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Title Page

Sediment toxicity assessment using zebrafish (*Danio rerio*) as a model system: historical review, research gaps and trends

Patrícia Saiki[a,b]; Francyelli Mello-Andrade[a,b]; Tânia Gomes [c]; Thiago Lopes Rocha[a*]

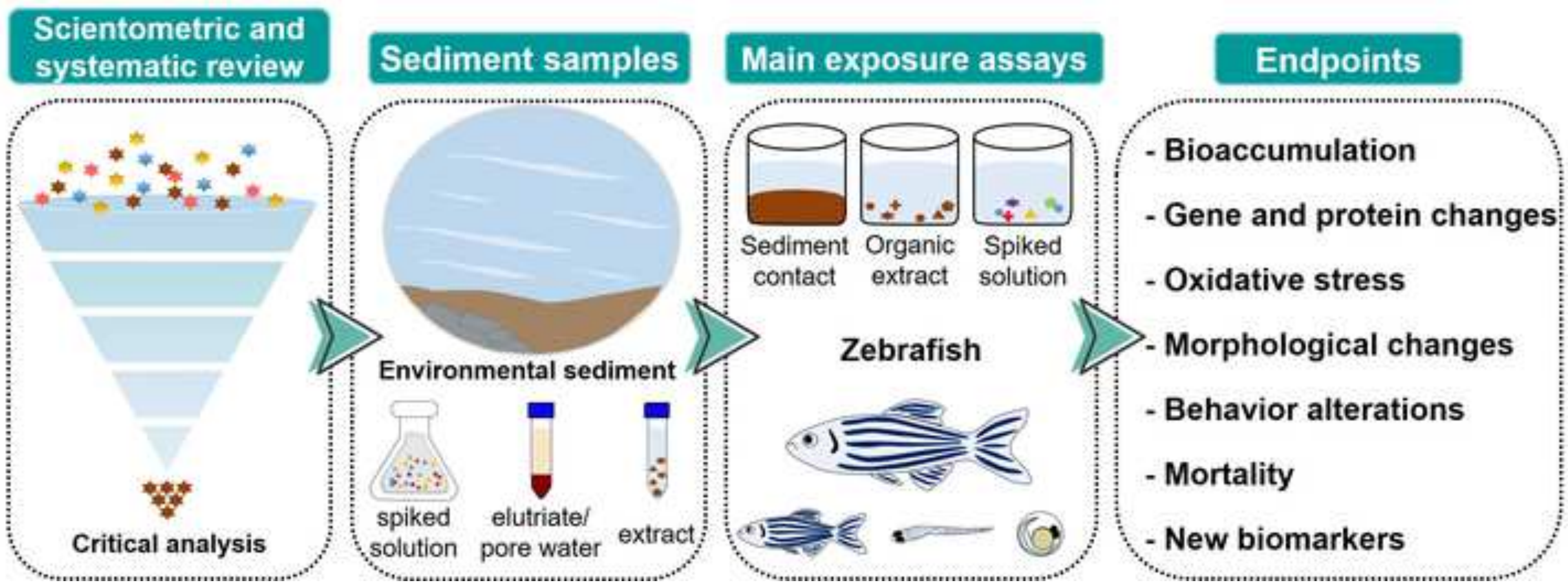
[a] Laboratory of Environmental Biotechnology and Ecotoxicology, Institute of Tropical Pathology and Public Health, Federal University of Goiás, Goiânia, Goiás, Brazil.

[b] Federal Institute of Education, Science and Technology of Goiás, Goiânia, Goiás, Brazil.

[c] Norwegian Institute for Water Research (NIVA), Section of Ecotoxicology and Risk Assessment, Gaustadalléen 21, N-0349, Oslo, Norway.

[*]Corresponding author at: T. L. Rocha, Universidade Federal de Goiás, Instituto de Patologia Tropical e Saúde Pública, Rua 235, Setor Universitário, Goiânia, Goiás, Brasil. CEP: 74605050. Tel.: +55 (62) 3209-6109. E-mail address: thiagorochabio20@ufg.br

Graphical Abstract



Highlights (for review : 3 to 5 bullet points (maximum 85 characters including spaces per bullet point)

Highlights

- State-of-the-art review on the use of zebrafish in sediment toxicity assessment;
- Pollutant-bound sediment exposure induces bioaccumulation and toxic effects on zebrafish;
- Sediment toxicity on zebrafish is mainly associated to oxidative stress and DNA damage;
- Zebrafish as an emerging model system to assess sediment toxicity.

Sediment toxicity assessment using zebrafish (*Danio rerio*) as a model system: historical review, research gaps and trends

Abstract

Sediment is an important compartment in aquatic environments and acts as a sink for environmental pollutants. Sediment toxicity tests have been suggested as critical components in environmental risk assessment. Since the zebrafish (*Danio rerio*) has been indicated as an emerging model system in ecotoxicological tests, a scientometric and systematic review was performed to evaluate the use of zebrafish as an experimental model system in sediment toxicity assessment. A total of 97 papers were systematically analyzed and summarized. The historical and geographical distributions were evaluated and the data concerning the experimental design, type of sediment toxicity tests and approach (predictive or retrospective), pollutants and stressors, zebrafish developmental stages and biomarkers responses were summarized and discussed. The use of zebrafish to assess the sediment toxicity started in 1996, using mainly a retrospective approach. After this, research showed an increasing trend, especially after 2014-2015. Zebrafish exposed to pollutant-bound sediments showed bioaccumulation and several toxic effects, such as molecular, biochemical, morphological, physiological and behavioral changes. Zebrafish is a suitable model system to assess the toxicity of freshwater, estuarine and marine sediments, and sediment spiked in the laboratory. The pollutant-bound sediment toxicity in zebrafish seems to be overall dependent on physical and chemical properties of pollutants, experimental design, environmental factor, developmental stages and presence of organic natural matter. Overall, results showed that the zebrafish embryos and larvae are suitable model systems to assess the sediment-associated pollutant toxicity.

Keywords: ecotoxicity; zebrafish embryotoxicity test; fish; elutriate, sediment-bound pollutant.

Introduction

Sediment is an important compartment in aquatic environments, where relevant biochemical transformations take place, and plays a critical ecological role as habitat and food source for countless species (Boulanger et al., 2019). Commonly known as the ultimate sinks for environmental pollutants (e.g., heavy metals, organic pollutants, xenobiotics, macro and micro(nano)plastics, nanomaterials and others), sediments are highly relevant in ecotoxicological assessments as they can provide a realistic scenario regarding environmental contamination (Schiwy et al., 2020). Most of these pollutants after ending in the sediment are expected to persist on aquatic ecosystems after interacting with the sediment matrix. Several pollutants can be released from the sediment to the water column when the sediment is changed by bioturbation and resuspension processes, thus eliciting long-term effects on sediment related/dwelling communities or benthic communities (Hollert et al., 2003; Schiwy et al., 2020).

Sediment quality studies evaluating the toxicity and resuspension of pollutants to the water column and its bioavailability for biota are very important to comprise the history, extent and trend of aquatic contamination (Hauer et al., 2018). Toxicological studies evaluating sediment toxicity and its potential impact on the aquatic environment has been widely carried out with primary producers (algae), bacteria and invertebrates (e.g., *Daphnia magna*) (Hollert et al., 2003). Thus, the need to integrate biomonitoring of aquatic ecosystems using a standardized vertebrate model system has emerged to fill knowledge gaps on impacts at higher ecological levels, and in some way, provide a parallel to human exposure as well.

The first reported fish-based studies evaluating sediment toxicity included *Pimephales promelas* (fathead minnow), *Oncorhynchus mykiss* (rainbow trout), *Lepomis macrochirus* (bluegill bream), *Micropterus salmoides* (largemouth bass), and *Carassius auratus* (goldfish) (Birge et al., 1977; Peddicord and McFarland, 1978; US EPA, 1981; Burton Jr, 1992). A large amount of sediment testing using fish species has been used to assess sediment-associated pollutants (Hallare et al., 2011; Feiler et al. 2013; Redelstein et al., 2015). Nonetheless, there is still a significant lack of whole sediment assays using an integrated approach and multiple biomarker response in vertebrate models.

In 1992 the Organization for Economic Cooperation and Development (OECD) published the test guideline for acute toxicity test of chemicals (OECD n° 203), recommending the use of zebrafish *Danio rerio* (Hamilton, 1822) in ecotoxicity testing strategies for aquatic environments (OECD, 2019). Zebrafish is considered a gold standard model for toxicity tests with water, effluents and sediments (Babić et al., 2017; Ribeiro et al., 2020). It features a small size, easy maintenance and reproduction in laboratory conditions, low maintenance cost, external embryonic development, high fertility, transparency of embryos and transgenic models available (Braunbeck et al., 2005; Muth-Köhne et al., 2012). In addition, due to highly conserved genetic and molecular processes across animals, many metabolic processes, as cell signaling and structure, anatomy, physiology, immunology, and development can be related to other vertebrates and even to humans, with which the zebrafish genome has approximately 70% similarity (Hill et al., 2005; Howe et al., 2013). Due to its advantages as a model system, multiple biomarker responses in zebrafish have been used to assess the ecotoxicological impact of traditional and emerging pollutants in Global North and South countries

(Campagna et al., 2013; Schweizer et al. 2018; Massei et al., 2019; Pereira et al., 2019; Trigueiro et al., 2020). Therefore, in combination with physico-chemical analyses, zebrafish can provide a real-time *in vivo* evaluation of the potential risk of sediments to aquatic ecosystems.

Accordingly, the current study aimed to evaluate the use of zebrafish as a model system in sediment toxicity assessments and describe the mechanisms of action and toxicity of pollutants-bound sediments. Besides, this study provides a comprehensive review on the data available in the scientific literature concerning the experimental design, type of sediment toxicity tests and approach (predictive or retrospective), zebrafish developmental stages, pollutants and stressors, bioaccumulation, and biomarkers responses in zebrafish applied in sediment toxicity tests. In addition, significant research gaps and recommendations for future research are also presented.

1. Methodological approach

A scientometric and systematic review was performed using the databases "ScienceDirect", "Scopus", "PubMed" and "Web of Science". The keywords "sediment", "extracts" and "elutriate" were combined with "zebrafish OR *Danio rerio*" and "toxicity" and "ecotoxicity", in both singular and plural forms. Papers until December 2020 were considered, while technical reports, review articles, academic theses, book chapters and scientific events summaries were not included (Figure 1). Initially, a total of 1,757 articles were found in the databases. After screening with the exclusion criteria (non-English records, reviews, technical reports, protocols, grey literature, do not fit the objectives, letters/short communications and duplicated documents), a total of 97 papers were systematically analyzed and summarized according to the following parameters: (*i*) year of publication; (*ii*) geographical location where the study was performed (identified from the mailing address of the corresponding author); (*iii*) sample type; (*iv*) experimental design (i.e., exposure time and system, extraction methodology); (*v*) developmental stages; (*vi*) biomarkers; (*vii*) type of approach (predictive or retrospective).

The data concerning the pollutants and/or stressors associated with the sediments, experimental design (i.e., zebrafish strain, control set up, exposure chambers, concentrations) and effects (i.e., mortality, hatching success, concentrations effects, bioaccumulation, behavioral changes, DNA damage, changes in gene expression and metabolism) were also summarized. The morphological alterations on zebrafish embryos and larvae induced by sediment-bound pollutants were classified into four reactional patterns (Rp): circulatory changes (Rp_1), pigmentation and tegumentary changes (Rp_2), musculoskeletal disorders (Rp_3), and yolk sac alterations (Rp_4), according to Pereira et al. (2019).

In order to understand relationship between the countries and the most influential researchers concerned with ecotoxicological assessment of sediments using zebrafish as a model, a cluster analysis among (*i*) the countries and (*ii*) the most influential researchers in the study area was performed using the VOSViewer© software (version 1.6.15, Centre for Science and Technology Studies, The Netherlands). The inclusion criteria for this analysis was that the author had at least 10 citations among the analyzed studies. The software generates a network whose visualization is based on nodes and connections, with the diameter of each node indicating the volume of (*i*) publications per country and (*ii*) citations of the referred author, while the distance between two nodes indicates the approximate intensity of the relationship between them (the higher relationship, the shorter the connection distance). Clusters are grouped by different colors (van Eck and Waltman, 2014).

2. Zebrafish use on sediment ecotoxicological assessments

3.1 Historical and geographical overview

Figure 2 presents the absolute and cumulative number of papers published until December 2020. The first studies using zebrafish as a model system to evaluate sediment toxicity were published in 1996, under predictive approach. Djomo et al. (1996) analyzed the toxic effects of polycyclic aromatic hydrocarbons (PAHs) evaluating uptake and depuration of 14C-radiolabeled compounds on zebrafish adults after exposure to spiked-sediment for a month. The main results indicated that more than 90 % of the compounds were sorbed to the sediment, decreasing the PAH bioavailability. Besides, Murk et al. (1996) analyzed the toxicity of pore water from 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-spiked sediment on zebrafish embryos and larvae for eight days, with reported $EC_{50} = 21 \pm 2.3$ ppm.

Revised data highlight the years 2014 and 2015, which together account for approximately 27% of the total number of publications. This finding seems to be associated with the publication of the OECD Guideline n° 236 in 2013 for testing of chemicals using the fish embryo acute toxicity (FET) test, which allowed the applicability of a faster and lower cost toxicity test to a wide range of substances (OECD, 2013). In addition, the availability of the full zebrafish genome also contributed to this increase, which has a great similarity to the genome of other vertebrates, including the human genome (Howe et al., 2013). The availability of transgenic strains may have also encouraged the increased use of zebrafish as a vertebrate model in sediment testing (Raftery et al., 2014). A similar growth in the number of studies using zebrafish was also reported for nanotoxicological (Pereira et al., 2019) and pesticide research (Gonçalves et al., 2020), confirming the wide application of zebrafish as a model in toxicological and ecotoxicological studies.

3.2. Geographical distribution, institutions and researchers

Regarding the geographical distribution of the studies carried out with sediments and zebrafish, Germany stands out (44.4% of the studies), followed by China (14.5%), the United States (10.3%), France and Brazil (both with 5.2%). Another 16 countries have articles published on that topic; however, 11 countries presented only one publication (Figure 3A). The cluster analysis performed with this data shows a strong relationship between Germany and China, for which the nodes are more expansive and with stronger interconnection (Figure 3B). Interestingly, among these 20 countries with publications evaluating sediment toxicity with zebrafish, 80% are classified with “very high human development” in the Human Development Index (HDI) and 20% with “high human development” (UNDP, 2020), suggesting a lack of investment in education, science and technology in countries with less economic development worldwide.

The institutions with the largest number of publications were University of Heidelberg (n = 15; 15.5%), Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen University (n = 7; 7.2 %), University of Tübingen (n = 6; 6.2%), Helmholtz Centre for Environmental Research (n = 4; 4.1%), all in Germany, followed by Tongji University in China (n = 3; 3.1%) and São Paulo University in Brazil (n = 3; 3.1%).

The cluster analysis among the researchers with the greatest centrality in this study area can be seen in Figure 4. The most cited author (largest diameter of the node) among all the studies raised was Hollert, H. (n = 30; 31%), followed by Braunbeck, T. (n = 18; 18.5%), Kosmehl, T. and Seiler, T. B. (both n = 8; 8.2%), all German researchers (RWTH

Aachen University and University of Heidelberg). Another important group visualized was formed by Chinese researchers, highlighted by Chen, L. (n = 4; 4.1%), from Tongji University. The network of connections points of cited authors highlighted Hollert, H. (Germany), as the most influential researcher in this field, with the highest number of citations, mainly due to the standardization of a sediment contact assay using zebrafish embryos for investigating whole sediments without extraction procedures (Hollert et al., 2003).

3.3 Experimental design

In terms of developmental stages, the sediment toxicity tests were conducted using mainly embryo-larval stages (77%) or only larvae (5%), while adults and juveniles were used in 15% and 3% of studies, respectively (Figure 5A), confirming the substitution of tests with adult animals for the early developmental stages. A similar trend has been reported regarding the use of zebrafish in effect-directed analysis (Di Paolo et al., 2015), further highlighting the higher sensitivity of early fish embryonic and larval stages to the effects of pollutants compared to juvenile and adult fish. Only one study evaluated transgenerational effects of pollutant-bound sediments (Vignet et al., 2014). These authors exposed zebrafish embryos to PAH-spiked sediment during 96 h and verified reproductive and behavioral effects in adults (after three and six months of development) and in the F2 generation.

Even though the use of whole sediment samples represents a more realistic environmental scenario under laboratory conditions, the use of elutriates and pore water have also been commonly used to determine the toxic potential of contaminated sediments. In the reviewed papers, studies involving sediment toxicity and zebrafish were conducted using different exposure procedures, such as whole-sediment contact assay (SCA) (45.1%), extract (31.3%), sediment with spiked solution (9.9%), microcosm with spiked sediment (5.3%), elutriate (3.8%), pore water (3.1%), and spiked food (1.5%) (Figure 5B). It is important to note that pore water is obtained by centrifuging fresh samples of sediment (interstitial water phase), while the elutriate phase intends to mimic the open-water remobilization of substances in sediments after resuspension and flood events through a water-extractable liquid-to-solid (usually 1:4 v/v) (Hallare et al., 2011).

The greater number of experiments exposing zebrafish to SCA can be explained due to the agreement that whole-sediment exposure can represent scenarios as close to reality to simulate exposures in the laboratory (Hollert et al., 2003). Organic sediment extracts enable the assessment of strongly absorbed compounds and may overestimate the bioavailability of pollutant-bound sediments to aquatic organisms or simulate worst-case scenarios. Nonetheless, it is a great technique for screening total chemical content in each fractionation step (Hallare et al., 2011). In general, it is believed that exposure to organic extracts imply greater toxicity in zebrafish than SCA (Hollert et al., 2003). Wu et al. (2010) comparing SCA and extracts from six environmental sites found higher mortality in exposed fish than the control group but with no differences between exposure methodologies and sites. In contrast, when assessing abnormalities, significant differences were found between both types of exposure for each site, with greater morphological changes in embryos exposed to the extracts than whole-sediments. Also, embryos exposed to extracts showed higher genotoxicity and gene expression changes (i.e., *cyp1a* and *cyp1c1*) than those exposed to the whole-sediment (Kosmehl et al., 2007; Bluhm et al., 2014). Even so, it is possible to find higher whole-sediment toxicity in relation to its extract, such as reported by Seopela et al. (2016). In this study, a higher mortality was found in zebrafish after exposure to whole-sediments (61.3 to 100%) in comparison with their extracts (1.67 and 3.34%). Another study did not find clear-cut differences in zebrafish responses to both acetonic extracts and native samples (Schulze et al., 2015). The toxicity of natural sediment samples may vary depending on their characteristics such as content of organic matter and grain size distribution (Höss et al., 2010), as well as the extraction procedure.

Revised data showed that the knowledge concerning the toxicity of pollutant-bound sediments on zebrafish under environmentally relevant conditions, such as micro- and mesocosms, mixture toxicity and multi-species exposure remain scarce and deserve further studies. Microcosms are intended to simulate natural environments, under control conditions, usually capable to understand bioavailability, uptake, bioaccumulation and bioturbation processes either in a binary system (i.e., water-sediment microcosm) or with more elements (i.e., water-sediment-zebrafish) (Chen et al., 2017). This simulated environment allows researching kinetic and thermodynamic behaviors of pollutants with a good reproducibility (Tian et al., 2020). Mesocosms are cutouts from a natural environment separated from the ecosystem by physical barriers, what provides more realism but at a higher cost (Amiard-Triquet et al., 2015).

Regarding the type of sediment samples analyzed with an integrated approach with zebrafish, there is a predominance on the use of freshwater samples (82.5%) followed by marine sediments (7.3%), sediments spiked in the laboratory (5.1%) and samples collected from estuaries (5.1%) (Figure 5C). Furthermore, sediment toxicity studies using zebrafish as a model were conducted under different exposure periods (Figure 5D). The exposures were performed mainly during 96 h (37.2%), as recommended in the FET Test Guidelines (OECD, 2013), followed by 48 h (18.6%) and 72 h (12.7%), with 69.5% of the studies under acute toxicity conditions. Revised data showed that sediment toxicity to zebrafish embryos and larvae is dependent on exposure time and that more chronic studies are needed.

The analysis of whether the reviewed studies carried out a retrospective approach to the possible contamination existing in the samples or a predictive approach to analyze the toxic potential of contaminants associated with sediments was also conducted. More than 75% of the studies assessed the toxic potential of sediments towards zebrafish using a retrospective approach, highlighting the analysis of multiple biomarkers in zebrafish as an important tool in quality assessment of environmental samples (Figure 5E).

3.4 Pollutants and stressors

Pollutants and stressors associated to sediment toxicity assessments with zebrafish were classified into 21 categories, based on their composition, physicochemical properties and usage. PAHs were the main pollutant class used on zebrafish pollutant-bound sediment toxicity testing (47.4%), followed by metals (40.2%), dioxin-like compounds (38.1%) and agrochemicals (19.6%), which include pesticides (such as Dichlorodiphenyltrichloroethane - DDT), herbicides and fungicides (Figure 6).

PAHs are substances formed by the incomplete combustion of organic material, present in complex mixtures in all environmental compartments, but mostly associated with suspended particulate matter which makes the sediment their main source of storage (Cousin and Cachot, 2014). In addition, they have great persistence in the environment and have carcinogenic and mutagenic potential (Hylland, 2006). PAHs induced several toxic effects in zebrafish under different exposure conditions, such as increased mortality rates, genotoxicity, morphological changes (i.e., pericardial and yolk sac edemas, tail malformations, underdeveloped eyes, lack of pigmentation), in addition to decreased hatching rates, circulatory functions and swimming behaviors (Yang et al., 2010; Perrichon et al., 2014; Li et al., 2016; Johann et al., 2020; Table S1).

Metals are widely used in human manufacturing processes and their tendency to ionization can enhance toxicity to aquatic organisms even at low concentrations by alterations in their absorption, distribution and metabolism (Donkin et al., 2000), with a great persistence and potential for bioaccumulation (Ali et al., 2019). Some examples of metals analyzed in the reviewed studies were cadmium (Cd), chromium (Cr), nickel (Ni), zinc (Zn), mercury (Hg) and lead (Pb) and their main effects to zebrafish were increased mortality, morphological changes, bioaccumulation, changes in genes expression related to metals metabolism and hatching rates (Béchard et al., 2008; Dedeh et al., 2014; Redelstein et al., 2015; Wang et al., 2015; Table S1).

Dioxins and dioxin-like compounds (DLCs) refer to polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), and PCBs with structure and effects similar to dioxins (dioxin-like PCBs - DL-PCBs) (Chung et al., 2018), which ring structures can be chlorinated to varying degrees. They emerge mainly from combustion reactions and industrial process, are persistent in the environment due to lipophilic, hydrophobic and chemical stability characteristics and can travel long distances from the source, causing countless effects in humans and environment life, like cancer, thyroid disturbance, reproductive fail, neurodevelopment diseases and biomagnification (Schiavon et al., 2016; WHO, 2019). Zebrafish exposed to DLCs showed morphological and histopathological changes in gill, liver, intestinal folds, head, kidney, spleen, swim bladder and blood cells (Yu et al., 2017; Qamar et al., 2020) and PCB bioaccumulation in lipids (Fadaei et al., 2015). In addition, DLCs induced mortality, development and hatching alterations, genetic damages, morphological changes and biochemical effects (Kais et al., 2017; Boulanger et al., 2019; Dong et al., 2019; Table S1).

Agrochemicals are a worldwide concern since their indiscriminate use and lack of proper regulation and monitoring of its trade in several countries. The problem hides in a lack of knowledge about their adverse effects on non-target organisms and the entrance of agrochemicals into aquatic ecosystems per run-off, which will increase due to frequent rain events as a consequence of climate change. Their very well-known consequences to biota are related to carcinogenic, mutagenic, reproductive and endocrine effects (Larramendy and Soloneski, 2015). Associated with sediments, agrochemicals cause increased mortality, teratogenicity, reproductive disorders, developmental delay, changes in swimming behavior, genotoxic and biochemical alterations in zebrafish (Nguyen and Janssen, 2001; Kais et al., 2015; Yan et al., 2015; Table S1).

3.5 Bioaccumulation

Few studies (12%) evaluated bioaccumulation in zebrafish after exposure to pollutant-bound sediments. Half of them evaluated bioaccumulation of metals and only four studies were carried out with early developmental stages (embryo and larvae) (Table S1). Two studies evaluating metal accumulation in zebrafish embryos after 48 h SCA exposure showed a decrease in bioaccumulation when metals were in mixture (Redelstein et al., 2015) or associated to an ion exchange resin (Mages et al., 2008), probably by causing a decrease in their bioavailability. In addition, pH was an important factor in determining toxicity of mixtures. Zebrafish larvae accumulated decabromodiphenyl ether (BDE-209), a flame retardant, 10-fold than the control, and yet did not show differences in morphology, morphometrics length and levels of T4 in thyroid follicles; apart from changes in swimming behavior (Garcia-Reyero et al., 2014). Trevisan et al. (2019) estimating PAH-mixture bioaccumulation in zebrafish after a 96 h co-exposure with nanopolystyrene particles (Nano-PS) observed a decrease in PAH bioavailability and uptake probably due to the absorption of PAHs to the surface of the Nano-PS.

Seeking to evaluate PCB bioaccumulation in fish lipid content, zebrafish juveniles were submitted to different sediment exposure setups undergoing treatment with and without coal-based fine granular activated carbon (AC). PCB uptake in zebrafish decreased by 87% in treatments with AC after 90 days, which is also consistent to percent reductions in porewater and overlying water (Fadaei et al., 2015). Bioavailability reduction of hydrophobic organic chemicals bound to sediments treated with AC was also evident to other organisms, as the freshwater oligochaete worm (*Lumbriculus variegatus*) (Beckingham and Ghosh, 2011) and benthic invertebrates, zooplankton and fish (*Leuciscus idus melanotus*) (Kupryianchyk et al., 2013).

The remaining papers evaluating bioaccumulation were performed in microcosms scenarios using zebrafish adults, in which several tissues were analyzed for bioaccumulation of sediment-bound pollutants. The relationship between sediments and its properties to sorb pollutants from the aquatic environment was analyzed by Djomo et al. (1996). This study showed that over 90% of PAHs (phenanthrene, pyrene, anthracene, benzo[a]pyrene) in spiked-medium were sorbed to the sediment, which resulted in the reduction of PAH bioavailability to zebrafish over time. The fate and bioavailability of total mercury (HgT) in the presence of sediment collected from a forest creek was investigated by Dominique et al. (2007), in which a significant HgT bioaccumulation was observed in the brain, gill, liver and skeletal muscle of zebrafish exposed via microcosms. In addition, after spiked-sediment exposure, the elimination of PAHs and nonylphenol was observed in zebrafish after depuration in a clean medium during 360 h (Djomo et al.,

1996) and 408 h (Huang et al., 2007). The authors suggest, however, that this decrease was probably associated with detoxification mechanisms present in fish that allowed the metabolization and transformation of these compounds. Trophic transfer of Cd from chironomids (*Chironomus riparius*) exposed via sediment to zebrafish was also observed, resulting in high concentrations in the gut and kidney, followed by the liver, gill and carcass of adult zebrafish, when compared to waterborne exposure (Béchard et al., 2008). Metal accumulation was observed in the digestive tract, gill and muscle of zebrafish, being ionic Au greater than Au nanoparticles (AuNP) (Dedeh et al., 2014), while Hg was poorly available to the fish at 168 hours of exposure because of the metal adsorption to the sediment (De Carvalho et al., 2006). Despite the adsorption of pollutants to the sediment, Chen et al. (2017) showed that the sediment sorption of pharmaceutical pollutants decrease their bioavailability to zebrafish, and is highly affected by sediment particle size and organic matter content similarly, as already reported in the literature (Bowman et al., 2002; Zhou and Broodbank, 2014).

3.6 Biomarkers

In addition to behavioral effects, mortality, hatching alterations and morphological changes, multiple biomarkers were identified in zebrafish exposed to pollutant-bound sediment at the molecular, genetic and biochemical levels, including genotoxicity (26%, n = 16), xenobiotic metabolism (24%, n = 15), oxidative stress (13%, n = 8), neurotoxicity (11%, n = 7), endocrine disruption (10%, n = 6), mitochondrial dysfunction (6%, n = 4), cytotoxicity (5%, n = 3), developmental toxicity (3%, n = 2), and immunotoxicity (2%, n = 1) (Table S2; Figure 7).

3.6.1 Behavioral biomarkers

Animal behavior is correlated to development and function of their neural systems and behavior assays can provide signs of disruptions and neurotoxicity. Several behavior assays with zebrafish are suggested in literature (Orger et al., 2004; Legradi et al., 2018; Shen et al., 2020); however, these studies have not yet been widely applied or standardized in sediment toxicity assessments. Only 8% of the reviewed studies analyzed behavioral changes in zebrafish after pollutant-bound sediment exposures (Table 1). The main assays used to evaluate behavioral changes in zebrafish exposed to pollutant-bound sediments were swimming activity (distance and velocity), touch-escape response and photomotor response (PMR), which are used as indicators of stress and anxiety (Vignet et al., 2014). In general, the studies found a decrease in zebrafish locomotor activity, swimming velocity and a reduced touch-escape response after pollutant exposure (Table 1). Only two studies analyzed behavioral responses in adult zebrafish (Vignet et al., 2014; Hafner et al., 2015). Strmac et al. (2002) observed a concentration-dependent reduction in motility of 96 hpf larvae exposed to sediment extracts polluted by metals, PAHs and pesticides, at concentrations ranging from 0.0125 to 0.1%.

The acclimation time, analysis and recordings varied widely between the studies, confirming the lack of standardization in this type of research. Larvae acclimation varied mainly between 5 and 10 min and up to 2 h. Time of analysis varied from 15 min to 1.75 h and recording periods varied from 15 min to 2.75 h, in addition to light/dark challenges (5 min to 1.5 h). Two software's were used to record zebrafish activities: EthoVision® XT video tracking software (version 8.0.516, Noldus Information Technology, The Netherlands) and VideoTrack for Zebrafish™ (ViewPoint Life Sciences, France). Just one study presented the illumination used on PMR assays, which corroborates, one more time, the lack of standardization for behavioral tests (Vignet et al., 2014).

3.6.2 Mortality, hatching inhibition and morphological changes

Almost 70% of papers evaluated zebrafish mortality after pollutant-bound sediment exposure (Table 1). Most studies that did not evaluate mortality used sub-lethal concentrations in order to assess genotoxic effects or changes at molecular levels in living animals. Half of these papers estimated LC_{50} (median lethal concentration), LOEC (lowest observed effects concentration) or EC_{50} (Effect Concentration 50%), seeking to understand the minimum concentrations that caused effects at the morphological level and mortality of 50% of the population (Table S1). Again, half of these studies were directed to determine PAH concentrations (43.8%), followed by metals (28.1%), dioxin-like compounds (25%) and agrochemicals (15.6%).

Decreased hatching rates were reported in 25% of the studies, indicating that several pollutants-bound sediments can inhibit zebrafish hatching and induce high mortality rates. Hatching inhibition was reported for zebrafish embryos exposed to PAHs, DLCs and metals (Vincze et al., 2014; Wang et al., 2015; Viganò et al., 2020) (Table S1). On the other hand, the mechanism of action of these pollutants on gene expression and enzymes responsible for hatching deserve further studies.

Of the 77% of studies carried out with zebrafish in embryo-larval stages, 57.7% analyzed morphological effects. Morphological alterations in zebrafish were grouped into general alterations and the four reaction patterns described by Pereira et al. (2019): circulatory changes (Rp_1), pigmentation and tegumentary changes (Rp2), musculoskeletal disorders (Rp_3) and yolk sac alterations (Rp_4) (Table 1). General edema was assigned when the authors did not detail the type of morphological changes. Musculoskeletal disorders and circulatory changes account almost 78% of the morphological effects reported, highlighting pericardial edema (12.6%), bradycardia (11.6%), abnormal circulation or vasculature (8.2%) and spine malformations (7.2%). Yolk sac edema and changes in pigmentation have also been detected frequently, 9.2% and 7.2%, respectively. Interestingly, only one paper presented changes in the swim bladder after DL-PCBs-sediment extracts exposure (Yu et al., 2017). The swimming bladder plays a fundamental role in coordination of larvae after hatching and locomotion for survival and escape predation (Lindsey et al., 2010) and its inflation is a relevant biomarker to assess the thyroid hormones disruption (Li et al., 2011; Stinckens et al., 2016; Wang et al., 2020).

3.6.3 Molecular and biochemical assays

Molecular and biochemical biomarker responses in zebrafish were assessed in 48% of studies with pollutant-bound sediment toxicity tests. Zebrafish at different developmental stages (i.e., embryo, larvae, and adult) were used in 36% (n = 35) of the studies (Table S2), while 12% (n = 12) of the studies were performed with other models. Most research using zebrafish evaluated the genetic and molecular parameters as a sediment toxicity endpoint (n = 21, 22%), while biochemical assays were performed in 6% of the studies (n = 6). Interestingly, 23% (n = 8) research of sediment toxicity using zebrafish evaluated both biomarkers (Figure 7, Table S1). Molecular assays evaluated genetic parameters, such as genome integrity and protein and genes expression, while biochemical assays included measurement of enzyme activity (e.g., ethoxyresorufin-O-deethlyase - EROD, acetylcholinesterase - AChE).

Results of the present study showed that genotoxicity was the most reported sediment toxicity biomarker using zebrafish embryos. Genotoxic studies using zebrafish as an experimental model have been recently reviewed, and sediment genotoxicity represented only 6.9% of all studies (Canedo and Rocha, 2021). The following techniques were applied to measure DNA damage as a sediment toxic effect in zebrafish: alkaline comet assay (Kosmehl et al., 2006, 2007, 2008; Boehler et al., 2017), global DNA methylation (Boulanger et al., 2019) and random amplified polymorphic DNA-PCR (RAPD-PCR) (Dedeh et al., 2014). Quantitative reverse transcription polymerase chain reaction (qRT-PCR) is another technique that was used to identify gene expression changes related to DNA repair mechanisms (Bluhm et al., 2014; Boulanger et al., 2019; Viganò et al., 2020). Similarly, the majority of genotoxicity studies adopted comet assay to evaluate DNA damage (Canedo and Rocha, 2021). The comet assay is a well-established technique useful in assessing the genotoxic potential of a wide range of pollutants (Frenzilli et al., 2009; Lapuente et al., 2015; Canedo and Rocha, 2021).

Zebrafish embryos exposed to whole sediments or their organic extracts proved to be sensitive to genotoxic effects of sediment pollutants, including heavy metals (Kang et al., 2014), organic pollutants (Kosmehl et al., 2006; Li et al., 2016; Sogbanmu et al., 2016), or both (Kosmehl et al., 2007, 2008). It is worthy to note that genotoxicity is a complex biological phenomenon implicated in multiple pathways, and DNA repair mechanisms as a response to adverse effects on a cell's genetic material and its integrity is often a rapid process. Therefore, the connection between DNA damage and other biomarkers becomes necessary to fully understand the extent of the mechanism behind the toxicity seen, as the case of xenobiotic metabolism, oxidative stress and general defense mechanism, cytotoxicity, among others (Canedo and Rocha, 2021). A study using zebrafish embryos observed that different sediment constituents probably led to differences in the embryotoxicity and genotoxicity of sediments organic extracts from different sampling sites in the Yangtze River estuary (Li et al., 2016). Whereas in another study, the genotoxicity was associated with cytotoxicity, i.e. cell death by apoptosis, as a toxic effect of exposure to whole sediment from Vering Kanal (Hamburg, Germany). As a consequence, bradycardia and pericardial edema were also observed on zebrafish embryos and larvae (Garcia-Käufer et al., 2015).

One of the most investigated biomarker responses in zebrafish exposed to sediments were related to the xenobiotic metabolism determined either by the expression of genes that encodes proteins or enzymes well established in the xenobiotic detoxification (e.g., *cyp1*) (Redelstein et al., 2015; Boulanger et al., 2019), or by enzymatic activity (e.g., EROD activity) (Perrichon et al., 2014; Boehler et al., 2018), or both (Schiwy et al., 2014; Bräunig et al., 2015). Xenobiotic-metabolizing enzyme CYP1A (cytochrome P450, family 1, subfamily A) is associated with the EROD activity. The EROD assay is widely used as a biomarker of xenobiotic metabolism in research toxicology, including aquatic ecotoxicology (Široká and Drastichová, 2004). However, based on cellular and subcellular responses induced by xenobiotic detoxification processes, an integrated biomarker approach is necessary to provide information about the process involved in toxicity response (Janz, 2013). For example, Schiwy et al. (2014) showed embryotoxicity in zebrafish exposed to sediment from the Rhine River (Altrip and Ehrenbreitstein, sites classified as low and moderately contaminated sites, respectively) and the Vering Kanal (highly contaminated site). Despite the fact that exposure to these sediments induced upregulation of *cyp1*, only Vering Kanal sediment exposure was able to induce the xenobiotic-metabolizing enzyme CYP1A1 (cytochrome P-450 1a1) in zebrafish embryos, curiously the sediment with highest embryotoxicity.

Xenobiotic detoxification comprises a central process in the metabolism of xenobiotic pollutants, such as planar aromatic substance classes, metals and pesticides. The well-known mechanism of CYP1A1 induction is mediated by binding of several xenobiotics, such as dioxins, PCBs and PAHs, to protein complexes formed by cytosolic aryl hydrocarbon receptor (AhR) and heat shock protein 90 (HSP90) (Whyte et al., 2000). A series of molecular events are initiated after AhR binding, leading to the expression of several genes that encode protein associated with xenobiotic's metabolism response, including increased expression and activity of CYP1A (Safe and Krishnan, 1995). Alterations in the xenobiotic metabolism of zebrafish embryos exposed to PAHs containing fraction of sediment extracts from the Vering Kanal was reflected by an increased cyp1a1 activity, upregulated *cyp1* gene expressions (*cyp1a*, *cyp1b1*, *cyp1c1*, and *cyp1c2*), as well as upregulated *ahr2* expression (Bräunig et al., 2015). Indeed, sediment contaminated with dioxin-like compounds, PBDEs, PCBs, PCDDs, and HCB can also act as inducers of zebrafish cyp1a (Kosmehl et al., 2012; Boulanger et al., 2019; Dong et al., 2019; Viganò et al., 2020).

As well as CYP1A1 have commonly been used as biomarkers for planar aromatic substance classes exposure (e.g., PAHs), so metallothioneins (MTs) have been used as biomarkers for trace metal exposure. MTs comprise a family of metal-binding protein involved in heavy metal detoxification and cellular antioxidative defense (Chan, 1995). Zebrafish embryos exposed to artificial Zn-spiked sediment caused changes in gene expression related to xenobiotic metabolism, including *mt1* and *mt2,* but not *cyp1a1* (Redelstein et al., 2015). In contrast, zebrafish larvae exposed to three sample of contaminated sediments with chemical mixtures (PAHs, PCBs, PCDDs and metals) from Lake Saint-Louis, Canada, increased the expression of *cyp1a* and *cyp1b1,* but not *mt2* gene. Although sediments contain high concentrations of organic contaminants and metals, molecular assays showed evidence of organic contaminants as the main responsible for the different biological level's effects. Notably, a significant increase in zebrafish mortality was associated to sediment exposure presenting higher PCDDs concentration (Boulanger et al., 2019).

3.6.4 Oxidative stress and antioxidant mechanisms

Pollutant-bound sediments can induce oxidative damage by intracellular reactive oxygen species (ROS) production and oxidative damage in proteins, lipids and DNA, leading to cell death (Lushchak, 2011). Defense antioxidant mechanisms are usually activated, such as heat shock proteins (HSP), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), to prevent cellular damage (e.g., DNA damage and cell death) (Lushchak, 2011, 2016). Zebrafish embryos exposed to zinc oxide nanoparticles (ZnO NPs) aggregates presented cellular oxidative stress, due to failure to upregulated of *gstp2* and *nqo1* (xenobiotic metabolism genes) and higher levels of ROS. These results were associated with hatching inhibition and high frequency of pericardial edema. Interestingly, zebrafish embryos exposed to ZnO NP aggregates in the presence of sediments were able to upregulate the expression of *gstp2* and *nqo1*, thus normalizing hatching rate and avoid cardiotoxic effects (Zhu et al., 2009).

Nevertheless, pollutant-bound sediments led to oxidative stress and changes in the antioxidant enzymes in zebrafish. For example, zebrafish embryos exposed to organic sediment extracts of Laguna Lake, Philippines, increased levels of hsp70 protein, resulting in delayed hatching and pericardial edema (Hallare et al., 2005). In addition to xenobiotic metabolism activation, oxidative stress responses resulted in the upregulation of the *hsp70* gene but not *sod1*, which regulates oxidative stress resistance, in zebrafish embryos exposed to Zn-bound sediments at sub-lethal concentrations (Redelstein et al., 2015). Similar effects were reported in adult zebrafish (Dedeh et al., 2014).

3.6.5. Endocrine disruption and neurotoxicity

Environmental pollutants and stressors may affect the normal secretion of hormones, influencing the growth, development, sexual differentiation and reproduction of aquatic organisms (Mouneyrac and Amiard-Triquet, 2013; Guo et al., 2019). Endocrine disruption was evaluated on the response to sediment exposure in zebrafish. Nevertheless, the effects caused by endocrine disruptors are not entirely clear from the revised data, probable due to the complexity of the sediment samples. Fetter et al. (2014) reported the estrogenic activity in transgenic zebrafish embryos tg(*cyp19a1b:*GFP), after exposure to sediment fractionated extracts from the river Bilina, Czech Republic. Alkylphenols and the natural steroid estrone present in the sediment-fractionated extracts were suggested as endocrine disruptors. Adult zebrafish exposed orally to organic extracts of sediments from Molnbyggen, a leachate-contaminated lake in Sweden, were evaluated for relationships between changes in sex steroid levels and index for assessing reproductive toxicity. Whole-body estradiol and testosterone levels were reduced, evidencing the presence of pollutants with endocrine-disrupting potential in the sediment; however, whole-body steroid concentration did not seem to affect body weight. No effects were observed on spawning capacity, gonadosomatic index (GSI), or liver somatic index (LSI) (Linderoth et al., 2006). Overall, selecting multiples endpoints at different biological levels may offer a comprehensive toxicological characterization of the sediment using zebrafish as a model system.

Alterations in AChE activity is a well-established biomarker of neurotoxicity in ecotoxicological studies (Payne et al., 1996). AChE inhibition in zebrafish embryos was also considered a suitable biomarker of neurotoxicity in sediment toxicity assessments (Kais et al., 2015). In contrast, sediments contaminated with organic pollutants and heavy metals from Gulf of Bothnia, in Sweden, caused developmental malformations, delayed hatching, bradycardia, and alterations of locomotor activity in zebrafish embryos; however, inhibition of AChE was not detected (Massei et al., 2019). Notably, neurotoxicity associated with an increase in AChE activity was also reported. Adult zebrafish exposed to Au NPs-bound sediment induced AChE activity, DNA damage and upregulation of gene related to oxidative stress (*sod2*, *hsp70*), mitochondrial dysfunction (*cox1*), DNA repair mechanisms (*gaad*), and neurotoxicity (*ache*). As mentioned previously, neurodevelopmental and reproductive toxicity could lead to the behavioral changes (He et al., 2014; Guo et al., 2019). In fact, revised data highlighted that neurodevelopment may be influence by several biological organismal levels.

3.6.6 Histopathological biomarkers

Alterations in tissue-level biomarkers were also reported in zebrafish exposed to contaminated-sediments, for example, which contains DLCs. Qamar and coworkers (2020) revealed alterations in spleen and kidney of adult zebrafish after 28 days exposure to DL-PCBs bound-sediment using classic histopathological analysis (hematoxylin and eosin staining). Several histological damages were reported in the spleen of zebrafish exposed to DL-PCBs, including decrease in spleen size, reduction of lymphocyte number and increased lysis of red blood cells. In addition, cell dissolution, tubular lumen dilatation and renal interstitial cell edema were detected in the kidney. Corroborating these findings, the increased white blood cells and reduced the number of red blood cells, lysozyme activity and immunoglobulin concentration were also reported as immunotoxic effect in zebrafish after exposure to DL-PCBs-bound sediments (Qamar et al., 2020).

Revised data showed that the use of new routine histological approaches, including immunohistochemistry and *in situ* hybridization, allows not only the detection of morphological and structural alterations in multiples organs, but their association with molecular events (Janz, 2013). For example, exposure to DLC-contaminated sediment extracts revealed the activation of cyp1a at transcriptional and protein levels in a concentration-dependent manner. The use of whole mount *in situ* hybridization (WISH) analysis by the authors allowed for the localization of *cyp1a* expression to the gill arches of larvae at 36 hpf (Dong et al., 2019).

3.6.7 OMICs approaches and transgenic zebrafish strains

OMICs approaches comprise of high-throughput technologies that measure the entirety of gene transcripts (transcriptome), proteins (proteome), or metabolites (metabolome) in a biological sample after xenobiotic exposure (Sukardi et al., 2010; Mushtaq et al., 2013). It is noteworthy to mention that the use of “OMICs” technologies associated with toxicological effects of different pollutant types in zebrafish have been reported (Schüttler et al., 2017; Piña et al., 2018; Zheng et al., 2018; Pereira et al., 2019; Farnsworth et al., 2020). Organic pollutants and heavy metals are major classes of pollutants identified in the sediment samples using OMICs approaches. OMICs technologies were also reported in sediment toxicity assessments, such as the use of microarrays (Kosmehl et al., 2012; Bluhm et al., 2014; Garcia-Reyero et al., 2014) and capillary column high resolution gas chromatography/high resolution mass spectrometry (HRGC/HRMS) (Linderoth et al., 2006).

Microarray is used as a transcriptome technology to monitor the concentration of specific mRNA molecules for a given cell, tissue, organ, or whole organism.

HRGC/HRMS can be used to describe the chemical composition of endogenous metabolites originating from biochemical pathways (Piña et al., 2018). These advances make it possible to observe the total system and explore the molecular mechanisms underlying a phenotype alteration, as well as identify new biomarkers of exposure and effect. This will in overall provide an insight into the possible mechanism of action related to the phenotypic changes as a direct or an indirect consequence of a toxicant exposure (Sukardi et al., 2010; Mushtaq et al., 2013). One example is the study by Garcia-Reyero et al. (2014), where several biological responses were evaluated after exposure to BDE-209 contaminated sediments in zebrafish. In this study, phenotypic and individual responses were linked to pathways regulated by molecules mainly associated with neurodevelopmental toxicity, even though differences in the thyroid function measured as intrafollicular T4-content by T4 immunofluorescence quantitative disruption test (TIQDT) and whole-mount immunohistochemistry, were not detected in zebrafish larvae. The first study using microarrays for the characterization of sediment toxicity, revealed a relationship between DNA damage (comet assay) and alterations in gene expression profiles in zebrafish embryos. These alterations in gene expression related to catabolic processes and neurodevelopmental processes, which responded to lipid binding and peptidase activity, visual perception, xenobiotic metabolism, and oxidative stress (Kosmehl et al., 2012).

Only one study used knockdown technology to assess the toxicity of pollutant-bound sediments, while transgenic zebrafish strains were used in three studies to analyze sediment toxicity assessment. The strains of tg(*cyp19a1b*:GFP), tg(*cyp1a*: mCherry), tg(*mlse*:GFP), and tg(*flk1*:EGFP) were used to evaluate endocrine disruption (Fetter et al., 2014), xenobiotic metabolism (Dong et al., 2019), mitochondrial dysfunction and cardiotoxicity (Trevisan et al., 2019), respectively. Wild-type zebrafish exposed to sediment demonstrated the activation of cyp1a at transcriptional and protein levels and cardiotoxicity, which are related to the presence of dioxin-like compounds in the sediment extracts and binding with AhR2 receptor. Confirming these findings, the use of the zebrafish *ahr2* morpholino knockdown did not show pericardial edema. Moreover, the induction of cyp1a promoter revealed by *mCherry* expression in heart position of the transgenic zebrafish larvae tg(*cyp1a*:*mCherry*) was also demonstrated as a toxic effect of exposure to dioxin-like contaminated sediments (Dong et al., 2019). In addition, the assessment of pollution monitoring using transgenic technology might reveal sediment toxicity mechanisms (Padilla, 2014).

4. Conclusion and perspectives

The present review summarized the data available in literature concerning the use of zebrafish (*D. rerio*) as a vertebrate model to assess the bioaccumulation and toxicity of pollutant-bound sediments. Overall, the revised data showed that zebrafish is an emerging model-system for testing the toxicity of traditional and emerging pollutant-bound sediments, of different contamination grades. The sediment toxicity in zebrafish is dependent on physical and chemical properties of pollutants, experimental design (i.e., exposure condition, concentration and exposure period), environmental factors (i.e., temperature, pH, conductivity), developmental stages and presence of organic natural matter. The sediment toxicity tests were conducted using mainly zebrafish embryos and larvae, focusing on the analysis of multiple biomarker responses, such as mortality rate, hatching rate, morphological alteration frequency, genotoxicity, neurotoxicity, xenobiotic metabolism, among others. Results showed that further studies with multiple biological targets at different levels of biological organization are needed to better understand the mechanism of action and toxicity of pollutant-bound sediments. To summarize, several research gaps that deserve further attention are highlighted, such as:

a) Assessment of sediment toxicity in more environmentally relevant conditions (i.e., multispecies exposure and microcosms);

b) Interactive effects of pollutants-bound sediments (mixture toxicity);

c) Transgenerational exposures and multigenerational effects;

d) Interaction between sediment microbiology and toxicity;

e) Development of standard protocols for assessing the toxicity of emerging pollutants (i.e., nanomaterials and endocrine disruptive compounds);

f) Investigate sediment toxicity under global changes.

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Figure captions

Figure 1. Systematic review methodology. A) Scoping; B) Planning; C) Identification; D) Screening; E) Eligibility assessment; F) Interpretation and Presentation. [1] Electronic databases: “ScienceDirect”, “Scopus”, “PubMed” and “Web of Science”. [2] Exclusion criteria: non-English records, reviews, technical reports, protocols, grey literature, do not fit the objectives, letters/short communications and duplicated documents.

Figure 2. Number of papers published (absolute and cumulative) concerning the use of zebrafish as a model system in sediment toxicity assessment from 1996 until December 2020.

Figure 3. A) Number of papers per country evaluating sediment toxicity and zebrafish, from 1996 to 2020, n = 97. B) Cluster analysis of the countries with studies evaluating sediments and zebrafish. The diameter of the node indicates the volume of publications and the connections indicate the intensity of the relationship between the countries.

Figure 4. Cluster of the most influential authors in research with sediment toxicity assessment and zebrafish, with at least ten citations, over the years. The diameter of the node indicates the volume of citations and the connections indicate the intensity of the relationship between the authors cited.

Figure 5. Number of papers (%) by experimental designs in sediment toxicity assessment using zebrafish. A) Zebrafish development stages used for assessing sediment toxicity. B) Sediment exposure procedures; C) Type of sediment sample; D) Exposure times; E) Approach evaluation of the sediment toxicity.

Figure 6. Number of papers (%) according to pollutant or stressor categories on sediment toxicity assessment using zebrafish as model system.

Figure 7. Trends in molecular and biochemical techniques using zebrafish as model to assess sediment toxicity.

Table caption

Table 1. Morphological alterations in zebrafish induced by pollutant-bound sediments, based on reaction patterns of Pereira et al. (2019), with modifications.

Supplementary materials

Table S1. General conditions and effects of sediment toxicity assessments using zebrafish as model system. N.d. = not described to assess.

Table S2. Biological responses carried out by molecular and biochemical assays using zebrafish as model system to assess sediment toxicity.

Table 1.

Reaction pattern	**Effects**	**n° of papers (%)**
General alterations	General edemas	7.2
	Reduced brain size	1.0
Circulatory changes (Rp_1)	Pericardial edema	26.8
	Bradycardia	24.7
	Abnormal circulation or vasculature	17.5
	Blood accumulation	1.0
Pigmentation and tegumentary changes (Rp_2)	Changes of pigmentation (weak/miss)	15.5
Musculoskeletal disorders (Rp_3)	Spinal malformation	15.5
	Absence or irregular size of eyes	11.3
	Defects in the somites	11.3
	Tail malformation	9.3
	Undetached tail	9.3
	Head malformation	6.2
	Underdeveloped ears	5.2
	General body structure malformations	14.4
	Development retardation	12.4
	Uninflated swim bladder	1.0
Yolk sac alterations (Rp_4)	Yolk sac edema	19.6
	Unresorbed yolk	3.1
	Yolk detachment	1.0

Figure 1 Click here to access/download;Figure;Fig 1.tif

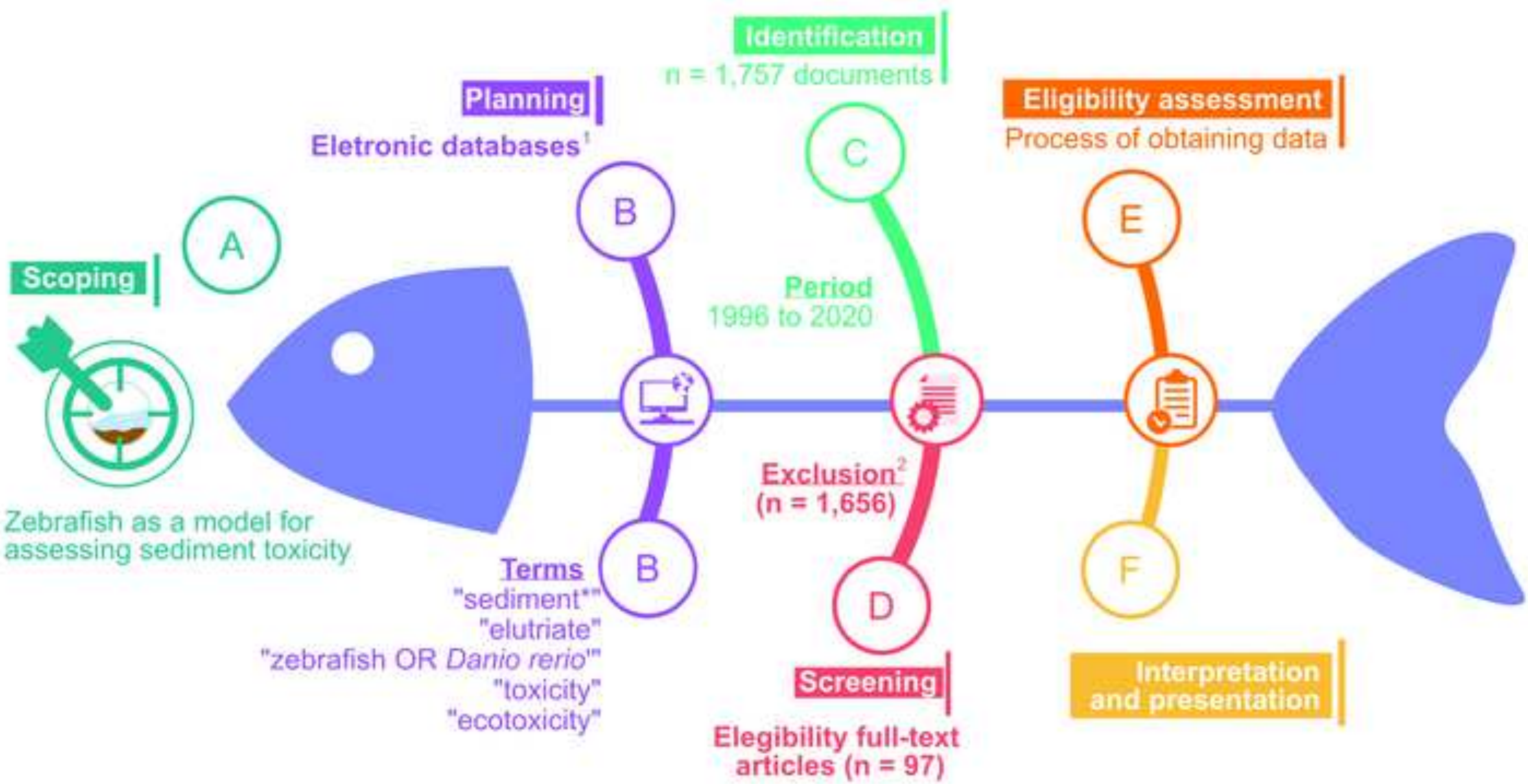

Figure 2

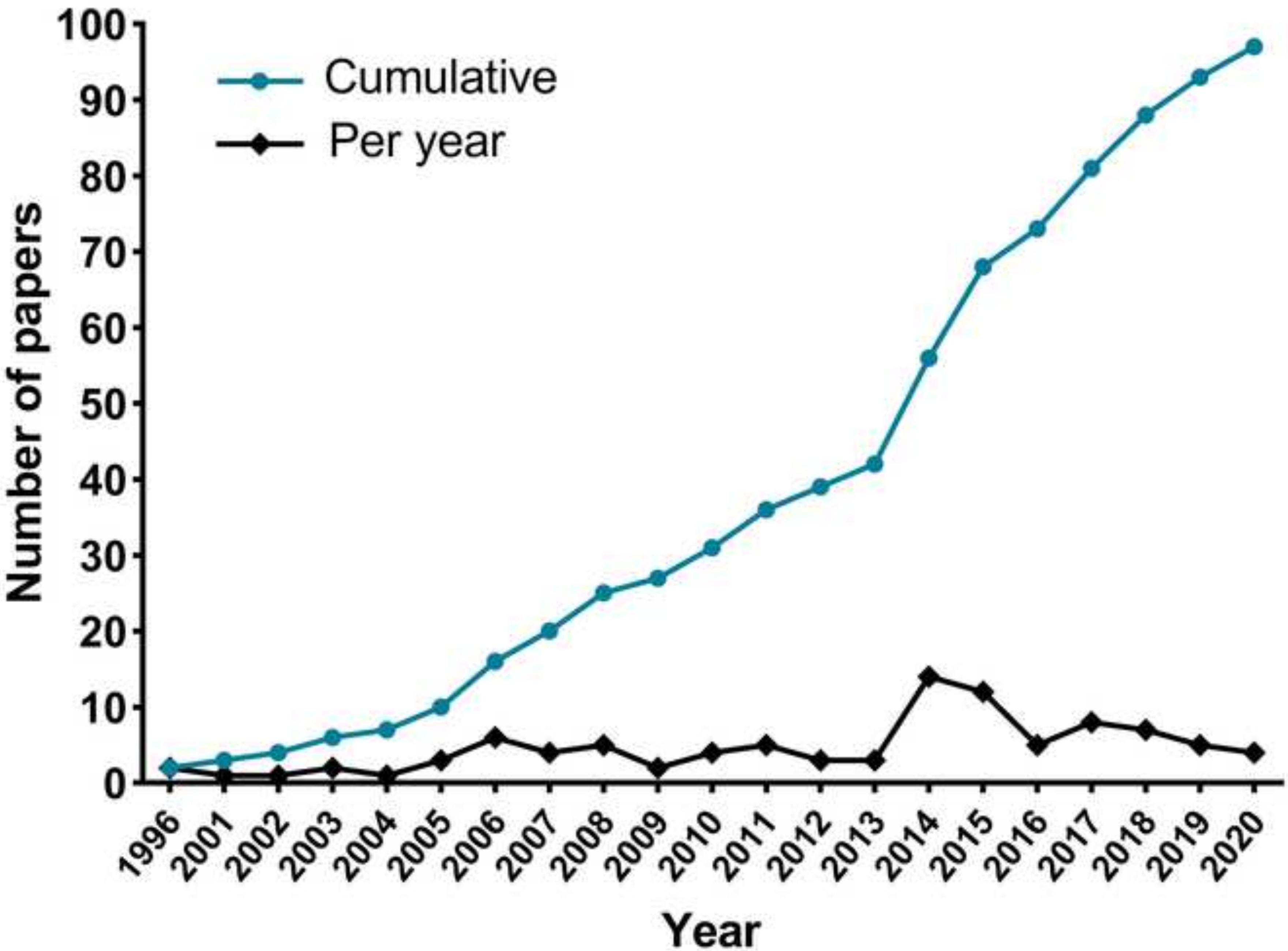
Number of papers
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Figure 3

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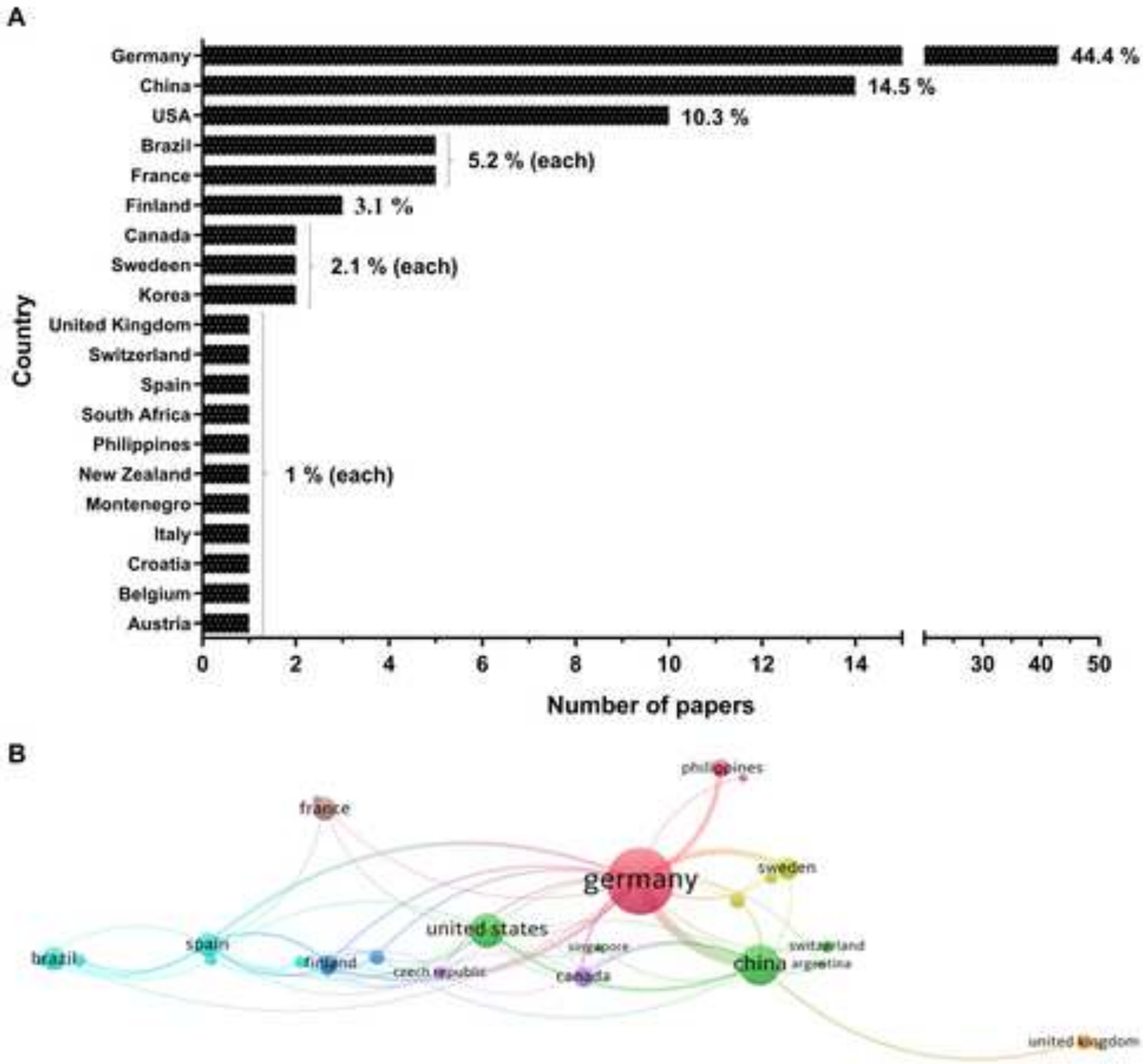

Figure 4

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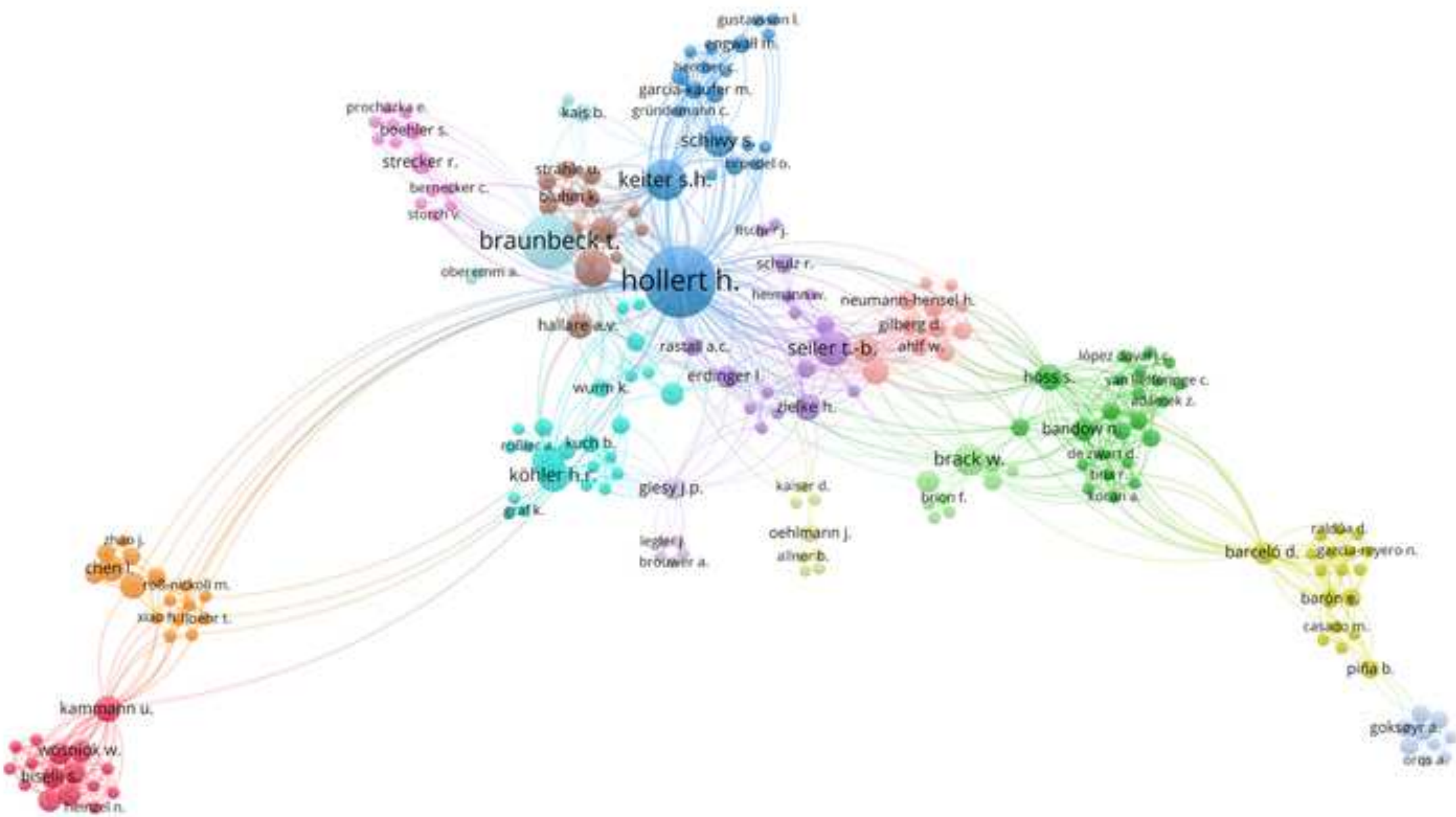

Figure 5

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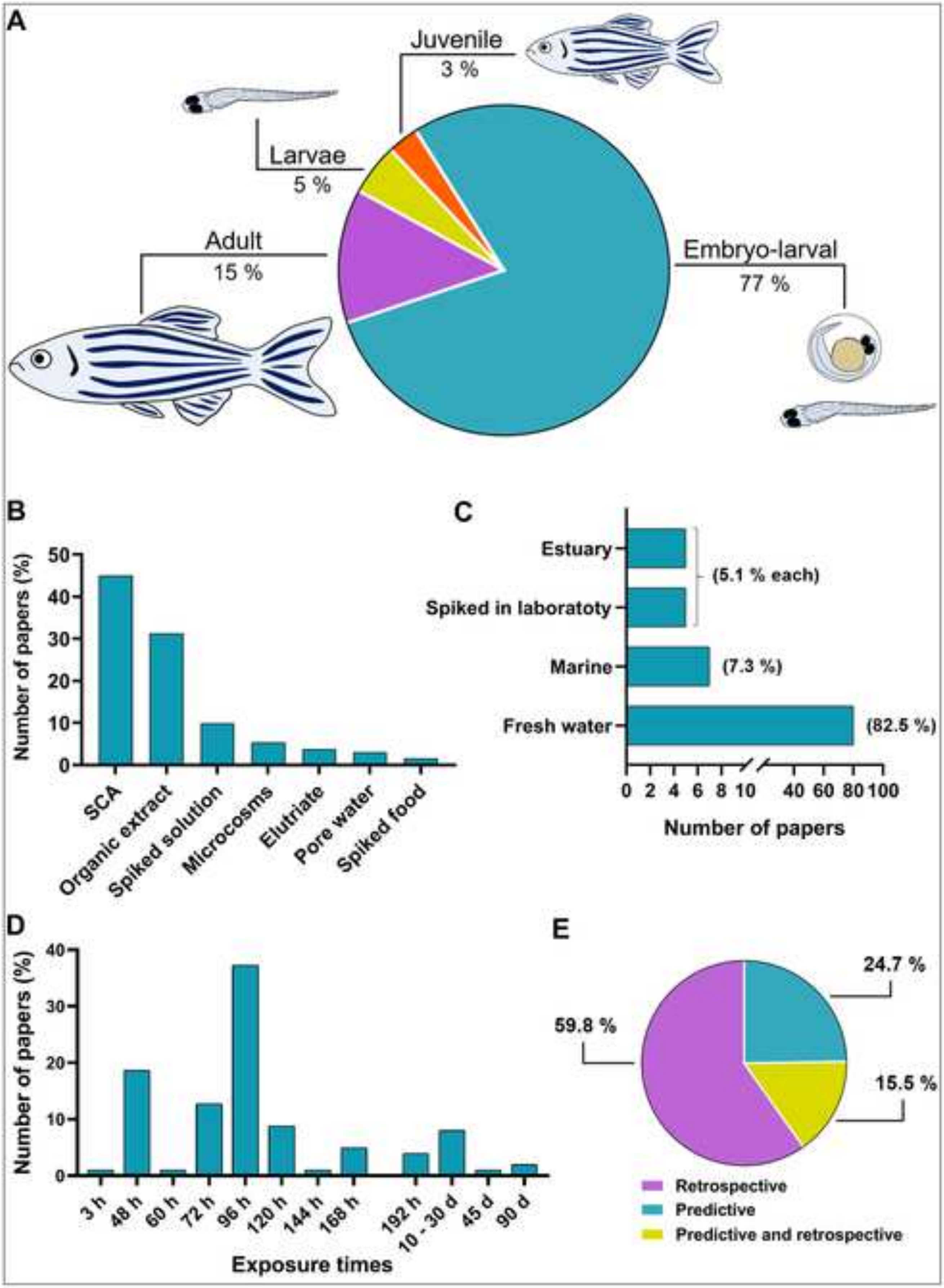
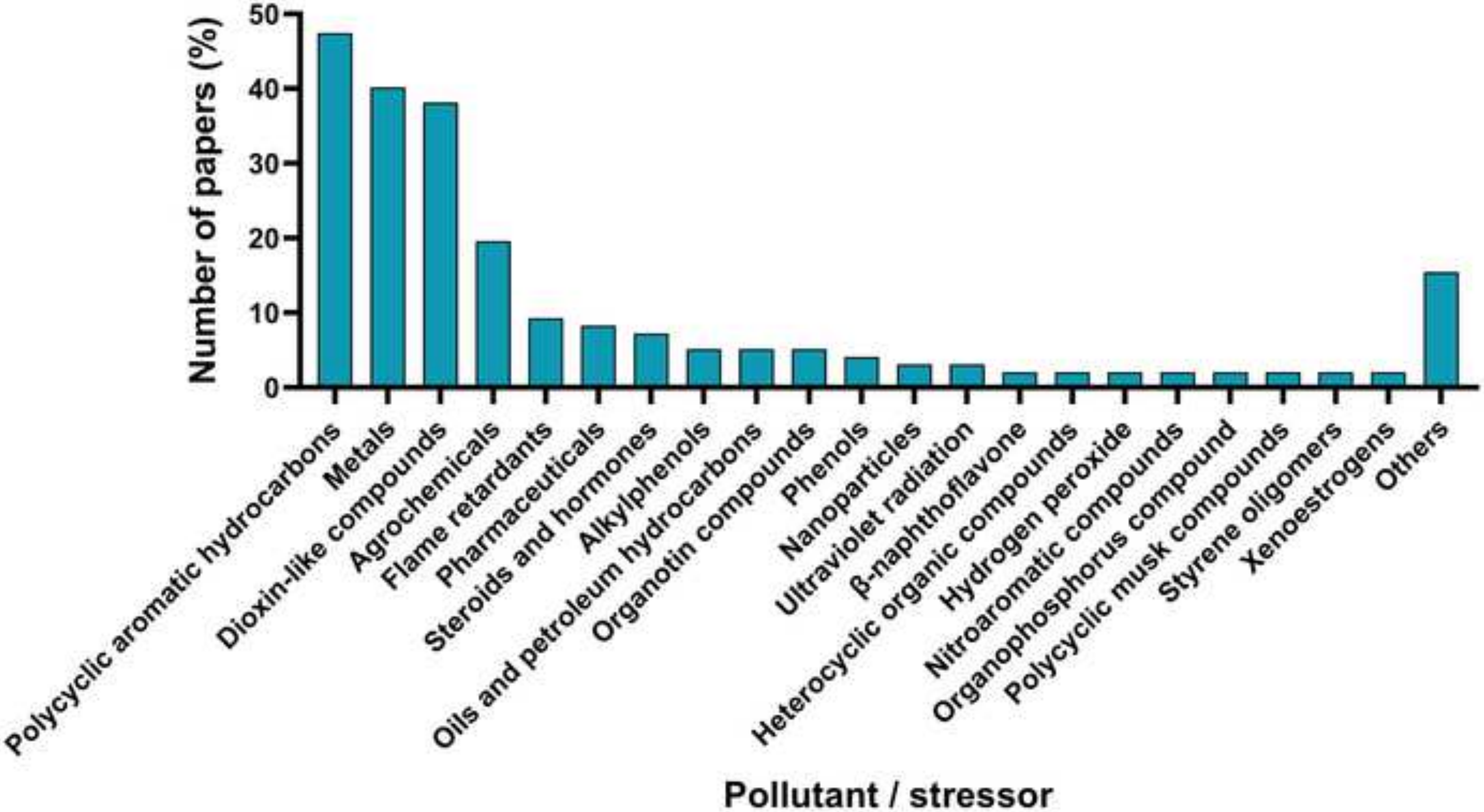


Figure 6


Number of papers (%)
50
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Polycyclic aromatic hydrocarbons
Metals
Dioxin-like compounds
Agrochemicals
Flame retardants
Pharmaceuticals
Steroids and hormones
Alkylphenols
Oils and petroleum hydrocarbons
Organotin compounds
Phenols
Nanoparticles
Ultraviolet radiation
β-naphthoflavone
Heterocyclic organic compounds
Hydrogen peroxide
Nitroaromatic compounds
Organophosphorus compound
Polycyclic musk compounds
Styrene oligomers
Xenoestrogens
Others
Pollutant / stressor

Figure 7

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