REVIEW ARTICLE

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Organ-Specific Toxic Effects and Biomarker Evidence of Pyrethroid in Vulnerable Populations: A Systematic Review

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Pyrethroid exposure through ingestion, inhalation, or dermal contact may trigger toxic effects in the human body, with severity potentially increasing in certain vulnerable populations. We aim to summarize the evidence regarding pyrethroid exposure and organ-specific toxic effects in children, pregnant and breastfeeding women, and the elderly. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this study. The search strategy was designed considering the population, exposure, controls, and outcomes (PECO). The scientific databases PubMed, Scopus, Google Scholar, and Science Direct were systematically searched for relevant literature published from 1990 to April 2025. Observational studies which meeting the inclusion criteria of were included. Two authors independently searched the database, assessed the risks of bias and extracted the data from the shortlisted articles. Out of the 7259 records collated, 25 studies were included in this review, there are 13 crossectional studies and 12 cohort studies. The studies investigated the related to the nervous system (n= 14), the endocrine system (n= 5), the lungs (n= 3), the reproductive organs (n= 2), and the auditory system (n= 1). The quality of the studies varied with overall grades derived from the bias analysis ranging from low to moderate bias. Selected articles revealed that the reproductive organs, lungs, ears, as well as the nervous and endocrine systems are particularly vulnerable to pyrethroid toxicity. All studies suggest a possible role for pyrethoid exposure and organ-specific toxic effects characterized by alterations in biochemical markers and organ function. Although further research is still needed, existing studies suggest that 3-phenoxybenzoic acid (3-PBA) is commonly used as a urinary biomarker of pyrethroid exposure.

Keywords: children, elderly, organ-specific effect, pregnant and breastfeeding women, pyrethroid

Introduction

Pyrethroid pesticides are extensively used in both household and agricultural environments. These compounds are synthetic derivatives of pyrethrins, which are natural insecticidal substances extracted from chrysanthemum flowers.[1] Pyrethroids, classified as synthetic organic insecticides, have been globally utilized since the 1980s due to their high efficacy and relatively low toxicity compared to organophosphate and carbamate pesticide groups.[2] The toxic effects of pyrethroids are primarily associated with their neurotoxic mechanisms, particularly

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their interference with the regulation of sodium and chloride ion channels. Although pyrethroids are generally regarded as safe due to their poor dermal absorption and rapid metabolism in humans compared to insects, recent studies have raised concerns regarding their potential toxicity in humans. These concerns include organ-specific effects such as endocrine disruption, delayed puberty, neurodevelopmental disorders, and respiratory conditions.[3–5]

Pyrethroid exposure may occur via ingestion, inhalation, or dermal contact, each of which can trigger toxic responses within the body 6. While pyrethroid toxicity has been examined in the general population, limited research has specifically explored its organ-specific effects in vulnerable groups such as children, pregnant and lactating women, and the elderly, despite their increased susceptibility. These populations possess distinct physiological and behavioral characteristics that heighten their vulnerability to pyrethroid exposure. Even without direct involvement in pesticide application, individuals in these groups may be exposed through environmental contamination, as pyrethroids can accumulate in the air and settle on surfaces in household settings.[7] The toxic effects of pyrethroids have been widely reported in clinical and epidemiological studies and are frequently associated with their metabolites. A case report described an association between pyrethroid exposure and acute pneumonitis in a 72-year-old woman, with histopathological evidence of edema and inflammatory cell infiltration in the alveolar septa.[8] Furthermore, a birth cohort involving 920 pregnant women reported a high prevalence of urogenital abnormalities among male offspring, including phimosis and hypospadias, with a relative risk of 1.58 (95% CI: 1.07–2.34).[9] Therefore, these findings highlight the urgent need for further investigation into pyrethroid-related health risks in vulnerable populations.

Previous studies assessing health effects of pyrethroids often relied solely on self-reported data via surveys or interviews.[10] This approach may have recall-bias, and may possible that exposure not only pyrethroid. Another hand, the usage of exposure biomarkers and pathological biomarkers is critical for guiding clinical and preventive interventions; however, inconsistencies in biomarker findings, such as those related to the impact of pyrethroid exposure on pubertal onset, remain controversial and unresolved.[5,11]

Considering the extensive literature on pyrethroid pesticide exposure and associated health problems, yet the limited number of synthesized reviews focused on specific populations, it is necessary to compile existing studies on pyrethroid exposure in paediatric, maternal (including breastfeeding women), and elderly populations to better understand its organ-specific toxic effects. Literature indicates that pyrethroids are widely used across various countries. In this context, the present study aims to conduct a systematic review of major published studies addressing the organ-specific toxic effects of pyrethroids in paediatric, maternal, and elderly populations. Additionally, data on exposure biomarkers and pathological biomarkers related to pyrethroid toxicity, as reported in the literature, are also presented.

Methods

Prior to conducting the literature search, a detailed review protocol was established following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). The PECO framework (Population; Exposure; Comparison condition; Outcome) was applied to arrange search strategy (**Table S1***: available as supplementary data*).

Search Strategy

The search for scientific publications in this review was searched using the PubMed and Scopus databases and also on Sciencedirect (https://www.sciencedirect.com/) and GoogleScholar (https://scholar.google.com) (Figure 1) following the PRISMA guidelines. Literature searching conducted in PubMed and Scopus on advance search using term Title/Abstract on PubMed or Article title, Abstract, Keyword on Scopus. The search terms entered were as follows: [Synonyms or truncation (*) for pediatric (0-18 years old), maternal and breastfeeding women, and geriatric (>60 years old)] AND [pyrethroid and its derivates (Pyrethroid* OR pyrethrin* OR dimefluthrin OR transfluthrin OR imiprothrin OR prallethrin OR deltamethrin OR cypermethrin OR permethrin OR allethrin OR cyhalothrin OR fenvalerate OR esfenvalerate)] AND [Synonyms or truncation (*) for organs or organ systems related to the integumentary (skin), skeletal, muscular, nervous, endocrine, cardiovascular, hematologic/ lymphatic/ immune, respiratory, digestive, renal, hepatic, reproductive, and sensory systems].

Eligibillity Criteria

All included articles were published between 1990 and April 2025 and were written in English. Publications reporting

adverse or toxic effects of pyrethroids on the human body were selected, with particular focus on: (1) populations including pediatric subjects (from birth to 18 years), pregnant and breastfeeding women, and geriatric individuals (60 years and older); (2) studies in which pyrethroids or their metabolites were measured in body fluids (blood or urine); and (3) clinically observable biological changes in organs or organ systems, including biochemical, functional, and structural parameters.

All observational studies (cross-sectional and cohort) published in English were included. However, descriptive or qualitative observational studies, as well as studies reporting adverse effects of pyrethroids due to accidental exposure, were excluded. We also excluded studies whose outcomes involved genetic changes, were associated with infections or cancer, or were associated with hereditary, or were not organ-specific (e.g., anthropometric measures, body mass index, nutrition status, etc.).

Screening, selection, and Data Extraction Process

Zotero ver6.0.36 was used to import all the references from the searched database and remove duplicates. Two reviewers (RA and JJ) independently assessed the quality of reporting in each study. A standard extraction format was used to extract the necessary data, such as first author, publication year, population & city, research design, measurable variable, result/finding, pyrethroid metabolite, observed organ, and siginifcant biomarker/clinical change. Statistical data, when available, were presented in result/findings as mentioned in the original article. Any screening, study selection, and data extraction disagreements were resolved through consensus.

Risk of Bias Assessment

Two independent reviewers assessed the quality of each included publication. The assessment was performed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist, specifically designed to appraise the methodological quality of crossectional, and cohort studies. The risks of bias were classified based on the total score; a score of 0 was assigned if the parameters coincided and 1 if they did not. The risk was low with a percentages of ≤ 25%, moderate at >25% and <50%, or high at ≥ 50% of total parameters. Only the articles with low and moderate risks of bias were included, (*Table S2: available as supplementary data*). Disagreements, if any, were resolved through discussion and consensus.

Results

A total of 7,259 records were identified through database searching. After removing 4,866 duplicates, 2,393 titles and abstracts were screened. Subsequently, 1,011 articles unrelated to pyrethroid exposure, 307 review articles, and 816 irrelevant studies (including qualitative observational studies, intervention studies in human, RCT protocols, intoxication case reports, and genetic, in-vitro, or animal studies) were excluded.

From 226 full-text articles assessed for eligibility, 33 were excluded due to inaccessible or unavailable full-texts, and 189 were excluded with the reasons: (1) absence of biochemical, functional, or structural organ changes as pathological biomarker measurements; (2) combined pesticide exposure without separate analysis of pyrethroid effects or no pesticide/metabolite analysis from body fluids; (3) study populations not including children (0–18 years), maternal, lactating, or geriatric individuals (>60 years), or lacking sub-analysis for these populations; and (4) outcomes not organ- or organ system-specific, or no association with the study outcome. In total, 25 articles met the eligibility criteria and were included in the review. A flowchart describing the selection of studies is shown in **Figure 1**, and the characteristics of each study are presented in **Table 1**.

Characteristics of Studies Included in the Review

Among the 25 studies published between 1990 and April 2025, 13 were cross-sectional studies and 12 were longitudinal cohort studies. Ten studies were conducted in the United States, seven in China, three in Africa, and one each in Denmark, France, South Korea, Spain, and Thailand. Result of the 25 studies, 13 involved pediatric populations, 10 focused on pregnant and breastfeeding women, and 2 targeted geriatric populations. Based on the target organ or organ system, 14 studies were related to the nervous system, 5 to the endocrine system, 3 to the lungs, 2 to the reproductive organs, and 1 to the auditory system.

Risk of Bias Assessment

The risk of bias across the 25 studies showed that 22 studies had a low risk of bias, while 3 studies had

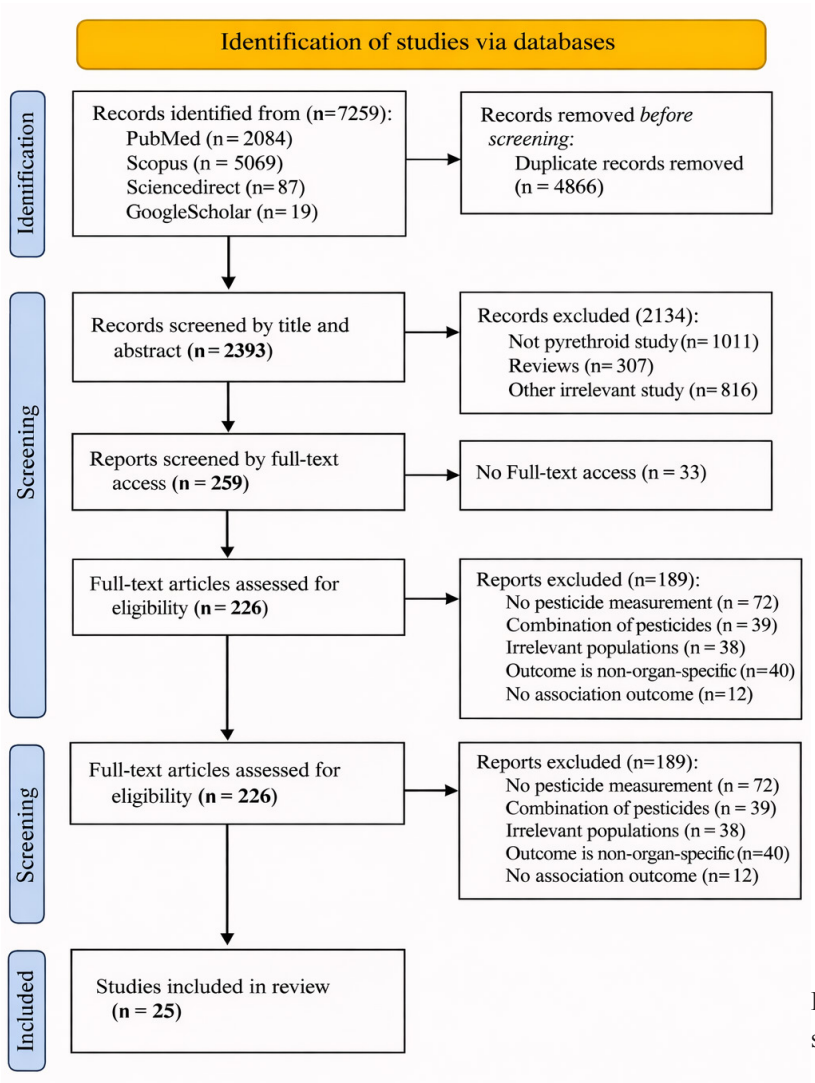

Figure 1. PRISMA flowchart of the study selection processs.

a moderate risk of bias. Risk of bias was identified in cohort studies due to their longitudinal or birth cohort design, which lacked a comparison between exposed and unexposed groups. Additionally, there were issues related to follow-up reporting, and some studies did not provide explanations for loss to follow-up.

General Characteristics

Table 1 summarizes the main characteristics of each study included in the review, including the authors and year of publication, study population, research design, measured variables, results/findings, exposure biomarker, and significant pathological biomarkers or clinical changes reported in the study.

Regarding exposure to the nervous system, seven studies were conducted in pediatric populations, six in pregnant and breastfeeding women, and one in a geriatric population. All 14 studies reported an association between pyrethroid exposure and impaired neuro-development and nervous system function. This was evidenced by the detection of urinary biomarkers such as 3-PBA, 4-F-3-PBA, cis-DBCA, cis-DCCA, or trans-DCCA, which indicated exposure to pyrethroids and were linked to adverse outcomes across several domains. These included declines in cognitive function (*e.g.*, reduced cognitive flexibility, lower full-scale IQ, slower processing speed, and diminished verbal comprehension, memory, and working memory), language and communication development (*e.g.*,cores, reduced expressive and receptive communication abilities, and impaired attention and inhibition control), motor and functions (*e.g.*, reduced locomotor skills and lower composite scores encompassing anguage, cognition).

Table 1. Characteristics of the article were included in review

Population & City	Research design	Measured variable	Result/ findings	Exposure biomarker	Observed organ	Siginifcant pathlogical biomarker	Ref
305 females adolescent (9-15 years old); China	Crossectional study	Physical pubertal development based on a series of external primary and secondary sexual characteristics	Negative association between 3-PBA level (1.42 ug/g creatinine) with later onset by being in breast stage-3 (B3), pubic hair stage-2 (P2) and delayed status of menarche	3-PBA	Reproductive organ	Delay onset of pubertal	[5]
215 pregnant woman; Limpopo, South Africa	Cohort Study with 1 year follow-up postpartum	Hypospadias in 1 year-old boys	cis-DCCA and trans-DCCA were associated with an increased risk for hypospadias (adjusted relative risk per 10-fold increase = 1.67 and 1.64) p-value <0.05	Cis-DCCA and trans-DCCA	Primary genital organ	Urogenital change (hypospadias)	[13]
797 pregnant women (10 – 15 GW); Denmark	Cohort Study with follow-up until gave birth (birth cohort study)	Tyroid hormone: TSH, fT4, fT3, and TPO antibody (TPOab) levels in serum of 12 weeks gestational	3-PBA tertile (>0.37 ng/ml) assoaciated with fT3 hormone level (p-value<0.05)	3-PBA	Endocrine system	Increase of fT3 hormone level in serum	[19]
463 males adolescent (9 – 16 years old); Hangzhou, Zhejiang, China	Cross-sectional study	Reproductive hormone: LH and FSH hormone levels Pubertal development based on Tanner stages and testicular volume	A positive association between 3-PBA and gonadotropins was found ($p < 0.001$), in which a 10% increase in 3-PBA was associated with a 2.4% and 2.9% increase in LH and FSH. And also increase genitalia stage G3 and G4, and testicular volume ($p<0.05$)	3-PBA	Endocrine system and reproductive organ	Increase LH and FSH hormone levels, and increase genitalia stage and testicular volume	[11]
717 Pregnant women (3 nd trimester) ; Limpopo,South Africa	Cohort Study with follow-up until gave birth (birth cohort study)	Thyroid hormones:TSH and T4 hormone levels in blood	Cis-DBCA, trans-DCCA, and 3-PBA were positively assoaciated with increase TSH levels 10.6% (0.5, 20.9); 12.3% (3.0, 23.3); and 14.0% (0.5, 30.2)	Cis-DBCA, trans-DCCA, and 3-PBA	Endocrine system	Increase TSH hormone levels in blood	[20]
134 males adolescent (15-17 years old); Granada, Spain	Cross-sectional study	Reproductive hormones: E2, DHEAS, SHBG, LH, FSH, AMH, and prolactin Tyroid hormones: fT4, TT3, TSH, IGF-1, ACTH, and cortisol	Positive associations between detectable 3-PBA (percentile 95 th is 0.253 ug/ml) and TT3 ($p<0.05$)	3-PBA	Endocrine system	Increase of TT3 hormone level in blood	[21]
400 pregnant womans; Costa Rica, America	Cohort Study with 10 weeks follow-up	Tyroid hormones: TSH, fT4 and fT3 hormone levels in serum	For the late-effect analysis, metabolites of pyrethroids (DCCA and 3-PBA was associated decreased TSH (non-linear regression)	DCCA and 3-PBA	Endocrine system	Lower of TSH hormone level	[14]
1023 children (6–11 years), 974 adolescents (12–19 years); Canada	Cross-sectional study	Lung function parameters: FVC, FEV1, FEV1 /FVC ratio and FEF 25-75%	Pyrethroid exposures (geometric mean of Σ PYR children= 3.56 nmol/g; of ΣPYR adolescent= 2.80 nmol/g) were associated with lower FEV_1($p=0.045$) 0.045) in children and lower FVC ($p= 0.05$) in adolescents	3-PBA, Cis-DCCA,Trans-DCCA	Lungs	Lower FEV $_1$ and FVC	[16]

Abbreviation: Gestational week [GW]; 3-phenoxybenzoic acid [3-PBA]; 4-fluoro-3-phenoxybenzoic acid [4-F-3-PBA]; Cis- or Trans-(3- (2,2- dichlorovinyl)- 2,2- dimethylcyclopropanecarboxylic acid) [Cis- or Trans-DCCA]; Cis-2,2-(dibromo)-2-dimethylvinyl-cyclo-propane carboxylic acid [Cis-DBCA]; gamma-aminobutyric acid [GABA]; Testosterone, 17 β -estradiol [E2]; dehydro-epiandrosterone sulfate [DHEAS]; sex hormone binding globulin [SHBG]; luteinizing hormone [LH]; follicle stimulating hormone [FSH]; anti-Müllerian hormone [AMH]; free triiodothyronine [fT3]; free thyroxine [fT4]; total triiodothyronine [TT3]; thyroid stimulating hormone [TSH]; insulin growth factor 1 [IGF-1], adrenocorticotropic hormone [ACTH]; forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC]; peak expiratory flow [PEF]; forced expiratory flow between 25% and 75% of FVC [FEF25-75%].

Indones J Basic Clin Stud. 2026; 1(1): 59-75

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Table 1. Characteristics of the article were included in review (continue).

Population & City	Research design	Measured variable	Result	Exposure biomarker	Observed organ	Siginifcant pathlogical biomarker	Ref
1174 children (6-17 years old); America	Cross-sectional study	Lung function parameters: FVC, FEV1, PEF	3-PBA (Geometricmean = 0.46 ug/L) associated with lower FEV 1:FVC ratio in girls (p=0.035) and lower PEF in boys adolescent (p=0.045)	3-PBA	Lungs	Lower FEV1:FVC and PEF	[15]
559 elderly (>60 years old); Seoul, Korea	Cross-sectional study	Lung function parameters: FVC, FEV1, and FEF25-75%	The FEV 1 (p-value < 0.01) and FVC p-value < 0.01) of females elderly (79.1% of participant) showed significant reductions by an increase of 3-PBA level (Geometric mean= 1.25 ng/mL)	3-PBA	Lungs	Lower FEV1 and FVC	[17]
720 adolescent (12-19 years old); America	Cross-sectional study	Pure-tone average	Pyrethroid exposure was significantly associated with increased hearing thresholds in both ears, indicating a higher risk of hearing loss. Adolescents in the highest tertile of urinary 3-PBA levels (≥ 0.52 μg/g creatinine) had over three times the odds of hearing loss (OR 3.12, 95% CI: 1.42–6.83) compared to those in the lowest tertile (<0.18 μg/g creatinine).	3-PBA	Ears	Increase of hearing threshold	[18]
263 children; Yunnan, China.	Cohort Study of (1 st trimester) with follow-up 1 year until 4 years postpartum	Neurodevelopment parameters: locomotor subscale, the personal social subscale, the language subscale, the eye-hand coordination subscale, the performance subscale, and the practical reasoning subscale	Higher 3-PBA level at 2-year- old was negatively associated with the quotient in locomotor (β= -14.61, 95 % CI: -24.93, -4.30) and language (β= -10.89, 95 % CI: -19.38, -2.41)	3-PBA, 4F-3PBA, DBCA	Nerveous system	Decrease of locomotor and language development	[22]
80 children; Bangkok, Thailand	Cross-sectional study	Urine GABA concentration	The 3-PBA concentration (1.46 ug/mL) was negatively correlated with GABA concentration (p < 0.05)	3-PBA	Nerveous system	Lower GABA concentration	[12]
179 children (mean age: 3.2 years old); Canada	Cohort Study with 2 years follow-up (2013-2015)	Neurodevelopment parameters: Behavioral outcomes and cognitive domains using WPPSI-III and BRIEF-P scales	Higher concentrations of cis-DBCA (median 0.02 ug/L) were significantly associated with lower verbal, performance and full-scale IQ scores in boys; 3-PBA (0.39 ug/L) was associated with lower verbal IQ scores; higher concentrations of cis-DCCA (0.12 ug/L) was assoaciated poorer BASC-2 Adaptive Skills scores with	cis-DBCA, cis-DCCA, trans-DCCA, 3-PBA, 4-F-3-PBA	Nerveous system	Lower verbal performance, adaptive skills and full-scale IQ	[23]
140 children; Costa Rica, America	Cross-sectional study	Neurodevelopment parameters: Cognitiveabilities, behavioral problems, sensory function (color discrimination), perception and memory, and motor function	Higher 3-PBA concentrations (median 0.8 ug/L) were associated with poorer processing speed scores, particularly in girls (β= -8.8, 95%CI: -16.1, -1.4).	3-PBA	Nerveous system	Lower processing speed score in cognitive abilities	[24]
140 children; Costa Rica, America	Cross-sectional study	Neurodevelopment parameters: Cognitiveabilities, behavioral problems, sensory function (color discrimination), perception and memory, and motor function	Higher 3-PBA concentrations (median 0.8 ug/L) were associated with poorer processing speed scores, particularly in girls (β= -8.8, 95%CI: -16.1, -1.4).	3-PBA	Nerveous system	Lower processing speed score in cognitive abilities	[25]

Table 1. Characteristics of the article were included in review (continue).

Population & City	Research design	Measured variable	Result	Exposure biomarker	Observed organ	Siginifcant pathlogical biomarker	Ref
241 children; Uruguay, South America	Cross-sectional study	Cognitive abilities parameters measured by IED scores	3-PBA (median 3.44 ng/mg creatinine) was inversely associated with IED Scores − 0.07 [−0.10, −0.04]	3-PBA	Nerveous system	Lower cognitive flexibility	[26]
336 elderly (60–84 years); America	Cross-sectional study	Cognitive function score	High concentration of 3-PBA (>0.30 µg/g creatinine) were associated with lower scores of cognitive function (−3.83 95% CI :−7.11,−0.54)	3-PBA	Nerveous system	Lower cognitive function	[27]
752 Pregnant woman; Limpopo, South Africa	Cohort Study with follow-up from early stage of labor until child at 1 and 2 years old	Neurodevelopment parameters: Cognitive, Language (Receptive and Expressive), Motor (Fine and Gross) and Social-emotional scores	Cis-DCCA, trans-DCCA, and 3-PBA were associated, respectively, with a − 0:70 (95% CI: −1:25, −0:15), −0:49 (95% CI: −0:96, −0:02), and −0:65 (−1:23, −0:06) decrement in Social-Emotional scores at 1 y of age. Maternal cis-DBCA levels was associated with significant decrements at 2 y of age in Language Composite scores and Expressive Communication scores	cis-DCCA, trans-DCCA, Cis-DBCA and 3-PBA	Nerveous system	Lower social-emotional, Language composite and expressive communication score	[28]
406 children (3–6 years); Nanjing, China	Cross-sectional study	Neurobehavioral parameters: Chinese Binet test, arithmetic test, picture completion test, maze test and cancellation test.	Higher urinary 3-PBA levels (geometric mean = 0.08 ug/g creatinine) were significantly associated with lower cancellation test scores, the Chinese Binet and arithmetic tests ($p<0.01$)	3-PBA	Nerveous system	Lower memory, ability concentration, and verbal discrimination	[29]
3421 pregnant women (GW<16); Brittany, Fance	Cohort Study with follow-up from GW <19 until 6 years old of child (Birth cohort study).	Cognitive development parameters: Verbal comprehension and working memory index	3-PBA and cis-DBCA concentrations were both negatively associated with verbal comprehension scores (P-trend = 0.04 and P-trend b 0.01, respectively) and with working memory scores (P-trend = 0.05 and P-trend b 0.01, respectively).	3-PBA and cis-DBCA	Nerveous system	Lower verbal comprehension and working memory	[31]
520 children (11-17 years); Ecuador, South America	Cross-sectional study	Neurobehaviour parameters: attention &inhibitory, language, memory & learning, visuospatial processing	The pyrethroid, 3-PBA was inversely associated with Language (β 50% = -0.13 [95%CI: -0.19, -0.01]) and had a negative quadratic association with Attention/Inhibitory Control.	3-PBA	Nerveous system	Lower language score, and attention/inhibition scores	[32]
419 pregnant woman (GW <12 $^{+6}$); Xuanwei, Southest China	Cohort Study with follow-up from GW <19 until 1 year postpartum	Neurodevelopment parameters: Cognition, Language, Motor, Social-Emotional, Adaptive Behavior	in the first trimester, Cognition and Motor scores were inversely associated with higher cis-DBCA [β= 7.19 (95% CI= -12.97, -1.41) and β= -8.20 (95% CI= -13.35, -3.05), respectively], Language scores were inversely associated with higher 3-PBA [β = -6.01 (95% CI= -10.96,1.06)]; in the second trimester, Cognition scores were inversely associated with higher cis-DBCA [β= -6.64 (95% CI= -12.51, -0.76)], Language scores were inversely associated with higher 3-PBA [β= -5.17 (95% CI= -10.07, -0.27)] and cis-DBCA [β= -5.40 (95% CI= -10.28, -0.52)].	3-PBA, 4-F-3-PBA, Cis-DBCA	Nerveous system	Lower language, cognition, and motoric scores	[33]

Only one study specifically examined the association between pyrethroid exposure and neurochemical parameters in urine. Kunno et al.[12] found a negative correlation between urinary levels of the neurochemical compound GABA and concentrations of 3-PBA in young children living in Bangkok. This finding suggests that increased urinary levels of 3-PBA, a biomarker of pyrethroid exposure, were associated with decreased GABA levels.[12]

Regarding exposure to the endocrine system, puberty, and reproductive organs, seven studies reported the effects of pyrethroid exposure on reproductive and thyroid hormone levels, as well as pubertal development. The outcomes related to pubertal disorders and reproductive organ maturation, such as hypospadias.[5,13] The remaining five studies reported disruptions in hormonal levels associated with pyrethroid exposure, including increased concentrations of fT3, TT3, LH, FSH, and TSH, as well as disturbances in the onset of puberty. Only one study reported that pyrethroid exposure was negatively associated with TSH levels.[14]

Three studies have reported on the effects of pyrethroid exposure on respiratory disorders, all of which found a correlation between pyrethroid exposure and decreased pulmonary function parameters, including FEV1, FVC, and PEF.[15,16] One of these studies focused on a geriatric population (>60 years), reporting that 79.1% of participants experienced significant declines in FEV1 and FVC ($p < 0.01$) in association with increased urinary concentrations of 3-PBA.[17]

Only one study included in this review reported the effects of pyrethroid exposure on the auditory system. A cross-sectional study conducted on a population of 720 adolescents, found a positive association between urinary 3-PBA levels and increased hearing thresholds, which may indicate a risk of hearing loss. The study compared hearing thresholds between adolescents in the lowest tertile of 3-PBA concentration (< 0.18 µg/g creatinine) and those in the highest tertile (≥ 0.52 µg/g creatinine).[18]

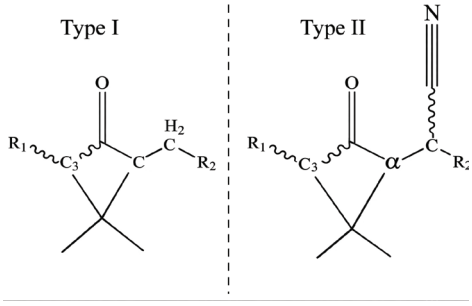

Figure 2. Alpha-cyano moiety in type-II pyrethroid structure.[35]

Discussions

Classification and Biotransformation of Pyrethroids in Humans

Pyrethroid devided into two groups based on chemical composition (presence of alpha-cyano moiety at the alpha-position), there are type-I lack an alpha-cyano group while type-II have alpha-cyano group in their structure.[2] At **Figure 2** illustrates the alpha-cyano group, which is a functional group characterized by a -C≡N structure attached to the alpha carbon atom.[35] Alpha-cyano play role to increase insectisidal properties. Therefore, type-I pyrethroid (*e.g.*, allethrin, resmetrhin, permethrin, transfluthrin, etc) more commonly used as household pesticides, while type-II (*e.g.*, deltamethrin, cypermethrin, cyhalothrin, etc) can be used even as agriculture pesticides.[36]

Pyrethroid are lipid soluble and photostable, any contact with the skin, digestive or respiratory tract result in their penetration into the body, although penetration in influence by the permability of the barrier.[1,37]Pyrethroid are generally rapid metabolized, major metabolic reaction have been found to be oxidation of the acid or alcohol moety, hydrolysis, and conjugation reaction.[38,39] A previous study conducted an experimental investigation comparing the metabolism of pyrethroids in rat and human hepatic microsomes. The study reported that microsomal metabolism in rats occurs more rapidly than in humans. There are notable differences in the isoforms involved in microsomal pyrethroid metabolism: in rats, it primarily involves CYP1A1, CYP2C6, CYP2C11, CYP3A1, and CYP3A2, whereas in humans, CYP2C19 exhibits the highest pyrethroid-metabolizing activity. In general, microsomal metabolism of pyrethroids involves both oxidation and hydrolysis. However, certain pyrethroids such as cis-permethrin, bifenthrin, and S-bioallethrin undergo predominantly oxidative metabolism, while hydrolysis is more common for compounds like bioresmethrin and cypermethrin.[40]

Many researchers have reported that the biotransformation of pyrethroids involves ester hydrolysis mediated by esterases/carboxylesterases and oxidation by several cytochrome P450 (CYP) enzyme isoforms,

including CYP2C9 and CYP3A4 in humans.[41]Among the resulting metabolites, 3-phenoxybenzoic acid (3-PBA) is the major compound most frequently detected in urine as a primary metabolite of pyrethroid derivatives. However, other metabolites can also be found in urine, such as 4-fluoro-3-phenoxybenzoic acid (4-F-3-PBA), cis- or trans-(3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid) (cis- or trans-DCCA), and cis-2,2-(dibromo)-2-dimethylvinyl-cyclopropane carboxylic acid (cis-DBCA).[42,43]

From the 25 articles reviewed, 24 of them utilized 3-PBA as a urinary biomarker for pyrethroid exposure. The 3-PBA metabolite is formed through ester bond cleavage in the pyrethroid structure, followed by oxidation reactions. As a result, 3-PBA can be detected as a common metabolite of various pyrethroids such as cypermethrin, deltamethrin, permethrin, cyhalothrin, and others.[44] In particular, 3-PBA is a metabolite derived from at least 20 different pyrethroid insecticides. In contrast, 4-F-3-PBA is a more specific metabolite that is exclusively formed from cyfluthrin. Additionally, permethrin, cypermethrin, and cyfluthrin can generate small amounts of cis- or trans-DCCA isomers, while DBCA is a metabolite specific to deltamethrin. Therefore, 3-PBA metabolite is considered the primary biomarker of choice when the specific type of pyrethroid exposure is unknown.[45–47]

Inter-organ Axis and Possible Mechanism of Pyrethroid Toxicity

The toxic effects of pyrethroids on organs are complex and remain challenging to fully elucidate, although several studies have linked these effects to inter-organ axis phenomena. Previous research has suggested the endocrine-disrupting effects of pyrethroids on the hypothalamic–pituitary–gonadal (HPG) axis. The human reproductive system is regulated by the HPG axis, which controls ovarian and uterine cycles in females and spermatogenesis in males [48]. Another study reported the toxic effects of deltamethrin on the neuro-organ axis in the auditory system, which were associated with neuroinflammation characterized by increased levels of neurofilament light chain (Nf-L) in the auditory cortex, ultimately leading to hearing impairment.[49] The microbiome–gut–brain axis has also been implicated, whereby pyrethroid exposure alters the gut microbiome, resulting in disrupted metabolism, including the synthesis and degradation of vitamins, amino acids, lipids, bile acids, and neurotransmitters. These alterations may affect the regulation of blood–brain barrier (BBB) development and influence the function of microglia and astrocytes.[50]

Inter-organ axis phenomena may occur in a discontinuous manner, and the precise mechanisms underlying pyrethroid toxicity have not yet been fully clarified. Nevertheless, several studies have broadly categorized pyrethroid-induced toxicity based on target-mediated toxicity where adverse outcomes arise from exaggerated pharmacological actions at the intended molecular target (on-target toxicity)—and non-target-mediated toxicity, which involves non-specific cellular damage such as oxidative stress, mitochondrial dysfunction, genotoxicity, and immune-mediated mechanisms (off-target toxicity).[51] Some studies have proposed that pyrethroid toxicity is mediated through actions analogous to those on voltage-gated sodium channels (VGSCs), resulting in continuous nerve firing (persistent depolarization) and paralysis.[52] However, other studies have challenged this hypothesis, citing differences in VGSC isoform composition and sensitivity to pyrethroids between insects and mammals.[53]

The characteristic toxic effects of pyrethroids are further classified based on the presence of an α-cyano moiety. Type I pyrethroids are associated with T-syndrome, presenting with symptoms such as tremors, incoordination, prostration, and seizures. A case of transfluthrin poisoning in a 25-year-old man was reported with hallmark symptoms of uncontrolled tonic–clonic seizures.[54] In contrast, Type II pyrethroids are associated with choreoathetosis syndrome (CS-syndrome), characterized by hyperactivity, hunched posture, salivation, tremors, and incoordination progressing to sinuous writhing movements.[55] These findings are consistent with *in vivo* studies in rats exposed to deltamethrin at a dose of 25 mg/kg, which exhibited tremors and hypersalivation.[56]

However, mechanistic hypotheses of pyrethroid toxicity extend beyond VGSC agonism. Several studies have reported off-target mechanisms involving oxidative stress and mitochondrial dysfunction resulting from excessive reactive oxygen species (ROS) production. In cases of pyrethroid-induced hearing loss, oxidative stress has been associated with increased lactate levels, leading to inner ear damage and an increase in pure-tone average (PTA), indicative of hearing impairment.[49] Exposure of Sprague–Dawley rats to cypermethrin resulted in pulmonary toxicity marked by elevated malondialdehyde (MDA)

levels and decreased activities of glutathione peroxidase (GSH), superoxide dismutase (SOD), and catalase (CAT). Additionally, cypermethrin induced apoptosis by regulating caspase-3 and Bax expression and downregulating Bcl-2 57. Hussein et al. (2011) further confirmed that cypermethrin exposure increased MDA levels while reducing GSH content and antioxidant enzyme activities in rat brain tissue. These changes were accompanied by histopathological alterations, DNA damage, and decreased activities of acetylcholinesterase and monoamine oxidase (AChE and MAO) in the brain 58. Deltamethrin exposure has also been linked to reproductive toxicity in rats, including reduced sperm count and motility, as well as decreased levels of testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) in the testes. Moreover, the activities of GSH, SOD, CAT, glutathione S-transferase (GST), glutathione reductase (GR), and glutathione peroxidase (GPx) were reduced in the testes, liver, and kidneys of deltamethrin-exposed rats.[59] Overall, although the mechanisms underlying pyrethroid toxicity have not yet been fully elucidated, available evidence suggests that these effects involve both disruption of neuronal depolarization via VGSCs and organ-specific oxidative stress, which may collectively contribute to inter-organ axis dysfunction.

Organ-Specific Toxicity and Pathological Biomarkers of Pyrethroid Exposure

The toxic effects of pyrethroid exposure may similar with time-cumulative toxicity princile, which low-dose exposure frequently over time can lead to adverse outcomes. This may involve compounds that slowly reversible bind to specific receptors or biological processes, resulting in cumulative effects with time of exposure.[60] Disruptions to biological processes may manifest as alterations in biochemical, organ function, or structural changes in both specific and non-specific organs.[61]

Nerveous System

Several studies have linked the neurotoxic effects of pyrethroids to two distinct syndromes: the "T syndrome" associated with type I pyrethroids and the "CS syndrome" associated with type II pyrethroids 2. Type I pyrethroids are typically associated with tremor-related symptoms, whereas type II pyrethroids are linked to choreoathetosis and salivation. Although both types exert their effects primarily through interactions with voltage-gated sodium channels in the nervous system, their mechanisms differ. Type I pyrethroids tend to bind to sodium channels in a reversible but short-lived manner, leading to repetitive depolarization. In contrast, type II pyrethroids exhibit more prolonged and less reversible binding, which also interferes with GABAergic signaling.[62] Furthermore, a study by Clark et al. demonstrated that the CS syndrome is also associated with increased calcium ion influx and enhanced glutamate neurotransmitter release.[63]

Our findings from 14 studies (**Table 1**) indicate that pyrethroid exposure is negatively associated with neurodevelopment, neurobehavior, and nervous system function, particularly in the domains of cognitive function, language and communication development, motor and psychomotor skills, and emotional and social functioning. These findings are consistent with the mechanism by which pyrethroids bind to the α subunit of voltage-gated sodium channels (VGSCs), disrupting their normal function and holding them open, thereby causing neuronal hyperexcitability. Similarly, Type II pyrethroids such as deltamethrin can also inhibit GABA receptors and voltage-gated chloride channels, further enhancing neuronal excitability. These conditions may underlie the pathogenesis of neurodevelopmental and neurobehavioral disorders, potentially contributing to intermediate pathways associated with symptoms of ADHD and autism. The case-control study conducted by Von Ehrenstein et al., involving 2,961 children, reported that prenatal exposure to permethrin was associated with an increased risk of autism and intellectual disability, with an odds ratio (OR) of 1.46 (95% CI: 1.20–1.78).[64,65]

Reproductive Organ and Endocrine System

Several studies have reported that pyrethroid exposure is associated with hyperthyroidism. Hypothyroidism is defined as an elevated TSH level accompanied by normal or decreased levels of T3 and T4. Structurally, pyrethroids and some of their metabolites, including 3-PBA, share similarities with thyroid hormones, namely thyroxine (T4) and triiodothyronine (T3).[19]

Based on **Table 1**, four studies reported increased levels thyroid hormones (TSH, fT3 or TT3) associated with pyrethroid exposure . However, a study by Corrales Vargas et al. (2022) reported a non-linear decrease in TSH levels in relation to urinary 3-PBA concentrations.[14] Interestingly, previous studies also reported that pyrethroid exposure was associated with lower T3 or T4 levels 66,67. Based on **Table 1** suggested that the association between 3-PBA and increased fT3 was influenced by the absence of thyroid

peroxidase antibodies (TPOab), which are commonly linked to autoimmune thyroid disease.[19] Meanwhile, in **Table 1** also reported that increased TT3 levels were associated with low pyrethroid concentrations (95th percentile = 0.253 µg/L) and a low detection frequency (19.4%) in a population of 134 participants.[21] Furthermore, a systematic review and meta-analysis conducted by Sirikul and Sapbamrer, which analyzed six studies, revealed that pyrethroid exposure was associated with an increased risk of hypothyroidism (adjusted odds ratio [aOR] = 1.15, 95% CI: 1.03–1.28), characterized by elevated TSH levels with normal or reduced levels of T3 and T4.[68]

On the other hand, the association between pyrethroid exposure and reproductive hormones as well as pubertal sign has been reported in three studies, there are increased levels of LH and FSH and disturbances in pubertal onset (**Table 1**). Physiologically, puberty is regulated by the secretion of gonadotropin-releasing hormone (GnRH), which stimulates FSH and LH secretion. In boys, FSH supports spermatogenesis, while LH stimulates Leydig cells to produce testosterone and androstenedione. In girls, FSH promotes ovarian follicle growth and estradiol synthesis, whereas LH stimulates androgen production by theca cells.[69] These gonadotropins (FSH and LH) further initiate physical changes such as the development of pubic hair, breast tissue, testicular volume, and the onset of menarche.

An animal study found that pyrethroid exposure did not affect GnRH gene expression but influence FSH and LH gene expression.[70] Furthermore, male and female adolescents revealed contrasting associations between pyrethroid exposure and pubertal timing, early puberty onset in males but delayed onset in females.[5,11] Consistently, these findings align with a meta-analysis which reported no statistically significant association between exposure to persistent organic pollutants (POPs) and pubertal timing in boys (RR: 1.18; 95% CI: 0.99–1.40; p=0.070), but a significant association with delayed pubertal timing in girls (RR: 0.85; 95% CI: 0.79–0.91; p<0.001).[71]

Respiratory System

Reduced pulmonary function (as indicated by lower FVC, FEV1, and PEF values) due to pyrethroid exposure has been reported in three studies (**Table 1**.), involving both pediatric and geriatric populations. Pyrethroid exposure in individuals with asthma has also been associated with increased disease severity.[72] This decline in pulmonary function is thought to be linked to the neuroexcitatory effects of pyrethroids on the respiratory tract. An experimental study in rats demonstrated that cyfluthrin triggered neuroexcitatory afferent sensory stimulation originating from peripheral nociceptors in the upper respiratory tract. An enxperimental study in rats, menunjukkan bahwa Cyfluthrin-induced neuroexcitatory afferent sensory stimulus from peripheral nociceptors in the upper respiratory.[73]

Two possible mechanisms may underlie the pulmonary toxicity of pyrethroids in humans. First, pyrethroids predominantly function by blocking voltage-gated sodium channels in insects. Several mammalian voltage-gated sodium channel isoforms are similarly sensitive to pyrethroid exposure, albeit with reduced sensitivity. Sodium transport channels present in alveolar epithelial cells types I and II may be disrupted by pyrethroids, disturbing osmotic balance and potentially resulting in mucosal or bronchial epithelial edema. Second, pyrethroids are metabolized through cytochrome P450 enzymes. At high concentration, these compounds may exeed enzymatic metabolic capacity, induce of oxidative stress and subsequent cytotoxicity. Animal models have shown that high-dose pyrethroid exposure can cause pulmonary edema, interstitial inflammation, and lymphocyte infiltration in lung tissue.[74]

Auditory System

The study of pyrethroid exposure on the risk of hearing loss are insufficiently studied, then underlying mechanisms still unclear. Hearing loss is defined as an increase in pure-tone average (PTA) >15 dB.[18] An experimental study in rats reported that cypermethrin 0.25 mg/L significantly decreased the amplitude of Distortion Product Otoacoustic Emissions (DPOAE), a commonly used method for assessing cochlear and inner ear cell damage.[75] The decline in auditory function may be associated with the neurotoxic effects of pyrethroids, which interfere with the activity of voltage-gated sodium channels (VGSCs). Consequently, certain pesticides may impair both cochlear function and central auditory pathways by disrupting the regulation of acetylcholine release in muscle tissue. This disruption occurs through the blockade of VGSCs involved in mediating the stapedius muscle reflex, a key protective mechanism of the middle ear.[76] Another theory explain that pyrethroids may contribute to ROS production, as they are primarily metabolized in the liver by enzymes such as cytochrome P450s and carboxylesterases, leading to the generation of reactive oxygen species (ROS) that can induce

oxidative stress and damage inner ear cells, particularly when exposure exceeds the body's metabolic capacity.[77]

Susceptibility of Vulnerable Populations to Pyrethroid Toxicity

The use of insecticides in indoor or agricultural environments poses a significant risk to human health, particularly for pregnant women, children, and the elderly. These populations have distinct physiological characteristics and behavioral patterns that make them more vulnerable to pyrethroid exposure. Although they may not be directly involved in agricultural or household pesticide application, these chemicals can accumulate in the air and settle as residues on household surfaces.[7] One study examined pyrethroid exposure by analyzing hand wipe samples and urinary 3-PBA levels in 80 children aged 2–3 years. The findings revealed that increased levels of 3-PBA metabolites were significantly associated with elevated cypermethrin levels in hand wipe samples. Additionally, gender and the frequency of walking barefoot indoors showed significant associations with urinary 3-PBA concentrations ($p=0.035$ and $p< 0.01$, respectively).[78] Unintentional ingestion by children may be at a considerably higher dose than an adult because of the greater intake of food or fluids per pound of body weight. Children exhibit frequent hand-to-mouth activity, and this is an important source of increased exposure in comparison with adults.[7]

Pregnant and breastfeeding women are closely associated with embryogenic processes and nutrient transfer through breast milk. Consequently, exposure to organic pollutants, including pyrethroids, has been frequently reported to interfere with embryogenesis, particularly during the first and second trimesters. Additionally, due to their hydrophobic nature, pyrethroids can be excreted through breast milk during lactation, as they can easily penetrate biological membranes. A study by Corcellas et al. reported pyrethroid concentrations in the breast milk of lactating women in Brazil ranging from 1.45 to 24.2 ng/g lipid weight.[79] In elderly individuals, physiological decline occurs across multiple organ systems, diminishing the body's capacity to maintain homeostasis under stress. Pyrethroid exposure has been linked to oxidative stress, resulting in the generation of reactive oxygen species (ROS). These free radicals accumulate over time, causing cellular damage and promoting cellular senescence, while the elderly exhibit diminished antioxidant defense and regenerative capacity.[80]

Clinical Implications and Recommendations

Pyrethrins are natural compounds, whereas pyrethroids are synthetic and tend to be more toxic. Exposure to high doses, primarily through ingestion, inhalation, and, less commonly, skin contact, can lead to toxicity. In severe cases, the symptoms may mimic those of other insecticide poisonings, making diagnosis and treatment more challenging. Managing toxic exposure to pyrethroids or pyrethrins involves careful monitoring, observation, and supportive treatment. It is common for patients to be unable to specify the insecticide involved. Early management should always include decontamination to limit further toxicity and reduce the risk of secondary exposure to medical personnel. Previous reports have noted that the hydrocarbon solvents in pyrethroid-based insecticides can lead to chemical pneumonitis, potentially resulting in respiratory failure and death following ingestion. Patients showing signs of respiratory distress should be given supplemental oxygen and closely observed. Skin exposed to the substance should be washed with soap and water to alleviate local irritation. Paresthesia has been treated with topical vitamin E, although this condition typically resolves on its own within 24 hours.[6]

The World Health Organization (WHO) advises that permethrin concentrations in drinking water should not surpass 20 micrograms per liter (μg/L). The Occupational Safety and Health Administration (OSHA) sets regulations for pyrethrin levels in workplace air, with an occupational exposure limit of 5 milligrams per cubic meter (mg/m^3) over an 8-hour workday within a 40-hour workweek. The Environmental Protection Agency (EPA) has also established recommended daily oral intake limits for ten different pyrethroids, ranging from 0.005 to 0.05 milligrams per kilogram of body weight per day.

Diagnosing severe pyrethroid poisoning can be difficult due to its clinical features closely resembling those of organophosphate toxicity. Currently, there is no specific antidote available, and most cases result in mild symptoms. Thorough washing of the skin with soap and water is a crucial step in managing dermal exposure. In patients presenting with systemic toxicity, treatment should prioritize stabilization of airway, breathing, and circulation. This may involve intravenous fluid resuscitation for hemodynamic support, oxygen therapy, decontamination to limit further absorption, and strategies to enhance toxin elimination. If ingestion has occurred

within one hour, administration of activated charcoal (50–100 g for adults) may be considered. Gastric lavage is not advised, as the solvents in many pyrethroid products pose a risk of chemical pneumonitis. A Cochrane review has shown that intravenous lorazepam is more effective than diazepam in stopping seizures and is preferred for treating prolonged convulsions. In cases of status epilepticus, a recent animal study found intravenous phenobarbital to be more effective than phenytoin.[81]

This systematic review underscores growing evidence that pyrethroid exposure, even at low levels is associated with organ-specific toxic effects in vulnerable populations, including children, pregnant and lactating women, and the elderly. A key take-home message is is the consistent use of urinary 3-PBA as a biomarker across studies, and the emerging link between pyrethroid metabolites and disruptions in neurological, endocrine, respiratory, and auditory systems. However, significant gaps remain in understanding the precise dose–response toxic effect relationship and long-term health implications. There is a pressing need for well-designed longitudinal studies that incorporate standardized exposure and pathological biomarkers to assess cumulative and delayed effects. Future research should also explore potential pyrethroid exposure-induced gene expression, or the integration of multi-omics technologies to explore biomarkers related pyrethroid. Nonetheless, challenges persist in translating biomarker-based evidence into clinical practice and public health policy, especially in low-resource settings. Addressing these gaps will be key to informing risk assessment, regulatory standards, and targeted interventions aimed at reducing the health burden of pyrethroid exposure in vulnerable groups.

Conclusions

This systematic review highlights evidence pyrethroid exposure to organ-specific toxic effect in vulnerable populations, particularly children, pregnant and lactating women, and the elderly. The toxicological impacts were observed across multiple organ systems, including the nervous, endocrine, reproductive, respiratory, and auditory systems. Urinary 3-phenoxybenzoic acid (3-PBA) emerged as the most frequently used biomarker of exposure, although its association with pathological changes varied among studies. Finally, this study provided an opportunity for a deeper understanding of the harm and health impacts of pyrethroid pesticide.

Authors' Contribution

RA, JJ and SK were involved in concepting and design of the study. RA and JJ performed the acquisition of data. RA, JJ, RGPP, MZC were involved in analysis and/or interpretation of data and drafting the manuscript. JJ and SK were involved in revising the manuscript critically for important intellectual content and editing assistance. All authors took parts in giving critical revision of the manuscript.

Conflict of Interest

All of authors declare no conflict of interest.

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