Abstract

The extensive use of pesticides in agricultural production has raised significant concerns about its impact on human health and the environment. Various types of pesticides, including fungicides, insecticides, and herbicides, have been associated with environmental pollution and health risks for non-target organisms. Infants and young children are particularly vulnerable to the harmful effects of pesticide exposure, given their early-life development stage.

Recent research has focused on understanding the health implications of early-life exposure to different types of pesticides, such as neonicotinoids, organophosphates, organochlorine insecticides, triazole fungicides, herbicides, and plant growth regulators. Studies have explored the effects of these pesticides on various organisms, including zebrafish, rats, mice, and humans, using advanced methodologies like gut microbiota analysis and multi-omics techniques. These methodologies help in comprehending the pathogenic mechanisms associated with environmental pesticide residues.

In addition to presenting a detailed account of the health impacts stemming from early-life exposure to pesticides, this comprehensive review emphasizes the need for future research endeavors. These endeavors should focus on identifying biomarkers that indicate early-life pesticide exposure, investigating intergenerational effects, and seeking effective treatments for diseases arising from such exposure. It underscores the importance of advancing our understanding of pesticide exposure and its long-term consequences to safeguard the health and well-being of future generations.

Introduction

Introduction：为什么生命早期？ 生命早期暴露对健康的影响

0）生命早期暴露（重新写了）

Focusing on early-life exposure is essential due to its significant and lasting impact on an individual's health and development. During the crucial stages of prenatal and early postnatal periods, the brain experiences rapid development, and any exposure to harmful elements can lead to future cognitive and neurological deficits[1]. Additionally, early-life conditions can cause epigenetic changes, which can affect gene regulation throughout one's life and even influence subsequent generations[2]. The formation and functioning of the immune system are also heavily influenced by exposures early in life. For instance, the right balance of microbial exposure can strengthen the immune response, whereas certain imbalances may lead to allergies or immune disorders[3]. Moreover, adverse conditions in early life, such as malnutrition or toxin exposure, can predispose individuals to chronic diseases like obesity, diabetes, and cardiovascular issues in adulthood[4]. Therefore, understanding and mitigating negative early-life exposures is paramount for ensuring long-term health and well-being.

Early life exposure

Early life exposure routes encompass transplacental transmission, lactational transfer through breast milk, ingestion of infant food and formula, consumption of drinking water, administration of medical products, and exposure to complex chemical mixtures[5]. Substances detrimental to health, such as illicit drugs, alcohol, and environmental toxins, possess the capability to permeate the placental barrier[6]. Additionally, fetuses are vulnerable to transmissions of viral and bacterial infections[7]. Neonates may receive contaminants via breast milk[8], and potential exposure to pollutants persists through infant formula and food intake. Airborne contaminants, including tobacco smoke and domestic chemicals, also pose a risk. Topical absorption of chemicals from products is possible, and contaminated water sources introduce children to deleterious chemicals or pathogens[9].

Within neonates, infants, and toddlers' periods, exposure to xenobiotics probably perturbs the gut environment, which drives or contributes to **microbial dysbiosis**, exerting a negative impact on adulthood health[10].

There's a direct relationship between in utero, perinatal, and postnatal exposures, and offspring's **depression**[11].

Prenatal exposure is related to the microbiome composition and **caries** prevalence during progenies' childhood[12].

In utero, platinum exposure induces **childhood hearing loss** in offspring[13], and intrauterine exposure to tobacco smoke is associated with congenital anomalies, obesity, and neuropsychiatric sequelae[14].

Pesticides

In 2020, the global pesticide usage was 2661124.23 tons, and the total pesticide usage in China was 273375.75 tons[15]. Widely used pesticides, such as neonicotinoid insecticides pose potential hazards to human health[16]. The negative effects of pesticides on food safety, soil and water safety, and human health have attracted global attention[17-19]. 18 Pesticides are discovered in Huangpu River, making the Huangpu River the area with the highest ecological risk for the Shanghai metropolitan area[20]. In the Eastern Mediterranean region, reported levels of pesticide residues are usually higher than the maximum residue levels in the Codex[21].

Pesticides can be classified into acaricides, insecticides, fungicides, herbicides, plant growth regulators, nematicides, and rodenticides[22]. Most research focuses on fungicides, insecticides, and herbicides.

Some literature shows that pesticide residues in small streams in **Germany** are relatively low, only within 10ng/L[23]. However, the pesticide residues in **Japanese** drinking water sources are very high, reaching over 6000ng/L[24]. *Table 1* shows the residual situation of some insecticides, fungicides, and herbicides in the water environment of various regions. On the

one hand, we can see that the residue of Glyphosate is the highest in the La Plata and **Argentina** regions, reaching 20040ng/L[25]. On the other hand, there is very little residue of Chloropyrifos in the **Maritime Region of Canada**, only 3.67ng/L[26].

It is true that pesticides have brought convenience to agriculture, increased production, and to some extent alleviated hunger. However, we cannot ignore its harm and threaten to the ecology and human health[27]. For example, exposure to fipronil, an **insecticide**, may lead to neurological, gastrointestinal, respiratory symptoms, acute kidney injury, epilepsy, and anuria[28] and endosulfan, an organochlorine insecticide, causes serious health problems, such as endocrine disruption, infertility, and neurological disorders[29]. **Fungicides** such as triazoles give rise to developmental toxicity, hepatotoxicity, neurotoxicity, and nephrotoxicity[30]. **Herbicides** such as glyphosate may be carcinogens[31]. **Rodenticides**, such as Salmonella serotype enteritis strains, are the main cause of human gastrointestinal diseases[31].

This review summarizes how early-life exposure to pesticides leads to adverse health effects on model organisms through gut microbiome, metabolomics, and transcriptomics.

Early life exposure to pesticides

一，生命早期农药暴露的研究进展

There is a little but not much research on the human health effects of early life exposure to pesticides. Prenatal or early exposure to **pesticides** tend to cause **autism spectrum disorder** (ASD)[32]. Early-life exposure to organophosphorus pesticides was associated with some **respiratory symptoms** like asthma in childhood[33]. Other studies suggest that pesticides and air toxins may be one of the causes of **cancer** in children[34] and early exposure to pesticides in life probably leads to **testicular germ cell tumors** during adulthood in the future[35]. Besides, **lymphoma, leukemia, and nephroblastoma** in children are possible consequences of pesticide exposure during pregnancy and early years[36]. Moreover, animal experiments have shown that early exposure to pesticides in life causes obesity in later life[37, 38], behavioral abnormalities[39], asthma [40], social novelty alteration[41], a reduced immune response[40, 42], suppressed neurodevelopment[32], metabolic disorder[38], and gut microbiome dysbiosis[43-45].

Perinatal exposure to dichlorodiphenyltrichloroethane (DDT), an organochlorine insecticide, causes a profound **decrease in epinephrine secretion** in adulthood of the posterity[46]. Contacting with bendiocarb, a type of insecticide, in infancy affects the **fetal immune system** and **response to vaccination**[47].

At the same time, prenatal exposure to chlordecone, another type of insecticide, affects the **neural development** of infants[48].

Other research contends that **respiratory diseases** like asthma, bronchitis, and persistent cough in children are associated with prenatal exposure to insecticides[46].

Fungicides also play a bad role in neonates' health since they corrupt their **neurogenesis**[49].

The herbicide Agent Orange, used in the Vietnam War, resulted in local children experiencing **epilepsy, deafness, speaking disability, slow mental development, mental illness, and eye disability** in later life[50].

Exposure to chlorocholine chlorine, a plant growth regulator, during pregnancy interferes with **reproductive function** in male offspring[51].

Many previous studies have only shown the adverse effects of pesticide exposure in early life, without elucidating the mechanism of such adverse effects. In this article, we conducted a more in-depth review of early exposure to life pesticides using a combination of omics techniques and gut microbiota.

Table1. Residual concentrations of some pesticides in water environments of different regions

pesticides	type	location	environmental concentration (ng/L)	Ref
Amitrole	herbicide	Athens, Greece	554	52
Climbazole	herbicide	Athens, Greece	790	52
Terbacil	herbicide	Athens, Greece	1135	52
Carbendazim	fungicide	German streams	8.2	23
Fenuron	herbicide	German streams	8.5	23
Flufenacet	herbicide	German streams	6.1	23
Metazachlor	herbicide	German streams	4	23
Azinphos-methyl	insecticide	Iberian Peninsula, Portugal	580.6	28
Cyhalofop-butyl	herbicide	Iberian Peninsula, Portugal	128.6	28
Difenoconazole	fungicide	Iberian Peninsula, Portugal	365.1	28
Edifenphos	fungicide	Japan water resources	6000	24
Fenthion	insecticide	Japan water resources	6000	24
Indanofan	herbicide	Japan water resources	9000	24
Chlorpyrifos	insecticide	La Plata, Argentina	2645	25
Glyphosate	herbicide	La Plata, Argentina	20040	25
Boscalid	fungicide	La Rioja, Northern Spain	57	53
Fluometuron	herbicide	La Rioja, Northern Spain	69	53
Fluopyram	fungicide	La Rioja, Northern Spain	72	53
Imidacloprid	insecticide	La Rioja, Northern Spain	46	53
Atrazine	herbicide	Maritime Region of Canada	29.1	26
Chlopyrifos	insecticide	Maritime Region of Canada	3.67	26
Clothianidin	insecticide	Maritime Region of Canada	19.4	26
Metribuzin	herbicide	Maritime Region of Canada	32.25	26
Atrazine	herbicide	Mogi Guaçu River Basin, Brazil	48.1	54
Carbofuran	insecticide	Mogi Guaçu River Basin, Brazil	56.9	54
Cyproconazole	fungicide	Mogi Guaçu River Basin, Brazil	15.8	54
Diuron	herbicide	Mogi Guaçu River Basin, Brazil	92	54
Flutriafol	fungicide	Mogi Guaçu River Basin, Brazil	14	54
Thiamethoxam	insecticide	Mogi Guaçu River Basin, Brazil	114.8	54
Chlorothiazide	insecticide	Ontario, Canada	2090	55

imidacloprid	insecticide	Ontario, Canada	700	55
Thiacloprid	insecticide	Ontario, Canada	460	55
Carbendazim	fungicide	Taihu Lake, China	35	56
Imidacloprid	insecticide	Taihu Lake, China	31	56
Metolachlor	herbicide	Taihu Lake, China	40	56
Azoxystrobin	fungicide	the Mediterranean Albufera de Valencia Natural Park	1027	57
Carbofuran	insecticide	the Mediterranean Albufera de Valencia Natural Park	60	57
Diuron	herbicide	the Mediterranean Albufera de Valencia Natural Park	110	57
Cypermethrin	insecticide	Punjab, Pakistan	1589	58
Fipronil	insecticide	Punjab, Pakistan	960	58
Profenofos	insecticide	Punjab, Pakistan	5665	58
Thiamethoxam	insecticide	Punjab, Pakistan	5812	58

2 Multi-omics Methodologies to Study the Effects of Early Life Pesticide Exposure

Multi-omics, a comprehensive approach comprising genomics, epigenomics, transcriptomics, proteomics, and metabolomics, offers a holistic understanding of biological systems.[59]. Within these, transcriptomics and metabolomics are most frequently employed in exposure studies. In contrast, lipidomics and proteomics find less frequent application.[60].

Transcriptomics employs techniques to analyze the transcriptome, reflecting the entire ensemble of transcripts in a cell at any given time[61]. Prominent among these are quantitative real-time polymerase chain reaction (QRT-PCR), microarray analyses, and next-generation sequencing[62].

on the other hand, delves into the complete set of proteins expressed by cells or organisms under specific conditions. Key methodologies here include mass spectrometry[63], two-dimensional gel electrophoresis[64], and protein microarrays[65]. Furthermore, proteomics plays an instrumental role in the identification of disease-specific biomarkers.

Metabolomics is pivotal in unveiling the pathogenesis related to early-life pesticide exposure, offering insights into diseases, such as obesity[66]. A typical metabolomic analysis involves stages of sample extraction, data collection, and analysis[67]. Crucial tools for data collection encompass mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy, and Fourier Transform Infrared spectroscopy (FT-IR)[68]. Notably, mass spectrometry have found extensive application in ecotoxicological studies, aiding in the identification of metabolic pathway disruptions[69] and stands out as a dominant analytical tool, extensively utilized in both metabolomics and lipidomics[70].

Given the myriad of metabolic pathways, understanding alterations due to early-life pesticide exposure is crucial. Several pathways, such as those involving tryptophan, dopamine, and lipid metabolism, have been implicated in pesticide-induced disruptions[71]. Given the vital roles of lipids in physiological processes, lipidomics, a subset of metabolomics, has gained prominence, especially in unveiling lipid metabolism pathways[70, 72]. Through metabolomics, it was found that the more **β- HCH** and **mecarbam** residue in serum of pregnant humans, the lighter the fetal weight, which may be due to the interference of these two insecticides with Glycerol metabolism and thyroid hormone metabolism[73].

A myriad of studies on model organisms, ranging from zebrafish to rodents, has elucidated the varied impacts of early-life pesticide exposures. These studies reveal disruptions in metabolic pathways, from retinol metabolism due to glufosinate ammonium exposure to the neurotoxic effects of chlorpyrifos, altering lipid components in the brain.

Glufosinate ammonium in the drinking water of prepregnant mice inhibits descendants' retinol metabolism and fatty acid biosynthesis, promotes pyrimidine metabolism, and enhances ubiquinone and other terpenoid-quinone biosynthesis[39]. Contact with **endosulfan** during gestation disturbs the glucose and lipid metabolism in descendants[38]. Mating period exposure to **a combination of pesticides**, including boscalid, captan, chlopyrifos, thiachloprid, thiophanate, and ziram, leads to changes in the metabolic fingerprints in urine, liver, and feces[74]. **Epoxiconazole** exposure to zebrafish larval affected lipid metabolism, glucose metabolism, and amino acid metabolism[42]. Rats getting in touch with **chlorpyrifos** during gestational and lactational periods alters fatty acid metabolism in progenies, which may be relevant to the potential risk of inducing neurotoxicity[41]. Discovered through proteomics, **chlorpyrifos** have neurotoxicity probably because it influences cholesterol esters, triglycerides, and phosphatidylcholine in the brain[75]. **Chlorpyrifos** altered endocannabinoid signaling, leading to changes in glutamatergic and GABAergic signaling in the amygdala[76]. In addition, other research contends that **chlorpyrifos** interferes Dio3b, a gene related to thyroid function in zebrafish embryos through transcriptomics[77]. **Nitenpyram** exposure to pregnant mice disturbs the descendants' purine metabolism, amino acid metabolism, and TCA cycle[78]. The combined exposure of **difenoconazole** and **tebuconazole** to zebrafish resulted in immune response and endocrine disruption, possibly because these two triazole fungicides affected the zebra larvae's arachidonic acid metabolism, linoleic acid metabolism, PPAR signaling pathway, and lipid metabolism[45]. Other research uses metabolomics combined with transcriptomics to find that **difenoconazole** exerts an adverse effect on zebrafish heartbeat by disturbing energy metabolism, lipid metabolism and immune-related pathway[79]. Environmental pesticide exposure in France of pregnant rats may lead to metabolic disorders and neurological effects on offspring rats later in life, including the disruption of amino acid metabolism, TCA cycle, and glucose metabolism[80]. Mother rats' exposure to **glyphosate** changes the levels of oxidative stress-related metabolites and genes in male offspring[80].

Procymidone influences the amino acid metabolism of mice pups, resulting in metabolic disorders[81]. Perinatal exposure to **fenvalerate** exerts a gender-dependent effect on neurodevelopment in offspring, which may be the result of the pentose phosphate pathway and starch and sucrose metabolism[32]. Juvenile mice exposure to **o，p'-DDT** tends to have a heavier uterine and higher luminal epithelial cell height (LEH) , partly due to changes in glycine,

choline, and phenylalanine, which can bind to the metabolite fumaric acid of o，p′-DDT[82].
Exposure to **cypermethrin** during pregnancy and perinatal period leads to neurodevelopmental defects in offspring male mice, such as the more slowly-acquired audit start reflex, which may be associated with the alternation of some genes related to protein synthesis, maturation, and degradation[83].
Early-life zebrafish exposure to **permethrin** makes F0 fish not active in adulthood, and F1 and F2 males exhibit reduced specificity for anxiety like behavior. That adverse reaction is related to histone acetylation and histone methylation/demethylation[84].
Gestational exposure to **flusilazole** disrupt male offspring's endocrine effects in vivo, probably due to the dysregulated Calb2 and Gsta2 expression[85], and **triticonazol**e alters genes related to hypospadias in humans of fetal male rat external genitalia[86].
Abamectin, Carbaryl, Chlorpyrifos, Fipronil, Imidacloprid, Methoxychlor are reported to influence the cardiac and neuronal development of zebrafish embryos.
Abamectin interferes zebrafish embryos' lipid metabolism. **Carbaryl** alters genes related to neurogenesis. While **fipronil** and **methoxychlor** influences nerve growth factor *vgf*[77].
Gestational exposure to **chlordecone** decreases the number of spermatogonia (SG) in F3, with meiotic defects in sperm cells and a decrease in the number of sperm in the F1 and F3 male offspring, and that is associated with protein-encoding genes disorders [87].
Although there's no significant changes in body weight, testes weight, or GSI on male offspring after zebrafish embryos' exposure to **atrazine,** transcriptomic analysis indicates that lipid metabolism, molecular transport, small molecule biochemistry, and cell morphology are changed[88]. At the same time, exposure of zebrafish embryos to **atrazine** resulted in a significant decrease in 5-hydroxyindoleacetic acid (5-HIAA) and serotonin turnover in adult female brain tissue[89]. Zebrafish eggs in water environments rich in **3,4-dichloroaniline**, an insecticide, may exhibit non-detachment of tail, lack of somite formation, and the absence of heartbeat, which may be related to several processes of cardiac function and development and metabolism[90]. Cry proteins from ***Bacillus thuringiensis*** induced minor disturbances in the proteome of zebrafish larvae, but they didn't cause malformations or mortality in zebrafish larvae[91].
Table 2 presents experimental information on early-life pesticide exposure using multi-omics methods.

To wrap up, multi-omics technologies play a pivotal role in studying the impacts of early-life exposure to organisms. Transcriptomics and metabolomics are frequently utilized in exposure studies, with techniques such as qRT-PCR and mass spectrometry being predominant. Metabolomics enhances our understanding of disease mechanisms, particularly with early-life pesticide exposure. Numerous studies, based on model organisms, have highlighted the mechanism of pesticides on metabolic pathways and physiological processes.

Table 2 Information about pesticides exposure experiment using metabolomics on mode organism.

Pesticides	Type	Organism	Exposure method	Dosage	exposure time	Organ	Methods	Mechanism	adverse effect on offspring	Ref
glufosinate ammonium	herbicide	Parent mice	drinking water	2 mg/kg per day	8 weeks before pregnancy	feces	metabolomics	*pyrimidine metabolism* *ubiquinone and other terpenoid-quinone metabolism* *retinol metabolism* *fatty acid metabolism*	Behavioral abnormalities	[39]
endosulfan	insecticide	Parent mice	gavage	0.03 mg/kg body weight	gestational day(GD) 6 to postnatal day(PND)21	feces	metabolomics	*lipid metabolism* *glucose metabolism*	Obesity, metabolic disorders	[38]
A combination of pesticides(boscalid, captan, chlopyrifos, thiachloprid, thiophanate, and ziram)	pesticides	Parent mice	diet	/	mating period	urine,liver and feces	metabolomics	none	Changes of the metabolic fingerprints	[74]
epoxiconazole	fungicide	zebrafish embryos	water environment	0, 1, 3, 5, 7, 9 and 11 mg/L	96h	larvae	metabolomics	*lipid metabolism* *glucose metabolism* *amino acid metabolism*	Develop morphological defects; Apoptosis	[42]
chlorpyrifos	insecticide	Offspring Rats	gavage	1 mg/kg/ml/day	PND10 to PND15	serum	metabolomics	*fatty acid metabolism*	Hyperlipidemic, hypoglycemic in female offspring; Altered the rat's reaction to social novelty	[41]

nitenpyram	insecticide	Parent mice	gavage	0, 0.4 and 4 mg/kg/day body weight	During pregnancy	feces	metabolomics	*purine metabolism* *amino acid metabolism* *TCA cycle*	A decrease in serum glucose of female offspring.	[78]
difenoconazole	fungicide	zebrafish embryos	water environment	405 μg/L	Larvae from 0 to 3 days post-fertilization	larvae	metabolomics	*arachidonic acid metabolism* *linoleic acid metabolism* *PPAR signaling pathway* *lipid metabolism*	Causes the immune response and the endocrine disrupting effect	[42]
tebuconazole	fungicide	zebrafish embryos	water environment	1135 μg/L	Larvae from 0 to 4 days post-fertilization	larvae	metabolomics	*arachidonic acid metabolism* *linoleic acid metabolism* *PPAR signaling pathway* *lipid metabolism*	Causes the immune response and the endocrine disrupting effect	[42]
acetochlor bromoxynil carbofuran chlormequat ethephon fenpropimorph glyphosate imidacloprid	herbicide herbicide insecticide plant growth regulator plant growth regulator fungicide herbicide insecticide	Parent rats	gavage	a total dose of 447 μg/kg bw/d	GD4 to GD21	urine, plasma, liver, and whole brain	metabolomics	*amino acid metabolism* *TCA cycle* *glucose metabolism*	It may cause metabolic disorders and neurological effects later in life.	[80]

glyphosate	herbicide	Parent rats	gavage	5 mg/kg per or day 50 mg/kg per day	GD18 to PND5	serum	metabolomics	/	Changes inflammation-related and oxidative stress genes in the cortex and the cerebellum of offspring	[92]
procymidone	fungicide	Parent mice	gavage	100 mg/kg body weight/day	During pregnancy and lactation	serum	metabolomics	*amino acid metabolism*	Metabolic disorder	[81]
fenvalerate	insecticide	Parent mice	gavage	30 mg/kg/day	D8 to D18 during pregnancy	serum	metabolomics	*Pentose phosphate pathway* *Starch and sucrose metabolism*	Exerts gender-dependent effect on neurodevelopment in offspring.	[32]
cypermethrin	insecticide	Parent mice	Intranasal exposure	5 and 20 mg/kg bw	GD 6–7 to PND 15	whole brain	transcriptomics	Genes related to protein synthesis, maturation, and degradation	Neurodevelopmental defects in male mice: the auditory startle reflex was acquired more slowly;	[83]
triticonazole	fungicide	Parent rats	gavage	450 mg/kg bw/day	GD17 or GD21	testis	transcriptomics	/	Disrupt endocrine effects in vivo	[85]
flusilazole	fungicide	Parent rats	gavage	45 mg/kg b w/day	GD17 or GD22	testis	transcriptomics	Dysregulated Calb2 and Gsta2 expression	Disrupt endocrine effects in vivo	[85]
triticonazole	fungicide	Parent rats	gavage	450 mg/kg bw/day	GD7 to GD17-21	fetal testes and the perineum	transcriptomics	Genes related to hypospadias in humans	Transcriptome changes in the external genitalia of fetal male rats	[86]
abamectin	insecticide	Zebrafish embryos	water environment	110, 220 ,440 μg/L	96 hours post fertilization(hpf)	larvae	transcriptomics	lipid metabolism	Affect cardiac and neuronal development	[77]
carbaryl	insecticide	Zebrafish embryos	water environment	275, 1100μg/L	96 hpf	larvae	transcriptomics	Genes related to neurogenesis: npas4a，egr1，btg2，ier2a 和 vgf	Affect cardiac and neuronal development	[77]

chlorpyrifos	insecticide	Zebrafish embryos	water environment	750, 3000μg/L	96 hpf	larvae	transcriptomics	Dio3b related to thyroid function	Affect cardiac and neuronal development	[77]
fipronil	insecticide	Zebrafish embryos	water environment	75, 300μg/L	96 hpf	larvae	transcriptomics	Nerve growth factor *vgf*	Affect cardiac and neuronal development	[77]
imidacloprid	insecticide	Zebrafish embryos	water environment	15000,30000, 60000μg/L	96 hpf	larvae	transcriptomics	Genes involved in immune system and inflammatory processes	Affect cardiac and neuronal development	[77]
methoxychlor	insecticide	Zebrafish embryos	water environment	20, 60, 180 μg/L	96 hpf	larvae	transcriptomics	Nerve growth factor *vgf*	Affect cardiac and neuronal development	[77]
β-HCH	insecticide	Human mothers	environmental exposure	/	/	serum	metabolomics	Glycerol metabolism and thyroid hormone metabolism	Weight loss	[73]
Mecarbam	insecticide	Human mothers	environmental exposure	/	/	serum	metabolomics	Glycerol metabolism and thyroid hormone metabolism	Weight loss	[73]
chlorpyrifos	insecticide	Offspring mice	gavage	1 mg/kg bw/day	PD10-15	brain	lipidomics	Cholesterol esters, triglycerides, phosphatidylcholine	Interference with neural development	[75]
permethrin	insecticide	Zebrafish embryos	water environment	1 μg/L	2 hours to 28 days after fertilization	brain	transcriptomics	Histone acetylation and histone methylation/demethylation	F0 fish are not active in adulthood, while males from F1 and F2 generations exhibit reduced specificity for anxiety like behavior	[84]
chlorpyrifos	insecticide	Offspring rats	gavage	0.75mg/kg bw/day	PND10 to PND16	brain	lipidomics	Altered endocannabinoid signaling	Changes in glutamatergic and GABAergic signaling in the amygdala	[76]
Bacillus thuringiensis	insecticide	Zebrafish embryos	water environment	1.1mg/L	3-99hpf	larvae	proteomics	/	Minor disturbances in the proteome of zebrafish larvae	[91]

chlordecone	insecticide	Parent mice	gavage	100 μg/kg bw/day	embryonic day(E) 6.5 to E15.5	larvae	transcriptomics	Gene encoding proteins disorders	The number of spermatogonia (SG) in F3 decreases, with meiotic defects in sperm cells and a decrease in the number of sperm in the F1 and F3 male offspring.	[87]
Atrazine	herbicide	Zebrafish embryos	water environment	0, 0.3, 3, or 30 ppb	1 to 72hpf	sexual gland and brain	transcriptomics	Lipid metabolism, molecular transport, small molecule biochemistry, and cell morphology	No significant changes in body weight, testes weight, or GSI on male offspring	[88]
atrazine	herbicide	Zebrafish embryos	water environment	0, 0.3, 3, or 31 ppb	2 to 72hpf	sexual gland and brain	transcriptomics	Alters gene expression of several genes throughout the serotonergic pathway	a significant decrease in 5-hydroxyindoleacetic acid (5-HIAA) and serotonin turnover in adult female brain tissue	[89]
3,4-dichloroaniline	insecticide	Zebrafish embryos	water environment	0.3mg / L	from 3hpf to 99hours	larvae	proteomics	Several processes of cardiac function and development and metabolism	Non-detachment of tail, lack of somite formation, and the absence of heartbeat	[90]
difenoconazole	fungicide	Zebrafish embryos	water environment	0.5, 5, 50, and 500 μ g/L	168h	larvae	transcriptomics and metabolomics	Energy metabolism, lipid metabolism and immune-related pathway	Adverse effects on zebrafish heartbeat	[79]
o，p′-DDT	insecticide	Parent mice	gavage	300 mg/kg bw	/	Brain and Uterine	metabolomics	Glycine, choline, and phenylalanine	Uterine wet weight increases and luminal epithelial cell height (LEH) increases	[82]

3 Gut microbiome and pesticides exposure in early life

The gut microbiome has garnered recognition as an autonomous organ, proving instrumental in elucidating health phenomena such as obesity, intestinal inflammation, and neoplastic conditions. The 16s rRNA technique stands as a cost-effective and facile methodology for the investigation of the gastrointestinal microbiome.[93].

Alterations in the gastrointestinal microbiota's compositional landscape can serve as harbingers for specific health anomalies. For instance, individuals diagnosed with ulcerative colitis (UC) and Crohn's disease (CD) typically manifest a diminished microbiota diversity, characterized by a decline in Bacteroides and Firmicutes populations, juxtaposed with an augmentation in Actinobacteria and Proteobacteria[94, 95]. Notably, a depletion of Firmicutes is frequently correlated with disruptions in intestinal ecology[95]. Furthermore, the ratio between Firmicutes and Bacteroides has been postulated as a potential indicator for obesity[96], albeit this hypothesis remains a subject of contention.[97].

Prenatal and early-life exposure to pesticides like paraquat, glufosinate ammonium, and permethrin disrupts the gut microbiome in rodents, leading to various health and behavioral implications.

Exposure to paraquat at birth alters the microbial composition, reducing Firmicutes while elevating Cyanobacteria levels, subsequently influencing body weight[37].

In utero exposure of mice to glufosinate ammonium shifts the gut flora by augmenting Bacteroidetes and diminishing Firmicutes, which is correlated with behavioral anomalies in their offspring[39]. Permethrin exposure in male rat neonates modifies the gut bacteria, reducing Bacteroides while elevating Lactobacillus and Enterobacteriaceae, which detrimentally affects gut flora[44]. When pregnant mice are exposed to Endosulfan and a high-fat diet, it adversely impacts offspring health by increasing intestinal Bacteroidetes, leading to obesity and metabolic disorders[38]. Early-life exposure to chlorpyrifos in mice and rats is associated with an increase in several bacterial strains, including Helicobacter and E. coli, and a decrease in beneficial strains like Lactobacillus. This imbalance can cause intestinal dysbiosis, poor gut development in the early stages[45, 98, 99], hyperlipidemia, hypoglycemia in female offspring, and diminished social novelty response in rats[41]. Glyphosate consumption in mice parents affects gut flora, particularly by elevating Odoribacter and Lachnospiraceae, which has been linked to asthma and weakened immune responses in progeny[40]. In new-born rats, glyphosate disrupts microbial equilibrium by increasing Blautia and decreasing both Streptococcus and Rothia, leading to altered gut flora in neonates[43]. Some studies also suggest that offspring exposed to glyphosate may exhibit autism spectrum disorder (ASD) symptoms, potentially mediated by gut microbiota[100].

Prenatal exposure to nitenpyram increases the abundance of Desulfovibrio in male offspring. This bacterium transforms sulfite into H2S via sulfite reductase (dsrA). Elevated H2S levels can erode the intestinal lining, compromising the intestinal barrier, which in turn can induce bacterial translocation and trigger a colonic inflammatory response[101]. Additionally, nitenpyram disrupts gut microbiota in female offspring and alters fecal metabolite profiles[78].

Table3 shows information on early-life pesticide exposure experiment through gut microbiota.

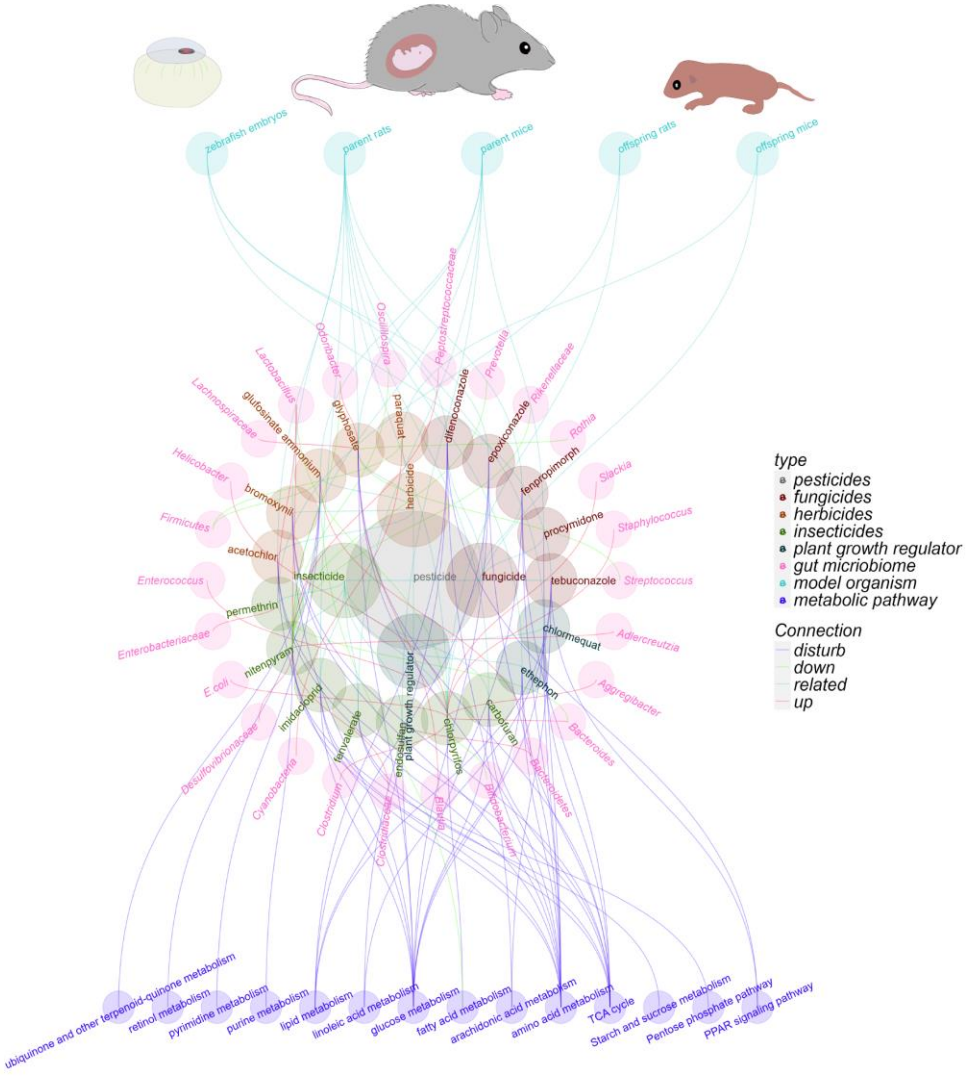
The gut microbiome, now acknowledged as a distinct organ, is central to our understanding of diverse health conditions, and the 16s rRNA technique is a key investigative tool. Specific shifts in microbiota can signal health challenges, such as UC and CD. A plethora of studies highlight the influence of pesticide exposure on the gut microbiota, connecting these changes to a spectrum of health outcomes, from behavioral anomalies to metabolic disturbances and a potential inclination towards ASD.

Figure2 shows how exposure to pesticides influences model organisms' gut microbiota and metabolic pathway.

Pesticides	Type	Organism	Exposure method	Dosage	exposure time	Changes in offspring gut microbiome	adverse effcet	References
paraquat	hebicide	Offspring mice	intraperitoneal injection	0.8 mg/kg body weight	postnatal day(PND) 5 to PND19	Cyanobacteria increases Firmicutes decreases	Adult body weight increased in male offspring	[37]
glufosinate ammonium	herbicide	Parent mice	drinking water	2 mg/kg per day	8 weeks before pregnancy	Bacteroidetes increases Firmicutes decreases	Behavioral abnormalities	[39]
glyphosate	herbicide	Parent mice	gavage	50 mg/kg body weight/day	pregnancy and lactation(A total of 95 days)	Odoribacter increases Lachnospiraceae increases	Asthma; a reduced immune response in females	[40]
glyphosate	herbicide	Parent rats	drinking water	1.75 mg/kg bw/day	gestation day (GD) 6 to the end of lactation	Blautia increases Streptococcus decreases Rothia decreases	Modifying the gut microbiota in rat pups	[43]
permethrin	insecticide	Offspring mice	gavage	34 mg/4 mL/kg body weight	PND6 to PND21	Bacteroides decreases Lactobacillus increases Enterobacteriaceae increases	Negatively affects the gut microbiota	[44]
endosulfan	insecticide	Parent mice	gavage	0.03 mg/kg body weight	gestational day 6 to PND21	Bacteroidetes increases	Obesity, metabolic disorders	[38]
chlorpyrifos	insecticide	Offspring mice	gavage	1 mg/kg in 1 μL/g of body weight	PND10 to PND15	Helicobacter increases	Dysbiosis at early ages	[98]
chlorpyrifos	insecticide	Parent rats	gavage	1 mg/kg bodyweight	four consecutive months before mating, the gestation periods and lactation periods	Lactobacillus decreases E. coli increases Enterococcus increses Staphylococcus increases	A lower live birth rate	[99]

						Enterococcus increases Clostridium increases Staphylococcus increases Bacteroides increases Lactobacillus decreases Bifidobacterium decreases		
chlorpyrifos	insecticide	Parent Rats	gavage	1 or 5 mg/kg body weight per day	throughout the gestation period to PND21		Affected intestinal development; Bacterial Translocation to liver and spleen	[45]
chlorpyrifos	insecticide	Offspring Rats	gavage	1 mg/kg/ml/day	PND10 to PND15	Slackia increases Aggregibacter increases	Hyperlipidemic, hypoglycemic in female offspring; Altered the rat's reaction to social novelty	[41]
						Adlercreutzia decreases Peptostreptococcaceae decreases Clostridiaceae decreases Lactobacillus decreases Desulfovibrionaceae decreases Oscillospira increases Odoribacter increases Rikenellaceae increases Prevotella increases		
nitenpyram	insecticide	Parent mice	gavage	0, 0.4 and 4 mg/kg/day body weight	During pregnancy		A decrease in serum glucose of female offspring.	[78]

Table3. Information about pesticides exposure experiment through gut microbiota on model organism.



Early life pesticide exposome, Gut microbiome, and metabolism

Figure2. The relationship between early-life model organism exposure to pesticides, gut microbiota, and metabolic pathway.

4 Treatment

Recent scholarly investigations have indicated that the utilization of prebiotics, probiotics, and traditional Chinese medicinal practices may mitigate the adverse consequences of pesticide exposure during early developmental stage[102]. Specifically, inulin supplementation has been observed to counterbalance detrimental outcomes, including metabolic anomalies, oxidative disturbances, and neurotoxic manifestations, originating from initial life exposure to insecticides such as Chlorpyrifos and Rotenone[99, 103, 104]. Besides, Furthermore, Catechin, a compound extracted from green tea, has been demonstrated to neutralize the deleterious effects of Chlorpyrifos on zebrafish larvae[105].

5 Perspectives:

In recent years, the impact of pesticide exposure on infants, young children, and adolescents has received increasing attention. Most studies explain the adverse health effects of pesticides through the alternation of gut microbiota, genes and metabolites. Further research on early life exposure of pesticides is needed to address the following issues.

1) Many articles focus on the display of experimental data, but seldom biomarkers have been found.

2) Most studies focus on studying the effects of early-life exposure on the next generation (F1), while a few studies have investigated the effects of transgenerational (F2)[84, 87], but there is little or no research on the third and fourth generation(F3 and F4).

3) Many articles have explained the mechanisms by which pesticide exposure affects early life health, but few studies propose treatment options. Research on finding treatments for pesticide induced diseases should be encouraged

4) At present, the relationship between pesticides, gut microbiota, metabolites, and genes is still relatively vague and has not been fully studied.

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