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Review

Multigenerational tests on *Daphnia* spp.: a vision and new perspectives☆

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ABSTRACT

Multigenerational toxicity testing is a valuable tool for understanding the long-term effects of contaminants on aquatic organisms. This review focuses on the use of multigenerational tests with *Daphnia*, a widely used model organism in aquatic toxicological studies. The review highlights the importance of studying multiple generations to assess *Daphnia* spp. reproductive, growth, and physiological responses to various contaminants.

We discuss the outcomes of multigenerational tests involving different contaminants, including nanoparticles, pesticides, and pharmaceuticals. The results reveal that multigenerational exposure can lead to transgenerational effects, where the impacts of contaminants are observed in subsequent generations even after the initial exposure has ceased. These transgenerational effects often manifest as reproduction, growth, and development alterations.

Furthermore, we emphasize the need for standardized protocols in multigenerational testing to ensure comparability and reproducibility of results across studies. We also discuss the implications of multigenerational testing for ecological risk assessment, as it provides a more realistic representation of the long-term effects of contaminants on populations and ecosystems.

Overall, this review highlights the significance of multigenerational tests with *Daphnia* in advancing our understanding of the ecological impacts of contaminants. Such tests provide valuable insights into the potential risks associated with long-term exposure to pollutants and contribute to the development of effective mitigation strategies for aquatic ecosystems.

1. Introduction

Daphnia is a small freshwater planktonic crustacean that is commonly employed in aquatic toxicology testing. In the late 1960s, scientific literature began to describe test protocols for performing acute toxicity tests (Persoone et al., 2009), and subsequently, standard test procedures were adopted by several federal agencies (e.g., OECD, ISO, U.S. EPA). While initially developed to assess the impacts of chemical compounds, *Daphnia* toxicity testing has demonstrated its applicability in evaluating the effects of various environmental stressors (Brausch et al., 2007). These stressors encompass not only chemical contaminants but also factors such as physical stressors and environmental conditions (Galdiero et al., 2019). The versatility of *Daphnia* toxicity tests makes them an essential tool for understanding the impacts of different stressors on aquatic organisms (Ebert, 2022).

Conducting acute and chronic toxicity tests on *Daphnia* provides a valuable mean to evaluate the detrimental impacts caused by chemical compounds present in the environment either naturally, intentionally released, or considered as waste. The evaluation of these chemicals is crucial for protecting the environment and public health (Galdiero et al., 2019; Galdiero et al., 2016; Pedrazzani et al., 2019; Persoone et al., 2009).

These tests play a crucial role as they are part of the fundamental set of biological assays required in several national and international regulations, such as the European Chemicals Agency (ECHA) and the European Food Safety Agency (EFSA) in Europe, the New Substances Notification Regulation (NSNR) in Canada, the Environmental Protection Agency in the United States, the Decree 591 in China, to name a few. Therefore, *Daphnia magna* is a commonly used organism as representative of freshwater invertebrates in environmental toxicity testing

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(Jonczyk & Gilron, 2005).

Typical *Daphnia* toxicity methods involve exposing organisms below 24 h old to a range of concentrations of a test item for a period ranging from 1 to 21 days (acute to chronic test), with an endpoint measurement (ISO, 2012; OECD, 2012). This approach allows direct analysis of chemical toxicity and provides mechanistic information useful for hazard assessment, as well as concentration-effect responses (McCarty et al., 2018).

Despite their important role in regulatory toxicology, there has been an increasing interest in the effects of long-term exposure to toxicants, particularly on emerging contaminants and the sub-lethal effects they can cause, in recent years. Emphasizing this aspect is crucial because organisms have the potential to acclimate to stressors, and prolonged exposure to contaminants, even at low concentrations, can lead to reduced or increased sensitivity over time (Falanga et al., 2018; Maselli et al., 2017). This adaptive response can mask the true impact of contaminants, emphasizing the need to consider adaptive mechanisms alongside acute effects in subsequent generations. Therefore, to make *Daphnia* methods more broadly useful for environmental contamination assessments, they need to be able to identify and characterize the toxicity that arises from repeated long exposure and also the effect on subsequent generations (Galdiero et al., 2019).

Exposing organisms to contaminants for several generations can simulate the real scenarios that organisms face in contaminated sites (Galdiero et al., 2019). Therefore, conducting toxic effect studies under multi-generational exposure conditions has the potential to provide a perspective that considers not only the sensitivity but also the potential changes over generations. Specific biological mechanisms, including gene expression, oxidative stress, and biomarkers, can serve as underlying factors in assessing organismal and population-level responses to low-dose exposures. These mechanisms might play a pivotal role in mitigating uncertainties for future risk assessments of pollutants in the environment (Clubbs & Brooks, 2007).

Extensive research has demonstrated that the sensitivity of daphnids to contaminants can differ from one generation to the next, despite their dominant clonal reproduction under ideal conditions (Alonzo et al., 2008; Guan & Wang, 2006; Muyssen & Janssen, 2004). Effects over several generations could reduce the mass of offspring, resulting in altered population dynamics with delayed reproduction and/or reduced egg mass (Alonzo et al., 2008; Galdiero et al., 2019; Maselli et al., 2017).

To gain a comprehensive understanding of current *Daphnia* multigenerational toxicity testing strategies, this review examined the impacts of some environmental contaminants on *Daphnia* populations through successive generations. By analyzing a range of studies, this review aimed to elucidate the effects of these compounds on reproductive success, growth, and other key parameters across multi-generations.

2. *Daphnia* spp. assays

Daphnia plays a crucial role as a primary consumer in the aquatic food chain, being an intermediary organism that consumes primary producers (such as algae) and is consumed by secondary consumers (such as fish). The most commonly used species in laboratory tests is the species *Daphnia magna*, although other species such as *Daphnia pulex* are included into acute exposure guidelines (OECD 202). One of the key advantages of using *Daphnia* in research is its relatively short lifespan, which typically lasts between 7 and 8 weeks at a temperature of 20 °C. Moreover, these organisms are capable of reaching sexual maturity within just 9–11 days after leaving the brood chamber, making them a highly convenient species to investigate aspects related to developmental and reproductive biology.

Daphnia is known for its unique reproductive strategy, called parthenogenesis, which involves the development of unfertilized eggs into offspring. This reproductive method results in genetic clones of the mother organism, as there is no contribution of genetic material from a male. This makes *Daphnia* an excellent choice for conducting multigenerational studies, as the genetic makeup of the organisms can be controlled and monitored with ease (Galdiero et al., 2016; Gonçalves et al., 2018).

2.1. *Multigenerational assay with Daphnia spp.*

In general, multigenerational tests are a modified and extended protocol of standardized tests. These tests evaluate the effects of contaminants on both the parental generation (F0) and filial generations (from F1 to Fn) of daphnids throughout their life cycle (Fig. 1). To begin the test, juvenile daphnids from the 3rd to 5th broods of a female in culture are chosen due to an expected more homogeneous size of neonates and reduce variability, ensuring more reproducible data (OECD, 2012). These daphnids, aged older than 6 h but younger than 24 h, are used to start individual cultures. (Gonçalves et al., 2018; Maselli et al., 2017; Nogueira et al., 2022).

Most of the experimental designs follow a modified exposure from the already standardized acute and chronic *Daphnia* tests. For the parental generation (F0) exposure, the neonates are distributed into different replicates (individually or pooled) in beakers and kept for a period of 21 days at a temperature of 20 ± 2 °C and a 16:8 h light-dark photoperiod. The daphnids are fed with unicellular green algae, and the media is renewed every 48 h to maintain semi-static conditions. The exposed daphnids are observed daily, and the number of surviving organisms, age at the first brood, and number of offspring per brood are recorded. Filial generations of daphnids are then selected mainly from the 3rd to 5th broods of the previous generations (Galdiero et al., 2019; Nogueira et al., 2022).

In most of the protocols, the concentration of the stressors (pollutant, environmental factors) are maintained in the same conditions over generations to evaluate the changes in the toxicity, if present. Moreover, the exposure of time it was usually maintained as a modification of the OECD 211 with 21 days of exposure to be able to measure the effects on reproduction, complemented sometimes with the differences on the acute toxicity of newborns.

Due to the lack of a standardized multigenerational exposure protocol, the conducted tests have exhibited diverse experimental designs. These designs may share certain conditions, yet they can vary across parameters such as the number of organisms per replicate, replicates per test, generations studied, exposure concentrations, and exposure duration. Because of the different modifications and adaptations performed, the endpoints analyzed vary between studies (e.g. endpoints might be limited in filial generations if the reproduction is impaired in parental generation), which as consequence limits also the comparison between generations of the same tests and between studies performed by different authors. In subsequent sections, multigenerational test applications, as well as advantages and disadvantages, are discussed.

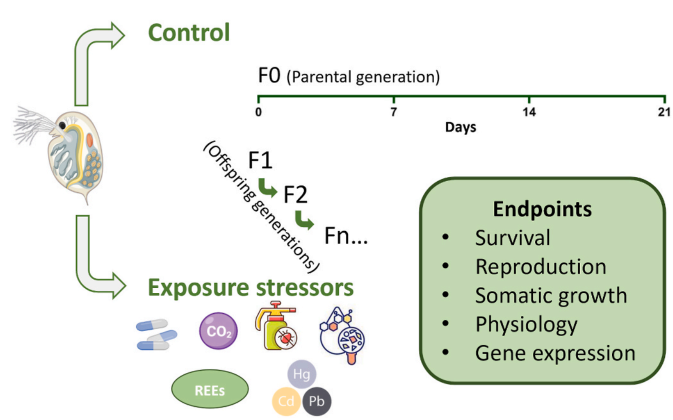

Fig. 1. Experimental design of the multigenerational assay with Daphnia spp.

2.2. Methodology and literature review

The existing literature for the compilation of this review paper was explored with a focus on studies available up until November 21st, 2022. To ensure a comprehensive coverage of available literature on the topic, the Scopus database (https://www.scopus.com/) was employed as a primary source due to its reliability in offering a wide range of scholarly articles.

To identify relevant studies, keywords were strategically employed during the search process. These keywords included "Multigenerational", "*Daphnia*," and "Multigeneration exposure".

The primary focus of our search was on studies that involved multigenerational exposures of *Daphnia* as the test organism. Studies meeting this criterion were categorized based on the different classes of contaminants under investigation. This categorization process facilitated the organization and synthesis of the findings, enabling a clearer understanding of the complex interactions between *Daphnia* and various contaminants.

Table 1 provides a summary of the studies identified during our literature review. The selection of these studies was guided by a set of specific criteria. To be included in the review, studies had to involve the exposure and assessment of multiple generations of daphnids.

3. Applications of multigenerational assay

3.1. Pharmaceuticals

Pharmaceuticals constitute the most important form of therapeutic modalities for combating diseases in living organisms (Chhabra, 2021). They include but are not limited to antibiotics, anticonvulsants, painkillers, cytostatic drugs, hormones, lipid regulators, beta-blockers, antihistamines, and X-ray contrast media (Ikehata et al., 2006). Different studies investigated the effects of pharmaceuticals on *D. magna* spanning from three to six generational timelines, shedding light on their ecological impacts (Yang et al., 2013; Dietrich et al., 2010; Dalla Bona et al., 2016; Kim et al., 2012; Maselli et al., 2017).

In the comprehensive six-generation studies, Yang et al. (2013) and Dietrich et al. (2010) delved into the pharmaceutical effects on *Daphnia* population. Dietrich et al. (2010) specifically examined the impact of carbamazepine, diclofenac, 17 α-ethinylestradiol, and metoprolol on the morphological parameters and reproductive outcomes of *D. magna* over six generations. Their findings revealed that 17 α-ethinylestradiol and metoprolol led to a reduction in body length, while carbamazepine and diclofenac delayed the first reproductive generation. Additionally, diclofenac induced an increase of body length in neonates of the F1 and F5 generations, and metoprolol decreased the number of offspring in the F0 and F4 generations.

In the case of Yang et al. (2013), who conducted a six-generation study exposing *D. magna* to sulfamethoxazole, ofloxacin, and ibuprofen at environmentally relevant concentrations, sulfamethoxazole, at concentrations of 0.8, 8.0, and 80.0 μgL^{-1}, did not exhibit significant effects on reproduction and growth. However, ofloxacin at 200 μgL^{-1} decreased the number of first reproduction in F3 and F4, while ibuprofen delayed the age of first reproduction and reduced offspring number at 900.0 μgL^{-1} in F3, F4, and F5. Furthermore, the administration of pharmaceutical mixtures at higher concentrations resulted in a delay in the age at which the first reproduction occurred and a decrease in the number of offspring in subsequent generations. Specifically, exposure to ofloxacin at concentrations of 2.0 and 20.0 μgL^{-1}, as well as ibuprofen at concentrations of 9.0 and 90.0 μgL^{-1}, had no observable effects on six consecutive clone generations. However, at higher concentrations, such as ofloxacin at 200.0 μgL^{-1} and ibuprofen at 900.0 μgL^{-1}, negative effects were evident, indicating a concentration-dependent and generational difference in their impact.

Similarly, Nguyen et al. (2021) investigated the effects of antibiotics, including ofloxacin, and found increased toxicity of ofloxacin exposure after four generations of *D. magna* at concentrations of 50, 500, and 5000 μgL^{-1} for each antibiotic. High antibiotic concentrations reduced fertility and led to degraded offspring, impacting oogenesis and brood size. Ciprofloxacin exposure, another antibiotic studied, resulted in both negative and stimulatory effects on brood size, suggesting that antibiotic toxicity and adaptation in *D. magna* can vary depending on the specific antibiotic, its concentration, and the duration of exposure.

Although long-term studies covering a greater number of generations could provide a more accurate understanding of the effects of drugs on organisms and populations, effects were observed with fewer generations. Building upon the research on fluoroquinolones, including ofloxacin and ciprofloxacin, a study by Dalla Bona et al. (2016) investigated the effects of Enrofloxacin (EFX), over four generations of *D. magna* exposure. Despite initial concerns about the environmental relevance of the EFX concentration used (2 mgL^{-1}), the results demonstrated that even commonly detected fluoroquinolone concentrations could not ensure the long-term survival of *D. magna* populations. Over the four generations, the toxicity of EFX increased, resulting in mortality rates reaching 100% in three out of four tested groups in the fourth generation. Furthermore, the study found that daphnid's ability to reproduce when born to EFX-exposed mothers was compromised, regardless of whether they were subsequently incubated in EFX-containing or pure medium.

Similarly, a study by Kim et al. (2012) evaluated on the effects of tetracycline on the growth and reproduction of *D. magna* over four generations. Authors found that higher tetracycline concentrations (10 mgL^{-1}) led to a decrease in reproduction, reducing the number of neonates by 60% in comparison to the control. The concentration to cause this effect, decreased with each successive generation, by the fourth generation, the lowest concentration of 0.1 mgL^{-1} was able to cause a 60% reduction in comparison to the control. The age at first reproduction was delayed in the highest concentration group (10 mgL^{-1}), but survival rates remained above 90%. Tetracycline also had a concentration-dependent effect on somatic growth, with a decrease observed in the parental generation and an increase with subsequent generations. The population growth rate (PGR) of *D. magna* was a sensitive parameter of toxicity to tetracycline, with a decreasing trend observed in all generations. Later studies (Kim et al., 2017; Kim et al., 2014) demonstrated that tetracycline induced decreased bioaccumulation and transcriptional responses in *D. magna* in a dose- and generation-dependent manner.

In addition to the aforementioned studies, Maselli et al. (2017) explored the effects of an antimicrobial peptide, indolicidin, complexed with quantum dots nanoparticles (QDs) on *D. magna*. This study stands out from the others due to its unique approach involving the exposure of D. magna to a sublethal concentration of 1.5 nM of QDs functionalized with 6.4 mM of indolicidin (Galdiero et al., 2016). Maselli et al. (2017) assessed various endpoints, including individual fitness, population growth, DNA alterations, and the expression of hemoglobin, vitellogenin, and two cytochrome P450 genes, across three generations. Notably, the indolicidin-QD complex exerted distinct effects, such as a reduction in the total number of broods per female, alterations in body lengths, up-regulation of hemoglobin and cytochrome P450 genes, and down-regulation of vitellogenin.

3.2. Abiotic environmental factors

Temperature, geomagnetic fluctuations, and CO_2 emissions are important environmental factors with the potential to influence the behavior and physiology of zooplankton. Climate change and global warming can cause thermal stress, while anthropogenic CO_2 emissions can lead to ocean acidification, which can affect the survival and reproduction of zooplankton (Barbarossa et al., 2021; Daufresne et al., 2009; Prakash, 2021). Despite the increased relevance of these environmental factors, it's noteworthy that there is a limited number of studies that have investigated their multigenerational effects on

Table 1
Studies on the application of multigenerational test with *Daphnia* for toxicity assessment of different classes of contaminants. The studies are categorized based on the type of contaminant examined. Arrows indicate the direction of change in response parameters across generations within each study (↑: increase, ↓: decrease, ↔: no significant change).

Stressor	Compounds	Exposure conditions	Duration of the test	Endpoints	References
Pharmaceuticals	Diclofenac 17 α-ethinylestradiol Metoprolol	0.36 μgL^{-1} 0.10 μgL^{-1} 1.20 μgL^{-1}	F0 → F6	Morphological and reproductive parameters (↓)	Dietrich et al., (2010)
	Ibuprofen Ofloxacin Sulfamethoxazole	9.0, 90.0 and 900.0 μgL^{-1} 2.0, 20.0 and 200 μgL^{-1} 0.8, 8.0 and 80.0 μgL^{-1}	F0 → F5	Reproduction (↓), growth(↓) and offspring number(↓)	Yang et al. (2013)
	Ofloxacin Ciprofloxacin	50, 500, and 5000.0 μgL^{-1}	F0 → F4	Survival(↔), maturity(↔), reproduction(↔) Survival(↓), maturity(↓), reproduction(↓) and offspring degradation	Nguyen et al., (2021)
	Enrofloxacin	2 mgL^{-1}	F0 → F4	Survival(↓) and reproduction(↓)	Dalla Bona et al., (2016)
	Tetracycline	0.1 and 10 mgL^{-1}	F0 → F4	Reproduction(↓) and growth(↓) Bioaccumulation(↓) and transcriptional responses(↓)	Kim et al. (2012) Kim et al. (2014); Kim et al. (2017)
	QDs-Indolicidin	1.5 nM in QDs and 6.4 mM in peptide.	F0 → F3	Growth(↓), survival(↓), reproduction(↓), consequently RAPD profiles(↓) and gene expression(↓↑)	Maselli et al., (2017)
Abiotic environmental factor	Temperature Salinity	15–30 °C 0–5 ppm	F0→F6	Reproduction (↓), growth(↓) and offspring number(↓)	Chen and Stillman, 2012
	Magnetic fields	15 nT, 50 Hz	F0 → F8	Body length(↑) and brood size(↑)	Krylov and Osipova, 2019
Plant protection products	Cyfluthrin	0.0026 to 0.02 μgL^{-}	F0 → F3	Survival, growth, reproduction, oxidative stress, and gene expression	Brausch and Salice (2011)
	Diuron Pentachlorophenol	0.1296 to 1.0 mgL^{-1} 0.0002 to 2 μmolL^{-1}	F0 → F2	Survival(↓), age at first reproduction(↓), fecundity(↓), Length of mothers(↓) and number of molts(↓)	Chen et al. (2014)
	Diazinon	0.05 to 1.0 ngL^{-1}	F0 → F2	Survival(↓) and reproduction(↓)	Sánchez et al. (2000)
	Chlorpyrifos	0.1 to 2.5 μgL^{-1}	F0 → F3	Survival(↔) and reproduction(↔)	Maggio and Jenkins (2022)
	Mancozeb and Pb	1.2 mgL^{-1}	F0 → F9	Reproduction(↓), feeding rate(↑), Acetylcholinesterase (AChE) activity(↑)	Araujo et al. (2019 a)
	Carbendazim	5 μgL^{-1}	F0 → F12	Immobility(↓), reproduction(↓), feeding activity(↑) and DNA damage(↑)	Silva et al. (2017)
	Cu Temperature	10, 34 and 25 μgL^{-1} 20 and 25 °C	F0 → F2	Multiple stressors(↑), reproduction(↓) and growth(↓) Multiple stressors(↑), reproduction(↓) and growth(↓)	Bae et al., (2016)
	Hg	3.8 μgL^{-1}	F0 → F2	Survival(↔)	Tsui and Wang, 2005
	Zn	13 to 800 μgL^{-1}	F0 → F9	Length(↔) and survival(↔)	Muyssen and Janssen, 2001
	U	10 to 75 μgL^{-1}	F0 → F2	Body length and dry mass(↓), brood size and dry mass (↓)	Massarin et al. (2010)
	Pb and Mancozeb	50 μgL^{-1}	F0 → F9	Malformations(↑), production of males(↑), epphipia(↑), aborted eggs(↑), change in color of eggs(G, W)	Araujo et al. (2019 a)
	Pb and Mancozeb under tow food regimes	50 μgL^{-1}	F0 → F9	Malformations(↑), production of males(↑), epphipia(↑), aborted eggs(↑), change in color of eggs(G, W)	Araujo et al. (2019 b)
	Ce Er	0.54 μgL^{-1} 0.43 μgL^{-1}	F0 → F2	Organisms' size(↓), reproduction(↓), survival(↓), determination of reactive oxygen species (ROS) (↔), enzymatic activity(↔)	Galdiero et al. (2019)
Wastewater and industrial effluents	Plant effluents	N.D	F0 → F21	Number of males(↑), endocrine system(↓) and disrupt sexual developmen	Baer et al. et al., 2009
	Organic contaminats	N.D	F0 → F4	Reproductive scenario(↓), compromised fitness, and affected global DNA methylation (hypermethylation)	Chatterjee et al. (2019)
	Ni, Pb, Cd, Zn, Cu	0.06 to 5.14 mgL^{-1}	F0 → F6	Growth(↓), reproduction(↓), and population dynamics (↓)	Sun et al. et al., 2021
Flame retardants and estrogens	1,3-dichloro-2-propyl phosphate (TDCIPP)	65 to 6500 ngL^{-1}	F0 → F1	reproduction (↓), growth (↓), gene transcription (↓↑)	Li et al. (2015)
	Tris(2-butoxyethyl) phosphate (TBOEP)	10 μgL^{-1}	F0 → F2	Gene transcription(↓↑), protein analyses(↓↑), survival (↔), reproduction(↔) and growth levels (↓)	Giraudo et al. (2017)
	17β-oestradiol diethylstilbestrol	2.87 mgL^{-1} 1.55 mgL^{-1}	F0 → F1	survival(↓) and fecundity(↓)	Brennan et al. (2006)
	bisphenol A and lignin-derived bisphenol (BPA, LD-BP)	2 to 2000 mgL^{-1}	F0 → F1	antioxidants genes, (↓)reproduction (↓), growth (↓) and molting (↓)	Li et al., (2018)
	17α-ethinylestradiol Faslodex	0.1 to 10 mgL^{-1} 1 to 100 mgL^{-1}	F0 → F1	Survival(↔), moulting(↔) and reproduction(↔) Survival(↔), moulting(↔) and reproduction(↔)	Clubbs and Brooks, 2007

(*continued on next page*)

Table 1 (*continued*)

Stressor	Compounds	Exposure conditions	Duration of the test	Endpoints	References
Microplastic and nanoparticles	Polyethylene microplastic and benzophenone-3	4.35 and 5.00 mgL^{-1}	F0 → F3	Mortality(↔),reproduction(↓)	Song et al. (2022)
	Polystyrene microplastics	5 μgL^{-1}	F0 → F1	Fecundity(↑) and growth rate(↑),heartbeat(↓) rate, and swimming speed(↑)	Chang et al. (2022)
	Polystyrene microplastics and roxithromycin	0.1 and 10 μgL^{-1}	F0 → F1	Reproductive(↓), swimming velocity(↓) and acceleration(↓)	Liu et al. (2022)
	Polystyrene microplastics	10,000 and 2000 particles mL^{-1}	F0 → F2	Survival(↓), reproduction(↓), and growth(↓)	Schür et al. (2020)
	AgNPs	0.017, 0.026, 0.04, 0.06, and 0.09 μgL^{-1}	F0 → F1	Survival, growth(↓), reproduction(↓), and age at first brood descendants (↑)	da Silva et al., 2021
	AgNPs	0.9 to 10.1 μgL^{-1}	F0 → F5	Number of offspring(↓), mortality(↑), and body size of adult(↓)	Hartmann et al. (2019)
	TiO_2NPs	1.0 to 10.3 μgL^{-1}			
	nTiO_2	1.19 to 6 mgL^{-1}	F0 → F5	mortality(↓), individual growth(↓), reproduction(↓) and population growth rates (PGR) (↓)	Jacobasch et al. (2014)

zooplankton.

In a study conducted by (Chen & Stillman, 2012), the *D. pulex* multigenerational responses were investigated under the combined influence of daily fluctuations in temperature (from 15 to 30 °C) and salinity variations (from 0 to 5 ppm). Decreased respiration rate and generation time persisted after six generations. The most extreme temperature conditions appeared to confer cross-tolerance to salinity stress, suggesting that temperature played a key role in metabolism, growth, and tolerance thresholds.

Krylov and Osipova (2019) investigated the possibility of a maternal effect in response to simulated natural geomagnetic fluctuations on *D. magna* lines. The analysis were performed on offspring from the subsequential generation (third, sixth and ninth) of exposed daphnids exposed to an artificial magnetic field (15 nT, 50 Hz). The results obtained suggested that the number of offspring produced was not affected but the size was smaller when *Daphnia* was exposed to different conditions for multiple generations. The full extent of any electromagnetic impact remains unknown, as it is not a factor considered during laboratory and field studies.

3.3. Plant protection products

Pesticides, insecticides, herbicides and fungicides are widely used chemicals in agriculture (de Montaigu & Goulson, 2020; Matowo et al., 2020). They are intentionally released into the environment in agricultural land, however, they might reach external ecosystems through runoff, drainage, and leaching, posing a threat to non-target organisms (Schleiffer & Speiser, 2022; Sharma et al., 2022). These chemicals can have a harmful effect, including reduced growth rates, reproductive failure, and increased mortality rates in various organisms such as humans, fish, and other non-target species. (Chakraborty, 2023; Rani et al., 2021; Schmidt-Jeffris et al., 2021). Although multigenerational studies involving *Daphnia* spp. and pesticides have been conducted, the majority have evaluated effects over a limited number of generations, often at environmentally relevant concentrations (Silva et al., 2017).

For instance, Brausch and Salice (2011) investigated the effects of an environmentally relevant pesticide mixture containing diuron and cyfluthrin on *D. magna* over two generations. The concentrations ranged from 0.1296 to 1.0 mgL^{-1} for diuron and from 0.0026 to 0.02 μgL^{-1} for cyfluthrin. The results showed that even at concentrations as low as 0.216 for diuron and 0.0043 μgL^{-1} for cyfluthrin, the mixture had significant and complex effects on *D. magna* survival, growth, reproduction, oxidative stress, and gene expression. Moreover, (Chen et al. (2014) also used environmentally relevant concentrations (0.0002–2 μmolL^{-1}) of an organochlorine pesticide, pentachlorophenol (PCP),to assess the survival, age at first reproduction, fecundity, length of dams and number of moults measured over three generations of *D. magna*. The study demonstrated that even at very low concentrations, such as 0.002 μmolL^{-1}, PCP had negative effects on the measured parameters, highlighting the need for careful monitoring and management of PCP contamination in aquatic ecosystems.

In the study performed by Sánchez et al. (2000), the toxicity of the insecticide diazinon on *D. magna* by exposing them to sublethal concentrations of the organophosphate, ranging from 0.05 to 1.0 ngL-1, spanning across two generations was evaluated. Diazinon exposure caused reductions in survival, reproduction, and growth, which were more pronounced in F1 (first and third brood) compared to F0. The study highlighted the intrinsic rate of natural increase (r) as an highly sensitive parameter for assessing toxicity. This sensitivity primarily stemmed from the parameter's ability to discern the influence of diazinon on both reproduction and survival. The maximum acceptable toxicant concentration (MATC), utilizing the intrinsic rate of natural increase (r) as the central evaluation parameter, revealed values of 0.62 and 0.07 ngL^{-1} for F0–F1 (first) generations and F2 (third) generation, respectively. One plausible hypothesis arising from these findings is the potential accumulation of the pesticide within the bodies of the parental generation (F0) exposed to sublethal diazinon concentrations. Subsequently, it is conceivable that the toxicant may have been transferred from the mothers to their offspring, particularly within the first and third broods, thus contributing to the observed effects.

Maggio and Jenkins (2022) exposed exposed *D. magna* to 0.1, 0.5, and 2.5 μgL^{-1} of chlorpyrifos (environmentally relevant concentrations) for four generarions in a multigenerarional exposure and a transgenerational exposure (only the first generation is exposed). Authors observed effects in a dose-dependent manner, with higher concentrations of the chemical causing more pronounced effects. This study observed that the effects of chlorpyrifos exposure on the daphnids were not always predictable based on the effects observed in the first generation, as differences in sensitivity were observed between the transgenerational and multigenerational assays. In the multigenerarional exposure, the fourth generation displayed a higher tolerance, while subsequential unexposed generations in the transgenerational assay did not display changes in their survival and reproduction.

Araujo et al. (2019 a) studied the sensitivity of two species, *D. magna* and *Daphnia similis* exposed to the fungicide mancozeb (1.2 mgL^{-1} as highest concentration and decreasing by a factor of two) for 48 h after a multigenerational exposure to 50 μgL^{-1} of Pb (F0 to F9). The exposure was also performed under the usual food regime of 3×10^5 cells·mL^{-1} and a restricted amount of 1.5×10^5 cells·mL^{-1}. The LC_{50} values showed no differences between different treatments (food regimes and between generations F0, F6, and F9) for both organisms. Moreover, a treatment group that had a recovery period from F6 to F9, showed a higher sensitivity compared to organisms continuously exposed to Pb for *D. magna*, while the *D. similis* group had a lower sensitivity.

Silva et al. (2017) conducted a multigenerational study to evaluate the effects of long-term exposure to carbendazim, a fungicide widely used in agriculture, on *D. magna*. Two isoclonal populations, one exposed to 5 μgL^{-1} of carbendazim (Dph_CBZ) and another kept under the same conditions with no carbendazim (Dph_clean), were used. The experiment lasted for approximately 34 weeks, corresponding to 12 generations. The researchers analyzed immobilization, reproduction, feeding activity tests, and comet assay for in vivo DNA damage evaluation. The results showed that feeding activity increased as a compensatory mechanism after stress. In terms of immobilization and reproduction, no clear effects were observed. DNA damage increased throughout the generations in a cumulative way. A later study by Silva et al. (2019) on carbendazim demonstrated that there were differences in the levels of three biomarkers - cholinesterase (ChE), glutathione S-transferase (GST), and lipid peroxidation (LPO) - between control populations (not exposed to carbendazim) and populations that were exposed to carbendazim. However, despite the differences in biomarker levels, the study was not able to identify a clear detoxification mechanism that could explain these differences.

3.4. Metals and rare earth elements

Metals and rare earth elements are naturally occurring elements that can be found in the aquatic environment, including oceans, rivers, lakes, and groundwater (Khatri & Tyagi, 2015; Noack et al., 2014). These elements can come from natural sources, such as rock weathering and soil erosion, or human activities, like mining, industrial processes, and agriculture (Pagano et al., 2015; Shah, 2021; Siciliano et al., 2021). While these elements are present in water, they can pose threats to both aquatic life and human health (Pagano et al., 2015; Pandey & Madhuri, 2014). Furthermore, these elements have the potential to accumulate in the food chain, and their effects can vary significantly, depending on the source and concentration of exposure (Pagano et al., 2015; Pandey & Madhuri, 2014).

The multigenerational studies investigated the effects of different and specific elements on *Daphnia* and examined various endpoints to assess toxicity. For instance, Bae et al. (2016) studied the effects of temperature and copper (Cu) exposure on three generations (F0–F2) of *D. magna* were investigated. The results showed that higher temperatures (25 °C) had a more detrimental impact compared to lower temperatures (20 °C), resulting in reduced growth and reproduction. Additionally, Cu exposure at a concentration of 10 μgL^{-1} induced higher levels of reactive oxygen species and lipid peroxidation, particularly pronounced at the higher temperatures (25 °C), and these effects escalated across generations, ultimately leading to decreased fitness in the offspring. Similarly, exposure to Cu at 25 °C resulted in an EC_{50} of 34 μgL^{-1}, in contrast to the lower value obtained by the 20 °C exposure with 25 μgL^{-1}, indicating a higher toxicity at lower temperatures. The difference in Cu toxicity at varying temperatures was attributed by the authors to the increased elimination rates associated with higher temperatures. However, an important finding was that as the temperature increased, the overall fitness of the daphnids declined. This resulted in a synergistic effect between the stressors of temperature and Cu exposure, compounding their detrimental impacts on *D. magna*'s health and well-being.

However, metals also induced adaptive effects on daphnia *D. magna* populations as demonstrated by Tsui and Wang (2005) that studied the toxicity of mercury (Hg) over three generations (F0–F2) showing that *D. magna* exhibited an ability to adapt to Hg-induced stress over multiple generations. Upon continuous exposure to Hg, they observed changes in the 48-h LC50 values. Initially, for the first generation (F0), the LC_{50} was higher (54 μgL^{-1}) than that the control group (46 μgL^{-1}). However, in the F1, the LC50 values remained relatively similar between the treatment group (49 μgL^{-1}) and the and control group (55 μgL^{-1}). The most significant change occurred, in the third generation (F2), where the LC50 significantly increased to 149 μgL^{-1} in contrast to the 40 μgL^{-1} of the control group. These findings indicated that *D. magna* adaption could be influenced by factors such as the ingestion rate and the induction of metallothionein-like proteins, which influences the detoxifying mechanisms. Similarly, Muyssen and Janssen (2001) exposed *D. magna* to zinc (Zn) in concentrations of 13–800 μgL^{-1} to assess the acclimation over seven generations. Results obtained showed that with increasing concentration of Zn, the length of organisms also increased, reaching a maximum size at concentration 450 μgL^{-1} and only reaching a smaller size than the control at concentration of 800 μgL^{-1}. Moreover, from the parental generation to the nineth generation (F9), daphnids were exposed to two concentrations of Zn, 3 μgL^{-1} zinc-deprived and 13 μgL^{-1} non deprived. No statistical effects were noticed, however, higher zinc concentrations resulted in a longer survival time.

Despite these studies, there is no clear evidence of continued adaptations to heavy metals, suggesting a lack of recovery mechanisms.

For example, Massarin et al. (2010) exposed *D. magna* over three generations (F0–F2) to uranium (U) at concentrations from 10 to 75 μgL^{-1}. The exposure over generations was performed in two different setups: Exposure experiment (A) where offspring were exposed to the same concentration as their parent; and Recovery of generations (B) where offspring were returned to a clean medium to assess their capacity of recovery from parental exposure. The highest concentration of exposure (75 μgL^{-1}) caused 100% mortality on days 16 and 17 of the F1 generations of the exposure and recovery tests, respectively. Moreover, the exposure caused a reduction in somatic growth and reproduction, which increased over generations, as lower concentrations of exposure (≤25 μgL^{-1}) caused similar effects to generations F1 and F2 as the highest concentration to F0. They observed that smaller neonates born from eggs of small mass had a higher sensitivity, which might be explained by the amount of reduced energy dedicated to the eggs or by the direct exposure of the embryos to uranium. This test highlighted that even after returning to clean media, offspring still could not fully recover from parental exposure, as their survival and reproduction decreased, and exhibited a higher body mass at concentrations ≤25 μgL^{-1}.

In the study conducted by Araujo et al. (2019 a), which investigated the effects of mancozeb as mentioned in section 3.3, *D. magna* and *D. similis* were also exposed for nine generations to 50 μgL^{-1} of Pb. Additionally, the study assessed the recovery in clean media over three generations and the effects of two food regimes (usual amount of 3×10^5 cells·mL^{-1} and restricted amount of 1.5×10^5 cells·mL^{-1}). The study aimed to estimate the 48 h LC_{50} for different generations (F0, F3, F6 and F9) after a continuous exposure to Pb. The results revealed that *D. magna* showed a decrease in sensitivity over generations. The LC_{50} values for *D. magna* changed from 0.43 mgL^{-1} (F0) to 2.11 mgL^{-1} for those on the usual food regime and 3 mgL^{-1} for those on the restricted food regime (F9). Similarly, in the case of *D. similis*, the LC_{50} increased from 0.29 mgL^{-1} (F0) to 0.94 mgL^{-1} for usual food regime and 1.76 mgL^{-1} for restricted food regime (F9). This study sheds light on the significant influence of food availability. It was observed that limited food supply led to decreased sensitivity to Pb exposure. This phenomenon can be attributed to a trade-off mechanism, as suggested by (Enserink et al., 1995). In this trade-off, a reduced food supply resulted in the production of fewer offspring. However, these offspring were larger in size and of higher quality. This increased size and quality made them less sensitive to other environmental stressors.

In the same test set up as in Araujo et al. (2019 a), *D. magna* and *D. similis* were exposed to Pb under two food regimes (usual and restricted) (Araujo et al., 2019 b). It was observed both species displayed a similar pattern of response to the stress. As for the bioaccumulation, it occurred faster when fed with a usual diet in contrast to a gradual increase under restricted conditions. During the recovery period, daphnids were able to exclude the amount of Pb, as there was no difference with the control group. The exposure of Pb caused diverse sublethal effects such as malformations in the carapace, aggregation of Pb in neonates, production of males, ephippia, aborted eggs, change in color of eggs (green and white). Moreover, this study highlighted that the adverse effects of Pb were influenced by the diet, as food restriction accounts for more stress for daphnids, this caused another adverse effect, the production of males.

Galdiero et al. (2019) exposed *D. magna* to two rare earth elements, Cerium (Ce) and Erbium (Er) over three generations (F0–F2) at measured concentrations of 0.54 μgL^{-1} for Ce and 0.43 μgL^{-1} for Er. The endpoints of survival, growth, reproduction, ROS, enzymatic activity, and uptake were evaluated. The toxicity of Ce and Er affected daphnids differently over the generations exposed. For mortality, Ce had a decreasing effect at each generation, as mortality was 48%, 21%, and 27% at generations F0, F1 and F2; for Er the effects were 40%, 45% and 22% for generations F0, F1 and F2. As for sub-lethal endpoints, Ce reduced the number of offspring, while Er caused a delay in the time of emergence but not in the number of offspring; the uptake for both elements did not vary across the generations; for the growth rate, Ce and Er had slight stimulatory effects that were more present in the first generation (F1). For ROS and enzymatic activity, there was not a clear trend regarding the Er exposure, while for Ce there was a slight decrease with exposure time but not across the generations.

3.5. Wastewater and industrial effluents

Wastewater can contain a wide range of toxic chemicals and pollutants that can have adverse effects on aquatic organisms(Akpor & Muchie, 2011; Edokpayi et al., 2017). Wastewater typically contains a mixture of organic and inorganic compounds, nutrients, and microorganisms, as well as various contaminants such as heavy metals, pesticides, and pharmaceuticals (Edwards & Kjellerup, 2013; Plöhn et al., 2021).

Baer et al. (2009) exposed *D. magna* to sewage treatment plant effluents, collected from a plant located in a heavily populated area of central Europe, for 21 generations, and the sex ratio of the population was monitored at each generation. The study found that exposure to the effluent resulted in a significant increase in the proportion of males in the population, with some populations reaching a male proportion of up to 90%. The researchers suggest that the increase in male proportion is likely due to the presence of EDCs in the effluent, which can interfere with the normal functioning of the endocrine system and disrupt sexual development.

Chatterjee et al. (2019) investigated the effects of contaminated water collected from the Gulpo stream (Bu-cheon-si, South Korea) on *D. magna* for five consecutive generations (F0–F4). The study found that exposure to contaminated water altered reproductive behavior, compromised fitness, and affected global DNA methylation without affecting survival. Additionally, the study found that continuous exposure to contaminated water led to an increase in size and a decrease in swimming speed, acceleration, and locomotive rate. The study also observed that the most significant increase in DNA methylation occurred in the first generation exposed to contaminated water, but this effect decreased towards normal levels in subsequent generations.

Sun et al. (2021) investigated the potential adverse effects of metal mixtures on *D. magna*, using water samples collected from Tai Lake in China. Samples were analyzed by ICP-MS and after determining the metal content, the mixture of exposure for the multigenerational test was then prepared on media spiked with a mixture of three ranges of concentrations, least medium and greatest. The ranges were from 0.06 to 5.14 μgL^{-1} of copper (Cu), lead (Pb), cadmium (Cd), nickel (Ni), and zinc (Zn). The multigenerational exposure approach and Maximum Cumulative Ratio (MCR) allowed the researchers to evaluate the potential long-term effects of metal exposure on the organism and its offspring by measuring the growth, reproduction, and population dynamics. These findings suggest that the metal cocktails in Tai Lake could have adverse effects on *Daphnia*. The reproduction was the most affected endpoint and the effects increased with increasing concentration, causing lower number of neonates and delaying the age of the first spawning (Sun et al., 2021).

3.6. Flame retardants and oestrogens

Flame retardants and oestrogens are two types of chemicals that are of concern in the environment due to their potential effects on human health and ecosystem and the increasing concentrations caused by anthropogenic use (Wojnarowski et al., 2021) Flame retardants are chemicals added to a wide range of consumer products to reduce their flammability and can enter the environment through various pathways, including leaching from products, wastewater effluent, and atmospheric deposition (Law et al., 2006; Rodriguez et al., 2006; Van der Veen & de Boer, 2012; Watanabe & Sakai, 2003). Environmental concern arises as they can persist for long periods and accumulate in the food chain, potentially posing a risk to human health and wildlife (Van der Veen & de Boer, 2012; Watanabe & Sakai, 2003). As for estrogens, they constitute hormones that are naturally produced in the body, however, human activities such as the use of contraceptives and hormone therapy (Adeel et al., 2017). Estrogens are known as endocrine disruptors, interfering with the normal functioning of hormones in the body, potentially leading to adverse effects on human health and wildlife (Ciślak et al., 2022).

Limited research has explored the impact of flame retardants on *Daphnia*, despite their frequent presence in the environment. (Li et al., 2015) studied the flame retardant tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) at environmentally relevant concentrations (ranging from 65 to 6500 ngL^{-1}) and observed dose- and time-dependent reductions in reproduction and development in *D. magna*. Transcriptomic analysis revealed significant changes in 57 genes, particularly at concentrations of 65 $\pm$ 7.1 and 550 $\pm$ 23 ngL^{-1}. Pathways related to protein synthesis, metabolism, and endocytosis were affected. These findings highlighted the adverse effects of environmentally relevant TDCIPP concentrations on *D. magna*, with development being the more sensitive endpoint, and identified specific genes and pathways involved.

In a separate study, Giraudo et al. (2017) exposed *D. magna* neonates (<24 h) to 10 μgL^{-1} of Tris (2-butoxy ethyl) phosphate (TBOEP) for three successive generations (F0, F1, and F2). TBOEP is an organophosphate ester, and is used as a substitute following the phase-out of brominated flame retardants, frequently detected in the environment and biota. *D. magna*, and effects were evaluated at the gene transcription and protein analysis levels, including catalase (CAT) activity, Juvenile hormone esterase (JHE), Vitellogenin (VTG), α-amylase (AMY), and survival, reproduction, and growth levels. Chronic exposure to TBEOP did not impact the survival or reproduction of *D. magna* but affected the growth output. The mean number of moults was also found to be lower in exposed daphnids, which can be related to significant differences in molecular responses in the transcription of genes related to growth, juvenile hormone signalling, proteolysis, and oxygenation.

As regard the estrogens, Brennan et al. (2006) assessed the effects of environmental estrogens, namely 17 b-oestradiol, diethylstilbestrol, bisphenol A (BPA), and 4-nonylphenol, on *D. magna* over two generations (F0 and F1) and found increased toxicity in the second generation, with decreased survival and fecundity.

Similarly, Li et al. (2018) studied the effects of BPA and lignin-derived bisphenol (LD-BP, a BPA analogue) were evaluated. Daphnids were exposed to BPA, LD-BP, and their binary mixture at concentrations (2–2000 mgL^{-1}) for 21 days. The expression of various biochemical markers, such as the activities of antioxidants (catalase (CAT), superoxide dismutase (SOD), and glutathione-S-transferase (GST)), a nervous system enzyme (acetylcholinesterase (AChE)), and a digestive system enzyme (α-glucosidase (α-Glu)), and the effects on growth, molting, and reproduction parameters were examined. The daphnids in the binary mixture treatment group had increased CAT activity. SOD activity in the daphnids was significantly inhibited in LD-BP- and the binary mixture-exposed animals. The activity of GST was not affected by BPA, LD-BP, and the binary mixture exposures. The binary mixture increased the activity of α-Glu of animals. BPA and LD-BP did not have effects on moulting and reproduction, except for the highest concentration of the mixture.

In contrast, Clubbs and Brooks (2007) found that *D. magna* exposed to other endocrine-active drugs (i.e. 17α-ethinylestradiol, faslodex, 20-hydroxyecdysone, and testosterone) developed resistance to these contaminants in the second generation of exposure, resulting in lower toxicity.

3.7. Microplastic and nanoparticles

Microplastics and nanoparticles are small particles that are often found in the environment, particularly in aquatic ecosystems, ranging from the micro-scale for particles in size less than 5 mm and nano-scale for those less than 100 nm in size (Nguyen et al., 2019). These particles come from a variety of sources, including the breakdown of larger plastic items, the wear and tear of tires and other materials, and the release of nanoparticles from industrial processes. Once these particles enter aquatic ecosystems, they can be consumed by a variety of organisms, who mistakenly confuse them with food, including fish, molluscs, and crustaceans (Kole et al., 2017; Lusher et al., 2017; Shruti et al., 2021).

In a recent study, Song et al. (2022) explored the transgenerational effects of polyethylene microplastic (MP) fragments containing benzophenone-3 (BP-3) on *Daphnia magna* over four generations. Only F0 was exposed to MP fragments, MP/BP-3 fragments, and BP-3 leachate to investigate potential transgenerational impacts in F3. The study revealed that the mortality of *D. magna* induced by MP and MP/BP-3 fragments returned to normal levels in the F3. However, somatic growth and reproduction significantly decreased in the F3 generation compared to the control group, indicating adverse transgenerational effects. These results confirmed transgenerational effects that appeared to accumulate across four generations for MP/BP-3 fragments, while an acclimation trend was observed for BP-3 leachate. It's important to note that there were no significant differences observed in global DNA methylation levels in D. magna across the four generations.

The effects of an environmentally relevant concentration of polystyrene microplastics (PS-MPs) (5 μgL^{-1}) on *D. magna* were investigated under six thermal conditions (2 mean temperatures and 3 daily temperature fluctuations) for two generations (Chang et al., 2022). At standard thermal conditions, microplastics had only a slight impact on the heartbeat rate. However, under challenging thermal conditions, microplastics affected life history, physiology, and behavior, including earlier maturation, higher fecundity and growth rate, decreased heartbeat rate, and increased swimming speed. High-latitude *Daphnia* populations showed a greater ability to adapt to microplastics under higher mean temperatures compared to low-latitude populations, highlighting the importance of daily temperature fluctuations and thermal evolution for a more realistic exposure accounting for more realistic conditions influenced by global warming. Another study on PS-MPs evaluated the effects of both single and combined exposures of PS-MPs and roxithromycin (ROX) on *Daphnia magna* (Liu et al., 2022) at environmentally relevant concentrations (0.1 and 10 μgL^{-1}). During single exposure, clearer and more straightforward adverse effects were observed compared to the combined exposure scenario. Combined exposure led to a shift in the inhibition of ROX on swimming velocity and acceleration of *D. magna* from inhibition to induction, while the feeding behavior continued to be inhibited. Notably, time to the first brood emerged as a sensitive indicator for reproductive toxicity.

Schür et al. (2020) cmpared the effects of PS-MPs and naturally occurring particles such as kaolin to model species *D. magna*. The findings indicated that when exposed to high concentrations of microplastics (10,000 and 2000 particles mL^{-1}), the survival of daphnids was significantly reduced. At the higher concentration, extinction occurred within a single generation, while at the lower concentration, it took four generations for extinction to occur. Additionally, the exposure to microplastics negatively affected reproduction and growth, leading to impairments in these vital processes. In contrast, an exposure to kaolin at similar concentrations did not induce negative effects. The study also found that food limitation did not affect the survival, but reproductive output was reduced in all treatment groups. Interestingly, the reproduction of animals in the high and low-food control, and the kaolin treatments recovered to the initial level after a marked decrease in reproduction from the first to the second generation across all groups. In a later study by Schür et al. (2021), they found that the sorption of dissolved organic matter is a key aging process that reduces the toxicity of microplastics. Toxicity testing using pristine microplastics may overestimate the effects of plastic particles in nature, resulting in the extinction of the third generation of daphnids as wastewater-incubated particles induced lower mortality.

da Silva et al. (2021) investigated the multigenerational ecotoxicological consequences of a binary mixture of silver nanoparticles (AgNPs) and glyphosate on *D. magna*. Neonates were exposed to different concentrations of glyphosate and AgNPs, individually or as a binary mixture. The survival, growth, reproductive capacity, and age at first brood were evaluated for both the parental generation and their offspring, with a distinction made between those exposed to the substances (F1E) and those not exposed (F1NE). The tests were performed using 5 concentrations of glyphosate (2.92–14.86 mg L-1) and 5 concentrations of AgNPs (0.017–0.09 μg L-1), resulting in 4 possible combinations of binary mixtures. The organisms subjected to a combination of two substances experienced a postponement in the onset of their first offspring and a noteworthy decline in reproductive capacity for both the parental generation and their offspring in F1E and F1NE. For the exposure to individual compounds, impairments on the reproduction were observed with no recovery for F1E and F1NE. Moreover, for the binary mixture exposure, a significant reduction on the reproduction for parents, F1E and F1NE was observed, indicating a higher toxicity when the components are present in mixture. Results obtained indicated that the binary exposure caused effects that differ from individual exposure, which needs to be further investigated for further comparison.

Hartmann et al. (2019) assessed the impact of wastewater-borne AgNPs and TiO_2NPs on *D. magna* in a multi-generation approach covering six generations. The effects of long-term exposure to pristine AgNPs and TiO_2 NPs on the reproduction, mortality, and body size of adult *Daphnia* were measured and compared to those caused by wastewater-borne AgNP and TiO_2NPs. In all six generations, exposure to environmentally relevant concentrations of pristine AgNPs (ranging from 0.9 μgL^{-1} to 10.1 μgL^{-1}) caused a significant reduction in the mean number of offspring compared to the control, while wastewater-borne AgNPs had no effect. No effects were observed following exposure to environmentally relevant concentrations of pristine and wastewater-borne TiO_2NPs (from 1.0 to 10.3 μgL^{-1}). The study used ASTM-medium and wastewater samples containing different concentrations of AgNPs and TiO_2NPs and the real concentrations were further determined by ICP-MS and ICP-OES. The study confirms that realistic exposure conditions are required for a reliable environmental risk assessment of NPs.

Jacobasch et al. (2014) exposed *D. magna* over six generations (F0–F5) to nanoscale titanium dioxide ($nTiO_2$). The mortality, somatic growth, reproduction and population growth rate were measured as endpoints. The nominal concentrations ranged from 1.19 to 6 mgL^{-1}, in which neither caused more than 40% mortality over the first five generations (F0–F4). However, at the sixth generation (F5) from the second lowest concentration (1.78 mgL^{-1}) to the highest concentration, there was 100% mortality. The size and reproduction of the daphnids was significantly decreased when exposed to TiO_2, this effect increased over generations, where lower concentrations would have a significant effect compared to the control. The population growth rate decreased over generations as well, because of the inhibition of the breeding, the populations became extinct. Because of the interactions of the particles with the daphnids' filter apparatus, this might have caused a reduction in food intake, which results in the reduced growth and subsequentially in reduced reproduction.

4. Advantages and limitations of multigenerational tests

Multigenerational toxicity tests with *Daphnia* were widely used to evaluate the chronic toxicity of chemicals in aquatic environments (Dietrich et al., 2010). Multigenerational tests provided a more realistic exposure scenario because they allow organisms to be exposed to chemicals over multiple generations, which means that the offspring of exposed organisms can be affected (Nederstigt et al., 2022; Schür et al., 2020). This is closer to the real-life situation in aquatic ecosystems, especially for chemicals that are constantly present in water bodies due to their persistent nature (metallic elements) or chemicals that might be repeatedly added (plant protection products or wastewater) or instrictic properties such as the temperature. These assays could be more useful than acute tests in detecting the effects of chemicals that may not cause immediate disruptions on the reproduction or survival but can cause effects on subsequent generations when constantly exposed (Galdiero et al., 2019; Maselli et al., 2017). By performing tests of longer periods and lower sublethal concentrations, they can provide a wider insight of trends that may be critical at population level (Galdiero et al., 2019).

Multigenerational tests can also provide information about the long-term population-level effects of chemicals by measuring the survival and reproduction of multiple generations of organisms. However, these tests can be time-consuming and more expensive than acute tests because they require monitoring of multiple generations of organisms, which can take several weeks or even months.

A guideline for these types of experiments might be difficult to establish due to the multiple factors that need to be considered when performing the tests and to maintain the reproducibility. Due to the wide of range of type of chemicals that can be tested, their properties and the concentrations used might limit the evaluation of some the endpoints such as the reproduction, as a high impairment will limit the number of offspring and by consequence the generations that can be exposed. Multigenerational tests may not be suitable for all chemicals, especially for those with short half-lives or that are rapidly metabolized but could give insight into the potential effects of being constantly exposed even if is for short periods of time.

Moreover, another important factor to consider is that different species of *Daphnia* may have different sensitivities to chemicals, which can affect the interpretation and generalizability of the results. However, some species of *Daphnia* might be more relevant for different types of exposure depending of the location and the risk of exposure to a type of chemical.

Despite the challenges arising from the high number of variables and parameters that can be tested, as well as potential variations in endpoints measured at different exposure times (Jonczyk & Gilron, 2005), multigenerational toxicity tests with *Daphnia* remain invaluable for providing insights into the potential chronic effects of chemicals in aquatic environments. Proper experimental design is crucial to ensure accurate interpretation of results.

5. Conclusions

Multigenerational tests with *Daphnia* are crucial for understanding the long-term effects of environmental stressors on population dynamics and evolutionary potential. These tests offer several benefits, including the ability to detect subtle effects, explore mechanisms underlying stressor effects, and identify critical windows of exposure. However, conducting multigenerational tests requires careful experimental design and control to address challenges and limitations. These include the potential for genetic drift and inbreeding depression in laboratory populations. Future studies should aim to overcome these limitations and consider innovative approaches, such as molecular biology and high-throughput sequencing, to enhance the sensitivity and resolution of multigenerational tests. Moreover, the development of standardized protocols for multigenerational testing is essential. Standardization will ensure comparability and reproducibility of results across studies, enabling better understanding and assessment of the ecological impacts of contaminants on aquatic ecosystems.

This review highlights the significance of multigenerational tests with *Daphnia* in providing insights into the effects of environmental stressors. It underscores the need for continued research in this field and the importance of standardized protocols to advance our understanding of the long-term ecological impacts and inform effective mitigation strategies.

CRediT authorship contribution statement

S. Pugliese: Writing – original draft. **E. Galdiero:** Supervision, Writing – original draft. **M. Guida:** Conceptualization, Funding acquisition, Project administration, Writing - review & editing. **G. Libralato:** Validation, Methodology, Writing - original draft. **C. Pappalardo:** Data curation. **A. Siciliano:** Supervision, Validation, Writing - original draft, Writing - review & editing.

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

No data was used for the research described in the article.

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