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THE ASSOCIATION BETWEEN PRENATAL PYRETHROIDS EXPOSURE AND CHILDREN'S HEALTH – CURRENT RESEARCH

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Abstract
Exposure to pyrethroids, a widely used agricultural, forestry, and household insecticide, is a major public health concern due to its potential health effects on children. The aim of this review was to summarize the current knowledge of the effects of prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children. A systematic and comprehensive search of the PubMed, Web of Science, and Scopus databases was conducted during January–February 2024. The review included original articles published in peer-reviewed English-language journals since 2015. Based on keywords, 198 studies were identified and screened for eligibility. Ultimately, the review analyzed 25 articles including 16 that assessed the effects of prenatal exposure to pyrethroids on children's neurobehavioural development, 3 studies that assessed the effects on the course and outcome of pregnancy, and further 3 focused on respiratory disease. In addition, 1 study analyzed the development of obesity and 2 studies examined the effects on children's growth, weight and body composition in early childhood. In conclusion, there is considerable uncertainty about the adverse effects of prenatal exposure to pyrethroids on children's health. The strongest evidence has been reported for neurobehavioural development although results are also inconsistent. Further research is needed to understand the mechanisms of action and health effects of pyrethroids in susceptible populations. Int J Occup Med Environ Health. 2024;37(4)

Key words:
obesity, prenatal exposure, respiratory diseases, pyrethroids, fetal growth, neurobehavioural development

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INTRODUCTION

Pyrethroids, both natural and synthetic derivatives of pyrethrin, are widely use as insecticides not only in agricultureor forestry but also in many households. They are promoted as a safer alternative to many chemicals such as organophosphates the use of which has been limited due to higher acute toxicity rates and long-term health concerns including developmental neurotoxicity [1]. Pyrethroids currently have an estimated 38% share of the global insecticide market [2,3]. Exposure to pyrethroids in the general population is common, with the key route of exposure being the ingestion of contaminated food and to a lesser extent, inhalation and dermal absorption [4,5]. The biomonitoring of exposure to pyrethroids is based on the measurement of the concentration of metabolites excreted in urine. Urine is a reliable marker for assessing integrated exposure from different sources and routes [6–8]. The widespread use of pyrethroids raises concerns about potential adverse health effects at low levels of exposure, especially among vulnerable populations such as pregnant women and children. Importantly children have higher pyrethroids exposure rates comparing to adults which can result from greater food consumption per unit of body mass, higher minute ventilation, larger relative body surface area, or age-specific behaviors including putting hands in the mouth, spending more time on the floor or near surfaces where pyrethroids were applied [9,10]. Moreover, pyrethroids can cross the placenta and the blood-brain barrier, raising concerns about health effects of *in utero* exposure, especially when combined with the potential greater susceptibility of the fetus and child (thereby impacting children's health and susceptibility to diseases later in life) [5,11,12].

Results from existing studies, summarized in systematic and narrative reviews by Elser et al. [13] (papers published up to 2022), Andersen et al. [14] (papers published up to September 2021) and Bliznashka et al. [15] (papers published up to 2015), suggest that exposure to pyrethroids during fetal life may cause a range of health effects, including the impact on the course and outcome of pregnancy and on neurobehavioural development in children, although the strength of the evidence varies.

The aim of this review is an attempt to summarize the current knowledge of the effects of prenatal pyrethroid exposure on children's health.

METHODS

This review was developed in alignment with the elements specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) guidelines [16].

Eligibility criteria

The following criteria were established for inclusion in the review:

- studies conducted with human participants,
- original articles published in full text in English-language, peer-reviewed journals within the last decade (≥2015),
- pyrethroid concentrations were measured in urine samples collected from the mother during pregnancy,
- the study analysed the effects of prenatal exposure to pyrethroids on pregnancy outcomes, children's health status, and development.

This review excluded meta-analyses and review articles, but utilized them as valuable sources of information.

Information sources search strategy

Epidemiological studies analyzing the effects of prenatal exposure to pyrethroids on pregnancy outcomes, health status, and child neurobehavioral development were identified through a comprehensive search of the PubMed, Scopus, and Web of Science databases conducted in January–February 2024. The search strategy utilized logical operators (AND, OR) to apply keywords with precision and efficiency: prenatal exposure, pyrethroids,

fetal growth, gestational age, birth outcomes, birth weight, abdominal circumference, obesity, neurobehavioural development, behavior, cognition, respiratory diseases, asthma, allergy.

Selection process and data collection process

A comprehensive and systematic search of the databases was performed independently by 2 reviewers. Based on the inclusion criteria using title and abstract, irrelevant reports were excluded and the full text was assessed. Verification of the search results and resolution of the resulting inconsistencies were discussed within the research team.

The following significant information was extracted from publications meeting the eligibility criteria: first author's name, year of publication, study design and population description (study name, country, period of recruitment, sample size, age of children), period of maternal exposure, metabolites determined, health outcomes observed, diagnostic tool, confounders, urinary pyrethroid metabolite concentrations and the results of analysis.

RESULTS

Study selection

In the search process utilizing keywords, 198 studies were identified and subjected to inclusion/exclusion verification. In the initial phase, following the analysis of titles and abstracts, 16 duplicates, 106 irrelevant studies, and 3 reviews were excluded. Subsequently, all publications selected during the title and abstract assessment phase underwent full-text review. The primary reasons for exclusion included the absence of original data, the analysis of pyrethroid metabolite concentrations in biological materials other than urine, and the evaluation of postnatal exposure. Ultimately, 25 publications were included in the review. Figure 1 presents a detailed flowchart of the study selection process for the review.

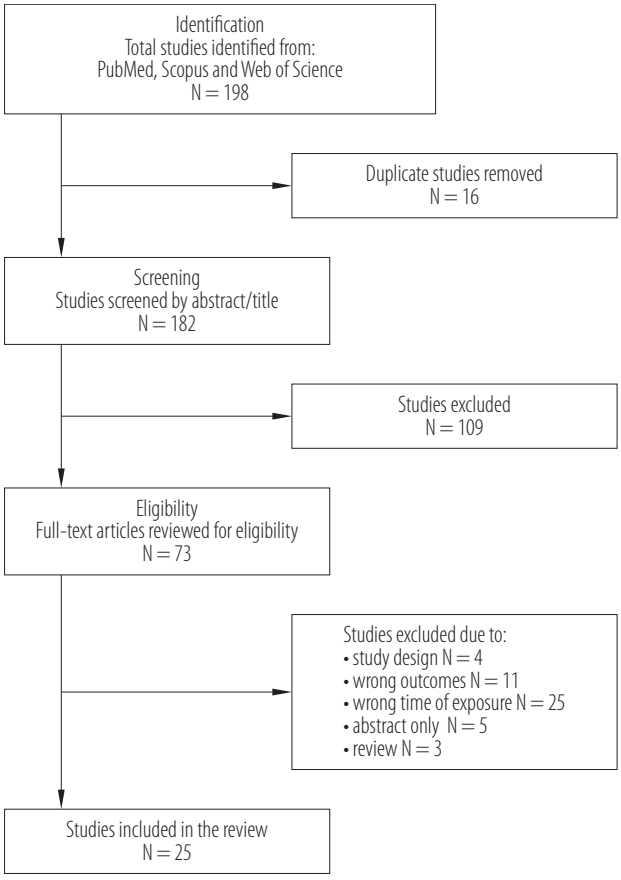

Figure 1. Study selection process for the review on the effects of prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children in 2015–2024

Characteristics of studies

Of the studies included in the review, 16 assessed the effects of prenatal exposure to pyrethroids on children's neurodevelopment, 3 studies assessed the effects on the course and outcome of pregnancy, and further 3 focused on respiratory and allergic diseases. In addition, 1 study analyzed the development of obesity and 2 studies examined the effects on children's growth, weight and body composition in early childhood (Table 1). Multiple analyses and publications may be available for some studies, therefore the quantity of publications does not always correspond to the number of cohorts. Finally, the data included in the review came from 18 different cohorts from 11 coun-

Table 1. Characteristics of studies published in 2015–2024 included in the review on the effects of prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children

Reference	Study/desing	Location	Time period	Sample size	Measurement	Exposure assessment	Outcome	Age of children at outcome assessment
Ding et al., 2015 [17]	birth cohort	China	2010–2012	454 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA	single urine sample at delivery	birth outcomes	birth
Dalsager et al., 2018 [18]	OCC (cohort)	Odense, Denmark	2010–2012	858 mother-child pairs	3-PBA	single urine sample (28 wk gest)	birth outcomes	birth, anogenital distance 3 months after the expected delivery
Jaacks et al., 2019 [19]	birth cohort	Bangladesh	2010–2013	289 mother-child pairs	3-PBA, trans-DCCA, 4-F-3-PBA	single urine sample (<16 wk gest)	birth outcomes	birth, 1–2 years
Viel et al., 2015 [30]	PELAGIE (cohort)	Brittany, France	2002–2006	287 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA, 4-F-3-PBA, cis-DBCA	single urine sample (between 6–19 wk gest)	neurodevelopment	6 years
Watkins et al., 2016 [25]	ELEMENT (cohort)	Mexico City, Mexico	1997–2001	187 mother-child pairs	3-PBA	single urine sample (third trimester)	neurodevelopment	2–3 years
Fluegge et al., 2016 [26]	prospective cohort	Ohio, USA	2002–2005	140 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA, 4-F-3-PBA, cis-DBCA, DMCA1, DMCA2, CIAA	2 urine samples (second, third trimester)	neurodevelopment	3 months
Viel et al., 2017 [21]	PELAGIE (cohort)	Brittany, France	2002–2006	287 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA, 4-F-3-PBA, cis-DBCA	single urine sample (between 6–19 wk gest)	neurodevelopment	6 years
Hisada et al., 2017 [34]	prospective cohort	Tokyo, Japan	2009–2011	102 mother-child pairs	3-PBA	single urine sample (10–12 wk gest)	neurodevelopment	18 months
Furlong et al., 2017 [20]	MSCEHC (cohort)	USA	1998–2002	162 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA	single urine sample (third trimester)	neurodevelopment	4, 6, 7–9 years
Eskenazi et al., 2018 [27]	VHEMBE (cohort)	Limpopo, South Africa	2012–2013	752 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA, 4-F-3-PBA, cis-DBCA	single urine sample pre- or post-delivery urine sample	neurodevelopment	1, 2 years
Dalsager et al., 2019 [22]	OCC (cohort)	Odense, Denmark	2010–2012	948 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA, 4-F-3-PBA, cis-DBCA	single urine sample (28 wk gest)	neurodevelopment	2–4 years

Tanner et al., 2020 [28]	SELMA (cohort)	Sweden	2007–2010	718 mother-child pairs	3-PBA	single urine sample (first trimester)	neurodevelopment	7 years
Guo et al., 2020 [31]	SMBCS (cohort)	Sheyang, China	2009–2010	326 mother-child pairs	3-PBA, trans-DCCA, cis-DCCA	single urine sample at delivery	neurodevelopment	7 years
Andersen et al., 2021 [32]	OCC (cohort)	Odense, Denmark	2010–2012	755 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA, 4-F-3-PBA, cis-DBCA	single urine sample (28 wk gest)	neurodevelopment	20–36 month
Qi et al., 2022 [35]	birth cohort	China	2016–2018	419 mother-child pairs	3-PBA, 4 F-3-PBA, cis-DBCA, ∑pyrethroids	3 urine samples (first, second, third trimester)	neurodevelopment	1 year
Lee et al., 2022 [23]	EDC (cohort)	South Korea	2008–2010	524 mother-child pairs	3PBA	single urine sample (second trimester)	neurodevelopment	2, 4, 6, 8 years
Chen et al., 2022 [33]	birth cohort	China	2016	173 mother-child pairs	3PBA, 4F3PBA, DBCA	single urine sample (third trimester)	neurodevelopment	2 years
Wang et al., 2023 [29]	prospective cohort	Wuhan, China	2014–2017	1041 mother-child pairs	3PBA, trans-DCCA, 4F3PBA	3 urine samples (first, second, third trimester)	neurodevelopment	2 years
Fage-Larsen et al., 2024 [24]	OCC (cohort)	Odense, Denmark	2010–2012	614 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA, 4-F-3-PBA	single urine sample (28 wk gest)	neurodevelopment	5 years
Gilden et al., 2020 [42]	HOME (cohort)	Cincinnati, Ohio, USA	2003–2006	367 mother-child pairs	3-PBA	2 urine samples (16, 26 wk gest)	respiratory health	4, 5, 8 years
Hu et al., 2022 [41]	LWBC (cohort)	China	2010–2013	233 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA	single urine sample (before delivery)	respiratory health	6–8 years
Islam et al., 2023 [40]	Infants' Environmental Health Study (cohort)	Costa Rica	2010–2011	303 mother-child pairs	3-PBA, DCCA, ∑pyrethroids	3 urine samples (<33 wk gest)	respiratory health	5 years
Lee et al., 2019 [36]	EDC (cohort)	Seoul, Gyeonggi, Republic of Korea	2008–2011	578 mother-child pairs	3-PBA	single urine sample (20 wk gest)	adiposity, growth	4 years
Kim et al., 2022 [38]	VHEMBE (cohort)	Limpopo, South Africa	2012–2013	628 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA, cis-DBCA	single urine sample (at the time of delivery)	anthropometric measurements, body composition analysis blood pressure	5 years

Table 1. Characteristics of studies published in 2015–2024 included in the review on the effects of prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children – cont.

Reference	Study/desing	Location	Time period	Sample size	Measurements	Exposure assessment	Outcome	Age of children at outcome assessment
Coker et al., 2019 [37]	VHEMBE (cohort)	Limpopo, South Africa	2012–2013	708 mother-child pairs	3-PBA, cis-DCCA, trans-DCCA, cis-DBCA	single urine sample (pre- or post-delivery)	length/height and weight	≤2 years

EDC – *Environment and Development of Children;* HOME – *Health Outcomes and Measures of the Environment;* LWBC – *Laizhou Wan Birth Cohort;* MSCEHC – *Mount Sinai Children's Environmental Health Center;* OCC – *Odense Child Cohort;* SELMA – *Swedish Environmental Longitudinal Mother and Child, Asthma and Allergy;* SMBCS – *Sheyang Mini Birth Cohort Study;* VHEMBE – *Venda Health Examination of Mothers, Babies and their Environment.*
3-PBA – 3-phenoxybenzoic acid; 4-F-3-PBA – 4- fluoro-3-phenoxybenzoic acid; ClAA – 4-chlorophenyl-2-isopropylacetic acid; cis-DBCA – cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; cis-DCCA – cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; DMCA1, DMCA2 – cis- and trans-3-(2,2-dimethylvinylcyclopropane-1-carboxylic acid); trans-DCCA – trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; Σpyrethroids – sum of pyrethroid metabolites.
wk gest – gestational week.

tries, Europe (7), America (5), Asia (10) and Africa (3). Pregnant women were recruited in 1997–2018, and urine samples were collected at different time points (pre-delivery, in the first, second and third trimesters of pregnancy). In 20 studies, the exposure assessment was based on a single urine sample, in 2 studies on 2 different samples, and in the remaining studies on 3 samples.

The level of exposure in urine samples collected from pregnant mothers was measured by determining the following biomarkers of exposure: cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (cis-DCCA, trans-DCCA), cis-3-(2,2-dicbromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (cis-DBCA), 3-phenoxybenzoic acid (3-PBA), 4-fluoro-3-phenoxybenzoic acid (4-F-3-PBA) and cis- and trans-3-(2,2-dimethylvinylcyclopropane-1-carboxylic acid) (DMCA1, DMCA2) (Table 2). Table 3 shows the concentrations of pyrethroid metabolites in maternal urine samples collected during pregnancy, the limit of detection (LOD) and the percentage of samples below LOD. Three-phenoxybenzoic acid, which represents the exposure to most pyrethroids, was the most commonly used biomarker. Direct comparison of the concentrations of pyrethroid metabolites in urine samples is difficult due to differences in analytical methods and LOD.

In all studies included in the review, adjustments for potential confounders were made, although the number of confounded varied (Table 4). The most commonly assessed confounders included the following data: maternal education, socioeconomic status, child sex and age.

Pregnancy and birth outcomes

Studies assessing the effect of prenatal pyrethroid exposure on the course and outcome of pregnancy focused on the following parameters: gestational age (weeks), preterm birth (<37 weeks gestation), birth weight (g), low birth weight (<2500 g), body length (cm), head and chest circumference (cm).

Table 2. Pyrethroids and their metabolites

Biomarker	Acronym	Description
3-Phenoxybenzoic acid	3-PBA	common metabolite of most pyrethroids (e.g., cypermethrin, cyhalothrin, deltamethrin, esfenvalerate, etofenprox, fenpropathrin, lambda-cyhalothrin, permethrin tau-fluvalinate, tralomethrin)
Cis-3-(2,2-dichlorovinyl)-2,2- dimethylcyclopropane-1-carboxylic acid	cis-DCCA	metabolites of the respective isomers of permethrin, cypermethrin and cyfluthrin
Trans-3(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid	trans-DCCA	metabolites of the respective isomers of cypermethrin, permethrin and cyfluthrin
Cis-3-(2,2-dibromovinyl)-2,2- dimethylcyclopropane-1-carboxylic acid	cis-DBCA	specific metabolite of deltamethrin
4-Fluoro-3-phenoxybenzoic acid	4-F-3-PBA	metabolite of cyfluthrin
Cis- and trans-3-(2,2-dimethylvinylcyclopropane-1-carboxylic acid)	DMCA1, DMCA2	metabolite of pyrethrin i (most abundant component of pyrethrin mix), tetramethrin, resmethrin, sumithrin

Table 3. Concentrations of the pyrethroid metabolites in maternal urine in studies on prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children published in 2015–2024

Reference	Exposure timing during pregnancy	Limit of detection (LOD) (% <LOD)	Urinary concentration
Ding et al., 2015 [17]	delivery	3-PBA 0.1 µg/l (18.0) cis-DCCA 0.1 µg/l (29.0) trans-DCCA 0.1 µg/l (23.0)	Me 3-PBA 0.68 µg/g creatinine cis-DCCA 0.51 µg/g creatinine trans-DCCA 0.65 µg/g creatinine
Dalsager et al., 2018 [18]	28 wk gest	3-PBA 0.03 µg/l (5.7)	3-PBA 0.20 µg/l
Jaacks et al., 2019 [19]	<16 wk gest	3-PBA 0.2 µg/l (80.2) 4F-3-PBA 0.2 µg/l (100) trans-DCCA 0.6 µg/l (93.8)	n.a.
Viel et al., 2015 [30]	6–19 wk gest	3- PBA 0.008 µg/l (69.8) 4-F-3-PBA 0.003 µg/l (91.2) trans-DCCA 0.01 µg/l (2.0) cis-DCCA 0.07 µg/l (35.1) cis-DBCA 0.07 µg/l (31.7)	Me 3-PBA <LOD 4-F-3-PBA < LOD trans-DCCA 0.14 µg/l cis-DCCA 0.09 µg/l cis-DBCA 0.011 µg/l
Watkins et al., 2016 [25]	third trimester, 21 women provided multiple urine samples (the first, second and third trimester)	3- PBA 0.25 µg/l (53.7)	Me 3-PBA <LOD
Fluegge et al., 2016 [26]	second and third trimester	n.a	urinary concentrations not presented, but used to estimate daily excretion per kg body weight
Viel et al., 2017 [21]	6–19 wk gest	3- PBA 0.008 µg/l (69.8) 4-F-3-PBA 0.003 µg/l (91.2) trans-DCCA 0.01 µg/l (2.0) cis-DCCA 0.07 µg/l (35.1) cis-DBCA 0.07 µg/l (31.7)	Me 3- PBA <LOD 4-F-3-PBA < LOD trans-DCCA 0.14 µg/l cis-DCCA 0.09 µg/l cis-DBCA 0.011 µg/l
Hisada et al., 2017 [34]	10–12 wk gest	n.a	Me 3-PBA 0.389 µg/l specific gravity corrected

Table 3. Concentrations of the pyrethroid metabolites in maternal urine in studies on prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children published in 2015–2024 – cont.

Reference	Exposure timing during pregnancy	Limit of detection (LOD) (% <LOD)	Urinary concentration
Furlong et al., 2017 [20]	third trimester	3-PBA 0.25 µg/l (70.4) trans-DCCA 0.20 µg/l (85.6) cis-DCCA 0.20 µg/l (79.0)	Me 3-PBA <LOD trans-DCCA <LOD cis-DCCA <LOD
Eskenazi et al., 2018 [27]	pre-delivery and post-delivery urine sample	3-PBA 0.0047 µg/l (0.0) trans-DCCA 0.0038 µg/l (0.0) cis-DCCA 0.0045 µg/l (0.0) cis-DBCA 0.0025 µg/l (0.0) 4-F-3-PBA 0.005 µg/l (87.5)	GM±GSD 3-PBA 0.712±2.80 µg/l trans-DCCA 0.357 (3.43) µg/l cis-DCCA 0.306 (2.95) µg/l cis-DBCA 0.223 (3.42) µg/l 4-F-3-PBA n.a. specific gravity corrected
Dalsager et al., 2019 [22]	28 wk gest	3-PBA 0.03 µg/l (5.7) 4F-3-PBA 0.2 µg/l (99.9) cis-DCCA 0.5 µg/l (97.2) trans-DCCA 0.4 µg/l (88.6) cis-DBCA 0.5 µg/l (97.0)	Me 3-PBA 0.24 µg/l 4F-3-PBA <LOD cis-DCCA <LOD trans-DCCA <LOD cis-DBCA <LOD
Tanner et al., 2020 [28]	first trimester	3-PBA 0.017 µg/l (1.0)	GM±GSD 3-PBA 0.16±2.7 µg/l
Guo et al., 2020 [31]	at delivery	3-PBA 0.1 µg/l (2.0) trans-DCCA 0.1 µg/l (1.6) cis-DCCA 0.1 µg/l (8.2)	Me 3-PBA 1.11 µg/l trans-DCCA 1.26 µg/l cis-DCCA 0.48 µg/l
Andersen et al., 2021 [32]	28 wk gest	3-PBA 0.03 µg/l (5.7) 4F-3-PBA 0.2 µg/l (99.9) trans-DCCA 0.4 µg/l (87.8) cis-DCCA 0.5 µg/l (97.4) cis-DBCA 0.5 µg/l (96.8)	Me 3-PBA 0.24 µg/g creatinine
Qi et al., 2022 [35]	first, second, third trimester	3-PBA 0.02 µg/l (n.a.) 4F-3-PBA 0.02 µg/l (n.a.) cis-DBCA 0.09 µg/l (n.a.)	Me first trimester: 3-PBA 0.24 µg/g creatinine 4F-3-PBA 0.14 µg/g cis-DBCA 0.21 µg/g ∑pyrethroids 0.88 nmol/g second trimester: 3-PBA 0.24 µg/g creatinine 4F-3-PBA 0.17 µg/g creatinine cis-DBCA 0.25, µg/g creatinine ∑pyrethroids 0.83 nmol/g third trimester: 3-PBA 0.21 µg/g creatinine 4F-3-PBA 0.15 µg/g creatinine cis-DBCA 0.19 µg/g creatinine ∑pyrethroids 0.81 nmol/g
Lee et al., 2022 [23]	second trimester	3-PBA 0.015 µg/l (0.8)	GM±GSD 3-PBA 0.7±3.7 µg/l
Chen et al., 2022 [33]	third trimester	n.a	Me 3-PBA 0.21 µg/l 4F-3-PBA 0.19 µg/l DBCA 0.15 µg/g creatinine

Table 3. Concentrations of the pyrethroid metabolites in maternal urine in studies on prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children published in 2015–2024 – cont.

Reference	Exposure timing during pregnancy	Limit of detection (LOD) (% <LOD)	Urinary concentration
Wang et al., 2023 [29]	first, second, third trimester	3-PBA µg/l (n.a.) 4F-3-PBA µg/l (n.a.) trans-DCCA µg/l (n.a.)	Me 3-PBA 0.19 µg/l 4F-3-PBA (n.a.) trans-DCCA 0.23 µg/l
Fage-Larsen et al., 2024 [24]	28 wk gest	3-PBA 0.03 µg/l (7.0) 4F-3-PBA 0.2 µg/l (n.a.) cis-DCCA 0.5 µg/l (n.a.) trans-DCCA 0.4 µg/l (n.a.) cis-DBCA 0.5 µg/l (n.a.)	Me 3-PBA 0.20 µg/l
Gilden et al., 2020 [42]	16 wk gest, 26 wk gest	n.a	GM (min.–max) $3\text{-PBA}_{16\text{ wk gest}}$ 0.4 (0.0–41.7) µg/l $3\text{-PBA}_{26\text{ wk gest}}$ 0.3 (0.0–37.4) µg/l
Hu et al., 2022 [41]	before delivery	3PBA 0.05 µg/l (18.5) trans-DCCA 0.23 µg/l (44.6) cis-DCCA 0.38 µg/l (78.1)	Me 3-PBA 0.44 µg/l trans-DCCA 0.17 µg/l cis-DCCA <LOD Me 3-PBA 0.94 µg/g creatinine trans-DCCA 0.72 µg/g creatinine cis-DCCA <LOD
Islam et al., 2023 [40]	<33 wk gest	3-PBA 0.03 µg/l (n.a.) DCCA 0.04 µg/l (n.a.)	Me 3-PBA 0.83 µg/l DCCA 1.32 µg/l ∑pyrethroids 2.26 µg/l specific gravity corrected
Lee et al., 2019 [36]	second trimester	3-PBA 0.013 µg/l (1.0)	GM±GSD 3-PBA 0.98±3.22 µg/g creatinine
Kim et al., 2022 [38]	at the time of delivery	3-PBA 0.0047 µg/l (0.0) cis-DCCA 0.0045 µg/l (0.0) trans-DCCA 0.0038 µg/l (0.0) cis-DBCA 0.0025 µg/l (0.0)	Me 3-PBA 1.03 µg/l cis-DCCA 0.45 µg/l trans-DCCA 0.53 µg/l cis-DBCA 0.32, µg/l specific gravity-corrected
Coker et al., 2019 [37]	pre- or post-delivery	cis-DBCA 0.0025 µg/l (0.0) cis-DCCA 0.0045 µg/l (0.0) trans-DCCA 0.038 µg/l (0.0) 3-PBA 0.0047 µg/l (0.3)	GM±GSD cis-DBCA 0.22±3.42 µg/l cis-DCCA 0.31 (2.95) µg/l trans-DCCA 0.36 (3.43) µg/l 3-PBA 0.71 (2.80) µg/l specific gravity corrected

3-PBA – 3-phenoxybenzoic acid; 4F-3-PBA –4-fluoro-3-phenoxybenzoic acid; cis-DBCA – cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; cis-DCCA – cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; trans-DCCA – trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; ∑pyrethroids – sum of pyrethroid metabolites.
GM – geometric mean; GSD – geometric standard derivation.
n.a. – not available.
wk gest – gestational week.

Table 4. Confounders included in the analyzes of the effects of prenatal exposure to pyrethroids on child development and health published in 2015–2024

Reference	Confounding factor
Ding et al., 2015 [17]	maternal age, child sex, family income, passive smoking, parity, pre-pregnancy BMI, pregnancy weight gain, length of gestation
Dalsager et al., 2018 [18]	weight-for-age Z-score and age-at-3-months examination
Jaacks et al., 2019 [19]	maternal education, family income, maternal total energy intake (log-transformed kcal/day) and maternal meat intake (log-transformed g/day)
Viel et al., 2015 [30]	maternal education, child sex, concentration of pyrethroid metabolites in childhood, urinary concentration of creatinine (mother and child), maternal concentrations of organophosphate metabolites, maternal IQ and HOME score
Watkins et al., 2016 [25]	maternal education, maternal IQ, family income, child sex, blood lead, urinary specific gravity
Fluegge et al., 2016 [26]	maternal education, gestational age, birth weight, also on some models TCPy
Viel et al., 2017 [21]	maternal education, child sex, concentration of pyrethroid metabolites in childhood, urinary concentration of creatinine (mother and child), maternal concentrations of organophosphate metabolites
Hisada et al., 2017 [34]	maternal age, gestational week, birth weight, maternal BMI, parity, child sex, concentration of TSH in the child's blood 5 days after birth, breastfeeding duration, age of child at examination, *Index of Child Care Environment* score; a second model also included fish consumption
Furlong et al., 2017 [20]	maternal education, maternal marital status, race/ethnicity, quality of the home environment – HOME scores, organophosphate metabolites (ΣDMPs), urinary concentration of creatinine visit, child sex
Eskenazi et al., 2018 [27]	maternal education, age, poverty status and marital status at delivery, breastfeeding, Raven's Coloured Progressive Matrices Z-score for the mother/caregiver, preterm birth, birth weight Z-scores, maternal depression risk score, U.S. Department of Agriculture *Food Insecurity Score*, modified HOME Z-score, the psychometrician administering the BSID-III
Dalsager et al., 2019 [22]	maternal educational, parental psychiatric diagnosis, child age, child sex, urinary concentration of creatinine
Tanner et al., 2020 [28]	maternal education, maternal IQ, weight, smoking status, child sex, urinary concentration of creatinine
Guo et al., 2020 [31]	maternal education, age of the mother at birth, family income, passive smoking during pregnancy, breastfeeding duration, child sex, doctors performing IQ assessment, marital status at assessment, urinary concentration of creatinine
Andersen et al. 2021 [32]	maternal education, breastfeeding duration, child sex, urinary concentration of creatinine
Qi et al., 2022 [35]	maternal education, maternal age, poverty status, perceived stress, weight gain, urine concentration of cotinine during pregnancy, child sex, birth weight Z-scores, primary caregiver and parenting time for children, breastfeeding, passive smoking
Lee et al., 2022 [23]	child's age, child sex, breastfeeding, family income, prematurity, diabetes during pregnancy, season of exposure, urinary concentration of creatinine for prenatal exposure analyses
Chen et al., 2022 [33]	n.a.
Wang et al. 2023 [29]	maternal education, prepregnancy BMI, maternal age, passive smoking, folic acid supplementation during pregnancy, number of deliveries, child sex, breastfeeding and mode of delivery
Fage-Larsen et al. 2024 [24]	maternal education level, parental psychiatric diagnosis, child sex, child age at assessment, urinary concentration of creatinine
Gilden et al., 2020 [42]	maternal education, age at delivery, maternal race marital status, employment status, parity, alcohol intake, daily fruit and vegetable consumption during pregnancy, child birth weight and sex, cotinine level
Hu et al., 2022 [41]	maternal education, maternal age, pre-pregnancy BMI, family income, child's age, child sex, BMI, height, and passive smoking, urinary concentration of creatinine
Islam et al., 2023 [40]	maternal smoking during pregnancy, child sex, parity, breastfeeding, maternal history of asthma

Table 4. Confounders included in the analyzes of the effects of prenatal exposure to pyrethroids on child development and health published in 2015–2024 – cont.

Reference	Confounding factor
Lee et al., 2019 [36]	height Z-scores included age, sex, gestational age, mid-parental height Z-score, paternal education, total energy intake, weekly physical activity, pre- and postnatal concentration of 3-PBA weight Z-scores included age, sex, gestational age, birth weight Z-score, maternal and paternal BMI, paternal education level, physical activity, total energy intake, pre- and postnatal concentration of 3-PBA BMI Z-scores included age, sex, gestational age, birth weight Z-score, maternal and paternal BMI, paternal education level and 3-PBA concentrations
Kim et al., 2022 [38]	maternal education, maternal age, height, post-delivery weight, household food poverty, food insecurity, wealth index, marital status, energy intake during pregnancy, alcohol use during pregnancy, HIV status at delivery, duration of exclusive breastfeeding, parity, child sex
Coker et al., 2019 [37]	maternal education, maternal age, maternal BMI, maternal parity, household poverty status, maternal HIV status

BSID-III – *Bayley Scales for Infant Development*, 3 edition; HOME – *Health Outcomes and Measures of the Environment*.
3-PBA – 3-phenoxybenzoic acid; TCPy – 3,5,6-trichloro-2-pyridinol (metabolite of chlorpyrifos).
TSH – thyroid stimulating hormone.
n.a. – not available.

Table 5. Associations between prenatal pyrethroid levels and birth outcomes – review of studies on prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children published in 2015–2024

Reference	Assessment timepoint	Birth outcomes	Outcomes assessment	Observed effect	Association
Ding et al., 2015 [17]	birth	birth weight, birth length, head circumference, gestation age	medical records, anthropometric measurements	maternal exposure to the sum of pyrethroid metabolites cis-DCCA, trans-DCCA, and 3-PBA was associated with lower (β: –96.76, 95% CI: –173.15–(–20.37), p = 0.013); no associations were between individual or total metabolite levels and birth length, head circumference or gestational duration	negative
Dalsager et al., 2018 [18]	birth	gestational age, birth weight, head circumference, abdominal circumference, anogenital distance	questionnaire, anthropometric measurement, birth records	maternal exposure to 3-PBA was associated with smaller abdominal circumference in female offspring (β: –0.3, 95% CI: –0.5–(–0.003) cm)	negative
Jaacks et al., 2019 [19]	birth, 1, 2 years	preterm birth, low birth weight, gestational age, stunting at 1 and 2 years of age	ultrasound (gestational age), anthropometric measurements (height, weight)	maternal urinary 3-PBA >LOD associated with lower risk for small for gestational age (OR: 0.13, 95% CI: 0.02–0.95)	positive

3-PBA – 3-phenoxybenzoic acid; cis-DBCA– cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid;
cis-DCCA – cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; trans-DCCA – trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid.
LOD – limit of detection.

Only 3 studies met the inclusion criteria and were included in this review [17–19] (Table 5). Ding et al. [17] and Dalsager et al. [18] observed a negative association for the relationship in question. An increase in the concentration of the sum of cis-DCCA, trans-DCCA and 3-PBA metabolites in maternal urine was associated with a significant reduction in the infant's birth weight, whereas no association was observed between the concentration

of individual metabolites and birth weight and between the total metabolite level and the infant's birth length or head circumference [17]. Dalsager et al. [18] demonstrated that higher concentrations of 3-PBA in maternal urine, collected during the third trimester of pregnancy, were associated with smaller abdominal circumference in girls. On the other hand, results from Jaacks et al. [19] suggest that mothers with detectable 3-PBA concentrations were less likely to give birth to a baby small for gestational age.

Prenatal exposure to pyrethroids and neurodevelopmental outcomes

Sixteen epidemiological studies were conducted to analyze the effects of prenatal pyrethroid exposure on child neurodevelopment (Table 6). The study population size ranged 102–1041 mother-child pairs. Neurodevelopmental assessments were carried out in a group of children using validated tools such as the *Wechsler Intelligence Scale for Children* (WISC), the *Bayley Scales of Infant Development* (BSID) and the *Strengths and Difficulties Questionnaire* (SDQ).

Four studies observed a significant association between prenatal pyrethroid exposure and poorer behavioural outcomes [20–24]. Furlong et al. [20] indicated an association between maternal urinary concentrations of 3-PBA, cis-DCCA and deficits in the *Internalizing*, *Depression*, *Somatization*, *Behavioral Regulation*, *Emotional Control*, *Shifting*, and *Monitoring* scales in children. Similarly, Viel et al. [21] found that maternal exposure to cis-DCCA was associated with the occurrence of more internalizing problems, particularly in girls. In contrast, Dalsager et al. [22] and Lee et al. [23] investigated potential associations between the exposure to pyrethroids and the incidence of attention deficit hyperactivity disorder (ADHD) in children. A doubling of 3-PBA concentrations in urine samples collected from mothers in the third trimester of pregnancy was associated with a 3% increase in ADHD score and a 13% chance of having an ADHD scores ≥90 [22]. Similarly, a doubling of 3-PBA concentrations during pregnancy was associated with a 2.7% increase in *ADHD Rating Scale-IV* (ARS) scores in children in 6 year olds [23]. Only, Fage-Larsen et al. [24] found no statistically significant association between prenatal exposure to pyrethroids and risk of ADHD in 5-year-old children.

Eleven studies analyzed the association between prenatal exposure to pyrethroids and children's cognitive and psychomotor development [25–35]. It is important to note that these findings are not conclusive. Of these, 5 found an inverse relationship, indicating a reduction in cognitive function in children with increasing maternal exposure to pyrethroids [25–29].

Watkins et al. [25] observed a decrease in mental development index (MDI) scores among 2 years old children who were prenatally exposed to mean levels of 3-PBA. However, this relationship was not observed in children at 3 years of age, nor for PDI scores at either 2 or 3 years of age. Fluegge et al. [26] observed a reduction in MDI with higher levels of 3-PBA in maternal urine during the third trimester of pregnancy but not during second trimester of pregnancy. Increase of cis-DCCA, trans-DCCA or 3-PBA (10-fold) in maternal urine was associated with a decrease in *Social-Emotional* scores in children at 1 year of age. On the other hand, an increase in cis-DBCA levels (10-fold) resulted in a decrease *Language Composite* and *Expressive Communication* scores at 2 years of age [27]. In addition, prenatal exposure to mixtures of potentially neurotoxic substances, including 3-PBA, was associated with lower intellectual functioning in children at the age of 7, although the authors did not provide a separate estimate of the effect for 3-PBA [28]. Four studies found no significant association between prenatal exposure and cognitive function in children [30–33].

Only Hisada et al. [34] demonstrated a positive correlation between maternal urinary 3-PBA levels and higher developmental quotient scores in children at 18 months of age.

Table 6. Associations between prenatal pyrethroid levels and neurodevelopmental outcomes in children in studies on prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children published in 2015–2024

Reference	Children's age at neurodevelopment assessment	Outcome	Neurodevelopment assessment		Observed effect	Association
			domain/subscale	tool		
Furlong et al., 2017 [20]	4, 6, 7–9 years	behavioral development	internalizing, externalizing behaviors, behavioral symptoms index, executive functioning, behavioral regulation index, metacognition index, global executive composite	BASC, BRIEF	maternal exposure to 3-PBA >LOD were associated with worse internalizing (β: −4.50, 95% CI: −8.05–(−0.95)), depression (β: −3.21, 95% CI: −6.38–(−0.05)), somatization (β: −3.22, 95% CI: −6.38–(−0.06)), behavioral regulation (β: −3.59, 95% CI: −6.97–(−0.21)), emotional control (β: −3.35, 95% CI: −6.58–(−0.12)), shifting (β: −3.42, 95% CI: −6.73–(−0.11)), and monitoring (β: −4.08, 95% CI: −7.07–(−1.08)) scales maternal exposure to cis-DCCA >LOD were associated with worse externalizing (β: −4.74, 95% CI: −9.37–(−0.10)), conduct problems (β: −5.35, 95% CI: −9.90–(−0.81)), behavioral regulation (β: −6.42, 95% CI: −11.39–(−1.45)), and inhibitory control (β: −7.20, 95% CI: −12.00–(−2.39))	negative
Viel et al., 2017 [21]	6 years	behavioral development	internalizing, externalizing behaviors, prosocial behavior	SDQ	maternal exposure to cis-DCCA was associated with more internalizing problems, with a more pronounced effect observed in females than in males (Cox $p = 0.05$); no significant associations were found for either trans-DCCA or 3-PBA	negative
Dalsager et al., 2019 [22]	2–4 years	behavioral development	6 ADHD problem items extracted from the CBCL for ages 1.5–5 years	CBCL	maternal exposure to 3-PBA was associated with increase ADHD score (ratio: 1.03, 95% CI: 1.00–1.07); maternal exposure to 3-PBA and trans-DCCA were associated with higher odds of scoring on the ADHD- scale score ≥90th percentile (OR: 1.13, 95% CI: 1.04–1.38)	negative
Lee et al., 2022 [23]	2, 4, 6, 8 years of age	behavioral development	18 items corresponding with the diagnostic criteria of ADHD in the DSM-IV	ARS	a doubling of prenatal 3-PBA levels was associated with an increase in ADHD symptoms at 6 years of age (2.7% change, 95% CI: 0.3–5.2)	negative
Fage-Larsen et al., 2024 [24]	5 years	behavioral development	100 problem items grouped into several scales and subscales	CBCL/1½–5	no associations between maternal pyrethroid exposure and ADHD score ≥90th percentile at age 5 years	no
Watkins et al., 2016 [25]	2–3 years	cognitive development	MDI, PDI	BSID-IIS	maternal exposure to 3-PBA (mean 3-PBA level only) was associated with decrement MDI scores in girls at age 2 years (β: −6.2, 95% CI: −12.3–(−0.14)), not associated with MDI scores at age 3 years or with PDI scores at age 2 and 3 years	negative
Fluegge et al., 2016 [26]	3 months	cognitive development	MDI, PDI	BSID-II	maternal exposure to 3-PBA was associated with decrement MDI scores, but not associated with PDI scores	negative

Table 6. Associations between prenatal pyrethroid levels and neurodevelopmental outcomes in children in studies on prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children published in 2015–2024 – cont.

Reference	Children's age at neurodevelopment assessment	Outcome	Neurodevelopment assessment		Observed effect	Association
			domain/subscale	tool		
Eskenazi et al., 2018 [27]	1, 2 years	cognitive development	cognitive, receptive communication, expressive communication, fine motor, gross motor, language composite, motor composite, social-emotional	BSID	maternal exposure to cis-DCCA, trans-DCCA, 3-PBA were associated, respectively, with β: –0.63, 95% CI: –1.14–(–0.12); β: -0.48, 95% CI: –0.92–(–0.05); β: –0.58, 95 % CI: –1.11–(–0.06) decrement in social-emotional scores at age 1 year; maternal exposure to cis-DBCA was associated with decrements at 2 years in language composite scores and expressive communication scores β: –1.74, 95% CI: –3.34–(–0.13) and β: –0.40, 95% CI: –0.77–(–0.04), respectively	negative
Tanner et al., 2020 [28]	7 years	cognitive development	FIQ	WISC-IV	FIQ scores were 1.9-points (95% CI: –3.6–(–0.2)) lower among boys for an inter-quartile-range change in the weighted quantile sum index for 26 EDCs included; maternal 3-PBA was estimated to contribute with a weight of 9% to the index but separate results for 3-PBA not provided	negative
Wang et al., 2023 [29]	2 years	cognitive development	MDI, PDI	BSID-CR	maternal exposure to trans-DCCA was associated with decrement MDI and PDI scores in boys	negative
Hisada et al., 2017 [34]	18 months	cognitive development	physical motor, manipulation, receptive language, expressive language, language concepts, social relationships with children, social relationships with adults, discipline, feeding	KIDS	maternal exposure to 3-PBA was associated with higher the KIDS score	positive
Qi et al., 2022 [35]	1 year	cognitive development	cognitive, language, motor, social-emotional, adaptive behavior	BSID-III	in the second trimester maternal exposure to 3-PBA were inversely associated with cognition scores (β: –3.34, 95% CI: –6.11–(–0.57)) and language scores (β: –2.90, 95% CI: –5.20–(–0.61)); adaptive behavior scores were inversely associated with cis-DBCA (β: –0.73, 95% CI: –1.27–(–0.19)); in the third trimester maternal exposure to 4F-3-PBA were positively associated with language scores (β: 6.04, 95% CI: 1.84–10.23), adaptive behavior scores were positively associated with cis-DBCA (β: 0.73, 95% CI: 0.29–1.17) and Σpyrethroids (β: 0.10, 95% CI: 0.01–0.20)	mixed effects
Viel et al., 2015 [30]	6 years	cognitive development	verbal comprehension index, working memory index	WISC-IV	no association between maternal pyrethroid exposure and children's cognitive scores	no

Guo et al., 2020 [31]	7 years	cognitive development	verbal intelligence quotient, performance intelligence quotient, full intelligence quotient	WISC-IV	no association between maternal exposure to 3-PBA, trans-DCCA and cis-DCCA and children's cognitive function	no
Andersen et al., 2021 [32]	20–36 month	cognitive development	vocabulary subscale, complexity subscale	MB-CDI	no association between maternal pyrethroid exposure and impaired language development. Maternal exposure to 3-PBA was associated with lower odds of scoring below the 15th percentile MB-CDI vocabulary score among boys	no
Chen et al., 2022 [33]	2 years	cognitive development	language	BSID-III	no association was observed between maternal exposure to 3-PBA, 4-F-3-PBA or DBCA in the 3rd trimester of pregnancy and language development	no

ARS – *ADHD Rating Scale IV*; BASC – *Behavior Assessment System for Children*; BRIEF – *Behavior Rating Inventory of Executive Functioning*; BSID-CR – Chinese revision of the *Bayley Scales of Infant Development*; BSID-III – *Bayley Scales for Infant Development*, 3 edition; BSID-IIS – *Bayley Scales for Infant Development* – Spanish version; CBCL – *Child Behavior Checklist*; DSM – Diagnostic and Statistical Manual of Mental Disorders IV; EDCs – endocrine-disrupting chemicals; FIQ – *Full-scale IQ*; KIDS – *Kinder Infants Development Scale*; MB-CDI – *MacArthur-Bates Communicative Development Inventories*; MDI – *Mental Development Index*; PDI – *Psychomotor Development Index*; SDQ – *Strengths and Difficulties Questionnaire*; WISC-IV – The *Wechsler Intelligence Scale for Children*, 4th edition.
3-PBA – 3-phenoxybenzoic acid; 4-F-3-PBA – 4-fluoro-3-phenoxybenzoic acid; CIAA – 4-chlorophenyl-2-isopropylacetic acid; cis-DBCA – cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; cis-DCCA – cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; DMCA1, DMCA2 – cis- and trans-3-(2,2-dimethylvinylcyclopropane-1-carboxylic acid); trans-DCCA – trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; Σpyrethroids – sum of pyrethroid metabolites.

The study conducted by Qi et al. [35] provided inconsistent and inconclusive results. Maternal exposure to 3-PBA during the second trimester was inversely associated with cognitive and language outcomes, while exposure to cis-DBCA was inversely associated with adaptive behaviour outcomes of children at 1 year of age. It is important to note that no such associations were found for exposure during the first or third trimester. However, it should be noted that maternal exposure to 4F-3-PBA during the third trimester was found to have a positive association with language scores. Similarly, adaptive behaviour scores were positively associated with cis-DBCA and sum of pyrethroids [35].

Children's health

The review included 6 studies that analyzed the impact of prenatal exposure to pyrethroids on the children's health, assessed based on anthropometric parameters and body composition analysis, the occurrence of respiratory diseases, including asthma, wheezing, or allergies (Table 7 and 8). Inconsistent and inconclusive results have been provided by studies focusing on the association between prenatal exposure to pyrethroids and anthropometric and body composition parameters (Table 7). According to Lee et al. [36], there is no correlation between maternal urinary 3-PBA concentrations during pregnancy and growth and adiposity parameters in early childhood. On the other hand, maternal concentrations of pyrethroid metabolites, specifically cis-DBCA and trans-DCCA, were negatively associated with body weight and composition in boys [37]. In contrast, Kim et al. [38] highlighted that prenatal exposure to pyrethroids can reduce body fat in children at 5 years.

Three studies focused on the association between exposure to pyrethroids during pregnancy and the frequency of respiratory diseases in children (Table 8). To diagnose respiratory diseases and allergies, the recommendations of the International Study of Asthma and Allergies in

Table 7. Associations between prenatal pyrethroid levels and anthropometric parameters and body composition in children in on prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children studies published in 2015–2024

Reference	Assessment timepoint	Outcomes	Outcomes assessment	Observed effect	Association
Lee et al., 2019 [36]	4 years	adiposity, growth	anthropometric measurements (height, weight)	prenatal urinary 3-PBA concentration exhibited no association with growth and adiposity parameters in early childhood	no
Kim et al., 2022 [38]	5 years	height and weight, body fat percentage, waist circumference, blood pressure	anthropometric measurements, body composition analysis, blood pressure	prenatal urinary concentrations of cis-DBCA, cis-DCCA, trans-DCCA, 3-PBA were associated with reduced adiposity including lower BMI Z-scores, smaller waist circumference and lower body fat percentage; reductions in BMI Z-score were observed only among children born to mothers with adequate energy intake during pregnancy ($\beta_{cis\text{-}DCCA,\ trans\text{-}DCCA}$ –0.4, 95% CI: –0.7–(–0.1), $p_{interaction} = 0.03$ and 0.04, respectively) but there was no evidence of effect modification for the other measures of adiposity	positive
Coker et al., 2019 [37]	≤2 years	weight, body composition	anthropometric measurements	maternal urinary pyrethroid metabolite concentrations (particularly cis-DBCA and trans-DCCA) were negatively associated with body weight and body composition in young boys	negative

3-PBA – 3-phenoxybenzoic acid; cis-DBCA – cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; cis-DCCA – cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; trans-DCCA – trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid.

Table 8. Associations between prenatal pyrethroid levels and respiratory and allergic diseases in children in studies on prenatal exposure to pyrethroids on the course and outcome of pregnancy, health status, and neurobehavioural development of children published in 2015–2024

Reference	Children's age at allergic diseases assessment	Symptoms	Allergic disease assessment	Observed effect	Association
Gilden et al., 2020 [42]	4, 5, 8 years	wheezing, whistling in chest, FEV_1	questionnaire, spirometry	no association between prenatal 3-PBA metabolites and child respiratory health outcomes	no
Hu et al., 2022 [41]	6–8 years of age	atopic dermatitis, allergic rhinitis, asthma, lung function (FEV_1 (l), FVC (l), FEV_1/FVC (%), $FEF_{25–75\%}$ (l/s), PEF (l/s))	ISAAC, spirometry	maternal exposure to 3-PBA was associated with a slight decrease in FEV_1/FVC among children aged 6–8 years, an association slightly more pronounced in girls than in boys. (girls: β: –0.01, 95% CI: –0.02–(–0.002), p-trend 0.011)	negative
Islam et al., 2023 [40]	5 years	wheezing, asthma, dry cough, lower respiratory tract infection (LRTI)	ISAAC-III	no significant association between prenatal pyrethroid exposure and children respiratory and allergic health at 5 years of age	no

ISAAC-III – International Study of Asthma and Allergies in Childhood.
3-PBA – 3-phenoxybenzoic acid; $FEF_{25–75\%}$ – forced expiratory flow 25–75% of FVC; FEV_1 – forced expiratory volume in 1 s; FVC – forced vital capacity; PEF – peak expiratory flow.

Children (ISAAC) were used or a spirometry test was conducted [39,40–42]. The study group consisted of children aged 4–8 years. Studies by Gilden et al. [42] and Islam et al. [40] suggested no association between prenatal exposure to pyrethroids and respiratory health outcomes. Only Hu et al. [41] indicated that maternal urinary 3-PBA concentrations were associated with a small decrease in FEV_1/FVC in school-aged children.

Interpretation of the results

In summary, the reviewed studies demonstrated a variable relationship between maternal exposure to pyrethroids during pregnancy and the occurrence of adverse health effects in children.

The strongest evidence was noted for an increased risk of adverse behavioural outcomes and cognitive decline, which was also supported by the findings in the narrative review by Elser et al. [13] (papers published 2011–2022) and the systematic review by Andersen et al. [14] (papers published 2011–2021). However, the authors emphasize the need for further research to fully understand the neurodevelopmental effects of prenatal exposure on the compounds in question. The results should be interpreted with caution because of the limited number of studies that met the inclusion criteria and the variable effects of pyrethroid exposure during pregnancy on the course and outcome of pregnancy, weight and height of the child, and the incidence of respiratory diseases. We found no papers with previous works (before 2015) with the reviewed literature on the effects of prenatal exposure to pyrethroids on the occurrence of respiratory diseases or the development of obesity in children. In contrast, the results of 15 studies (papers published in 2003–2020) which analysed the relationship between prenatal exposure to pyrethroids and pregnancy outcome yielded mixed results [13].

Limited evidence and inconsistent results may be due to, the magnitude of exposure, the main routes of exposure, analytical methods, and the inability to separate the effects of exposure during fetal life from those occurring after birth. In addition, studies varied in the choice of health outcomes assessed (e.g., birth weight, low birth weight), the tools used to assess them (particularly in relation to neurodevelopmental outcomes and respiratory disease), and the age groups of children. It should also be noted that many studies characterized exposure based on the common metabolite for most pyrethroids, 3-PBA, which may makes it difficult to identify specific health effects for individual insecticides. In addition, most studies have relied on a single urine sample to assess exposure, which may not fully describe the exposure given the short half-life of pyrethroids in the body. The mechanisms linking the occurrence of adverse health effects in children to prenatal exposure to pyrethroids are not fully understood. Studies in animal models have provided evidence of the effects of pyrethroids on systems and processes critical for brain and nervous system development. The developing brain is particularly vulnerable to neurotoxic substances, and increased sensitivity occurs not only during fetal life but also after birth [43,44]. The main mechanism of action of pyrethroids is related to modification of sodium channel function (slower opening and closing), binding to voltage-gated calcium channels, chloride channels and the lambda-aminobutyric acid receptor chloride ionophore [45].

The biological mechanisms linking prenatal exposure to pyrethroids to reduced lung function in the offspring are not fully elucidated. It is noteworthy that a key stage of respiratory development occurs during the second and third trimesters of pregnancy and lasts until about 3 years of age, so exposure to environmental contaminants during this critical period for lung development may influence the occurrence of long-term health consequences. Furthermore, 3-PBA-induced disruptions in related systems – autonomic, neuroendocrine and immune – during perinatal development may increase susceptibility to airway inflammation and reactivity which can lead to

reduced lung function in late childhood and even adulthood [46,47].

The mechanisms linking prenatal pyrethroid exposure to anthropometric parameters and body composition are also unclear, possibly due to the small number of studies published available and inconsistent results in this area. The adverse effects of pyrethroid exposure on pregnancy outcome may be due to greater susceptibility to toxicity in rapidly growing and developing fetal organs and lower levels of detoxifying enzymes than in adults. However, it should be noted that the exact mechanism of the potential effects of prenatal exposure to pyrethroids on the course and outcome of pregnancy is not fully understood [48].

Knowledge and understanding of the mechanisms of action of pyrethroids is essential for both risk assessment and the development of strategies to minimize the occurrence of adverse health effects.

Strengths and limitations

This review aims to synthesize recent reports on the association between prenatal exposure to pyrethroids and the occurrence of adverse health outcomes in children. The majority of the studies included in this review are prospective cohort studies, which permit the tracking of changes in exposure levels and may provide evidence of a causal relationship between exposure and outcomes. Furthermore, a number of publications included in this review assessed multiple health effects and disorders (e.g., low birth weight, overweight/obesity, respiratory diseases, neurobehavioural and cognitive development) in children. This is crucial for a complete health risk assessment of prenatal exposure to pyrethroids.

The use of questionnaires to collect data on the prevalence and course of respiratory diseases and allergies in children has some important limitations, i.e., reduced reliability of the data (answers given by parents may be subjective and may not reflect the child's true health status), incompleteness of the data (parents may not remember all relevant details regarding symptoms, time of onset and response to treatment), flawed questionnaire design (questions in the questionnaire may be interpreted differently by respondents, resulting in inconsistencies in responses). Therefore, it is worth noting that to address the above limitations, Islam et al. [40] used a standard questionnaire (ISAAC study) to assess children's health status and Gilden et al. [42] and Hu et al. [41] additionally used clinical tests (spirometry).

The main limitation of the review is the small number of epidemiological studies that examined the association between prenatal exposure to pyrethroids and effects on pregnancy and pregnancy outcomes, weight and height, and incidence of respiratory disease in children, which did not allow firm conclusions to be drawn about the prevalence of associations. In addition, the characterization of exposure based on a single urine sample collected at different stages of pregnancy (pre-delivery, first, second, third trimester), different age groups of the children and different tools and methods used to assess the health outcomes analyzed may be a limitation that affects, the reliability of the exposure assessment and, the reliability of the observed health effects.

CONCLUSIONS

In conclusion, there is a considerable uncertainty regarding the adverse effects of prenatal exposure to pyrethroids on children's health. Further research is needed to understand the mechanisms of action and the effects of pyrethroids on the health of susceptible populations.

Author contributions

Research concept: Agnieszka Jankowska, Jolanta Dominowska

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