disruption to neurobehavior and kidney dysfunction in early developing embryo-larval zebrafish. Solid lines denote the endpoints measured in this study. Dotted lines indicate endpoints not measured in the present study or a mechanistic information gap that requires future investigations.

regulation of *ttr* gene after AVB, OC, and OMC exposure may be interpreted as a compensatory effort to reduce whole-body elimination of the THs (Fig. 4 and Fig. S5-S8). In fish, Ttr is a crucial carrier protein for TH. The unbound forms of free THs are physiologically active, but also easily metabolized and eliminated, leading to a decrease in circulating THs levels (Fernie et al., 2005). The observation of significant down-regulation of *nis* gene following exposure to AVB and BP-3, could be considered a primary response that led to decreased TH synthesis in the larval zebrafish. Down-regulations of *dio1* or *dio2* genes further explain lowered T3 (Fig. 4), because the enzymes coded by both genes are responsible for the bioconversion of T4 to T3 (Ka and Ji, 2022).

Our observations show that exposure to the test OUVFs affected neurobehavior and kidney function in larval fish, while lowered THs at the same time (Fig. 1-3). Neurological and kidney-related outcomes, shown in the present study, may be due to toxicological pathways which are independent of thyroid disruption. However, one may not ignore the possibility that the observed thyroid disruption at the early stages of life may have implicated the neurodevelopmental changes, which may further influence the behavior of the larval fish (Gilbert et al., 2020). THs are responsible for the differentiation and maturation of neuronal and oligodendrocyte cells (Remaud et al., 2017). Moreover, during the early developmental stage, THs are considered an important driver for both kidney morphology and function (van Hoek and Daminet, 2009). In line with these relationships, hypothyroidism has been associated with changes in protein synthesis and cellular development, resulting in a reduced cell number, density, and size of the kidneys (Canavan et al., 1994; Slotkin et al., 1992), and eventually their function, in several experimental and epidemiologic studies (Benedetti et al., 2019; Kim et al., 2020; Mansourian, 2012). However, attempts to mechanistically link TH disruption to kidney consequences have been scarcely made.

4.2. Developmental neurobehavioral toxicity of UV filters

Decreased locomotor activity or increased anxiety observed in the larval fish indicates that all test OUVFs are neurobehavioral toxicants, mediated by generally similar modes of action (Fig. 2). Behavioral changes can provide evidence of not only disrupted normal neuronal development (Moser, 2011), but also a measure of emotional status such as anxiety or aggression (Mughal et al., 2018). Except for BP-3, neurobehavioral responses to OUVFs have been seldom evaluated previously. For BP-3, several studies investigated behavioral changes in fish, but the results were inconsistent: For example, waterborne exposure to BP-3 significantly increased mean velocity (mm/s) in larval zebrafish (Tao et al., 2020), however, hypoactivity and/or shoal preference were observed in larval clown anemonefish (Chen et al., 2018) and adult zebrafish (Moreira and Luchiari, 2022). The discrepancy in behavioral responses in the larval zebrafish following BP-3 exposure, between Tao et al. (2020), which reported non-monotonic but increased activities, and the present study, which exhibited concentration-dependent decreases of activity, could stem from different exposure designs, e.g., age, species, and light/dark cycles (Demin et al., 2019; Hurd et al., 1998; Krylov et al., 2021). However, it should be noted that the hypoactivities of larval fish, observed in the current study following BP-3 exposure, are biologically plausible, and supported by decreased THs and down-regulations of their downstream genes (Tables S12-S15). Thigmotaxis, a wall-hugging behavior, or a tendency to favor the edges of the arena, has been employed as an indicator of anxiety of both fish and rodents, and reported in both larval and adult fish previously, following exposure to BP-3 and its major metabolite, benzophenone-1 (BP-1) (Moreira et al., 2024; Song et al., 2022). Exposure to AVB and OMC could also inhibit the locomotor behavior of zebrafish (Liu et al., 2022; Yang et al., 2024).

Transcriptional changes of *mbp* and *gfap* genes that coincided with TH disruption in the current study suggest a potential link between decreased TH levels and the observed neurobehavioral changes in larval zebrafish (Fig. S5-S8). The *mbp* is often employed as a biomarker of axon myelination and is expressed in oligodendrocytes in both central and peripheral nervous systems (Wang et al., 2015). THs are required for the normal process of oligodendrocyte differentiation and maturation (Fernandez et al., 2004). It was reported that *mbp* gene was significantly down-regulated under a hypothyroid state induced by TR$^{-/-}$ deletion (Farsetti et al., 1991) and thyroidectomy, which could be restored by T4 administration (Farsetti et al., 1992). Moreover, *gfap* which is highly expressed in astrocytes, translates an intermediate filament protein, and hence expression of this gene is associated with TH status. Under insufficient THs, *gfap* gene is significantly down-regulated in the brain of rat models (Faivre-Sarrailh et al., 1991; Kumar et al., 2018). A recent literature has also reported that exposure to BP-1 significantly down-regulated *mbp* and *gfap* genes, and inhibited locomotor or cognitive behavior in larval or adult zebrafish (Moreira et al., 2024). The present observations suggest that decreased THs by OUVF exposure could be at least partially responsible for behavioral changes of the larval fish, through regulatory alteration of myelination and astrocyte maturation.

Significant down-regulation of the *syn2a*, *syt1a*, and *stxbp1b* genes observed in the larval zebrafish also supports potential links between TH disruption and neurogenesis (Fig. S5-S8). Syn2a, Syt1a, and Stxbp1b are components of presynaptic proteins that facilitate both synaptogenesis and neurotransmitter release in zebrafish (Roy-Carson et al., 2017). The essential role of THs in synaptogenesis is well characterized (Di Liegro et al., 1995; Hosoda et al., 2003; Thompson, 1996; Thompson and Potter, 2000). For example, Sprague-Dawley (SD) F1 rats, born to dams with maternal hypothyroidism induced by a low-iodine diet and consumption of 0.025 % methimazole in drinking water, demonstrated significant down-regulation of *Srg1*, which was attenuated after T3 injection (Thompson, 1996). Similarly, in fetal rat cortical cells, T3 addition increased synapsin I (SYN1) protein levels and up-regulated *Syn1* gene (Di Liegro et al., 1995). Thus, decreased TH levels observed in the present study, could lead to disrupted synaptogenesis in larval fish. The significant positive relationship observed among TH levels, TH-regulating genes, and neurotransmitter-related genes, supports the link between hypothyroidism and impaired synaptogenesis (Table S12-S15).

The results of PCA analysis also support the potential influence of TH disruption on the neurobehavioral alterations: Following exposure to each test OUVF, the genes that translate presynaptic proteins, e.g., *syn2a* and *syt1a*, were grouped with key genes of HPT axis (i.e., TH synthesis (*trhr*, *nis*, or *tg*), and TH metabolism and elimination (i.e., *dio1* and *sult1st5*), in major PCs (Fig. S9). Moreover, those genes that were identified to have partial correlations in a chord diagram generally agree with the results of the PCA results (Fig. S10).

Transcriptional alterations in several other neuronal genes also support the neurotoxic potentials of the OUVFs, which may be independent of THs. Down-regulation of *gap43* gene in larval zebrafish suggests that the OUVFs could impair axonal regeneration following potential neuronal injury (Fig. S5-S8). Axonal membrane protein Gap43 (*gap43*) is used as a marker for the process of reinducing axonal regeneration following injury (Fan et al., 2010), which contributes to plasticity and the growth of the presynaptic terminal (Holahan, 2017). Up-regulation of *c-fos* gene by AVB or OMC exposure may explain increased thigmotaxis of the larval fish. The early immediate gene (IEC) (*c-fos*) is considered a reliable marker for measuring neuronal activity (Chatterjee et al., 2015), psychiatric conditions, such as anxiety, and in association with fear memories in the brain (Gallo et al., 2018). Therefore, its up-regulation could account for increased thigmotaxis, or anxiety-like behavior (Butler et al., 2011). It is noteworthy that BP-3 and OC exposure did not cause the changes in thigmotaxis of the larval fish and showed a different pattern of regulation of the *c-fos* gene (Fig. S5-S8), suggesting different patterns of neurological effects. One limitation of our study is that we did not include neurotransmitter measurements, which may provide additional evidence supporting developmental neurotoxicity of OUVF exposure.

4.3. Kidney toxicity of UV filters

Concentration-dependent increases of proteinuria observed by most OUVFs along with regulatory alterations in nephrogenesis genes, indicate that OUVFs could disrupt the normal development of kidneys and their filtration function in the larval zebrafish. Proteinuria is one of the typical phenotypes of kidney dysfunction (National Kidney Foundation, 2022) and has been employed as an indicator of kidney toxicity in zebrafish following exposure to nephrotoxicants, like gentamicin and aristolochic acid (Naylor et al., 2022). Experimental studies for kidney toxicity have rarely been conducted for OUVFs. Only BP-3 has been reported for a positive association with albuminuria in a healthy female human population (Kang et al., 2019).

We hypothesized that observed proteinuria in the larval fish could be in part related to thyroid disruption. During early life stages, nephrogenesis is influenced by THs. Impaired neonatal kidney development and CKD were characterized by low T3 levels (Basu and Mohapatra, 2012), and these adverse outcomes were reversible with TH treatments in CKD patients (Iglesias et al., 2017; Weerakkody and Lokuliyana, 2019). In neonatal rats, kidney development was disrupted by the treatment of propylthiouracil, an anti-thyroid drug, and later recovered with thyroxine (T4) treatment (Ali and Clos, 1986). Moreover, in a human proximal tubular epithelial cell line (HK-2), triiodothyronine (T3) exposure inhibits fibrosis of the cells (Lu et al., 2013). The current observations made in our study, i.e., a significant negative relationship between THs and proteinuria levels, and a positive relationship between hypothyroid status and *wt1a* genes in zebrafish larvae, after exposure to OUVFs, suggest a potential association of THs with kidney function (Table S16-S19). Moreover, the results of PCA analysis that exhibited the clustering of major genes related to HPT axis (i.e., *tshb*, *trhr*, *dio2*, *ugt1ab*, and *ttr*) and nephrogenesis (i.e., *wt1a, nephrin*, and/or *podocin*) in the same PCs, support possible involvements of THs in nephrogenesis and kidney function (Fig. S9). However, chord diagram analysis showed that only *sult1 st5* gene was partially correlated with *wt1a* and *nephrin* (Fig. S10).

Significant down-regulation of several nephrogenesis related genes (Fig. S5-S8), e.g., *wt1a*, *podocin*, *nephrin*, *kim-1*, *sim1a*, and *cdh17*, suggests that the OUVFs may, independently of the thyroid pathway, inhibit proper neurogenesis or induce kidney injury in larval fish (Table S11), eventually leading to dysfunction of the larval kidney indicated by increased protein contents in urine (Fig. 3). Although the extent of transcriptional changes varied by compound, the directions of adverse outcomes were generally similar, suggesting that the OUVFs could damage normal kidney function by disrupting nephrogenesis in both glomeruli and proximal tubules (Fig. S5-S8). Proteinuria is considered to be induced by effacement of the podocyte foot process, including functional loss of podocin (Nakatsue et al., 2005), deletion of a slit diaphragm protein known as nephrin, and diminished reabsorption by injured proximal tubules (Kalluri, 2006; Parikh et al., 2010). Therefore, the down-regulation of *wt1a*, *nephrin*, and *podocin* genes is in line with the observed proteinuria (Fig. S5-S8). As an important regulator of the fate of kidney progenitors (Kreidberg, 2010), Wt1 plays essential roles in podocyte growth, glomerular development, and renal filtration in the urogenital system (Dong et al., 2015); previous studies reported that *wt1a* knockout zebrafish embryos did not undergo podocyte differentiation, ultimately failing to express *nephrin* and *podocin*, which are the main components of the podocyte foot process and slit diaphragms (O'Brien et al., 2011; Perner et al., 2007), essential for maintaining the structure and function of the glomerulus.

Concentration-dependent up-regulation of the *kim-1* gene by BP-3 exposure also supports its nephrotoxic effect (Fig. S5-S8). Kim-1 is widely used as a biomarker for both acute kidney injury (AKI) and CKD (Yin and Wang, 2016). Significant induction of Kim-1 following exposure to nephrotoxicants, such as rapamycin in zebrafish (Yin et al., 2016) and gentamycin in Wistar rats (Medić et al., 2019) has been reported. Down-regulation of *sim1* and/or *cdh17* genes observed following exposure to AVB, BP-3, OC, and OMC supports the disrupted kidney function of the fish (Fig. S5-S8). A Previous study reported that the knockdown of *sim1a* gene in zebrafish caused defects in proximal tubule development and reduced renal clearance (Cheng and Wingert, 2015). The *sim1a* gene translates Sim1a, which regulates *cdh17* gene, of which protein product is essential for morphogenesis of the kidney (Horsfield et al., 2002). Lack of histopathological observations on the larval kidneys is a limitation in the present study, because it would help support the link between the observed transcriptional and phenotypic changes.

4.4. Nominal versus measured concentrations

We observed the discrepancies between nominal and measured concentrations of the OUVFs in the test solutions, while the extent of difference in the concentrations varied by chemical (Table S5). Rapid dissipation of OUVFs has been reported in several studies. Significant losses of OUVFs including AVB, OC, and OMC, were observed over the experimental periods, and were explained by degradation or loss of the analyte in the test chambers, as well as losses during sampling, processing, analysis, or a combination of these factors (Fel et al., 2019; He et al., 2019a; He et al., 2019b; He et al., 2021; NASEM, 2022; Wijgerde et al., 2020). The difference observed in the current study may be due to several reasons, such as rapid photodegradation in the experimental setting, the loss of the chemical by being absorbed into the organism, binding to suspended particles and/or precipitating out of the solution, absorption into containers, or degradation by abiotic/biotic processes (Ahmed et al., 2017; Cho et al., 2019; NASEM, 2022). Unlike other chemicals, we found that BP-3 was photostable and was not degraded after 24 h, as also reported in a previous review (Ahmed et al., 2017).

5. Conclusions

Overall, our study demonstrated that exposure to the test OUVFs could disrupt thyroid, neurological, and kidney functions, and alter the regulation of related genes in the larval zebrafish. Significant transcriptional changes in injury marker genes, such as *c-fos* and *kim-1* genes, in neuronal and kidney systems, respectively, may suggest direct neuronal- or kidney toxicities of the OUVFs. However, significant alterations in neurogenesis, synaptogenesis, and/or nephrogenesis-related genes, which were associated with reduced TH levels, showed suggestive evidence of the potential links between TH dysfunction and neurological or kidney function in the larval zebrafish. As direct mechanistic links of TH disruption with neurobehavioral or kidney impairment remain an open question, further investigations on possible mechanistic links, such as cellular transport and uptake of THs, and their signaling pathways at the target tissues (e.g., brain and kidneys), are required. As an initial attempt, the current study provides evidence that several OUVFs that have been widely used could cause adverse effects on thyroid, neurological, and kidney systems during early life stages, and TH disruption may be partly responsible for behavioral and kidney outcomes.

CRediT authorship contribution statement

Ba Reum Kwon: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Ah-Reum Jo:** Methodology, Investigation, Formal analysis. **Inae Lee:** Methodology, Investigation, Formal analysis. **Gowoon Lee:** Methodology, Investigation, Formal analysis. **Young Joo Park:** Writing – review & editing, Resources. **Jung Pyo Lee:** Writing – review & editing, Resources. **Na-Youn Park:** Validation, Methodology. **Younglim Kho:** Validation, Methodology. **Sungkyoon Kim:** Writing – review & editing, Resources. **Kyunghee Ji:** Writing – review & editing, Resources. **Kyungho Choi:** Writing – review & editing, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109030.

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