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How pesticides affect neonates? - Exposure, health implications and determination of metabolites

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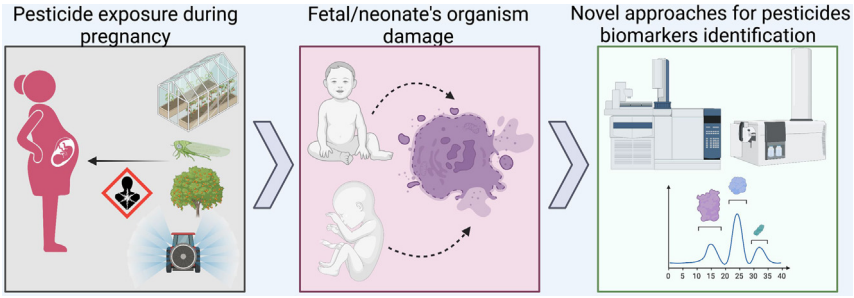
HIGHLIGHTS

- Exposure to pesticides and their metabolites starts in fetal period through placenta.
- Neonates exposure to pesticides can lead to life-long abnormalities and diseases.
- Pesticide determination in neonates biofluids should differ from those from adults.
- Novel analytical approaches focus on low volume analysis and high throughput.
- Untargeted analysis gives information for toxicity assessment in biological systems.

GRAPHICAL ABSTRACT



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ABSTRACT

This review covers key information related to the effects of pesticides on fetal and child health. All humans are exposed to environmental toxicants, however child's health, due to their high vulnerability, should be of special concern. They are continuously exposed to environmental xenobiotics including a wide variety of pesticides, and other pollutants. These compounds can enter the child's body through various routes, both during fetal life, in the first days of life with breast milk, as well as during environmental exposure in later years of life. Consequently, in the body, some of them are metabolized and excreted with urine or faces, while others accumulate in tissues causing toxic effects. This review will provide information on the types of pesticides, their pathways of uptake and metabolism in children's bodies. Determination of the impact of them on children's organism performance is possible through effective identification of these compounds and their metabolites in children's tissues and biofluids. Therefore, the main procedures for the determination of pesticides are reviewed and future trends in this field are indicated. We believe that this comprehensive review can be a good starting place for the future readers interested in the impact of environmental xenobiotics on the health of children as well as the aspects relates with the analytical methods that can be used for analysis and monitoring of these pollutants in children's tissues and biofluids.

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Contents

1. Introduction

According to the World Health Organization (WHO), children are the most vulnerable of the world's population (World Health Organization, 2011). It is well-known that some environmental factors play a critical role in children's health (Zayas Mujica and Cabrera, 2007). Every year, about three million infants under five years old die from preventable environment-related causes (World Health Organization and United Nations Environment Programme, 2010), which is more than 30 % of child deaths annually (WHO, 2002).

Due to the vulnerability of the child population, an important number of research studies and social programs have been developed in recent years, which primarily contributes to the development of methodologies for the risk assessment in children and the identification of priority research areas in this matter (World Health Organization, 2011; WHO, 2002). During the embryo, fetus, infant, and adolescence stages are widely considered to be at an increased risk from environmental threats (Winchester et al., 2016). Due to their developmental physiology and immature systems they receive higher exposure to pollutants from different sources with major consequences, besides, the exposure to these hazards in the early stages of life can alter the normal development and growth in critical phases (de Zwart et al., 2002). Because of their higher life expectancy, children have more time to develop diseases with long latency periods such as neurological diseases, cancer, endocrine alterations, and kidney dysfunctions (Perlroth and Castelo Branco, 2017).

The common understanding of exposure to the environmental xenobiotics needs to be reconsider in the terms of detrimental effect on children, especially neonates. Neonates, according to WHO, children under 28 days of age has different exposure routes than older human beings (Cresteil, 1998; Committee et al., 1993).

The intake of xenobiotics is mostly during fetus stage (placental transfer) (Souza et al., 2005; Porpora et al., 2013) as well as with mother's breast milk in the early days of life (Yusa et al., 2015; Yildizdas et al., 2018). Therefore, the transfer of toxicants is indirect and the accumulation factor of them in child's and mothers body is also crucial. Maternal exposure to chemicals increases the prevalence of prematurity, birth defects, neurological and behavioral disorders (Grandjean and Landrigan, 2014), blood cancers, respiratory and endocrine (Ünüvar and Büyükgebiz, 2012) alterations in neonates. Exposure to environmental toxicants can be assessed with the characterization of specific biomarkers of these environmental xenobiotics in the human body (Ferguson et al., 2017; Delano and Koren, 2012). The identification of biomarkers is useful for clinicians to detect exposure to several chemical compounds including pharmaceutics, food, and environmental toxicants in different biological matrices such as hair, saliva, urine, blood, and breast milk which could provide clinically relevant information to early diagnosis and for the identification of prenatal exposure (Perlroth and Castelo Branco, 2017).

Up to date, the hundreds of environmental xenobiotics are classified and their toxic effects are studied (Embrandiri et al., 2016). Those chemicals could be both inorganic substances, such as heavy metals and their salts as well as organic substances like pesticides, fire retardants, plasticizers, drugs, dyes to name a few. Based on the great availability, with over 2.5 billion t used worldwide each year (Alavanja, 2009), and unstoppable intake, the pesticides can be consider as one of the key xenobiotics that mother can be exposed to and which can lead to neonate health problems. Since the pesticides are the group of structurally different chemicals, with different biocidal properties and different metabolism in human body. Some of the pesticides are known of their toxic properties and thus are prohibited to use, such as organochlorines (e.g. DDT), but other pesticides also exhibit toxic effects and are still greatly used for crops both in poorly and well-developed countries.

Pesticides is a wide group of compounds that are used in agriculture to “prevent, destroy, repel or mitigate any pest ranging from insects (i.e., insecticides), rodents (i.e., rodenticides) and weeds (herbicides) to microorganisms (i.e., algicides, fungicides or bactericides)” (Alavanja, 2009). These chemical compounds have many different functions, hence manifest different mechanisms of action as well as completely different chemical structures. This in turn may imply different routes of bioaccumulation and metabolism of these compounds in the mother's and neonate's body. Among organic pesticides we can distinguish organochlorine (OCs) and organophosphate (OPs) pesticides, carbamates, pyrethrins and pyrethoids (Hassaan and El Nemr, 2020). In recent years, the novel, less known for their toxicity pesticides are developed such as succinate dehydrogenase inhibitors (SDHI; fungicides), nicotinic and diamide insecticides or herbicides possessing acetolactate synthase mode of action (Umetsu and Shirai, 2020). The wide range of in-use pesticides requires a customized approach in the development of analytical methods for the determination of these compounds and their metabolized derivatives.

The aim of this state-of-the-art review is to cover key information related to the effects of pesticides on neonates health, as well as the description of the novel trends in the determination of pesticides and their metabolites in biological samples. Determining pesticides and their metabolites in neonates biological samples needs the introduction of mainly non-invasive sample collection procedures as well as highly-sensitive analytical methods. The perspectives of application of metabolomics approaches in terms of pesticides determination is also addressed.

2. Potential health hazards in fetuses and neonates due to pesticide exposure

Compared to adults, neonates, and fetuses are more susceptible to environmental exposures. That might be because children are not fully developed, thus they are particularly vulnerable to environmental xenobiotics' effects (Goldman, 1995). Exposition to pesticides during fetal and childhood life is particularly dangerous because these are the most vulnerable periods of life, due to organ formation and thus rapid cell division during these periods (Sly and Carpenter, 2012). This disruption can lead to lifelong abnormalities, diseases, and alterations such as cognitive function, behavior, growth, reproductive and immune system alterations. The impact of the xenobiotics varies whether it is an embryo, fetus, or child, and it is related to the window of susceptibility (WOS). As different organs and systems develop during different periods of fetal life, harm to any organ or system will be at a specific time of exposure (Terry et al., 2019). Exposure during the embryonic and fetal period can lead to abnormalities and alteration of systems and organs that are in development during these critical periods of life, shown in Fig. 1 (L Keith More . Embriología Clínica. 10th ed. (Elsevier, n.d.).

A critical period of brain development occurs during weeks 3 to 16. However, brain development can also be disrupted after this period because it is an organ that still undergoes growth and differentiation at birth (Connect, 2019). Thus, exposure to pesticides during embryonic and fetal periods can lead to mental deficiency. Moreover, most of the development that occurs during the first 4 weeks is related to the formation of extra-embryonic structures, such as the amnion, the umbilical vesicle, and the chorionic sac (Nakano et al., 2018). During the period of organogenesis which occurs between the fourth and eighth weeks, teratogens can induce important birth defects such as physiological defects and morphological malformations (G, 2000). During the fetal period after the ninth-week functional disorders like mental deficiency and minor morphological malformations in the ears can occur (Chung, 2004).

Some teratogenic chemicals can enter the body through the placental barrier to the fetus, which can be harmful to it (Myllynen et al., 2007). The first months of infants' life are critical too, due to their susceptibility to toxic compounds delivered via breast milk (Howard and Lawrence, 2001).

The accumulation of pesticides in milk compartments depends on a wide variety of factors such as infant factors, maternal factors (which can be the stage of lactation, dose, and toxicokinetics), and the xenobiotic's physicochemical properties (Bitman et al., 2018).

The mammary gland is capable of concentrating lipophilic compounds. For example, some pesticides have highly lipophilic properties such as p,p'-DDT and its main metabolite p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) which has been employed as a biomarker for the assessment of exposure to OCPs (Elserougy et al., 2013).

In terms of lethality, pesticides such as organophosphates or pyrethroids, and rat poisons which use is not authorized are important components that contribute to children's acute intoxication in developing countries (Bucaretchi and Baracat, 2005).

2.1. Health implications of organophosphate pesticides

Several authors have described OPs as endocrine-disrupting chemicals (ECDs) (Viswanath et al., 2010). Animal studies have suggested that early exposure to these chemicals is related to changes in reproductive hormones such as follicle-stimulating hormone (FSH) estradiol (E2), luteinizing hormone (LH), and testosterone (T) (Ventura et al., 2016). Epidemiological studies have suggested that early exposure to OPs can be associated with lower levels of E2 and T and increased levels of FSH (Sundukov, 2006).

Clinical observations have shown that OPs exposure may lead to hyperglycemia, which induces a concomitant increase in insulin secretion (De Cock and Van de Bor, 2014). Murine model studies have shown that early-life exposure of rats to chlorpyrifos leads to hyperinsulinemia but with normal glucose levels, suggestive of insulin resistance (Ventura et al., 2016).

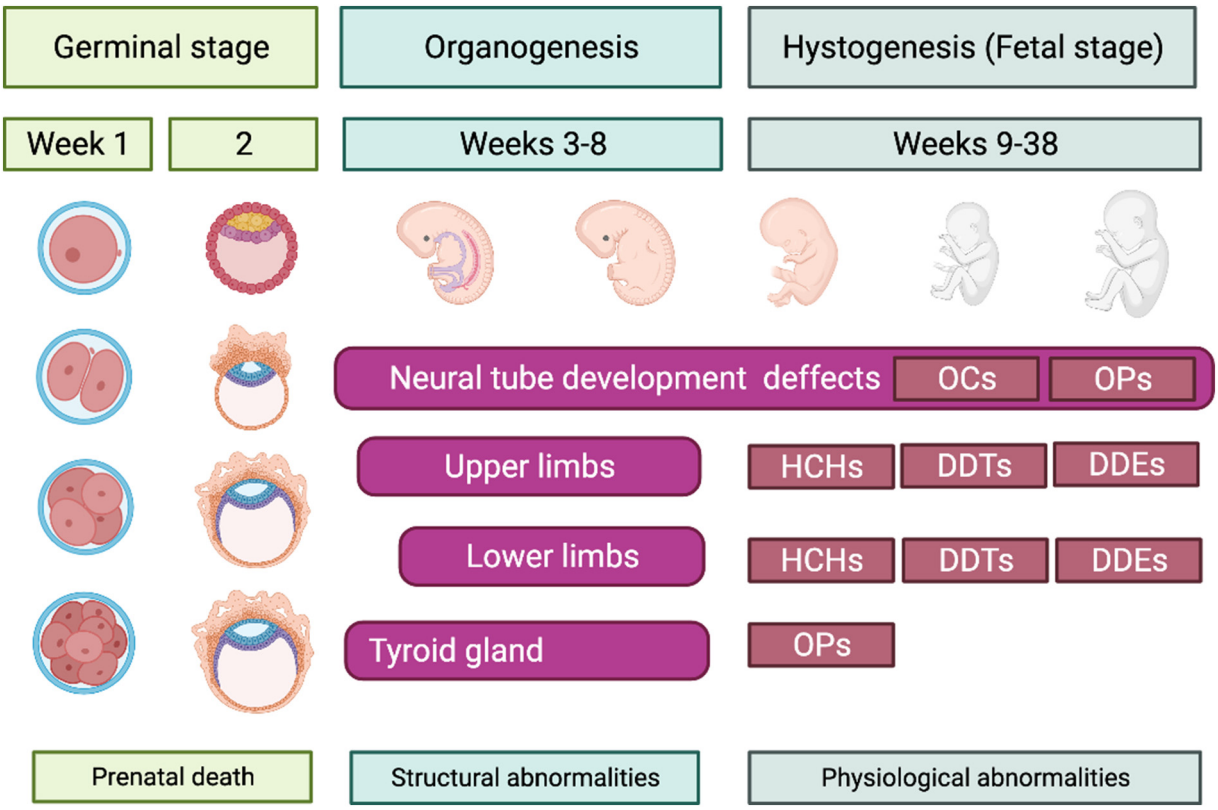

Fig. 1. Schematic illustration of critical periods of human prenatal development (different WOS) and xenobiotics that can affect specific organs growing during these periods.

Dibutyl phosphate (DBP) and diethyl phosphate (DEP) metabolites were recently associated with neurocognitive dysfunction, inattention associated with attention deficit and hyperactivity disorder (AHDH), aggressive behavior, and the development of depressive and anxious episodes in children (Engel et al., 2021).

In some cases, organophosphate pesticides may cause acute intoxication, due to their Acetylcholinesterase (AChE) inhibition potential (Riordan et al., n.d.; Abbruzzi and Stork, 2002).

2.2. Organochlorine pesticides health outcomes

Studies have suggested that OCs pesticide residues in the placenta, may influence anthropometric measures on infants. Thus, pregnant women who are exposed to OCs have shown an increased prevalence to deliver low birth weight babies (Anand and Taneja, 2020). According to Yang's longitudinal study prenatal exposure to β-HCH shown a strong association with increased body mass index (BMI) z-score and elevated risk of overweight in infants at 12 and 24 months of age (Yang et al., 2021).

In recent evidence, it is shown that early exposure to OCs has an important association with neuropsychological and neurodevelopment impairments through to effects mediated by the thyroid hormone (TH) which plays an important role in neurodevelopment. Some evidence has shown that higher levels of thyroid-stimulating hormone (TSH) in 2–5 days after birth infants were associated with higher levels of ΣDDTs in serum (Chevrier et al., 2008).

In Keiko Yamazaki's study reported that *cis* and *trans*-nonachlor significantly influenced maternal and child-free thyroxine (FT4) levels (Yamazaki et al., 2020).

Moreover, a neurodevelopmental impairment that takes place via prenatal exposure to OCs, and breastfeeding is related to postnatal toxicity in newborns. Neurobehavioral and neurodevelopmental disorders such as attention deficit and hyperactivity disorder (ADHD), anxiety, depression, autism spectrum disorder (ASP), and impaired psychomotor and cognitive development (IPCD) had been related to early exposure to OCs such as endosulfan, aldrin, DDTs and HCBs (Saeedi Saravi and Dehpour, 2016).

Other studies suggested that exposure to OCs during pregnancy elevates the risk of developing drinking and smoking behaviors during adolescence. However, there is still not enough evidence to confirm this association (Dickerson et al., 2022).

2.3. Other pesticides health outcomes

Neonicotinoids (NEOs) pesticides exposure during pregnancy had been related to developmental neurotoxicity (Sheets et al., 2016), reproductive toxicity, and hepatoxicity in murine models (Toor et al., 2013). However, these hypotheses haven't been proven in human populations.

NEOs are suggested to produce toxicity via oxidative stress through the generation of reactive oxygen species (ROS) (Sastre-Serra et al., 2010).

Despite the mechanisms of xenobiotic carcinogenesis are still unknown, a wide variety of these compounds are related to DNA damage, as changes in DNA molecule properties can cause a disordered growth of cells which can invade and destroy other tissues of the body (Anon, n.d.). In children, the toxicodynamics of environmental xenobiotics is a matter of concern, because the time of exposition to the toxicants during their life is greater than in adults. Pesticides are closely related to carcinogenic effects, and some studies suggest a relationship between childhood brain cancer, neuroblastomas, Non-Hodking lymphoma, and Ewing's sarcoma with parental pesticide exposure (Feychting et al., 2001).

3. Metabolism of pesticides

Most pesticides have to be transformed to be eliminated from the body, and this process mainly occurs in the liver but can take place in other organs as well, such as the kidneys, skin, and lungs (Almazroo et al., 2017).

During metabolism, phase I and II biotransformation can occur simultaneously or sequentially. Phase I biotransformation reactions are cytochrome P-450 (CYP) monooxygenases, esterases, and dehydrogenases-dependent (Meyer, 1996). Phase I metabolism products are mainly excreted in the urine (Anders, 1980). In phase II metabolism, synthesis and conjugation reactions are the most important (Sterling et al., 2021). Reactions mechanisms and enzymatic systems in phase I and II metabolism are listed in Table S1.

3.1. Metabolism of pesticides at fetal stages

During intra-uterine life, due to fetal liver immaturity, the maternal liver and kidney are responsible for biliary compound and xenobiotic biotransformation and elimination (Cecchi et al., 2012). Some studies have shown that the placenta can metabolize xenobiotics in less proportion than the mother liver, however, its role to transform xenobiotic agents is not well elucidated yet (Juárez-Olguín et al., 2014).

Placenta maternal biotransformation highly influences transference and elimination of xenobiotics during the gestational period. Regarding neonates, the concentration of CYP-450 oxidase and conjugation enzymes is 30–50 % less than in adults, and glucuronic acid achieves adult concentrations until the fourth year of life, thus neonates have less capability to metabolize drugs and xenobiotics than adults (Juárez-Olguín et al., 2014; Dellschaft et al., 2020). For example, CYP1A2, CYP2C19, CYP2C9, and CYP3A4 are mainly responsible for DDT, pharmaceuticals and, hydrocarbons biotransformation presented major expression in maternal than in fetal liver tissue (Robinson et al., 2020; Zota et al., 2019). Sulfotransferases (SLUTs) catalyze conjugation by transferring an SO_3 group from a donor molecule. SLUTs are relevant in the sulfonation of dimethylaniline (DMA) which is a toxic product present in some dyes and pesticides, and other hydroxysteroids prevenient from endocrine disruptor compounds such as organophosphate pesticides (Nandini, 2014). SLUT1A2 for example, showed a non-significative difference in mRNA relative expression in maternal and fetal liver samples (Ekstrom and Rane, 2015).

In fetuses, elimination transporters such as P-Glycoprotein coming from ABCB 1 or MDR-1 gene are present as well. Mainly in fetal liver and brain tissues (Fakhoury et al., 2009).

N-acetyltransferases (NATs) isoenzymes NAT1 and NAT2 are also involved in phase.

II metabolism of endogenous and exogenous compounds (Zusterzeel et al., 2005; Fessler et al., 2008). These are expressed in fetal tissues as well, such as the duodenum, and fetal liver. However, NAT2 had higher expression than NAT1 and was predominant in the fetal liver (Fakhoury et al., 2009).

The expression of elimination and enzymes in maternal blood and cord can lead to a better understanding of xenobiotics elimination patterns during intrauterine life. Examples of pesticides metabolites and their properties are listed in Table S2 (Supplementary materials).

4. Biomarkers as indicators of pesticides exposure

According to WHO, the term biomarker is referred to any substance, process, structure, or its products that can be measured in the human body which can modify, influence, or predict the development of an outcome disease (Strimbu and Tavel, 2010). Actually, due to a recent understanding of the interpretation of biomarkers, the use of biomarkers as indicators of some diseases and exposure is very limited. According to the EPA, biomarkers can be classified as exposure, effect or susceptibility (United States Environmental Protection Agency, 2001). Each type of biomarker can be useful to evaluate and measure the health status of a human being or an ecosystem.

Biomarkers of exposure serve as indicators for assessment of concentrations of toxic compounds in fluids. On the other hand biomarkers of susceptibility asses specific sensitivity to environmental xenobiotics effects, whereas biomarkers of effect shows physiological changes in organisms due to exposure to certain environmental xenobiotics respectively. General workflow for assessing the impact of environment xenobiotics in children in schematically perented in Fig. 2.

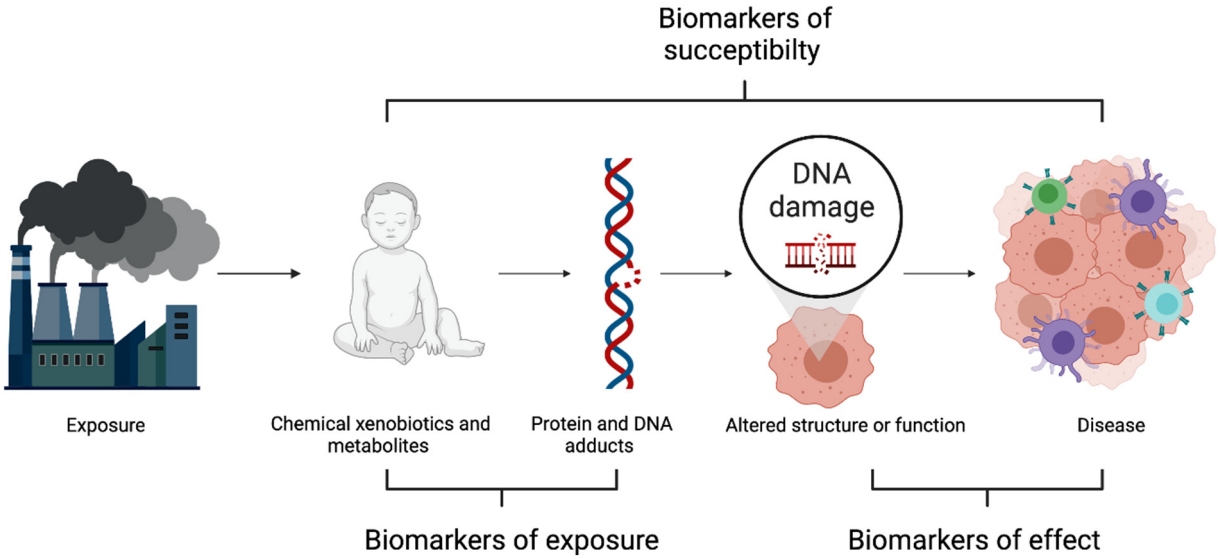

Fig. 2. General workflow for assessing the impact of environment xenobiotics in children.

Biomarkers of exposure serve as indicators for assessment of concentrations of toxic compounds in fluids; biomarkers of susceptibility asses specific sensitivity to environmental xenobiotics effects, and biomarkers of effect shows physiological changes in organisms due to exposure to certain environmental xenobiotics respectively.

Selected examples of the pesticides and their metabolites representing biomarkers of each type are given in Table 1, and complementary information with detailed examples are shown in Table S3, Supplementary materials.

5. Sample types and sample handling

There is a general aspect that needs to be considered, which is the selection of an adequate sample type. As was mentioned before, there is a number of biological samples that could be selected for the analysis, namely blood (whole blood, serum), urine, stool (for neonates – meconium), hairs and nails, among others. A blood sample could be considered as a time-correlated sample (as it is in equilibrium with the childs' tissues) (To-Figueras et al., 2000). For other types of samples, the accumulation should be taken into account; for urine due to the bladder volume (form minutes to hours of accumulation), stool daily (except meconium) and for nails and hairs long-term environmental pesticides accumulation. Urine is worth considering while biomarkers, especially phase I metabolites, are determined, whether stool finds its application in phase II metabolites (Kluwe, 1982). Both urine and stool samples could be considered as non-invasive ones, which is a key for children, especially newborns (Neu et al., 2007). Another non-invasive sample could be saliva, which can be easily collect for youngsters, but in terms of newborns sampling could be problematic. The solution could be placing filtration paper under the tongue of a baby for a couple of minutes (Koppel et al., 2017). For the determination of non-metabolized xenobiotic, the blood analysis is the most suitable option (Wagner et al., 2016). The alternative to whole blood could be dried blood spots analysis, which allows much easier sampling. The dried capillary blood from heel (neonate) and fingertips (mother) is deposited on the paper card. Historically, it was used in 1960s in phenylalanine analysis, but now it gains popularity in many branches of medical diagnosis (Molina-Villalba et al., 2015). In recently published articles the usage of blood, hair, nails and feces decreased, which can be explained by the importance of labour-intensive sample handling including steps such as digestion, centrifugation, precipitation, etc. (Cequier et al., 2016a)

To obtain representative biological sample the selection of an appropriate sampling protocol as well as transporting and storing procedures needs to be consider. The storage procedure selection depends on both the sample type and the physicochemical properties of the target metabolites. According to guidance approved by the European Council of Legal Medicine, there are well-established protocols the sampling and storage of breast milk, meconium, peripheral blood, urine, hair and nails (To-Figueras et al., 2000). There, special attention is paid to an appropriate sample pH, sample collection time, preservation and storage temperature.

It is recommended to store biological samples in sealed containers at 4 °C for short-time storage (up to few hours) and from −20 °C to −80 °C (second is preferable) for long-time storage. In some instances, storage conditions may be more relaxed, especially in situations where highly persistent environmental xenobiotics, such as pesticides, are sought in the sample. However, it is recommended to freeze or refrigerate samples whenever possible. Exceptions are nail, hair and dried blood spot samples which can be easily stored and transport at room temperature.

In general, biological samples have a highly complex and heterogeneous composition, including macromolecules, proteins, and salts that can hinder the identification and quantification of pesticides and their metabolites and damage the analytical instrument of analysis. In addition to the complexity of the sample, the low concentration levels of target compounds prevent direct instrumental determination (López-García et al., 2017). To address these limitations, extraction, cleaning, and concentration steps are necessary to separate the compounds from the matrix components, providing an adequate concentration level and a cleaner extract, preferably free of interferents. This challenge requires efficient sample preparation to handle the complex sample and obtain accurate and reliable results (Ye et al., 2017).

6. Analytical procedures

Biological monitoring of acute or chronic pesticide poisoning helps identify evidence of children's health problems. However, monitoring children's exposure to pesticides requires sensitive and precise instrumental analytical techniques to carry out their determination in biological samples (Cequier et al., 2016b).

Previously published studies on pesticide biomonitoring are reported here (Table 2), focusing on instrumental analytical techniques and sample preparation approaches, making a call between contemporary microextraction and usual extraction techniques for different classes of pesticides in biological samples. We present studies that we consider useful and notable that can serve as a valuable tool for analysts who focus on biomonitoring studies of pesticides and their metabolites and guidance for the development of new analytical methods. The findings were obtained by searching through the most popular available databases (Google Scholar,

Table 1
Selected examples of pesticides biomarkers in fetal and maternal tissues.

Pesticides or metabolites	Samples number	Key findings	Type of biomarker	Reference
Aldrin, β-HCH and γ-HCH HCB *c/t* Nonachlor α/γ Chlordane Oxychlordanes DDE, DDT Mirex Toxaphenes Parlar 26 and 50	1983 (maternal blood)	DDE and oxychlordane were the most abundant compounds in maternal blood.	Biomarker of exposure	(Fisher et al., 2016)
DMP, DMTP, DMDTP, DEP, DETP, and DEDTP TSH or FT4, TT4 and TPOAb	800 (urine from pregnant women)	No association of DAPs with maternal TSH, FT4, TT4 or TPOAb during pregnancy. No association between DAPs with cord blood TSH or FT4.	Biomarkers of exposure and effect.	(Mulder et al., 2019)
CYP1A1, −1A2, −2B6, −2C9, −2C19, −2E1, −2 J2, −3A4 and −19A1	92 (adult liver tissues) and 12 (fetal liver tissues; *in-silico* tests)	Significant CYP-specific differences in expression activity between an adult and fetal tissues. CYP2E1 and CYP3A4 were expressed significantly lower in fetal than in adult livers.	Biomarkers of susceptibility	(Robinson et al., 2020)
AChE β-Glucuronidase Cortisol and progesterone AST and ALT Albumin	407 (pregnant women blood samples)	Plasma and erythrocyte cholinesterase (AChE) decreased significantly during the 6 months of spraying period. CT values increased significantly in the first trimester.	Biomarkers of exposure and effect.	(Araki et al., 2018)
Aldrin, Chlordanes DDT, DDE and DDD, Dieldrin and endrin Heptachlors HCB, HCHs Mirex, Thoxaphenes Steroids and reproductive hormones	514 (maternal blood) and 295 (infant cord blood)	15 OCs were detected in over 80 % of the samples Testosterone-androstenedione ratio tended to decrease with the presence of higher concentrations of OCs.	Biomarkers of exposure and effect	(Wren et al., 2021)
c/t-DCCA *t*-CDCA *c*-DBCA FPBA 3PBA	63 (cord serum; maternal-fetal dyads)	Non-specific metabolites, 3PBA, t-DCCA, and t-CDCA, were detected most frequently	Biomarkers of exposure.	(Alvarado-Hernandez et al., 2013)
DDT, DDE, α/β Endosulfan, HCHs and HCBs Aldrin Heptachlor epoxide Oxychlordane *c/t*- Chlordanes, *c*-Nonachlor Mirex	50 (maternal and umbilical cord blood)	Significantly higher pesticide levels in umbilical cord plasma than in mothers' plasma	Biomarkers of exposure and effect.	(Dinis-Oliveira et al., 2016)

PubMed, ScienceDirect, Springer Nature) for the scientific papers related topic of this manuscript. Here, we focused on papers after 2016 and indicated an in-depth description of the methodology. The publications where the analytical procedure wasn't well-described were omitted. The searched keywords were 'neonates', 'urine', 'metabolites', 'pesticides', 'infants', 'blood', and 'insecticides', among others. For omics-based procedures, we searched for keywords like 'metabolomics', 'mass spectrometry' and 'NMR'.

Cequier et al., presented a new method for determination of the six non-specific metabolites dimethyl phosphate (DMP), diethyl phosphate (DEP), dimethyl thiophosphate (DMTP), diethyl thiophosphate (DETP), dimethyl dithiophosphate (DMDTP), and diethyl dithiophosphate (DEDTP) in the urine based on *off-line* solid-phase extraction (SPE) in the 96-well plates modality, which allows high analytical frequency, followed by ion-pair ultra-high performance liquid chromatography time-of-flight mass spectrometry. The application of 96-well plates enable the analysis of up to 96 samples per day, considering the instrumental analysis stage (Akramipour et al., 2020).

Akramipour et al., developed a new method of Dispersive Liquid-Liquid Microextraction based on a Double-Solvent System (DLLME-DSS) for the extraction and preconcentration of organophosphate pesticides in the blood of children, followed by high performance liquid chromatography (HPLC). The dual solvent idea is based on the mixture of two alcohols (1-undecanol/1-decanol; 1:1 v/v) that presents superior performance than any of its components alone and does not require dispersing solvent, reducing the number of solvents used. The authors used 50 μL of the extractant solvent mixture. And the results show that DLLME-DSS is a simple, inexpensive, ecologically correct, fast, and efficient method for preconcentration of target compounds in blood samples. In addition, when compared to Extraction Liquid-Liquid (LLE), DLLME presents a significant reduction in the volumes of organic solvents used (Shin et al., 2019).

Shin et al., developed a unique analytical method for the simultaneous determination of 260 pesticides. The extraction method was performed by QuEChERS (Quick, Easy, Cheap, Effective, Rustic, and Safe) in human urine, followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The optimized method applied 100 μL of human urine in the QuEChERS procedure. This is an advantage to consider in a realistic situation where a small urine sample is available. In addition, the method presented adequate LOQ for the determination of target compounds and may be an attractive alternative to current analytical techniques (Pirard et al., 2020).

Garcia et al., applied an online TurboFlow™ extraction approach, and ultra-high performance liquid chromatography (UHPLC) coupled to Orbitrap high-resolution mass spectrometry to determine neonicotinoids (imidacloprid, acetamiprid, clothianidin, dinotefuran, nitenpyram, thiacloprid, and thiamethoxam) and of the acetamiprid-*n*-desmethyl metabolite in urine samples. Briefly, 1 ml of the sample was diluted to 2 ml with a mixture of methanol:water (50:50, v/v). The mixture was centrifuged for 10 min at 4500 rpm. Finally, the pre-treated sample was filtered

Table 2
Studies reported in the literature on the identification and quantification of pesticides and their metabolites in biological samples.

Analytes	Number of analytes	Sample	Number of samples	Sample preparation	Technique	LOD	LOQ	Linear range	Identified pesticides (mean values)	Ref.
Pesticide metabolites	6	Urine	56	SPE (format of 96-well plates)	UPLC-TOF	0.15–1.20 ng mL^{-1}	n.d.	0.1 to 416 ng mL^{-1}	2.1 to 5.2 ng mL^{-1}	(Akramipour et al., 2020)
Pesticides	4	Blood	6	DLLME-DSS	HPLC	1–2 μg L^{-1}	3–6 μg L^{-1}	3 to 600 μg L^{-1}	not detected	(Shin et al., 2019)
Pesticides	43	Urine	258	SPME Derivatization	LC–MS/MS and GC–MS/MS	–	0.05–0.92 μg/l	0,5 to 40 pg μL^{-1} for LC-MS/MS to 100 ng mL^{-1} for GC–MS/MS	<LOQ-661.8 μg L^{-1}	(Gao et al., 2021)
Pesticides	260	Urine	10	QuEChERS	LC-MS/MS	–	10 ng mL^{-1}	10–250 ng mL^{-1}	–	(Pirard et al., 2020)
Neonicotinoids	3	Urine	36	TurboFlowTM	UPLC-HRMS	–	0.2 pg mL^{-1}	0.2–2 pg mL^{-1}	0.23–1.57 μg L^{-1}	(Ye et al., 2017)
Pyrethroids, organophosphorus pesticides, fipronil, and metabolites	26	Urine	25	SPE	LC-MS/MS	–	0.4–1616 pg mL^{-1}	0.01 to 33,535 pg mL^{-1}	1–448 pg mL^{-1}	(Ein-Mor et al., 2018)
Organophosphate pesticide metabolites	6	Urine	107	Freeze drying LLE (Acetonitrile) Derivatization	GC–MS/MS	0.1 μg L^{-1}	0.03–0.3 μg L^{-1}	n.d	0.02–1.06 μg L^{-1}	(Glorennec et al., 2017)
Pesticide metabolites	5	Urine	245	SPE Derivatization	LC-MS/MS GC–MS	0.003–0.008 μg L^{-1}	n.d.	n.d.	0.02 to 1.75 μg L^{-1}	(Fiserová et al., 2021)
Pyrethroids metabolites	2	Urine	305	Enzymatic hydrolysis (β-glucuronidase) LLE (Haxane)	UPLC/MS-MS	0.005–0007 μg L^{-1}	n.d	n.d	1.11 μg L^{-1}	(Cequier et al., 2016b)
Pesticide metabolites	15	Urine	20	Enzymatic hydrolysis (β-glucuronidase) QuEChERS and SPE	LC-MS	0.02–0.87 ng mL^{-1}	0.06–2.91 ng mL^{-1}	0.01 to 200 ng mL^{-1}	<LOD to 10.94 ng mL^{-1}	(Bravo et al., 2019)
Metabolites of organophosphate and pyrethroid pesticides	8	Urine	199	SPE	UPLC/MS-MS	0.014–0.069 ng mL^{-1}	0.021–0.039 ng mL^{-1}	2.5 to 800 ng mL^{-1}	0.36–6.60 ng mL^{-1}	(Li et al., 2019)
Organophosphate and pyrethroid pesticide metabolites, and herbicides and metabolites	19	Urine	400	Freeze drying LLE (Acetonitrile) Derivatization SPE	GC–MS/MS UPLC/MS-MS	0.00085 to 1.3 ng mL^{-1}	–	–	0.012–2.7 ng mL^{-1}	(Jacobson et al., 2021)
Organophosphate pesticide metabolites	6	Urine	618	SPE	HPLC	0.0024–0.0054 ng mL^{-1}	–	–	0.05–17.99 ng mL^{-1}	(Li et al., 2022)
Organophosphate pesticides,pyrethroid pesticides, miscelaneous herbicides, instecs repellent.	20	Urine	953	Freeze drying Derivatization SPE	GC–MS/MS LC-MS/MS	0,0050 a 0,70 ng mL^{-1}	–	0,05 a 50 ng mL^{-1}	0.049–13 μg/g	(Liu et al., 2022)

through a 0.2 μm nylon econofilter and injected into the online extraction procedure. This procedure injected 100 μL of the sample into the extraction column (TurboFlow™) connected with an analytical column for online extraction. The process is carried out in 14 min. The authors' proposal is relevant for the determination of analytes due to the simplicity of the procedure (Ye et al., 2017).

6.1. Metabolomics approach for pesticides monitoring

While targeted analysis brings valuable information on pesticide exposure, sometimes a broader picture is needed, such as determining the toxicity of newly emerging pesticides. A solution may be to look to metabolomics, which is effectively applied to finding metabolic changes in complex biological systems. This approach is to comprehensively analyze the metabolic profile and then apply bioinformatics tools to characterize metabolites and the interactions between them. The most commonly used analytical techniques in metabolomics are NMR and MS. (Aliferis and Chrysayi-Tokousbalides, 2011) The use of NMR is often associated with ease of sample preparation and high-throughput analysis, while metabolomics studies often employ two-dimensional (2D-NMR), such as correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY), and J-RESolved (JRES) experiments (Aliferis and Jabaji, 2011). In turn, MS is often coupled with LC and GC. The analysis results in datasets composed of thousands of variables, which are the input for statistical analysis. Common bioinformatics tools are multivariate statistics and pattern recognition algorithms. Algorithms such as principal component analysis (PCA), hierarchical analysis (CA), heatmaps, molecular networks, partial least squares-discriminant analysis (PLS-DA) or artificial neural networks (ANN), are commonly used for this purpose. In fact, the data processing is complex and includes spectral deconvolution, baseline correction, noise filtering, data alignment, outliers removal, normalization, data reduction, and application of data mining protocols (Aliferis and Chrysayi-Tokousbalides, 2011). The results obtained can then be confronted with biological databases such as KEGG, SMPDB or HMDB. The general workflow of metabolomics in human biofluids is shown in Fig. 3.

There are many examples of metabolomics applications in studying the effects of pesticides on organisms, however, there are no applications directly related to the study of neonates samples. On the one hand, some researchers refer to seeking pesticide metabolites that can serve as modes-of-action (MoA) biomarkers (Keum et al., 2010), as well as to the assessment of pesticide toxicity in different animal biological systems (Aliferis and Chrysayi-Tokousbalides, 2011; Aliferis and Jabaji, 2011; Benbrook et al., 2021). Metabolomics was also used in determining the health effects of pesticides, which has been reported in recently published review papers (Zhou and Zhao, 2021; Yan et al., 2021). Based on the current knowledge, it should be assumed that metabolomics can be used to link pesticide exposure with metabolic disorders related to oxidative stress, lipid and fatty acid metabolism, mitochondrial energy metabolism, neurotransmitter precursors and body inflammation (Bonvallot et al., 2013).

There are also findings on the use of metabolomics in determining pesticide exposure in pregnant women. An example study of 83 pregnant proved that exposure to pesticides can cause statistically significant changes in the concentration of glycine, threonine, lactate, glycerophosphocholine and citrate in the urine (Yang et al., 2020). NMR spectral data was used in this study, which was then processed using the PLS-DA algorithm. In another study, researchers correlate the metabolic profile of mothers exposed to pesticides with the weight of babies born and length of gestation (Cheng et al., 2022). The decreased birth weight was correlated with increasing concentration of mecaramb and β-HCH. The authors of the cited study believe that the problems with the weight of newborns may be related to disorders of thyroid hormone metabolism. The determination of the metabolome of children exposed to pesticides was made by Cheng et al., who examined the metabolic profile of children aged 3 to 11 years subject to an organic diet and a diet rich in food from products treated with pesticides.[106] It was found that an organic diet was associated with a reduction in inflammatory responses and detoxification demands.

7. Conclusions and future trends

In this review, it has been demonstrated that it is necessary to reconsider the understanding of pesticides' impact on human health in the fetal and neonates stages of life. Since the exposure routes are different, namely transplacental and via breast milk, as well as the metabolism of pesticides is not the same as for adults, there is a vital need to modify or develop new strategies related to toxicity determination and detection of pesticides metabolites.

Exposure of the mother to pesticides via contaminated food and water consumption can have health-related consequences for fetuses during the perinatal period as well as breastfed neonates. This is why the understanding of the transmission of pesticides, and their effect on the organism of children needs to be studied.

Exposition to pesticides can be monitored either by determination of their native form in blood or tissues or analysis of their metabolites or biomarkers in biofluids and excrements. In the last ten years novel, fast, robust and sensitive analytical procedures were developed which can be easily applied to neonates exposure studies. These include the application of mostly LC-MS and GC-MS together with miniaturised and efficient sample preparation protocols. The newest trend is to provide a holistic view of metabolic

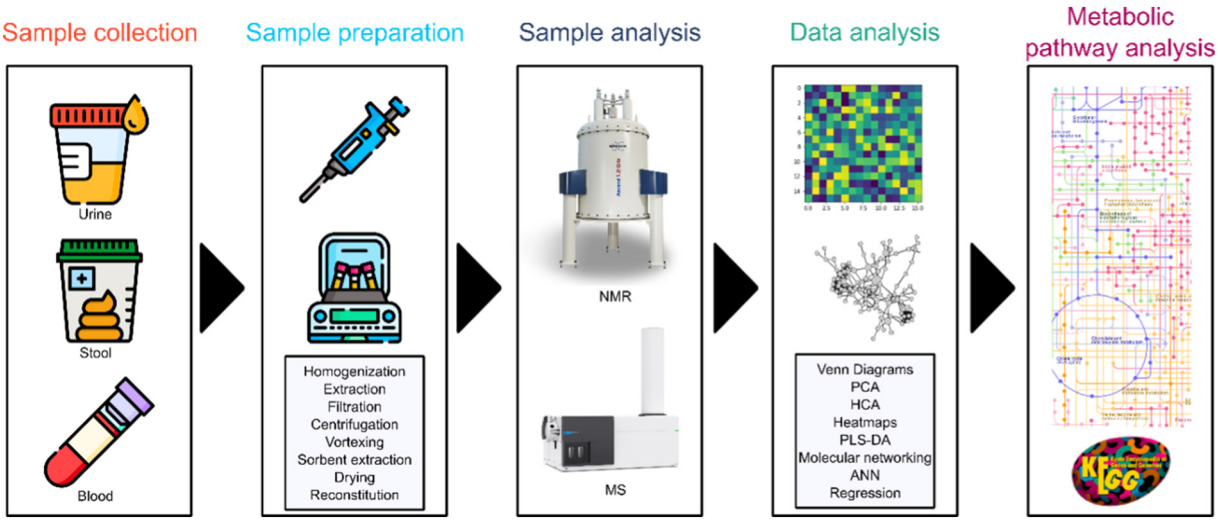

Fig. 3. General scheme of the metabolomics workflow.

profile, thus omics pipelines, with a strong emphasis on metabolomics are increasingly popular. This approach makes it possible to identify biomarkers of exposure, and indeed, it is useful in the evaluation of chronic exposure to low levels of pollutants.

Nevertheless, there are still many challenges to overcome, such as the efficient, non-invasive and child-friendly sampling, the determination of long-term effects of exposure, and synergistic effects of pesticides and other xenobiotics. Future efforts should concern with the impact of pesticides on infants' microbiota and their interaction with emerging contaminants, such as nanoplastics, nanomaterials, viruses, heavy metals, antibiotics residues, etc. The development of analytical procedures based on a non-invasive sampling of urine, sweat or breath could be a new direction in pesticide research. Other challenges are due to the complicated sampling, mainly due to the small volume of biofluid and lack of full awareness of the neonate during sample collection. Thus, procedure miniaturization and novel alternative sampling protocols could be applied, for instance using diapers as a collector of urine for further analysis. From a global perspective, large use of organic solvents and other chemicals during sample preparation and derivatization could be an issue, therefore alternative greener analytical procedures should be considered. All the mentioned challenges are worth solving in the nearest future, as concern for the safety and health of neonates is one of the worldwide priorities.

CRediT authorship contribution statement

María José Santoyo Treviño, and Tomasz Majchrzak conceptualized and writing of the original draft, writing (reviewed and edited the manuscript).

Marina Pereira-Coelho, and Andrea Guadalupe Rodríguez López wrote the original draft.

Sergio Zarazúa Guzmán, Luiz Augusto dos Santos Madureira critically reviewed the manuscript.

Justyna Płotka-Wasylka conceptualized and design the original draft, supervised, and reviewed the manuscript, project administration and founding acquisition.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data availability

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

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.

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Appendix A. Supplementary data

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