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REVIEW ARTICLE

Caenorhabditis elegans: a model organism in the toxicity assessment of environmental pollutants

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Abstract

The unfavorable effects of environmental pollutants are becoming increasingly evident. In recent years, *Caenorhabditis elegans* (*C. elegans*) has been used as a powerful terrestrial model organism for environmental toxicity studies owing to its various advantages, including ease of culture, short lifespan, small size, transparent body, and well-characterized genome. In vivo bioassays and field studies can analyze and evaluate various toxic effects of the toxicants on the model organism, while emerging technologies allow profound insights into molecular disturbances underlying the observed phenotypes. In this review, we discuss the applications of *C. elegans* as a model organism in environmental toxicity studies and delineate apical assays such as lifespan, growth rate, reproduction, and locomotion, which are widely used in toxicity evaluation. In addition to phenotype assays, a comprehensive understanding of the toxic mode of action and mechanism can be achieved through a highly sensitive multi-omics approach, including the expression levels of genes and endogenous metabolites. Recent studies on environmental toxicity using these approaches have been summarized. This review highlights the practicality and advantages of *C. elegans* in evaluating the toxicity of environmental pollutants and presents the findings of recent toxicity studies performed using this model organism. Finally, we propose crucial technical considerations to escalate the appropriate use of *C. elegans* in examining the toxic effects of environmental pollutants.

Keywords Model organism · *Caenorhabditis elegans* · Environmental pollutants · Toxicology · Biochemical assay

Introduction

With technological advances, products that improve the quality of life, such as plastics, have significantly increased worldwide. In addition, the use of pharmaceuticals and personal care products (PPCPs) is escalating with an increase in the world population, and the public's interest in improving modern lifestyles (Kasprzyk-Hordern 2010; Tkaczyk et al. 2021). Increased product usage promotes deposition in aquatic and terrestrial environments (Nizzetto et al. 2016). Moreover, these pollutants can interact with each other to induce a more severe impact on the environment. For example, microplastics in aquatic environments can transport organic pollutants, leading to accumulation in marine organisms (Chua et al. 2014; Zarfl and Matthies 2010). Due to this severe phenomenon, many research groups have investigated the toxic effects of environmental pollutants on humans and wildlife (Chae and An 2018; Savoca et al. 2021).

Environmental pollutants can be characterized by their intended usage. Pharmaceuticals are structurally-diverse chemicals designed to positively affect specific biological pathways (Ankley et al. 2007). Nonetheless, they can trigger side effects in humans and may render toxic effects in non-target organisms. When organisms are exposed to pharmaceuticals, their harmful effects should be investigated based on the characteristics of such drugs. Certain plastic materials and their constituents may become significant environmental pollutants that can cause serious problems. Low recycling rates and high dependence on plastics have resulted in the generation of large quantities of plastic waste (Di et al. 2021; Lee 2019). Plastics discharged into the environment are decomposed into micro- or nano-sizes by physical and

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biochemical forces. These micro- and nanoplastics negatively impact the environment (Auta et al. 2017). In previous studies, frequent detection of plastic debris was confirmed in the ocean and soil (Scheurer and Bigalke 2018; Shen et al. 2019). Humans can be exposed to these small-scale plastic particles via the food chain by consuming fish or seafood contaminated with the plastics. Additionally, small size, large surface area, and hydrophobic properties can facilitate the absorbance of other toxic substances; this increases the probability of exposure to other toxic contaminants that are absorbed onto plastics (Bhagat et al. 2021a). Other than pharmaceutics and plastics, there are still various types of contaminants, most of which are included in products and processes used to improve daily life. These pollutants are called emerging contaminants, mostly anthropogenic chemicals widely detected in environments with trace concentrations (Ahmed et al. 2021; Chen et al. 2022). Therefore, those emerging contaminants need to be carefully monitored and evaluated.

Although excess waste is detected in landfills, most studies have focused on toxicity effects targeting aquatic organisms. Environmental pollution in the soil is as severe as that in aquatic environments, and the detection of pharmaceuticals, plastics, and various pesticides has been reported in the soil environment (Qi et al. 2020; Rillig 2012). Such soil contamination can significantly affect the biogeochemical cycle, microbial, water circulation, and food production and requires considerable attention (Bhagat et al. 2021b; Sizmur and Richardson 2020; Tang et al. 2019; Tripathi et al. 2017).

Caenorhabditis elegans (*C. elegans*) is a good model organism for evaluating the toxic effects of soil organisms. The first investigation of *C. elegans* was reported by Sydney Brenner in 1974 (Brenner 1974) for genetic characterizations. Since then, it has been widely used as a model organism owing to several advantages, including ease of maintenance, short life cycle, convenient use in the laboratory environment, and well-characterized genome (Lucanic et al. 2018; Salzer and Witting 2021). These nematodes play crucial roles in essential soil processes, such as energy flow and nutrient mineralization (Höss et al. 2009). *C. elegans* is a preferred experimental model in soil organisms than *Eisenia fetida* because of its advantages of well-characterized genome and plentitude of in vivo and in vitro laboratory methods. (Bhagat et al. 2021b; Queirós et al. 2019). Various parameters affected by toxicity, such as survival, growth rate, reproduction, neurotoxicity, DNA damage, and metabolic perturbations, have been studied in *C. elegans*. Pioneering studies utilized *C. elegans* as a model organism to investigate its responses to food sources, environmental factors, heavy metals, and pharmaceuticals (Höss and Weltje 2007; Klass 1977; Popham and Webster 1979). These studies have provided proof-of-concept evidence and relevance regarding the suitability of *C. elegans* as a toxicological model organism (Hägerbäumer et al. 2015; Leung et al. 2008; Williams et al. 2022; Wilson and Khakouli-Duarte 2009). Various review papers have emphasized the importance of *C. elegans* as an important soil organism. However, there has been a lack of comprehensive discussion focusing on the adverse effects of various environmental pollutants on *C. elegans*.

This review discusses the advantages of *C. elegans* as an environmental toxicity research model. An in-depth description of the behavior examination and various physiological and biological parameters used in evaluating toxicity are described. We also present and discuss the main findings of recent studies. Finally, perspectives for future studies are provided to facilitate the appropriate use of *C. elegans* for the toxicity assessment of environmental pollutants.

C. elegans is a robust model organism for toxicity assessment

This promising model organism has received considerable attention in environmental toxicology by evaluating the toxic effects caused by exposure to environmental pollutants, such as plastics, persistent organic pollutants (POPs), and pesticides (Chowdhury et al. 2022; Li et al. 2020a; Wei et al. 2021; Yu et al. 2022). Their behavior and physiological assays have been utilized to evaluate the severity of toxic effects (Neher 2001). Under normal conditions, *C. elegans* is mainly characterized by small size, simplicity, and rapid culture speed (Bhagat et al. 2021b). When maintained in usual laboratory conditions, it has a rapid life cycle, and it takes 3 days to grow from eggs to adult worms ready for fertilization, and the lifespan of an individual is 2–3 weeks depending on the culture conditions (Salzer and Witting 2021). They are cultured in a small plate on a solid medium called nematode growth media (NGM), and *Escherichia coli* OP50 is used as a food source (Brenner 1974). Owing to this growth condition, it consumes less space and can be cultured inexpensively compared to other model organisms. *C. elegans* has two sexes, a self-reproducing hermaphrodite and a male; the male populace has a low frequency. Hermaphroditic reproduction has the advantage that the gene mutation occurs in a small percentage of the culture process, and each hermaphrodite has a constant number of 959 somatic cells. After hatching, *C. elegans* develops into an adult worm after proceeding through the four larval stages (L1-L4). *C. elegans* contains a system that can survive harsh conditions. During the growth process, if food is insufficient or the density is extremely high, it stops the normal growth stage and transforms into dauer larvae. By turning into the dauer stage, it exhibits resistance to external stimuli, survives several months without nutrient supply, and grows again to become a reproductive adult when the energy source is re-supplied (Hu 2007). Approximately 60–80% of human

gene homologs exist in *C. elegans*. Accordingly, research corresponding to human health and diseases in *C. elegans* is of great significance. Research on the genome of *C. elegans* is underway using genetic tools, such as RNA interference (RNAi) and CRISPR-Cas9 (Arribere et al. 2014; Dickinson and Goldstein 2016; Paix et al. 2015). Furthermore, studies using metabolomics, which can perform an in-depth evaluation of the metabolic process of *C. elegans*, are being actively conducted (Kim et al. 2019b; Molenaars et al. 2021; Yin et al. 2020). By combining genetic studies and metabolomics of *C. elegans* and various biochemical phenotype assays, we can advance our knowledge of the metabolic regulation and physiological behavior of nematodes. Furthermore, combining the behavioral examination, physiological assay, and multi-omics approaches on *C. elegans* is readily applicable. Altogether, *C. elegans* has shown to be a powerful model organism that advances our insights into the molecular processes underlying a phenotype of interest.

Assays used in *C. elegans* for toxicity assessment

Toxic effects from exposure to external substances appear in various forms in *C. elegans*. The events can be confirmed by evaluating the biological and physiological factors and detecting molecular markers. Through in-depth biological and behavioral assays, the toxic effects of pollutants can be evaluated, and the corresponding metabolic changes can be confirmed by detecting the biochemical markers. Typical phenotypic assays are helpful in understanding the observable effects of the toxic compounds on *C. elegans*. Furthermore, molecular and biochemical assays capable of measuring apoptosis, mitochondrial dysfunction, cell cycle disruption, and DNA damage give more profound insights into the mechanisms of the toxicity (Allard et al. 2013; Behl et al. 2016; Leung et al. 2010). As such, the biomarkers or endpoints discussed in this section will play an important role in the evaluation of toxic effects. Besides, comparing sensitivities for these assays is an essential factor to consider. For example, Li et al. identified endpoints such as lethality, body volume, lifespan, food intake, and excretion behavior, and confirmed that the degree of toxicity is different according to the type of assays (Li et al. 2023).

In this section, we discuss methods for evaluating the toxicity of *C. elegans*, which are summarized in Fig. 1 and Table 1.

Uptake and accumulation

Contaminants are widespread and persistent in the environment; hence, living organisms are increasingly exposed to these pollutants. The uptake and accumulation of these substances should be assessed to evaluate the degree of exposure to pollutants. One of the key features of *C. elegans* is transparency (Liu et al. 2014). Owing to this feature, the internal structure of the worm can be observed under a microscope. Therefore, the uptake of pollutants could be monitored and visualized. These characteristics have been widely used in toxicity studies of micro- and nanoplastics. After exposing the nematode to fluorescently labeled nanoplastics, their uptake can be tracked by monitoring the organism under a fluorescence microscope (Chu et al. 2021; Kim et al. 2019a). Previous studies have confirmed the uptake of nanoplastics in *C. elegans* by observing the accumulation in the buccal cavity, pharynx, intestine, and rectum site (Mueller et al. 2020; Scharf et al. 2013). In addition to visualization, bioaccumulation of contaminants in nematodes can be evaluated by determining the internal concentrations. Chen et al. successfully analyzed the internal concentration of perfluorinated compounds using LC–MS/MS (Chen et al. 2018). Monitoring internal concentration could be significant, since this parameter would indicate the actual levels of contaminants in the nematode, which can help determine the actual behavior of toxicants in *C. elegans*.

Typical physiological parameters

Lifespan and survival

A representative parameter for evaluating the comprehensive toxicity of pollutants is lifespan. Exposure to contaminants can cause tissue disruption, intestinal damage, and metabolic dysregulation, which induce lethal damage with abnormalities in the digestive and circulatory systems, and various cellular processes (Liu et al. 2019b; Shao and Wang 2020; Wang 2020). In addition to lifespan assays, survival studies are frequently used to evaluate survival rates upon exposure to toxicants. This survival study is performed by counting dead worms using a microscope, and has been used in several studies as an indicator of toxicity evaluation (Table 2). In a previous study, Lei et al. used five different-sized microplastics and attempted to determine the size of microplastics responsible for short lifespans and low survival rates. Accordingly, *C. elegans* showed the shortest lifespan and survival rate when exposed to 1 μm polystyrene (Lei et al. 2018a). Another study evaluated the lethality assay to assess the toxicity of triclosan, a pharmaceutical that is frequently detected in the environment. Lifespan was significantly reduced in the organism exposed to 1 mg/L of triclosan (11.3 days) compared to the control group (14.5 days) (Kim et al. 2019b). These parameters can be used as an index to compare overall toxicity after exposure to environmental pollutants.

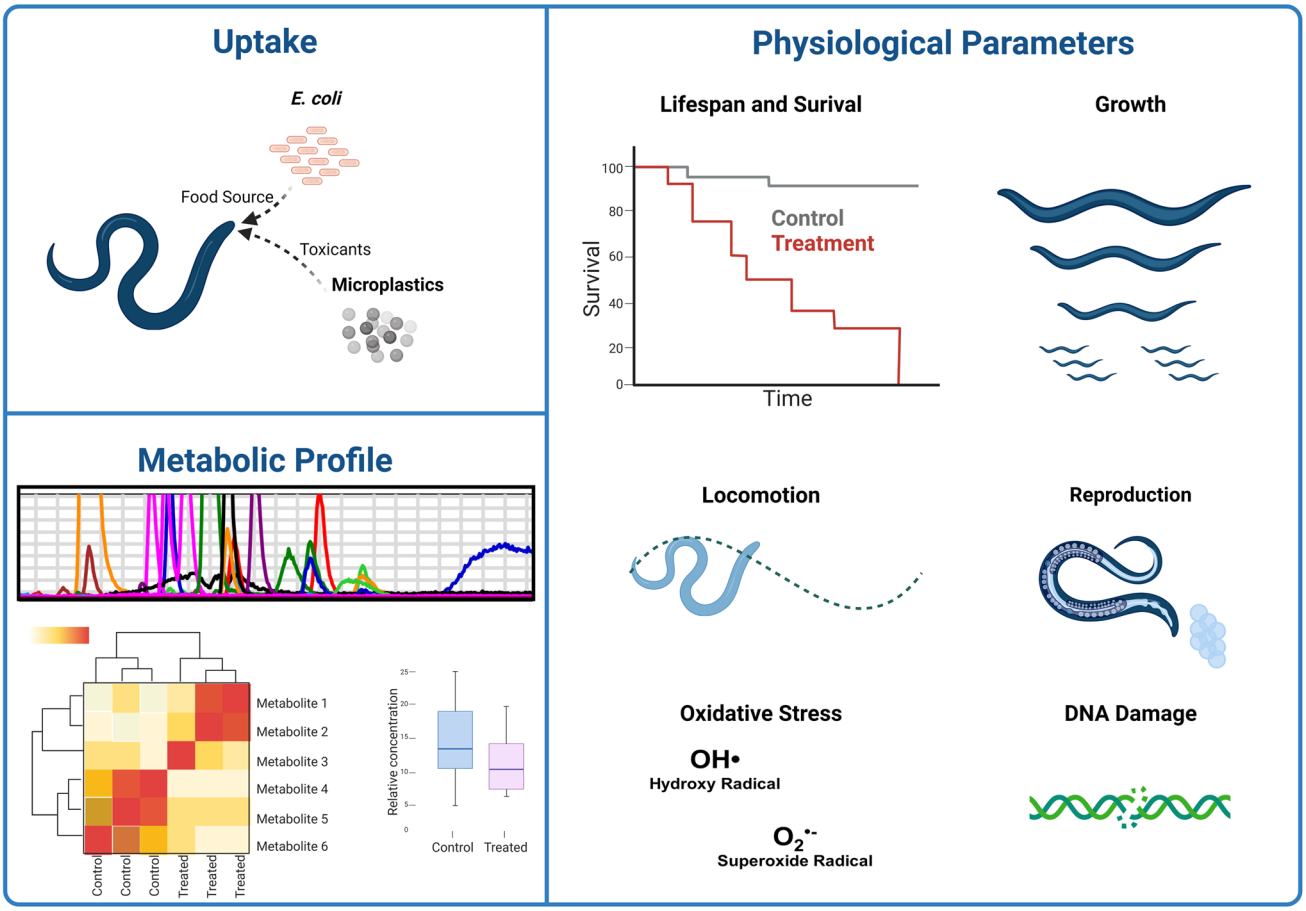

Fig. 1 Parameters of *C. elegans* used in toxicity assessment

Growth rate

The growth rate is one of the parameters that can be affected by exposure to environmental pollutants. Contaminants evidently reduce the growth rate of *C. elegans*. For example, when organisms are exposed to plastics, they delay their feeding and deplete their energy (Huerta Lwanga et al. 2016; Wright et al. 2013). This phenomenon inhibits the growth and development of organisms. In addition, flame retardants significantly decrease larval development. The severity differed according to the type of flame retardant; among them, polybrominated diphenyl ethers (PBDEs) severely affected the growth rate (Behl et al. 2016). Bisphenol S (BPS), used in a variety of products such as food packaging and personal care products, affects the growth rate at concentrations higher than 0.01 µM. Xiao et al. evaluated the growth rate by measuring the body length of the nematode (Xiao et al. 2019). BPS is known to affect thyroid hormone homeostasis, which affects the growth rate in *C. elegans* (Crump et al. 2016; Rochester and Bolden 2015). Since toxic substances could seriously impact the growth rate with various toxic mechanisms, this parameter can be used as an index to evaluate the toxicity by monitoring the rate and stage of development in *C. elegans.*

Locomotory ability

Another toxic mechanism of environmental pollutants is neurotoxicity. In. *C. elegans*, the nervous system is the most complex and consists of one-third of all somatic cells. Accordingly, various evaluations of the nervous system are being conducted. A phenotype assay to assess neurotoxicity includes pharyngeal pumping and locomotion assays (head thrashes, body bends, and crawling speeds). A reduced locomotor effect was confirmed in *C. elegans* exposed to microplastics, which affected the GABAergic neurons (Kim et al. 2019a; Qiu et al. 2020). Li et al. evaluated the multigenerational toxic effect of di(2-ethylhexyl) phthalate (DEHP) on locomotive behaviors (Li et al. 2018). Prolonged exposure can adversely affect locomotory behavior across generations. This study implies the potential ecological risk of multigenerational effects, which could pose a severe environmental issue. Additionally, numerous pesticides affect locomotor behavior in *C. elegans*. Exposure to the organophosphorus

Table 1 Summary of assays used in *C. elegans* for toxicity assessment

Assays	Evaluation	Biological effect	Advantages	Reference
Uptake	Confirm uptake of environmental pollutants upon exposure to the model organism	By specifying the organ where pollutants are accumulated, an estimation of the toxic mechanisms and their target organ can be conducted	*C. elegans* has a transparent body. Therefore, the uptake of pollutants can be visualized using a microscope	Chu et al. 2021 Mueller et al. 2020
Lethality	Determine the concentration of environmental pollutants, which show the lethal toxic effect	By confirming the lethality, the optimal concentration of pollutants can be defined	The lethal effect could be monitored via a microscope	Lei et al. 2018a
Lifespan	Assess the effects of environmental toxicants on the lifespan of the nematode	By assessing lifespan in *C. elegans*, the long-term effects of environmental pollutants can be evaluated	*C. elegans* has a short life cycle, which significantly reduces the time needed for lifespan assay	Kim et al. 2019b
Growth	Examine developmental stage or body length to evaluate the developmental speed	The development rate can be decreased upon exposure to environmental toxicants by disturbing the absorbance of energy sources	The short life cycle of *C. elegans* helps reduce the measurement time of the growth rate	Xiao et al. 2019
Locomotion	Measure the movement rate of the nematode	Locomotory dysfunction could be a sign of neurotoxicity	Locomotory ability could be measured in a lab environment due to the small size of *C. elegans*	Li et al. 2018
Reproduction	Measure brood size, and the number of eggs or germline cells for reproductive toxicity	Damage to reproductive organs upon exposure to environmental toxicants can be evaluated	A transparent body makes it possible to visualize the damage to the reproductive organ The small size of the nematode eases the measurement of brood size	Schöpfer et al. 2020 Lei et al. 2018b
Intestinal damage	The intestinal damage can be measured by various approaches, including autofluorescene, gene expression, permeability, development, and accumulation	The intestine is the primary organ exposed to toxicants upon intake. Uptake of nutrients can be disturbed upon damage in the intestine	Transparent characteristic helps evaluate the damage to the intestine, permeability of the intestine, and accumulation of toxicants	Shao and Wang 2020 Yu et al. 2020a
Oxidative Stress	Measure internal ROS using reagent or evaluate the accumulation of lipofuscin	The balance of ROS is essential in the organism. An increased amount of ROS can cause damage to cellular composition in organisms	The transparent body makes it possible to visualize the oxidative stress status	Kim et al. 2019a Wang et al. 2018b
DNA damage	DNA damage can be evaluated by transgenic strain, qPCR, or measurement of oxidative DNA damage	Genotoxic effects by environmental toxicants could induce genomic mutations	The availability of diverse mutant strains enables in-depth evaluation of genotoxicity	Imanikia et al. 2016 Yin et al. 2018

Table 2 List of environmental pollutants tested toxicity for physiological parameters

Environmental pollutants	Concentration	Tested parameters	Effects on tested parameter	References
Polystyrene (PS) (0.1, 0.5, 1.0, 2.0, 5.0 µm)	1.0 mg/L	Survival Body length Lifespan Motor behavior Motor behavior Cholinergic neuron GABAergic neuron Oxidative damage	Decreased (0.5, 1.0, and 5.0 µm PS) Decreased (1.0 µm PS) Decreased (1.0 and 5.0 µm PS) Increased (0.1 and 0.5 µm PS) Decreased (1.0, 2.0, and 5.0 µm PS) Damaged (0.5 and 1.0 µm PS) Damaged (1.0 µm PS) Damaged (0.1, 0.5, 1.0, 2.0, and 5.0 µm PS)	Lei et al. 2018a
BDE-47	0.1–100 µM	Larval Development Feeding assay Reproduction assay	Decreased (LEC[a]: 0.4 µM) Affected (LEC: 6.3 µM) Affected (LEC: 13 µM)	Behl et al. 2016
Bisphenol S	0.25–2 mM	Lethality Locomotion Growth rate Reproduction Lifespan Oxidative stress	LC_{50}: 2.18 mM Decreased (LEC: 0.01 µM) Decreased (LEC: 0.01 µM) Affected (LEC: 0.01 µM) Decreased (LEC: 0.01 µM) Affected (LEC: 0.01 µM)	Xiao et al. 2019
Polystyrene (PS) (50, 200 nm)	0.01–86.3 mg/L	Locomotion Oxidative stress Reproduction	Decreased (17.3 mg/L PS-50, 200 nm) Affected (17.3 mg/L PS-50 nm) Affected (17.3 mg/L PS-50 nm)	Kim et al. 2019a
Di(2-ethylhexyl) phthalate (DEHP)	0.2–100 mg/L	Locomotion Reproduction	Decreased (LEC: 0.2 mg/L) Affected (LEC: 0.2 mg/L)	Li et al. 2018
Quinalphos	0.0034–0.034 mM	Lethality Locomotion Feeding assay Oxidative stress	LC_{50}: 0.0323 mM Decreased (0.00344 mM) Inhibited (0.00344 mM) Affected (0.00344 mM)	Govindarajan et al. 2019
Tetrabromobisphenol A	0.01–100 µg/L	Growth rate Locomotion Oxidative Stress	Decreased (LEC: 10 µg/L) Decreased (LEC: 0.1 µg/L) Affected (LEC: 1 µg/L)	Liu et al. 2019a
Triclosan (TCS) Triclocarban (TCC)	1–5 mg/L 0.05–5 mg/L	Lethality Reproduction Hatching time Lifespan Stress response Germline toxicity	LC_{50}: 3.65 mg/L (TCS) LC_{50}: 0.91 mg/L (TCC) Decreased (LEC: 0.1 mg/L) (TCS) Decreased (LEC: 0.01 mg/L) (TCC) Delayed (LEC: 0.1 mg/L) (TCS) Delayed (LEC: 0.01 mg/L) (TCC) Decreased (LEC: 0.5 mg/L) (TCS) Decreased (LEC: 0.05 mg/L) (TCC) Affected (LEC: 0.1 mg/L) (TCS) Affected (LEC: 0.01 mg/L) (TCC) Affected (LEC: 0.1 mg/L) (TCS) Affected (LEC: 0.01 mg/L) (TCC)	Lenz et al. 2017
Lindane	0.01–100 ng/L	Growth rate Reproduction Locomotion Oxidative stress	Decreased (LEC: 100 ng/L) Affected (LEC: 100 ng/L) Decreased (LEC: 10 ng/L) Affected (LEC: 10 ng/L)	Yu et al. 2020b
Methomyl	500–6000 mg/L 83–1917 mg/L	Lethality Motor behavior AChE activity	24 h LC_{50}: 2482 mg/L 48 h LC_{50}: 2151 mg/L Affected (LEC: 83 mg/L) Increased (LEC: 83 mg/L)	Queirós et al. 2019
Triadimenol	3–300 µg/L	Lifespan Growth rate Reproduction Locomotion Oxidative stress	Decreased (300 µg/L) Decreased (LEC: 3 µg/L) Decreased (LEC: 30 µg/L) Decreased (LEC: 3 µg/L) Affected (300 µg/L)	How et al. 2018

[a]*LEC*, lowest effective concentration

pesticide, quinalphos, led to defects in the locomotion of *C. elegans*. The expression level of genes associated with locomotion (*unc-47*, *unc-13*), was also downregulated (Govindarajan et al. 2019). Flame retardants, tetrabromobisphenol A (TBBPA), also influenced the locomotory effect and oxidative stress. The expression levels of *sod-3* and *ctl-2* increased, which implies that these genes play a vital role in toxicity induction (Liu et al. 2019a). Collectively, locomotor dysfunction related to neurotoxicity is a phenotype that must be evaluated to confirm the toxicity of contaminants. Perturbations in the expression levels of various genes were confirmed depending on the toxic substance, and although the mechanism could evidently vary, the locomotion is reduced as an endpoint.

Reproductive ability

Another behavioral assay in *C. elegans* is its reproduction ability. *C. elegans* is a hermaphrodite with a short reproduction cycle, which makes *C. elegans* a valuable model organism for evaluating reproductive toxicity. To evaluate reproductive ability, brood size, number of eggs, and reduction of germline cells can be monitored. After exposure to environmental pollutants, the reproduction ability will confirmed to be significantly affected by the reduction in energy production, energy source absorption, and inhibition of feeding activity. A reduction in egg numbers has been reported in *C. elegans* exposed to different types of microplastics (Schöpfer et al. 2020). Furthermore, exposure to microplastics reduced the embryo number and brood size (Lei et al. 2018b). Lenz et al. assessed the germline toxicity induced by triclosan and triclocarban by evaluating the number of progeny, hatching time, and monitoring transgenic strain xol:GFP (TY2431). Therefore, the endocrine disruption effect of these antibiotics was assessed using *C. elegans* (Lenz et al. 2017).

Intestinal damage

The intestine is the organ responsible for the absorption of xenobiotics and the intake of nutrients. Accordingly, it is a major organ involved in xenobiotics toxicity. In addition, since *C. elegans* is transparent, intestinal damage can be evaluated visually using a microscope. In particular, microplastics absorbed in the intestine induce toxicity via abrasion of intestinal tissue and blockage of the alimentary canal (Lei et al. 2018b; Shao and Wang 2020; Yu et al. 2020a). In a previous study, the effects of the absorption of five different types of plastic polymers were studied. This resulted in the cracking of villi, damage to enterocytes and a significant decrease in calcium concentration in the intestines from four species (polyamides, polypropylene, polyethylene, polyvinyl chloride) (Lei et al. 2018b). Exposure to organochlorine pesticide, lindane, induces intestinal damage with high permeability. This was assessed using Nile red and blue food dye staining. In addition, the expression levels of genes related to intestinal development (*mtm-6* and *opt-2*) was significantly downregulated (Yu et al. 2020b). Most studies have shown a combination of oxidative stress and intestinal damage. Oxidative stress causes inflammation and altered signaling pathways, damaging tissues (Qu et al. 2018).

Oxidative stress

Oxidative stress is the most preferred endpoint in toxicity studies and has been evaluated in many studies on *C. elegans*. Oxidative stress is a widely known toxic mechanism in various types of environmental pollutants. An increase in reactive oxygen species (ROS) causes severe damage to biomolecules, such as proteins, lipids, and DNA. ROS in *C. elegans* can be measured by evaluating the accumulation of lipofuscin, a marker compound of ROS, or by using a reagent named 2′,7′-Dichlorofluorescin diacetate (H_2DCFDA), which is widely used in quantifying intracellular ROS. The damage caused by ROS has been reported to have a mutual effect on locomotion, body length, and brood size (Yu et al. 2020a). ROS levels are maintained through redox reactions by enzymes such as glutathione S-transferase (GST) and superoxide dismutase (SOD). When their balance is disrupted by exposure to environmental pollutants, the ROS level increases, resulting in severe damage to the body. Upon exposure to nanoplastics, glycine was significantly decreased, possibly due to oxidative stress, which affected the role of glycine as a ROS scavenger (Kim et al. 2019a). Induction of oxidative stress was also observed upon exposure to flame retardants, such as hexabromocyclododecane (HBCD). Increased ROS production and lipofuscin levels were also monitored. It was simultaneously confirmed that the toxicity caused by oxidative stress was alleviated by treatment with the antioxidant, N-acetyl cysteine (Lei et al. 2018a; Wang et al. 2018b). An imbalance of scavengers or antioxidants causes an increase in ROS production. Since ROS can damage cellular composition, oxidative stress induced by environmental pollutants can cause serious damage to organisms in the environment.

Stress marker with transgenic strains

One of the advantages of *C.elegans* is that it has diverse mutant strains; its genetic manipulation is relatively simple. This advantage enables in-depth research on genotoxicity. Since *C. elegans* shares several genes with humans, studies on the genotoxicity of environmental pollutants using *C. elegans* can help elucidate its effect on humans. Several studies have confirmed that ROS production induced by environmental pollutants can cause DNA damage (Imanikia et al. 2016; Yin et al. 2018). These damages have been

shown to be relieved upon treatment with antioxidants (Hornos Carneiro et al. 2020). Among various mutant strains of *C. elegans*, certain types of mutants tagged with GFP can be used to visualize the toxic effects and stress response. For example, the TJ356 [daf-16p:daf-16a/b:GFP] transgenic strain is widely used in stress response evaluation. DAF-16 is an essential element that regulates forkhead box O (FOXO) transcription factor and is typically inactivated, but can activate under external stimuli, such as oxidative stress or thermal stress. DAF-16 moves from the cytoplasm to the nucleus to regulate genes that increase resistance to stress (Henderson and Johnson 2001). Translocation of GFP was identified by fluorescence microscopy. Furthermore, GFP translocation into the nucleus has been monitored in several different toxicity studies, which confirmed the stress responses of *C. elegans* upon exposure to environmental contaminants (How et al. 2018; Kronberg et al. 2018). This advantage makes *C. elegans* a powerful model organism for evaluating genotoxicity.

Metabolic profiles

An essential parameter for evaluating toxic mechanisms in *C. elegans* is metabolic profiling using a metabolomics approach. Metabolomics is a comprehensive method for analyzing small molecule metabolites that study toxic mechanisms by identifying statistically significant metabolites between the control and exposed groups (Holmes et al. 2008; Long et al. 2020). Detected metabolites are further analyzed using pathway analysis or other omics techniques to evaluate biochemical changes in the model organism when exposed to environmental pollutants. One of the additional omics tools is lipidomics (Wan et al. 2019). Lipidomics is a branch of metabolomics studies that characterizes and analyzes lipid compositions in organisms. Although metabolites and lipids have diverse chemical properties, recent development in analysis methods has enabled simultaneous analysis of metabolites and lipids with single sample preparation (Molenaars et al. 2021). Therefore, a comprehensive understanding of the toxic mechanisms of environmental contaminants could be achieved. Metabolomics and lipidomics have been widely used in biological samples to evaluate the perturbation of metabolites and lipids upon toxic effects induced by environmental pollutants. Measurements of these metabolites enabled the investigation of metabolic disruption, which could serve as key marker compounds upon exposure. The application of omics approaches to *C. elegans* has now started to draw attention to the suitability of models to study metabolism. The results of the omics approach can be used to interpret the data by combining the phenotype assays, as mentioned earlier, which provides valuable data on toxic mechanisms. With the advantages of analyzing hundreds of metabolites simultaneously, researchers studying *C. elegans* have recently applied metabolomic approaches to toxicology studies (Table 3). It has been reported that when *C. elegans* is exposed to nanoplastics, it affects the energy-related metabolism, such as the TCA cycle and lipid metabolism (Hughes et al. 2009; Kim et al. 2019a; Liu et al. 2020; Ratnasekhar et al. 2015; Sudama et al. 2013; Yang et al. 2020). Ingestion of plastics affects the absorbance of the energy source, which eventually induces dysregulation of energy metabolism. Perturbation of metabolites was also observed when exposed to atrazine; in particular, metabolites involved in glycolysis, pyrimidine metabolism, and glycerophospholipid metabolism, consisting of amino acids and lipids and energy metabolism, were affected (Yin et al. 2020). Additionally, *C. elegans* were exposed to the antibiotic triclosan, a popular antibacterial agent in household and personal care products. Triclosan mainly affects the TCA cycle intermediates, carbohydrates, amino acids, and polyamines. Other phenotypes such as locomotion, reproduction, and ROS were monitored, and stress response was also confirmed in the transgenic strain (Kim et al. 2019b). This study refers to the risk of pharmaceuticals being exposed to soil environments.

Currently, there are few publications regarding metabolomics studies on *C. elegans*. Since metabolic profiling can provide a comprehensive evaluation of toxic effects on biological mechanisms, it is encouraged to apply metabolomics in *C. elegans* to assess the toxicity of diverse compounds.

Toxicity of environmental pollutants using *C. elegans* as a model organism

With the development of science and technology, environmental pollutants, such as plastics and pharmaceuticals, have become easily accessible through mass production. These contaminants are continuously detected in various environments, such as aqueous, soil, and wastewater; accordingly, there is a growing interest in assessing the toxic effects of these pollutants on the environment and humans. *C. elegans* has been widely used in toxicity research for a long time. After treatment with various environmental toxic substances, various phenotypic analyses, and changes in metabolic processes were elucidated using a metabolomics approach. This section discusses the types of environmental toxicants and their toxic mechanisms in *C. elegans*.

Plastics are among the most widely detected environmental pollutants; their uptake and potential toxic effects on model organisms are attractive to researchers. Therefore, several studies have elucidated the toxic mechanisms of plastics in many different ways. Lei et al. studied the toxic effects of polystyrene depending on the size of plastics, which ranged from 0.1 ~ 5.0 μm (Lei et al. 2018a). Accordingly, 1.0-μm sized polystyrene had the most severe toxicity, displaying the lowest survival rate and significantly

Table 3 Representative environmental pollutants tested toxicity for metabolic profiles

Environmental pollutants	Concentration	Affected metabolic pathways	References
Particles			
Nanopolystyrene (PS) (50, 200 nm)	17.3, 86.8 mg/L	TCA cycle Valine, leucine, and isoleucine biosynthesis Glycine, serine, and threonine metabolism Alanine, aspartate, and glutamate metabolism	Kim et al. 2019a
Titanium dioxide nanoparticles (< 25 nm)	7.7 and 38.5 mg/L	Glycine, serine and threonine metabolism Cyanoamino acid metabolism Oxalate glyoxalate metabolism Alanine, aspartate, and glutamate metabolism Glutamine, Glutamate metabolism Inositol phosphate metabolism Ascorbate and aldarate metabolism	Yin et al. 2020
Chemicals			
Triclosan	0.1 and 1 mg/L	Glycine, serine and threonine metabolism Tyrosine metabolism Starch and sucrose metabolism Valine, leucine, and isoleucine biosynthesis Alanine, aspartate, and glutamate metabolism	Kim et al 2019a, b
Atrazine	4 mg/L	Glycerophospholipid metabolism Glycolysis/gluconeogenesis Folate biosynthesis Glycine, serine, and threonine metabolism Pyrimidine and purine metabolism	Ratnasekhar et al. 2015
Perfluorooctane sulfonate (PFOS) Perfluoroctanoate (PFOA)	0.5 mg/L 2.0 mg/L	Aminoacyl-tRNA biosynthesis Phenylalanine, tyrosine, and tryptophan biosynthesis Valine, leucine, and isoleucine biosynthesis Lipid metabolism	Kim et al. 2020
Cadmium	12 µM	Transsulfuration pathway Phytochelatin synthesis	Hughes et al. 2009
Lead	0.66, 1.32, 2.64, and 5.27 mM	Pyrimidine and purine metabolism Phenylalanine, tyrosine, and tryptophan biosynthesis	Sudama et al 2013

decreased body length and lifespan. Gene expression studies confirmed toxic mechanisms. Downregulation of *unc-17* and *unc-47* implied the induction of damage in cholinergic and GABAergic neurons. Additionally, *gst-4*, which encodes a key enzyme in oxidative stress, was significantly increased, implying that oxidative damage was induced upon exposure to microplastics. Since plastics are eminent pollutants, several studies were conducted using C. elegans, confirming the findings above (Hu et al. 2020; Jewett et al. 2022; Yang et al. 2021). Collectively, plastics show comprehensive toxic effects, including oxidative stress, locomotion, and lifespan reduction, in a size-dependent manner.

Bisphenol A (BPA) is widely used in the production of thermal paper, bottles, packaging, and many other products. It is frequently detected in the environment and needs to be carefully studied because it is an endocrine-disrupting chemical (EDC) (Björnsdotter et al. 2017; Lombó et al. 2015). Zhou et al. evaluated the chronic toxicity of bisphenol A (BPA) in *C. elegans* to investigate the biological effects of long-term exposure (Zhou et al. 2016). Exposure to BPA higher than 0.1 µM significantly affected the growth, locomotion, and lifespan of *C. elegans*. An additional gene expression study revealed that *cep-1*, which regulates the stress response in the soma and mediates apoptosis in the germline, is related to the BPA-induced toxicity mechanism (Zhou et al. 2016). Due to the known toxicity of BPA, various types of bisphenol analogs have been used as a substitute (Catenza et al. 2021; McDonough et al. 2021). However, their effects on model organisms remain exclusive, and an in-depth study of those compounds should be conducted.

Engineered nanoparticles are frequently used in daily consumer products, including sunscreens and cosmetics. Titanium dioxide (TiO_2) nanoparticles are the most frequently used (Wang et al. 2018a). Upon exposure to TiO_2 nanoparticles, fertility and survival were affected, and gene expression of *cyp35a2* was upregulated. This gene is related to fat storage pathways, which may be a defensive response to the TiO_2 nanoparticle-induced toxicity (Roh et al. 2010). Since plastics are one of the highest contaminants in the environment, their combinational effect also needs to be studied. Dong et al. evaluated the combined effect of TiO_2 nanoparticles and nanopolystyrene (Dong et al. 2018). Synergistic toxic effects were observed under oxidative stress, while there was no enhancement in locomotion or brood size. This study implies a possible enhancement of the toxicity of nanopolystyrene particles. To understand the actual environmental conditions, these types of combined toxic effects should be further studied with other types of contaminants.

Some studies have focused on the toxicity of POPs, ubiquitous compounds in the environment (Chen et al. 2019). POPs are hardly degraded and prone to bioaccumulation, inducing higher toxicity. Since POPs can negatively impact the environment, assessing the toxic effect of these compounds is gaining interest and is widely studied in various model organisms, including *C. elegans*. Perfluorooctane sulfonate (PFOS) is a type of POPs extensively used in industrial applications due to its water- and oil-repellent properties and thermal and chemical stability (Kim et al. 2020). Exposure to PFOS-induced retardation of gonad development, DNA damage in germ cells, and ROS production. These results suggested that ROS caused DNA damage, which might cause reproductive toxicity in *C. elegans* (Guo et al. 2016).

Antibiotics are vital to treat infectious diseases in humans and animals. Overuse of these antibiotics can cause these chemicals to reach the environment, adversely affecting the organisms. Various monitoring studies have reported the detection of antibiotics in various environmental backgrounds. It has been frequently detected in aquatic and soil environments, and food sources (Li et al. 2020b; Majdinasab et al. 2020; Zhi et al. 2019). Therefore, many studies have been conducted to elucidate these unintended effects. Yu et al. evaluated the adverse effects of sulfonamide antibiotics on food availability (Yu et al. 2018). Exposure to sulfonamide-induced growth inhibition and oxidative stress. These effects were enhanced by high food availability, indicating that sulfonamide uptake was facilitated by dietary exposure. Since the availability of food and other types of contaminants can affect the behavior of toxicants, these combination effects should be carefully considered. Triclosan is a bactericidal agent in numerous health care and consumer products. Overuse of this antibiotic lead to its detection in human biospecimens, including plasma, urine, and breast milk (Bilal et al. 2020). Therefore, many model organisms have been applied to evaluate the effect induced by exposure to triclosan, and *C.elegans* was one of the model organisms to evaluate the effect on soil organisms. Exposure to triclosan induced perturbation of key metabolic pathways, including carbohydrates and amino acids metabolism related to energy production, and affected phenotype of organisms such as reproduction, locomotion, and oxidative stress (Kim et al. 2019b). As discussed in this section, environmental pollutants have chemical diversities that induce different toxicity mechanisms. Additionally, they can interact with each other to exert synergistic effects in actual environmental conditions. Therefore, in-depth toxicity studies of these various environmental contaminants are encouraged for environmental risk assessment.

C. elegans holds considerable promise for the environmental toxicity study

An essential advantage of using *C. elegans* is the ease of culturing and handling and the low maintenance cost (Hunt 2017). Additionally, the phenotype research method is well established, and it has the advantage of being able to conduct research in a short time using a minimal sample volume (Boyd et al. 2010a, b, 2012; Xiong et al. 2017). Furthermore, ethical approval is generally not required for this study, unlike other animal studies.

C. elegans has various mutants, and genes orthologous to humans render *C. elegans* a powerful model organism for environmental toxicity research, which also presents several advantages (Hochbaum et al. 2010; Kutscher and Shaham 2014). Transgenic strains using fluorescent proteins can interact with genes and respond to external stress (Henderson and Johnson 2001; Wang et al. 2012). Additionally, RNA interference (RNAi) gene silencing using bacteria can be studied using this model (Kamath and Ahringer 2003; Tabara et al. 1998).

With these advantages, *C. elegans* has been applied in various research fields. Nonetheless, to strengthen the research process, it is necessary to validate the research method used in the toxicity evaluation with factors through repeatability and inter-laboratory precision. In addition, it is essential to standardize the culture conditions, such as the medium recipe or temperature used in the experimental method, for their extensive use by research groups dedicated to *C. elegans* studies.

Future perspective

The increasing occurrences of environmental pollutants have been reported, significantly increasing research on assessing their toxic effects on the environment. As emphasized many

times in this review, *C. elegans* is an experimental model that can rapidly and conveniently confirm the effects of toxicants on the environment. Toxic responses can be identified through various phenotypic assays and advanced omics technologies can shed light on comprehensive biochemical effects. To date, various research groups have widely conducted environmental science research using *C. elegans*, but there are significant research areas that necessitate in-depth investigation. Most studies on *C. elegans* have conducted toxicity investigation under laboratory conditions using NGM or liquid medium. The high ionic strength of NGM also promotes plastic aggregation and can interact with other contaminants. Therefore, it is essential to study how the culture conditions used in laboratory environments affect the results of toxicity studies.

A typical workflow and considerations for a study using *C. elegans* are shown in Fig. 2. As mentioned, *C. elegans* culture condition should be first optimized for the environmental contaminants. Then, treatment concentration needs to be optimized with a lethality assay along with prior knowledge of the environmentally practical concentrations. Treatment conditions could be categorized as single-dose or dose-dependent treatment and acute or chronic exposure. The developmental stage for the experiment should also be selected. Furthermore, the influences of the toxicants on the later generations of living species could also be readily investigated using *C. elegans*.

When toxicity is evaluated by functional omics approaches, such as metabolomics and lipidomics, extraction methods, analytical parameters, and other aspects of metabolomics should be considered carefully. Multi-omics data integration is arguably an all-inclusive framework for giving better insights into the dysregulations of *C. elegans* exposed to the toxicant at the molecular level. Furthermore, the role of genetic variants, including mitochondrial mutations, should also be examined for a comprehensive understanding of the effects of pollutants on living species. In natural environments, organic compounds co-exist with contaminants. Accordingly, more effort should be put into the interactions between organic and toxic substances in the environment. In some instances, it is necessary to study these effects because they can influence the mechanism of exposure by interacting with each other. This will help us understand the effects of the actual natural environment. Additionally, there could be a difference in experimental conditions between in situ environments and lab studies. These potential differences are important factors that need to be considered when conducting lab assays using model organisms.

In conclusion, *C. elegans* has been increasingly studied as an alternative in vivo model for toxicity studies. Nonetheless, it is still developmental compared with conventional experimental models such as rodents or zebrafish. Further technical standardization and method optimization are still

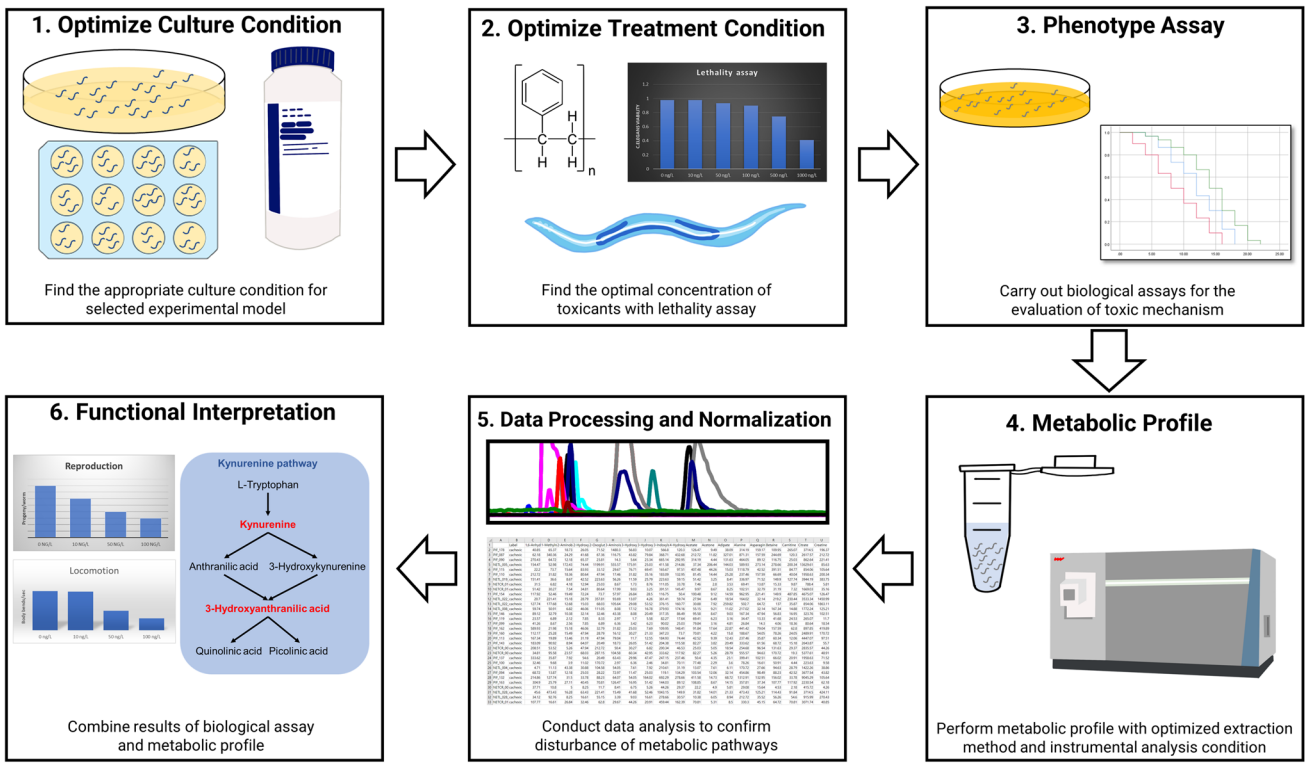

Fig. 2 A typical workflow of enviromental toxicology study using *C. elegans* as model organism

required to maximize the acquisition of biological variance and reduce technical noise. A comprehensive understanding of the environmental toxicants and living species can be achieved by combining proper experimental conditions, advanced techniques for data acquisition, and appropriate functional interpretation.

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