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Zebrafish as a Model for Toxicological Perturbation of Yolk and Nutrition in the Early Embryo

Karilyn E. Sant and **Alicia R. Timme-Laragy**

Department of Environmental Health Sciences, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA 01003, USA

Abstract

Purpose of Review—Developmental toxicity assessments often focus on structural outcomes and overlook subtle metabolic differences which occur during the early embryonic period. Deviant embryonic nutrition can result in later-life disease, including diabetes, obesity, and cardiovascular disease. Prior to placenta-mediated nutrient exchange, the human embryo requires maternally-supplied nutritional substrates for growth, called yolk. Here, we compare the biology of the human and zebrafish yolk, and review examples of toxicant-mediated perturbation of yolk defects, composition, and utilization.

Recent findings—Zebrafish embryos, like human embryos, have a protruding yolk sac that serves as a nutritional cache. Aberrant yolk morphology is a common qualitative finding in fish embryotoxicity studies, but quantitative assessment and characterization provides an opportunity to uncover mechanistic targets of toxicant effects on embryonic nutrition.

Summary—The zebrafish and the study of its yolk sac is an excellent model for uncovering toxicant disruptions to early embryonic nutrition and has potential to discover mechanistic insights into the developmental origins of health and disease.

Keywords

Yolk; yolk sac; embryonic nutrition; developmental toxicology; malabsorption

INTRODUCTION

In the first trimester of human development, the embryo undergoes dynamic and rapid growth and organization. Because of this rapid rate of growth and increasing physiological demands, the embryonic period is highly metabolically taxing and requires ample energetic substrates. During this early window, the human embryo can rely on a supply of maternally-

CORRESPONDING AUTHOR: Dr. Alicia R. Timme-Laragy, aliciat@umass.edu, Phone: +1 (413) 545-7423, Department of Environmental Health Sciences, University of Massachusetts, School of Public Health and Health Sciences Goessman 171, 686 N Pleasant St., Amherst, MA 01003.

COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST

Karilyn E. Sant and Alicia R. Timme-Laragy declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

All reported studies with animal subjects performed by the authors have complied with all applicable ethical standards. All procedures were approved by the University of Massachusetts Amherst IACUC committee (Animal Welfare Assurance Number A3551-01).

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supplied substrates collectively referred to as yolk, containing bulk proteins and lipids used for synthesis and metabolism. The developmental origins of health and disease paradigm proposes that the early life nutrient and chemical environment plays a critical role in establishing later-life health and susceptibility to diseases, including metabolic dysfunction as occurs in diabetes and obesity [1–3]. Nutrient restrictions that occur during the early period of hyperplastic growth (blastocyst stage) are associated with obesity later in life [4, 5]. It is therefore critical for embryonic success and for the long-term health of the organism that yolk content and utilization is not compromised. This review will first highlight why the zebrafish is a useful model to understand the role of the yolk in embryonic development, and how the yolk is a susceptible target of toxicological modulation.

THE ZEBRAFISH IS A MODEL FOR HUMAN YOLK NUTRITION

For multiple ethical and practical reasons, the yolk and nutritional processes cannot be studied in the human embryo. Therefore, the majority of our knowledge about embryonic nutrition has been accumulated from studies using model organisms. These models can all be compared and contrasted to the anatomy, physiology, and metabolism of the human embryo. One important point of comparison is the intrauterine environment, which differs between rodents and humans in numerous ways such as in uterine shape (bicornuate in rodents) and litter size (multiparous in rodents) (for an extensive review of mammalian reproductive anatomy, please read [6]). Despite these differences, the rodent models become fairly congruent to human nutritional processes during the fetal period with a functioning placenta and onset of hemotrophic nutrition (maternal and fetal exchange of nutrients via circulation). However, during the early embryonic period (up to 8 weeks post fertilization in humans, corresponding to the end of peak organogenesis) there are substantial differences between rodent and human nutrition. Rodent embryos instead rely solely on histiotrophic nutrition- the uptake of proteins and nutritive cargoes secreted by the maternal endometrium and endometrial glands by the yolk sac of the conceptus [7]. Rodent embryos are completely surrounded by a thin, metabolically active inverted yolk sac epithelium, and lack maternally-supplied yolk. Therefore, the rodent embryo has a much more dynamic nutritional environment than a human embryo at this stage, since they cannot rely on an existing cache of nutrients. In contrast, a human embryo has a protruding yolk sac more structurally akin to that found in a zebrafish embryo.

Zebrafish (*Danio rerio*) are a commonly used model for embryonic development, and widely used in health research [8]. There are numerous reasons why the zebrafish is an excellent model in which to study toxicant effects on early embryonic nutrition. As a vertebrate, zebrafish embryos are structurally and functionally similar to humans, and the contributions of genetics, anatomy, and physiology to embryonic nutrition can be explored. Importantly, zebrafish embryos—like human embryos—have a protruding yolk sac, which contains a supply of protein, lipids, and micronutrients to sustain metabolic function and growth until the onset of exogenous feeding in the zebrafish, or placental-fetal exchange in humans (Figure 1). There are also logistical advantages to the zebrafish such as large clutch sizes that provide ample embryos for experimentation and transparency for easy visualization of organogenesis using fluorescent probes and transgenic strains. The zebrafish embryo develops rapidly; while the human embryonic period spans most of the first trimester, or

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roughly 10 weeks, the zebrafish embryonic period lasts approximately 3 days, and the resulting larvae begin feeding exogenously as early as 4–5 days post fertilization when the yolk is mostly expended [9]. Further, female zebrafish produce large clutches (averaging 100 eggs), allowing for large sample sizes of embryos with synchorinzed fertilization [10]. For these reasons, the zebrafish is an ideal high-throughput model for studies at the intersection of developmental biology, toxicology, and nutrition.

While the congruence between the zebrafish and human embryo is substantial, there are also some notable differences with respect to the yolk. First, the zebrafish is purely lecithotrophic, relying entirely on a finite supply of yolk supplied prior to external fertilization [11]. In contrast, the human embryo begins with a small supply of yolk granules, and histiotrophically acquires more nutrients into the protruding yolk and vitelline vasculature (reviewed in [12, 7]). Second, the major proteins within the yolks of zebrafish and human differ; the primary content of human yolk is albumin whereas the primary content of zebrafish yolk is vitellogenin. However, bulk proteins are typically cleaved shortly after uptake from the yolk into the embryo to supply amino acids for protein synthesis, so the original source of these amino acids (including albumin in humans and vitellogenin in zebrafish) are likely degraded into free amino acids soon after uptake [12]. Because zebrafish embryos are fertilized and develop externally, they are not an appropriate model for the intrauterine environment, histiotrophic function, or fetal haemotrophic nutrition, which occurs after the embryonic period once the placenta is active (end of first trimester and beyond).

Despite these differences, the external fertilization and development of these transparent zebrafish embryos provide a unique opportunity to visualize early embryonic nutritional processes *in vivo* in a vertebrate species that shares numerous structural, genetic, and metabolic similarities with human embryos. The zebrafish model provides researchers a number of tools and strategies to better study and understand embryonic nutrition, and how it is affected by toxicant exposures. First, because the zebrafish yolk contains a finite supply of nutrients, embryonic nutrition can be approximated observing the rate of yolk utilization using standard light microscopy as the volume of the remaining yolk visually decreases. Second, the accessibility of the protruding yolk sac provides the opportunity to characterize yolk composition biochemically, and large clutch sizes can conveniently and affordably provide an ample amount of yolk. Third, the transparency of embryos allows use of fluorometricaly-tagged nutrients to visualize uptake and distribution processes *in vivo* [13, 14], as well as the generation of transgenic zebrafish lines with fluorescently tagged transporters or bulk proteins (such as zebrafish expressing fluorescent Vitamin D binding protein, as described in [15]). Lastly, external development of zebrafish embryos enables utilization of water exposures, which are easy to administer. These water-based exposures can minimize inter-individual variability by reducing exposure variability due to position in the bicornuate rodent uterus. Though water-based exposures may not be as precise as other methods such as direct injection (which can also be done in the zebrafish), they are more high-throughput and minimize confounding variables such as animal distress. It is important to consider study design when performing water exposures, as exposing embryos to the parent compound or metabolites should differ based upon examination of ecotoxicological risk or human health risk, respectively. *In utero*, embryos are likely exposed to metabolites

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as well as parent compounds, as many toxicological compounds are first metabolized in the maternal liver before entering circulation. Water exposures allow administration of metabolite dose-responses, removing variability contributed by maternal bioaccumulation or metabolic variance. For all of these reasons, the zebrafish is an ideal model to study the role of the yolk in early embryonic nutrition as well as toxicant-induced perturbations of these processes.

YOLK COMPOSITION & SYNTHESIS

The major constituents in yolk, regardless of species, are proteins and lipids. Lipids mediate cell signaling and provide building blocks of plasma and cell membranes. In the zebrafish, the majority of yolk lipids are cholesterol (40% of total lipid), phosphatidylcholine (17%), and triglycerides (9%) [16]. Triglycerides can be cleaved into free fatty acid species for purposes including membrane synthesis and energy metabolism. Fatty acids are a class of lipids that provide the main source for ATP generation in the oocyte and embryo; for example, palmitate oxidation can generate 106 ATP molecules vs only 30 generated from glucose [17]. Because of this high ATP yield, high lipid content in the yolk is advantageous to maximize energy yield per unit volume in the yolk.

The early zebrafish embryo (through gastrulation) contains over 50 μg of protein, more than 90% of which is contained in the yolk [18]. The majority of yolk protein is comprised of vitellogenins, a family of phospholipo-glycoproteins, which are important for oocyte maturation [18–20]. Vitellogenins are synthesized in the maternal liver and transported to the ovary via the vasculature, where they are deposited into the oocyte via receptor-mediated endocytosis in a process known as vitellogenesis [21]. Across species, maternal circulating lipid concentrations greatly impact yolk lipid deposition. For excellent reviews on the maternal synthesis and genes involved in vitellogenesis among different species, we refer the reader to [22, 23].

There is substantial evidence to support that the yolk and yolk sac are metabolically active. First, lipid species can be processed and metabolized prior to embryonic uptake and distribution; for example, the yolk concentrations of several lipid species, such as cholesterol and sphingomyelins, have been shown to actually increase throughout embryonic development, demonstrating metabolic function in the yolk [16]. Second, there is abundant evidence suggesting that maternal mRNA and miRNA transcripts are deposited into the zebrafish oocyte, and regulate developmental processes in the oocyte, zygote, and embryo (reviewed in [24]). Studies investigating early RNA transcripts in the recently fertilized zebrafish zygote have provided evidence that maternally-deposited RNAs have a parent-of-origin signature, and contribute to embryonic metabolic processes such as proteolysis and lipid metabolism [25]. These maternally-patterned metabolic signatures could potentially contribute to inter-individual susceptibility, and underscore the importance of the maternal ovarian environment in the metabolic programming and yolk composition of offspring.

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TOXICANTS AFFECTING MATERNAL YOLK DEPOSITION

One of the most direct ways that toxicants can influence maternal yolk deposition is via disruption of maternal vitellogenin production [26]. Vitellogenin gene promoters contain Estrogen Response Elements (ERE), transcription factor binding domains for estrogen receptors (alpha and beta) [27]. Therefore, expression of vitellogenins is highly inducible (by as much as 300%) by estrogenic compounds in the environment [28–30]. This inducible response allows females to increase vitellogenin production to support deposition into the yolk of developing oocytes. For this reason, yolk vitellogenin can be a sensitive target for toxicants—especially endocrine disrupting compounds. Several studies have demonstrated that the endocrine disrupting compounds 2,4,6-tribromophenol [31] and bisphenol A [32] increased the accumulation of vitellogenin in oocytes following maternal toxicant exposures in fish species including zebrafish. Others demonstrated that vitellogenin expression in the liver and in circulation is a sensitive biomarker of exposures to toxicants and endocrine disrupting compounds such as: perfluorooctanesulfonic acid [33] (unpublished data), di(2-ethylhexyl) phthalate [34], bisphenol A and tetrabromobisphenol A [33, 35, 36], endosulfan [35], heptachlor and methoxychlor [35], flutamide [37], betulinol [38], and pharmacological agents such as: diethylstilbestrol [37], 17α-ethinylestradiol [39, 40, 36], 17β-trenbolone [40], and gallic and pelargonic acids [41]. The zebrafish embryo provides an excellent model to study vitellogenesis, as fluorescently-labeled vitellogenin can be injected into maternal fish and incorporation into eggs can be quantified [29].

TOXICANTS ACCUMULATE IN THE YOLK

The yolk can selectively aggregate lipophilic xenobiotics from the maternal-embryonic environment (humans) or in the surrounding aquatic environment (fish). Several studies have quantified xenobiotic bioaccumulation specifically in the yolk resulting from waterborne exposures to estradiol [42], selenium [43], graphene oxide [44], and hydrogen sulfide [45]. Uptake of these compounds could involve passive or active movement of the molecule across the yolk sac epithelium. The yolk sac epithelium contains several active receptors, which stimulate receptor-mediated endocytosis or pinocytosis of nutrients and their cargoes, such as the multiligand endocytotic receptor complex [46]. The arrangement and function of transporters on the yolk sac epithelium, and their vulnerability to toxicological perturbation, require further characterization.

Toxicants can also be deposited into the yolk following maternal exposure. For example, zebrafish studies have demonstrated that maternal exposure to perfluorooctanoic acid (PFOA) [47] and selenium [48] results in xenobiotic deposition into the oocyte or embryonic yolk. This has important implications for trans- and multigenerational studies, many of which focus upon underlying heritable mechanisms (such as epigenomic modification) or indirect (disrupted maternal signaling cascades) as the driving causes of developmental origins of health and disease (DoHaD) outcomes in subsequent generations. Maternal deposition of toxicants into the yolk results in direct exposure of the embryo to these toxicants, thus complicating interpretations of exposure timing including generational, since the initial exposure. For this reason, DoHaD studies investigating multigenerational paradigms can benefit from a better understanding of yolk as a source of exposure.

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TOXICANTS IMPACT YOLK UTILIZATION

Oocytes contain a finite store of yolk that must sustain the embryo until additional sources of nutrition are available, such as implantation and histiotrophic acquisition of nutrients in the human embryo, or hatching and exogenous feeding in the zebrafish. In addition to toxicant impacts on the amount and composition of the maternally deposited yolk, toxicants can also alter the rate at which these nutrients are used. This can have important implications for the developing embryo's perception of nutrient availability and metabolic programming. For example, an embryo that has a higher metabolic demand due to toxicant exposures might exhaust its yolk prematurely and thus perceive a starvation environment in which calorie resources need to be conserved. Alternatively, if yolk uptake transporters are inhibited, or if there are not enough of them, then the yolk utilization is impaired, similarly resulting in a perceived starvation environment. Thus, both increased and decreased rates of yolk utilization can prove detrimental.

Nutrient storage and utilization is directed by several important pathways, such as the Peroxisome Proliferator-Activated Receptor (PPAR) pathway. PPARs are nuclear receptors that activate transcription of genes involved in processes such as lipid metabolism, glucose metabolism, and adipogenesis. All PPAR isoforms (α, δ/β, γ) are expressed in both the human and the zebrafish embryo, and tissue-specific expression, genetic sequence and synteny, and function are conserved across vertebrate species [49, 50]. However, an evolutionary genome duplication event [51] resulted in zebrafish having two isoforms for the *PPARα* (*pparaa*, *pparab*) and *PPARδ/β* (*pparda*, *ppardb*) genes, resulting in potential neofunctionalization (having new potentially divergent functions) and subfunctionalization (having the function of their non-duplicated ancestor), respectively [52]. PPAR binding sites can be found in the promoters of vitellogenin genes, suggesting that PPAR-disrupting contaminants may directly impact vitellogenesis [53]. Many environmental contaminants such as endocrine disrupting compounds (including perfluorinated compounds, bisphenol A, and phthalates) act by disrupting PPAR signaling, potentially diverting metabolic and cellular fates.

The zebrafish embryo relies solely on a finite amount of maternally deposited yolk for embryonic nutrition, which presents opportunities to gain insight into processes of embryonic nutrition and their disruption by toxicant exposures. Measurement of the yolk dimensions of individual zebrafish embryos over the first four days of development can be used to calculate the rate of nutrient uptake and identify agents that interfere with nutrient mobilization from the protruding yolk sac into the embryo proper (Table 1). For example, we have found that exposure to PFOS during embryonic development resulted in an increase in the rate of yolk utilization over the first four days post fertilization [54]. However, it is more common for toxicology studies to rely on single-endpoint sampling times rather than collecting this morphometric data on a daily basis.

There are several categories of yolk phenotypes reported in zebrafish developmental toxicology studies that are not universally defined. One common observation includes yolk sac edema (fluid in the yolk syncytial layer); however, this is not always distinguished from yolk edema (fluid pockets observed within the yolk sac, or in some cases distended yolk

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content). Another common finding is that of yolk retention, also referred to as decreased yolk mobilization/utilization or malabsorption. Here the yolk sac area is typically larger than that of age-matched control fish, indicating that yolk uptake has been impaired. Conversely, another finding is that of accelerated yolk utilization, resulting in a smaller yolk area and indicating increased yolk mobilization or utilization. While studies often report yolk observations qualitatively, many recent studies have quantified yolk dimensions in order to better characterize these phenotypes. Table 1 presents examples of recent studies that have quantified the yolk area following toxicant exposures.

Nutrition during the embryonic period can establish a foundation for metabolism throughout the lifecourse, as described by the "thrifty phenotype" hypothesis. Because the rate of yolk utilization can be used to approximate early embryonic nutrition, quantification of this rate is an important study outcome with implications for later-life metabolic dysfunction. Additional longitudinal studies are necessary in order to more directly link yolk with later-life growth and health outcomes in the zebrafish model.

TOXICANTS INDUCING YOLK SAC EDEMA

The yolk sac environment is highly lipophilic, and has low water and solute permeability [60]. The zebrafish embryo relies on a coordinated 'water barrier', maintaining an osmotic gradient compared to the surrounding aqueous environment [61]. Until the kidney becomes functionally active during the subsequent larval stage of zebrafish embryonic development, osmoregulation must be maintained in part by the gills and the digestive system [62]. However, impaired maintenance of this osmotic gradient can result in excessive water uptake into the embryo, or edema.

Yolk sac edema is a commonly observed pathology in zebrafish developmental toxicity screens. Compounds including TCDD classically induce "blue sac syndrome," a pathology characterized by yolk sac and pericardial edema [61]. However, a wide array of toxicants including polycyclic aromatic hydrocarbons [63, 64], polychlorinated biphenyls [65, 66], polybrominated flame retardants [67], poly- and perfluorinated compounds [68, 69] (unpublished data), organophosphates [70–73], herbicides [74–76], and nanoparticles [67, 77–79] among others have been demonstrated to cause yolk sac edema in zebrafish embryos. The wide range of chemical properties demonstrated by these chemicals suggests that yolk sac edema is an especially sensitive toxicological outcome for embryonic evaluation. While these phenotypes are not commonly observed in humans, clinical data has shown an increased rate of yolk sac edema in pregnancies, resulting in spontaneous abortion [80].

UNCOVERING THE ROLE OF EMBRYONIC NUTRITION IN THE DEVELOPMENTAL ORIGINS OF DISEASE

While some concentrations of toxicants can cause yolk sac edema and other malformations in the embryo, subtle alterations to embryonic nutrition are more difficult to assess unless specifically examined, but later-stage growth parameters are commonly measured. Toxicologists, epidemiologists, and environmental health scientists often include neonatal measures such as birth weight, head circumference, and infant length as health outcomes.

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Based upon consensus measures from clinical data, human infants born with the lowest scores for these measure are often designated as “small for gestational age” or intrauterine growth restricted (fetal measures, *in utero*), or low birth weight (infant). Though we are unable to probe the relationship between the human embryonic yolk and these parturition outcomes, the use of models such as the zebrafish may help to elucidate this relationship. Epidemiology studies have associated numerous environmental toxicants with reduced birth weight or size, including bisphenol A [81], phthalates [82], perfluorinated compounds [83, 84], and fine particulate matter [85]. However, the mechanisms underlying this relationship remain unknown. Because growth is strongly correlated with nutrition during the fetal, postnatal, and juvenile periods in humans, it is also possible that nutrition during the embryonic period could be predictive of intrauterine growth. Because little is known about these processes, the relationships currently remain unknown. Using microscopy, the zebrafish model is ideal to explore this correlation quantitatively.

CONCLUSIONS

The zebrafish is an excellent model for uncovering toxicant disruptions to early embryonic nutrition due to its structural similarities with the human embryonic yolk sac. Thorough characterization of yolk defects, composition, and utilization has potential to provide mechanistic insights into the developmental origins of health and disease. Several studies have now demonstrated that the yolk is metabolically active [16, 86], and thus should be recognized as another target tissue for developmental toxicology studies. Because the yolk is lipophilic, it also provides an ideal compartment in which hydrophobic toxicants may accumulate and facilitate embryonic exposures throughout the yolk-based feeding period. Perturbations to the utilization of yolk may potentially be indicative of other metabolic conditions, and should be closely examined in the etiology of the ‘thrifty phenotype’ and metabolic dysfunction such as diabetes and metabolic syndrome.

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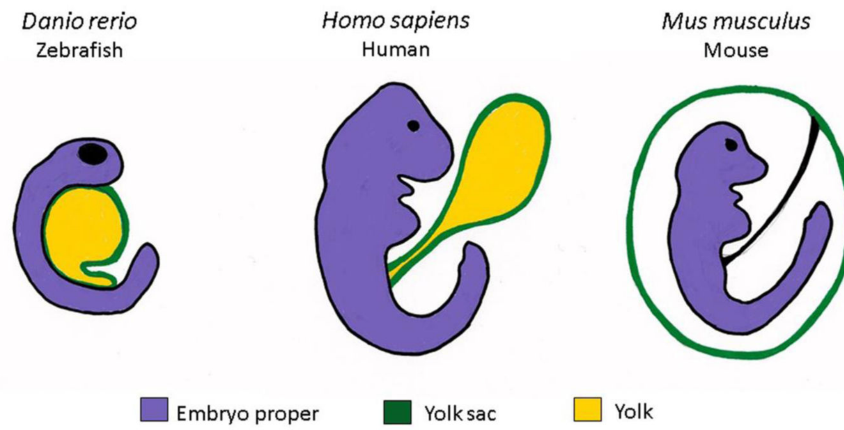

Figure 1.
Comparative yolk sac anatomy of the zebrafish (*Danio rerio*), human (*Homo sapiens*), and mouse (*Mus musculus*).

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Table 1

Recent studies that have quantified increased or decreased yolk utilization with different chemical exposures

Zebrafish yolk effect	**Exposure agent**	**Exposure concentrations**	**Ref.**
Increase yolk mobilization	Tetrabromobisphenol A (TBBPA; flame retardant)	1 nM	[55]
	Tetrachlorobisphenol A (TCBPA; flame retardant)	1 nM	[55]
	Butralin (herbicide)	10 nM, 100 nM, 1 μM	[55]
Increase or decrease yolk mobilization	Clofibrate (antilipidemic pharmaceutical)	Increase yolk mobilization (100 nM) Yolk retention (20 μM)	[55] [56]
	Tributyl tin (aquatic anti-fouling agent)	Yolk retention (10–100 pM) Increase yolk mobilization (1 nM)	[55]
Decrease yolk mobilization (yolk retention	Fine particulate matter ($PM_{2.5}$)	100, 200 μg/mL	[57]
	Prochloraz (fungicide)	100 nM- 10 μM	[55]
	Gemfibrozil (antilipidemic pharmaceutical)	20 μM	[56]
	Brefeldin A (fungal product, inhibits protein transport)	1 mg/L	[56]
	Copper (metal)	190 μg/L–464 μg/L	[58]
	Copper pyrithione (Aquatic anti-fouling agent)	64 μg/L	[59]