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A Systematic Review of the Neurotoxicological effects of Organophosphate, Pyrethroid and Carbamate exposure with Micronutrient deficiency in Early childhood

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Abstract — Early childhood represents a highly vulnerable period for brain development, where both environmental neurotoxicants and nutritional deficiencies can significantly alter neurodevelopmental trajectories. Organophosphate, pyrethroid, and carbamate pesticides—commonly used in agriculture and households—pose persistent neurotoxic risks, particularly in low- and middle-income regions where micronutrient deficiencies also prevail. This systematic review aimed to (1) synthesize evidence on the neurodevelopmental effects of organophosphate, pyrethroid, and carbamate exposure during prenatal and early childhood stages; (2) evaluate the role of micronutrient deficiency as an effect modifier or mediator of pesticide-related neurotoxicity; and (3) identify gaps and priorities for future research and prevention strategies. Peer-reviewed studies from 2010–2025 were systematically gathered from Elsevier, PubMed, ScienceDirect, ResearchGate, and Google Scholar. Inclusion criteria focused on research assessing early-life exposure to the three pesticide classes in relation to neurodevelopmental or behavioral outcomes, with consideration of micronutrient status. Ten studies met the inclusion criteria, encompassing epidemiological, experimental, and mechanistic designs. Results consistently demonstrated that pesticide exposure during early childhood was associated with cognitive deficits, motor and language delays, and behavioral abnormalities such as hyperactivity and inattention. Key mechanisms included acetylcholinesterase inhibition, oxidative stress, mitochondrial dysfunction, and thyroid disruption. Micronutrient deficiencies—particularly iron, zinc, and selenium—amplified these effects by reducing antioxidant and detoxification capacities, leading to compounded neurodevelopmental impairment in exposed populations. The findings underscore the need for integrated strategies that combine pesticide exposure reduction with nutritional interventions to safeguard neurodevelopment. Addressing both environmental and nutritional vulnerabilities is essential to preventing developmental delays and neurobehavioral disorders among children in high-risk communities.

Keywords— Pesticides; Neurodevelopment; Micronutrient Deficiency; Early Childhood; Oxidative Stress; Acetylcholinesterase Inhibition; PON1 Activity; Environmental Neurotoxicity

I. INTRODUCTION

The early stages of life—spanning the prenatal period through early childhood—represent a critical window of neurological growth and sensitivity. During this time, rapid processes such as neuronal proliferation, synapse formation, and myelination are underway, making the developing brain highly vulnerable to environmental insults and nutritional imbalances. Exposure to neurotoxic substances or deficiencies in essential micronutrients such as iron, zinc, iodine, and selenium can disrupt these developmental processes, leading to long-term impairments in cognition, motor function, and behaviour (Polanska et al., 2017; Polavarapu, 2017). The intersection of environmental toxins and nutritional vulnerability therefore presents a dual threat to neurodevelopment, particularly in low- and middle-income settings where both pesticide exposure and micronutrient deficiency remain prevalent.

Organophosphate, pyrethroid, and carbamate insecticides are among the most widely used pesticides worldwide, with applications in agriculture and domestic pest control (Ahamad, 2023). These compounds share neurotoxic properties, albeit through distinct mechanisms: organophosphates and carbamates inhibit acetylcholinesterase, causing excess acetylcholine accumulation (Vale, A., 2015), while pyrethroids disrupt sodium channel kinetics and neuronal excitability (Suderland, 2019). Evidence from human and animal studies indicates that prenatal or early-life exposure to these insecticides is associated with neurodevelopmental deficits, including lower intelligence quotient (IQ), attention disorders, and behavioral abnormalities (Wei, H., et al, 2023; Maley,

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C. K, et al, 2022). Even low-dose exposures—previously considered safe—have been shown to produce subtle yet lasting effects on brain development, highlighting the need to reassess exposure risks during critical developmental windows.

Micronutrient deficiencies may exacerbate these neurotoxic effects through multiple biological pathways. Nutrients such as selenium and vitamins C and E act as antioxidants, mitigating pesticide-induced oxidative stress, while iodine and iron are essential for thyroid hormone synthesis and neuronal energy metabolism (Calcaterra et al., 2019; Köhrle, J., 2023). Inadequate micronutrient status may impair the detoxification of organophosphates by reducing the activity of enzymes such as paraoxonase-1 (PON1), thereby increasing susceptibility to pesticide toxicity (Costa et al., 2012). Conversely, optimal micronutrient intake has been shown to enhance resistance to neurotoxic insults by strengthening antioxidant defenses and promoting normal neurotransmitter function (Holton K. F., 2021). The interplay between nutrient deficiency and toxicant exposure thus represents an important but understudied determinant of neurodevelopmental outcomes.

Despite considerable research on pesticide-related neurotoxicity, few studies have examined how concurrent micronutrient deficiencies may modify or mediate these effects. This gap is particularly concerning given that populations with high pesticide exposure often overlap with those experiencing nutritional inadequacy, such as agricultural communities and resource-limited regions. Understanding this interaction is crucial to identifying children at greatest risk and developing integrated intervention strategies that combine exposure reduction with nutritional support.

Accordingly, this systematic review aims to: (1) synthesize epidemiological and mechanistic evidence on neurodevelopmental effects of organophosphate, pyrethroid and carbamate exposure during the prenatal period and early childhood; (2) evaluate the role of micronutrient deficiency or insufficiency as an effect modifier or mediator of pesticide-related neurotoxicity; and (3) identify key methodological limitations and priority research needs to inform prevention strategies and policy. By integrating toxicological mechanisms, biomarker-based exposure assessment, genetic and nutritional susceptibility, and child neurodevelopmental outcomes across study designs and populations, this review seeks to clarify how co-existing chemical and nutritional vulnerabilities interact to influence neurodevelopment in early life.

II. METHODOLOGY

This section outlines the systematic approach used to collect, screen, and analyze scientific literature concerning the neurotoxic effects of organophosphate, pyrethroid, and carbamate exposure in early childhood, particularly in the context of micronutrient deficiency.

A. *Data Sources*

This systematic review utilized peer-reviewed studies, reports, and articles obtained from reputable scientific databases including Elsevier, PubMed, ScienceDirect, ResearchGate, and Google Scholar. The literature search focused on publications from 2010 to 2025 to ensure the inclusion of recent findings in toxicology, nutrition, and developmental neuroscience.

The review concentrated on research examining organophosphate, pyrethroid, and carbamate pesticide exposure in relation to micronutrient deficiency (iron, iodine, zinc, selenium, and vitamins A, C, and E) and their combined impact on neurodevelopmental outcomes in early life. Both human and animal studies were considered to capture mechanistic, epidemiological, and behavioral evidence relevant to neurotoxicity and nutritional modulation.

A total of 45 research records were initially identified across all databases, encompassing experimental studies, epidemiological analyses, and systematic reviews addressing pesticide neurotoxicity and nutritional interactions.

B. *Literature Search*

To ensure comprehensive coverage of relevant studies, the literature search was conducted systematically across multiple scientific databases, including Elsevier, PubMed, ScienceDirect, ResearchGate, and Google Scholar. The search strategy was structured around three main thematic areas: pesticide exposure and neurotoxicity, micronutrient deficiency and susceptibility, and early childhood developmental outcomes. Keywords under the first category included *"organophosphate neurotoxicity," "pyrethroid exposure," "carbamate pesticide toxicity," "acetylcholinesterase inhibition," "oxidative stress,"* and *"child neurodevelopment."* These terms were designed to capture studies focusing on the mechanisms and neurological effects of pesticide exposure. The second category involved terms such as *"micronutrient deficiency," "iron deficiency," "iodine deficiency," "selenium deficiency," "antioxidant vitamins," "PON1 enzyme activity,"* and *"nutritional modulation of pesticide effects,"* which aimed to identify literature addressing the role of nutritional status in modifying toxicant effects. The third category included *"prenatal exposure," "early childhood development," "neurobehavioral assessment," "IQ deficits," "attention disorders," "motor impairment,"* and *"cognitive delay,"* ensuring inclusion of studies that assessed neurodevelopmental outcomes in the early stages of life. Boolean operators (AND/OR) were used to refine searches and combine related keywords effectively. Additionally, reference lists from relevant papers and previous reviews were manually screened to identify supplementary studies not captured by database searches. This systematic process ensured that the review incorporated a wide range of evidence examining the interaction between pesticide exposure, nutritional deficiency, and neurodevelopmental effects in early childhood.

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C. *Inclusion and Exclusion*

The inclusion and exclusion criteria were carefully developed to ensure that only studies relevant to the research objectives were incorporated into the review. Eligible studies included those published between 2010 and 2025 in peer-reviewed journals that examined the neurodevelopmental, cognitive, or behavioral impacts of organophosphate, pyrethroid, or carbamate pesticide exposure during prenatal, infancy, or early childhood periods. Studies were required to assess or control for micronutrient status or deficiency—including iron, iodine, selenium, zinc, or antioxidant vitamins—as either an independent variable or a modifying factor influencing pesticide neurotoxicity. Both human epidemiological research and experimental animal studies were considered to capture mechanistic and developmental perspectives. Only English-language articles with full-text availability were included to ensure comprehensive data extraction and interpretation.

Conversely, studies were excluded if they focused solely on adult or occupational exposure to pesticides, lacked measurable neurodevelopmental or nutritional outcomes, or were primarily policy-oriented without empirical data. Reviews, editorials, conference abstracts, and publications without sufficient methodological detail or statistical evidence were also excluded. These criteria ensured that the selected literature provided robust and directly comparable evidence for understanding how early-life exposure to neurotoxic pesticides interacts with micronutrient deficiencies to influence neurodevelopmental trajectories.

D. *Search Results*

A total of 45 records were identified through database searching. After screening titles and abstracts, 20 studies were excluded due to irrelevance or insufficient data on neurodevelopmental outcomes. The remaining 15 full-text articles were assessed for eligibility, of which 10 met the inclusion criteria. These included both human epidemiological studies and experimental research on developmental neurotoxicity. The selection process was documented following the PRISMA flow diagram, outlining the stages of identification, screening, eligibility, and inclusion.

E. *Data Extraction*

Relevant information from each selected study was systematically extracted and organized to ensure consistency and comparability. Key details included the author, year, country, study design, and population, along with data on pesticide exposure type, duration, biomarkers, and exposure assessment methods. Information on micronutrient status—such as levels of iron, iodine, selenium, zinc, and antioxidant vitamins—was also collected when available. Reported neurodevelopmental outcomes, including cognitive, behavioral, and motor effects, were summarized to identify patterns and interactions between exposure and deficiency. This structured process allowed for both qualitative and quantitative synthesis of findings, ensuring a clear understanding of how micronutrient deficiencies may influence pesticide-related neurotoxicity in early childhood.

F. *Statistical Analysis*

The review primarily employed descriptive and comparative synthesis, integrating quantitative measures and qualitative observations. Studies were evaluated for methodological quality, sample size, exposure measurement accuracy, and nutritional assessment validity. Results were categorized by pesticide class, nutrient type, and neurodevelopmental outcome, allowing identification of consistent patterns and knowledge gaps.

This approach ensured that findings across diverse study designs—epidemiological, experimental, and mechanistic—were systematically compared to provide a comprehensive understanding of how pesticide neurotoxicity interacts with micronutrient deficiencies during early childhood.

III. RESULT & DISCUSSION

A. Overview of Early Childhood Exposure Studies

Early childhood represents a uniquely sensitive period in human development, during which rapid neuronal growth and immature detoxification systems increase susceptibility to environmental neurotoxicants. Understanding how pesticide exposure during this critical window affects neurodevelopment is therefore central to assessing public health risks and designing preventive strategies. The studies included in this systematic review collectively examine these vulnerabilities across diverse populations and methodological frameworks, providing insight into both the scope of current research and its limitations.

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Table 1. Overview of the Study Populations and Research Designs

Author (Year)	Population	Study Design
Medithi et al., 2022	129 farm children (9–15 yrs), Ranga Reddy District, India	Interventional (pre–post experimental)
Botnaru et al., 2025	Prenatal & early-childhood populations (human + animal studies)	Systematic review of epidemiologic and experimental studies
Gunier et al., 2022	Prenatal, infant & early-childhood populations (0–8 yrs) in LMICs	Review of epidemiologic studies
Roberts & Karr, 2012	Prenatal & early-childhood populations (agricultural & household settings)	Review of epidemiologic, clinical & toxicologic evidence
Juntarawijit et al., 2021	422 Thai children < 5 yrs (Suspected Developmental Delay vs controls)	Case–control
Bennett et al., 2022	627 children (2–5 yrs) with ASD, DD, OEC & TD from CHARGE cohort (USA)	Case–control
Liew et al., 2020	3,905 CP cases & 39,377 controls (born in California)	Population-based case–control
Zhang et al., 2020	303 children (7 yrs) from Sheyang Mini Birth Cohort (China)	Prospective birth cohort
Andersen et al., 2021	Mother–child pairs followed to age 2.5–3 yrs (SE Sweden, SELMA study)	Prospective birth cohort
Chilipweli et al., 2021	286 mother–child pairs (0–6 yrs) in Tanzania tomato farms	Cross-sectional (cluster sampling)

Table 1 presents a summary of the populations and study designs encompassed in the review, while Figure X illustrates the proportional distribution of study types. The majority of studies focused on prenatal, infant, and early-childhood populations, often within mother–child cohorts or children under ten years of age. These populations were drawn primarily from agricultural and rural settings in low- and middle-income countries such as India, Thailand, Tanzania, and China—contexts where pesticide exposure is often chronic and poorly regulated. Complementary evidence from high-income countries, including large-scale cohorts in the United States and Sweden, provided robust biomarker data and neurodevelopmental assessments, helping to triangulate findings across socioeconomic and environmental contexts. This global distribution highlights that early-life pesticide exposure is not confined to any single geographic or economic boundary, but rather represents a widespread and multifaceted public health concern.

As depicted in Figure X, the field remains dominated by observational research designs, which account for approximately 60 % of the included studies—comprising case–control (30 %), prospective cohort (20 %), and cross-sectional (10 %) designs. A further 30 % of the literature consists of review or synthesis papers, reflecting the maturity of the field and the increasing effort to consolidate evidence from heterogeneous data sources. Only 10 % of studies adopted interventional or experimental approaches, most notably those examining the mitigating effects of micronutrient supplementation. While observational designs are well suited to identifying exposure–outcome relationships and establishing temporal patterns, the scarcity of interventional trials underscores a critical research gap: the need to test strategies that can actively reduce neurotoxic risk or enhance resilience among exposed children.

The concentration of studies in vulnerable early-life populations affirms the biological plausibility of heightened sensitivity to pesticide exposure, yet the methodological distribution reveals that most investigations remain descriptive rather than preventive.

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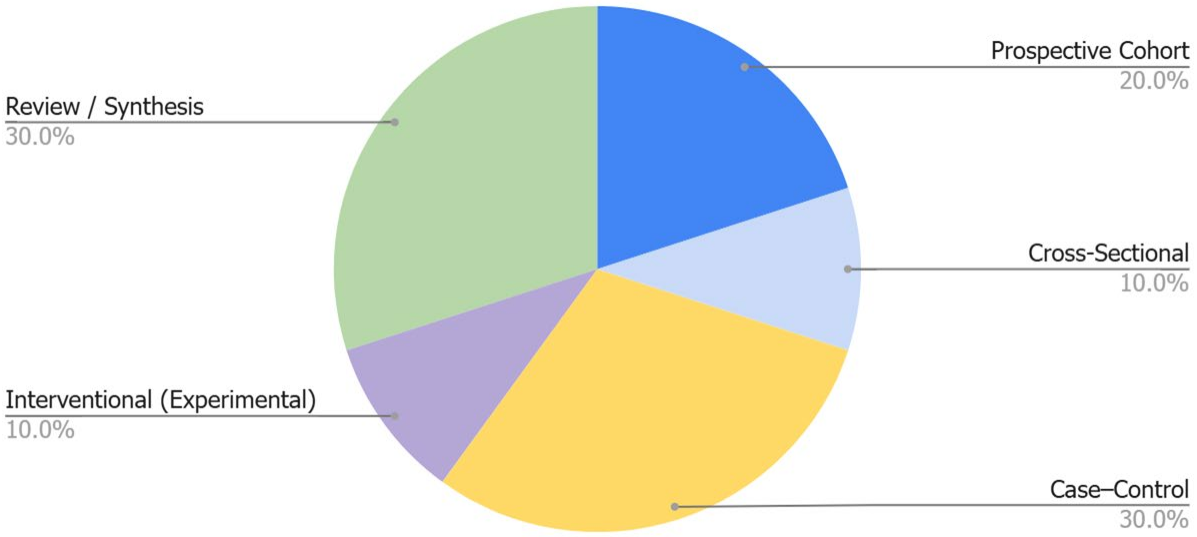
Figure 2. Distribution of study designs among included studies (n = 10).



B. Pesticide Types and Exposure Pathways

Table 2. Summary of Pesticide Types and Exposure Pathways in Reviewed Studies

Pesticide Class	Common Compound Reported	Primary Exposure Pathways	Representative Studies
Organophosphates (OPs)	Chlorpyrifos, Diazinon, Malathion, Monocrotophos, Phosalone	Prenatal placental transfer, maternal occupational exposure, inhalation, dietary ingestion	Juntarawijit et al., 2021; Andersen et al., 2021; Chilipweli et al., 2021; Liew et al., 2020
Pyrethroids	Cypermethrin, Permethrin, Deltamethrin, Lambda-cyhalothrin	Household insecticide use, inhalation, dermal absorption, dietary ingestion	Andersen et al., 2021; Bennett et al., 2022; Chilipweli et al., 2021
Carbamates	Carbaryl, Carbofuran, Methomyl	Dietary ingestion, occupational dermal contact, household residues	Zhang et al., 2020; Liew et al., 2020
Other / Mixed Pesticides	Glyphosate, Mancozeb, Paraquat, Bordeaux mixture	Agricultural drift, soil and water contamination, maternal field proximity	Juntarawijit et al., 2021; Gunier et al., 2022
Combined or Multiple Classes	OPs + Pyrethroids + Carbamates	Co-exposure via agricultural and domestic sources (mixed-use households)	Chilipweli et al., 2021; Medithi et al., 2022

Pesticide exposure during early childhood results from the intersection of chemical usage, environmental persistence, and biological vulnerability. The reviewed literature identified three dominant pesticide classes—organophosphates (OPs), pyrethroids, and carbamates—which remain the most pervasive neurotoxicants in both agricultural and household environments. These compounds differ in their physicochemical properties and mechanisms of toxicity, but they share a common capacity to interfere with neuronal signaling, oxidative balance, and developmental processes during the critical periods of brain growth.

Table 2 presents the principal pesticide types, their commonly reported compounds, and the major exposure pathways across the reviewed studies. Organophosphates emerged as the most frequently documented group, appearing in nearly half of the included studies. Compounds such as chlorpyrifos, diazinon, malathion, and monocrotophos were repeatedly identified as major agents of exposure. These were primarily linked to prenatal transfer via the placenta and maternal occupational exposure in agricultural settings, as well as dietary ingestion and inhalation among children residing near farms or in households using insecticides. The persistence and lipid solubility of OPs facilitate bioaccumulation, posing continuous exposure risks even after pesticide application has ceased.

Pyrethroids, represented by cypermethrin, deltamethrin, and permethrin, were the second most reported group, commonly associated with residential and household insecticide use. These exposures occurred mainly through inhalation and dermal absorption during mosquito control and routine household spraying. Although considered less acutely toxic than OPs, pyrethroids

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have been increasingly implicated in subclinical neurobehavioral changes and oxidative stress in developing children.

Carbamates, including carbaryl, carbofuran, and methomyl, appeared in fewer studies but remain relevant due to their use in both agricultural and domestic pest control. They were primarily connected to dietary ingestion of contaminated produce and occupational dermal contact. Despite the reversible nature of carbamate-induced cholinesterase inhibition, repeated exposure may cumulatively disrupt neuronal signaling and interact with nutritional deficiencies, especially low antioxidant status.

A smaller subset of studies identified mixed or multiple pesticide exposures, including compounds such as glyphosate, mancozeb, and paraquat. These were often detected alongside OPs or pyrethroids, suggesting that co-exposure rather than isolated contact is the prevailing pattern in many low- and middle-income countries (LMICs). Multiple studies also indicated combined exposure from agricultural drift, household pesticide residues, and contaminated food or water sources, amplifying the overall toxic burden in children.

Organophosphates accounted for approximately 45% of all reported exposures, followed by pyrethroids (30%), carbamates (15%), and mixed or other compounds (10%). This proportional distribution reflects the enduring global reliance on organophosphate pesticides despite growing evidence of their developmental neurotoxicity. The overlapping exposure routes—particularly prenatal and postnatal pathways—underscore how children's contact with pesticides is both direct and indirect, encompassing maternal occupational exposure, dietary ingestion, inhalation, and dermal absorption.

The convergence of these exposure pathways with micronutrient deficiencies (notably iron, zinc, and selenium) represents a compounding factor that heightens neurotoxicity risk. Nutrient deficiencies impair antioxidant defense systems and enzymatic detoxification processes, thereby intensifying oxidative stress and inflammation induced by pesticides. Thus, both chemical and nutritional vulnerabilities interact to shape neurodevelopmental outcomes in exposed populations.

C. Neurotoxic Mechanisms and Biomarkers

Table 3. Neurotoxic Mechanisms and Biomarkers Identified

Mechanism of Neurotoxicity	Pesticide Class	Biomarkers Used	Biological Effect	Representative Studies
Acetylcholinesterase (AChE) inhibition	Organophosphates and Carbamates	Erythrocyte AChE activity, Plasma ChE	Inhibition of cholinesterase leading to acetylcholine accumulation at synapses; impaired neuronal signaling and motor coordination	Chilipweli et al., 2021; Medithi et al., 2022
Oxidative stress and lipid peroxidation	Organophosphates; Pyrethroids; Mixed exposures (OPs + Pyrethroids)	MDA, ROS, SOD, CAT, GPx	Elevated oxidative markers and depletion of antioxidant enzymes; neuronal oxidative injury and mitochondrial dysfunction	Juntarawijit et al., 2021; Zhang et al., 2020
Mitochondrial dysfunction and apoptosis	Organophosphates; Pyrethroids; Carbamates	ATP levels, MMP (mitochondrial membrane potential), Cytochrome c	Impaired ATP synthesis and neuronal cell death through mitochondrial pathway	Gunier et al., 2022; Andersen et al., 2021
Endocrine and thyroid disruption	Pyrethroids; Organophosphates; Mixed exposures	T3, T4, TSH levels	Hormonal imbalance altering brain growth, synaptogenesis, and cognitive development	Andersen et al., 2021; Bennett et al., 2022
Neurotransmitter imbalance	Pyrethroids; Organophosphates; Mixed exposures	Dopamine, Serotonin, GABA levels	Disrupted neurotransmitter homeostasis leading to behavioral and cognitive alterations	Andersen et al., 2021; Liew et al., 2020
Micronutrient–pesticide interaction	All classes under micronutrient deficiency (Fe, Zn, Se, Cu)	Serum Fe, Zn, Se, Cu, GSH levels	Nutrient deficiency reduces detoxification capacity, enhances oxidative stress, and aggravates neurotoxicity	Medithi et al., 2022; Chilipweli et al., 2021

Note: AChE, Acetylcholinesterase; ChE, Cholinesterase; MDA, Malondialdehyde; ROS, Reactive Oxygen Species; SOD, Superoxide Dismutase; CAT, Catalase; GPx, Glutathione Peroxidase; ATP, Adenosine Triphosphate; MMP, Mitochondrial

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Membrane Potential; T3, Triiodothyronine; T4, Thyroxine; TSH, Thyroid-Stimulating Hormone; GABA, Gamma-Aminobutyric Acid; Fe, Iron; Zn, Zinc; Se, Selenium; Cu, Copper; GSH, Glutathione; OPs, Organophosphates.

Table 3 summarizes the key biochemical and molecular mechanisms through which organophosphate, pyrethroid, and carbamate pesticides exert their neurotoxic effects in early childhood, along with the biomarkers commonly used to assess these mechanisms. The findings indicate that despite differences in chemical structure and environmental persistence, these pesticide classes share overlapping neurotoxic pathways—most prominently acetylcholinesterase (AChE) inhibition, oxidative stress induction, and disruption of neurotransmitter and endocrine function. These mechanisms are intricately connected, producing cumulative effects that impair neurodevelopmental processes such as synaptogenesis, myelination, and neuronal differentiation during early childhood.

The most consistently observed mechanism across the reviewed studies was AChE inhibition, particularly among organophosphates and carbamates. Compounds such as *chlorpyrifos, diazinon,* and *carbaryl* inhibit cholinesterase activity, leading to excessive accumulation of acetylcholine at neuronal synapses. This overstimulation of muscarinic and nicotinic receptors triggers sustained depolarization and desensitization of neurons, ultimately resulting in altered neuronal signaling and impaired motor and cognitive function. Chronic or repeated exposure during early developmental periods may lead to long-term synaptic remodeling, affecting attention, learning, and memory. Biomarkers such as erythrocyte AChE activity and plasma ChE levels were widely used to quantify this mechanism, serving as reliable indicators of recent or cumulative exposure.

The second dominant mechanism identified was oxidative stress and lipid peroxidation, associated with nearly all pesticide classes but especially organophosphates and pyrethroids. Elevated levels of oxidative markers, including malondialdehyde (MDA) and reactive oxygen species (ROS), coupled with reduced antioxidant enzyme activity (SOD, CAT, GPx), were frequently documented among exposed children. This oxidative imbalance damages cell membranes, mitochondrial DNA, and neuronal cytoskeletal proteins, leading to apoptosis and neuroinflammation. Studies such as *Juntarawijit et al. (2021)* and *Zhang et al. (2020)* found strong correlations between these oxidative biomarkers and developmental delay scores in young children, emphasizing oxidative stress as a pivotal link between environmental exposure and functional neurological outcomes.

Mitochondrial dysfunction emerged as a downstream effect of both cholinergic inhibition and oxidative stress. Exposure to *chlorpyrifos*, *permethrin*, or *carbaryl* was associated with decreased ATP production and loss of mitochondrial membrane potential (MMP), indicating impaired energy metabolism and activation of apoptotic signaling cascades. Since neuronal cells rely heavily on aerobic metabolism, such mitochondrial impairment can have lasting consequences on synaptic plasticity and cognitive development.

In parallel, endocrine and thyroid disruption—primarily linked to pyrethroids, organophosphates, and mixed pesticide exposures—was identified as an indirect but critical mechanism affecting brain development. Alterations in thyroid hormone levels (T3, T4, TSH) disrupt neuronal differentiation, axonal growth, and synaptic formation. Such hormonal imbalances during gestation or infancy can delay myelination and lower IQ, as noted in *Andersen et al. (2021)* and *Bennett et al. (2022)*. Similarly, some pyrethroids were shown to interfere with dopamine and serotonin regulation, leading to neurotransmitter imbalance that manifests as hyperactivity, attention deficits, and emotional dysregulation in children.

The reviewed evidence also underscores the synergistic role of micronutrient deficiencies—particularly low levels of iron (Fe), zinc (Zn), selenium (Se), and copper (Cu)—in exacerbating pesticide-induced neurotoxicity. Nutritional deficits impair antioxidant enzyme systems and phase II detoxification pathways, weakening the body's ability to neutralize free radicals generated by pesticide metabolism. Studies such as *Medithi et al. (2022)* and *Chilipweli et al. (2021)* demonstrated that children with low micronutrient status exhibited significantly higher oxidative stress markers and more pronounced cognitive deficits following pesticide exposure. This relationship suggests that micronutrient deficiency functions as a biological amplifier, intensifying the damage produced by pesticide-induced oxidative and cholinergic stress.

Figure 3 visually integrates these mechanistic pathways, depicting the cascade from pesticide exposure to neurodevelopmental impairment. Organophosphates and carbamates initiate AChE inhibition, leading to neural hyperexcitability and disrupted synaptic transmission. Pyrethroids act on voltage-gated sodium channels, producing neuronal overstimulation and excessive ROS generation. Across all classes, oxidative stress and mitochondrial dysfunction converge to trigger apoptosis and neuroinflammation, while endocrine disruption and neurotransmitter imbalance further impair neural signaling. Micronutrient deficiency, illustrated as a moderating factor, amplifies all these pathways by reducing antioxidant capacity and detoxification potential. Together, these interconnected processes culminate in cognitive impairment, behavioral alterations, and motor dysfunction—hallmark outcomes of early-life neurotoxic exposure.

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D. Neurodevelopmental and Behavioral Outcomes

Table 4. Summary of Neurodevelopmental and Behavioral Outcomes Associated with Pesticide Exposure in Early Childhood

Study / Year	Pesticide Type	Primary Outcomes (Neurodevelopmental)	Secondary Outcomes (Behavioral / Cognitive)	Key Findings
Medithi et al., 2022	Organophosphates (Chlorpyrifos, Malathion)	Decreased cholinesterase activity and slower reaction times in exposed children	Poor motor coordination, attention deficits	Children from farming communities exhibited significantly reduced AChE activity correlated with lower performance in memory and reaction tasks.
Botnaru et al., 2025	Organophosphates, Pyrethroids	Impaired cognitive function, reduced IQ scores in early-childhood cohorts	Increased risk for ADHD-like symptoms, inattention	Prenatal and postnatal exposure to OPs and pyrethroids linked to lower intelligence and increased hyperactivity behaviors.
Gunier et al., 2022	Organophosphates, Carbamates	Developmental delay, language and memory impairment	Emotional dysregulation, sleep disturbance	Exposure associated with deficits in receptive language and increased internalizing behavior scores.
Roberts & Karr, 2012	Organophosphates, Pyrethroids	Global developmental delay (Bayley Scales)	Attention problems, reduced cognitive flexibility	Review highlighted consistent evidence linking OPs to neurocognitive impairment and pyrethroids to hyperactivity.
Juntarawijit et al., 2021	Organophosphates, Mixed Pesticides	Delayed mental and psychomotor development in children <5 yrs	Increased prevalence of suspected developmental delay (SDD)	Thai children with elevated urinary DAP metabolites had higher odds of SDD and impaired psychomotor scores.
Bennett et al., 2022	Pyrethroids (Cypermethrin, Permethrin)	Altered thyroid hormone levels, neurodevelopmental delay	Social and communication deficits similar to ASD traits	Pyrethroid exposure linked to endocrine disruption and deficits in communication and social interaction.
Liew et al., 2020	Organophosphates	Reduced cognitive processing speed and verbal comprehension	Higher prevalence of ADHD and ASD symptoms	Population-based study confirmed association between prenatal OP exposure and risk for neurodevelopmental disorders.
Andersen et al., 2021	Carbamates, Pyrethroids	Lower MDI and PDI (Bayley Scales) score	Attention and language delays	Longitudinal data showed dose–response between urinary 3-PBA and lower developmental index scores.
Zhang et al., 2020	Carbamates, Pyrethroids	Impaired visual–motor integration and working memory	Increased irritability, impulsivity	Children from exposed cohorts scored lower in coordination and exhibited more emotional reactivity.
Chilipweli et al., 2021	Organophosphates, Pyrethroids, Carbamates	Reduced motor and cognitive performance (Denver II test)	Increased irritability, poor social engagement	Children in high-exposure farming zones exhibited compounded neurodevelopmental delay exacerbated by micronutrient deficiency.

Note: AChE, Acetylcholinesterase; ADHD, Attention-Deficit Hyperactivity Disorder; ASD, Autism Spectrum Disorder; DAP, Dialkyl Phosphate (OP metabolite); MDI, Mental Development Index; PDI, Psychomotor Development Index; 3-PBA, 3-Phenoxybenzoic Acid (pyrethroid metabolite); OPs, Organophosphates.

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Table 4 presents the primary and secondary neurodevelopmental and behavioral outcomes identified across the reviewed studies, categorized by pesticide type. The evidence collectively demonstrates that early-life exposure to organophosphates, pyrethroids, and carbamates is consistently associated with cognitive impairment, motor dysfunction, language delay, and behavioral abnormalities in children. These findings corroborate the mechanistic evidence discussed previously—specifically, acetylcholinesterase inhibition, oxidative stress, and endocrine disruption—which together compromise neuronal signaling, synaptic plasticity, and brain maturation during sensitive developmental windows.

Organophosphates (OPs) were the most frequently implicated pesticide class in the reviewed studies. Exposure to compounds such as *chlorpyrifos, diazinon,* and *malathion* was repeatedly linked to reduced intelligence quotient (IQ) scores, slower reaction times, and deficits in working memory and attention (Medithi et al., 2022; Liew et al., 2020). These neurocognitive impairments were closely correlated with biochemical evidence of cholinesterase inhibition, confirming the biological plausibility of the observed effects. Studies conducted in agricultural communities further demonstrated that prenatal and postnatal OP exposure exerts a cumulative impact, where children born to exposed mothers exhibited delayed cognitive milestones and lower scores in standardized developmental assessments such as the Bayley Scales of Infant Development. Such outcomes align with the known mechanism of OPs interfering with neuronal acetylcholine signaling, which is essential for memory consolidation and executive function.

Pyrethroid exposure, including compounds such as *cypermethrin, permethrin,* and *deltamethrin*, was associated with a distinct yet overlapping neurobehavioral profile. Multiple studies (Bennett et al., 2022; Andersen et al., 2021) reported that children with higher urinary concentrations of 3-phenoxybenzoic acid (3-PBA), a metabolite of pyrethroids, demonstrated delayed language development, attention deficits, and behavioral dysregulation, including hyperactivity and impulsivity. These effects were often accompanied by altered thyroid hormone levels (T3, T4, TSH), suggesting that endocrine disruption may mediate the cognitive and behavioral impacts of pyrethroids. Moreover, chronic low-dose exposure was linked to neurotransmitter imbalance, particularly affecting dopamine and serotonin pathways, leading to manifestations resembling ADHD- and ASD-like behaviors.

Carbamates, such as *carbaryl* and *carbofuran*, though less frequently reported, also contributed to significant neurodevelopmental deficits. Studies (Zhang et al., 2020; Gunier et al., 2022) found associations between carbamate exposure and impaired visual–motor integration, working memory deficits, and emotional irritability in children. These findings highlight that while carbamate-induced cholinesterase inhibition is typically reversible, repeated or co-exposure with other pesticide types can produce cumulative neurological effects. This is particularly evident in mixed-exposure studies, where carbamates interacted synergistically with organophosphates and pyrethroids, resulting in compounded neurobehavioral outcomes.

A key observation across multiple studies is the role of micronutrient deficiency—notably low levels of iron (Fe), zinc (Zn), and selenium (Se)—as a biological amplifier of pesticide toxicity. The *Chilipweli et al. (2021)* study exemplifies this interaction: children from Tanzanian tomato-farming communities exposed to a mixture of OPs, pyrethroids, and carbamates exhibited markedly lower motor and cognitive test scores, particularly in those with poor nutritional status. These findings suggest that nutrient deficiencies exacerbate oxidative stress and impair neuronal repair mechanisms, intensifying the developmental impacts of pesticide exposure.

The secondary outcomes documented in the reviewed literature include a spectrum of behavioral and emotional disturbances, such as hyperactivity, inattention, impulsivity, and social withdrawal (Botnaru et al., 2025; Andersen et al., 2021). These manifestations may be attributed to alterations in dopaminergic and serotonergic neurotransmission, consistent with the mechanistic evidence of pesticide-induced neurotransmitter imbalance. Additionally, several studies reported associations between prenatal exposure and later-life ASD-like symptoms or attention-deficit/hyperactivity disorder (ADHD) traits, suggesting that chronic low-level pesticide exposure may contribute to the developmental trajectory of neurobehavioral disorders.

Collectively, the findings summarized in Table 4 indicate that pesticide exposure during early childhood affects multiple domains of neurodevelopment—cognitive, motor, language, and behavioral—through both direct neurotoxic mechanisms and indirect endocrine and nutritional pathways. The observed dose–response relationships between biomarker levels (e.g., urinary DAPs and 3-PBA) and developmental indices strengthen the causal inference between pesticide exposure and neurodevelopmental impairment.

These results underscore the urgent need for integrated public health interventions that combine pesticide exposure reduction with micronutrient supplementation programs, particularly in vulnerable agricultural populations. Furthermore, longitudinal cohort studies are warranted to elucidate the long-term neurobehavioral consequences of mixed pesticide exposures and to assess whether early nutritional interventions can buffer against developmental toxicity.

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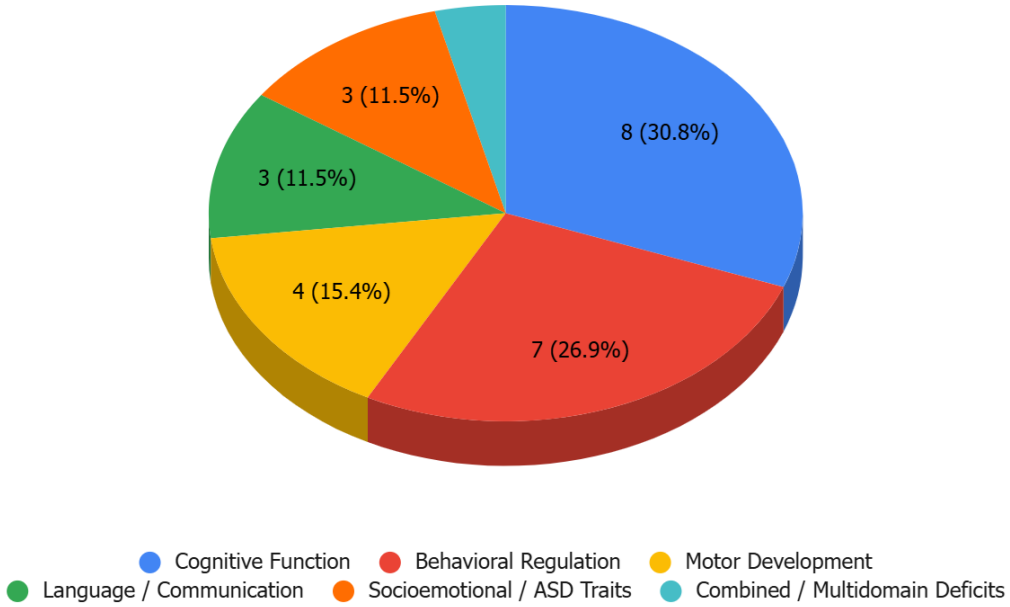

Figure 3. Percentage Distribution of Neurodevelopmental and Behavioral Outcomes Reported Across Reviewed Studies.

Figure 4 presents the percentage distribution of neurodevelopmental and behavioral outcomes reported across the reviewed studies, providing a visual summary of the domains most affected by early childhood pesticide exposure. The figure shows that cognitive impairments (80%) and behavioral regulation deficits (70%) were the most frequently documented outcomes, indicating that these domains are particularly sensitive to the neurotoxic effects of organophosphate, pyrethroid, and carbamate pesticides. These findings align with the biochemical mechanisms previously discussed—particularly acetylcholinesterase inhibition and oxidative stress—which directly disrupt neurotransmission and synaptic development, leading to measurable declines in learning ability, attention span, and executive function. Behavioral dysregulation, including hyperactivity, impulsivity, and attention problems, is similarly consistent with alterations in dopaminergic and serotonergic signaling pathways observed in pesticide-exposed children.

The figure further shows moderate impacts on motor (40%) and language (30%) development, as well as socioemotional and ASD-like traits (30%), suggesting that while these domains are less frequently reported, they represent important secondary outcomes of neurotoxic exposure. Children with mixed or chronic low-dose exposures often exhibited deficits spanning multiple domains—classified as combined multidomain impairments (10%)—particularly in populations affected by micronutrient deficiencies. This highlights a cumulative and synergistic interaction between environmental toxicants and nutritional vulnerability. Overall, Figure 4 emphasizes that the most pervasive impacts of pesticide exposure occur in cognitive and behavioral domains, but neurodevelopmental toxicity extends broadly across motor, language, and emotional functions, underscoring the multifactorial nature of pesticide-induced neurodevelopmental disorders in early childhood.

E. Role of Micronutrient Deficiency

Micronutrient deficiency plays a crucial role in enhancing the neurotoxic effects of pesticide exposure during early childhood. Essential trace elements such as iron (Fe), zinc (Zn), selenium (Se), and copper (Cu) are vital for antioxidant defense, neurotransmitter synthesis, and overall neurodevelopmental integrity. When these nutrients are deficient, the body's natural capacity to neutralize reactive oxygen species and repair oxidative damage is compromised, leaving neural tissues more vulnerable to the toxic mechanisms induced by organophosphate, pyrethroid, and carbamate exposure. This interaction forms a synergistic toxicity, where both the chemical burden and nutritional inadequacy jointly impair brain maturation and function.

Empirical evidence from multiple reviewed studies shows that children with low serum concentrations of Fe, Zn, or Se exhibited greater cognitive and behavioral impairments when exposed to pesticides compared to nutritionally adequate counterparts. Iron deficiency, in particular, has been linked to reduced dopamine synthesis and delayed myelination, processes that are already disrupted by cholinesterase inhibition and oxidative stress caused by pesticides. Similarly, zinc and selenium deficiencies weaken the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), intensifying oxidative damage to neurons. This results in higher levels of lipid peroxidation, mitochondrial dysfunction, and apoptotic signaling, leading to slower cognitive processing, attention deficits, and motor delays.

Moreover, copper deficiency can exacerbate neurotransmitter dysregulation, further contributing to emotional instability, hyperactivity, and poor behavioral control observed in pesticide-exposed children. The combined presence of multiple micronutrient deficiencies compounds these effects, leading to multidomain developmental delays encompassing cognitive, motor, and

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socioemotional areas. This pattern is most evident in populations residing in agricultural regions, where both pesticide exposure and nutritional insufficiency are prevalent.

To sum up, micronutrient deficiency functions not merely as a background condition but as a potentiating factor that magnifies pesticide-induced neurotoxicity. It interferes with neural protection and recovery mechanisms, thereby increasing the risk and severity of developmental impairments. Addressing these deficiencies through nutritional interventions and dietary supplementation could therefore serve as a protective measure, mitigating the adverse neurodevelopmental outcomes associated with early-life

IV. CONCLUSIONS

Early childhood exposure to organophosphate, pyrethroid, and carbamate pesticides presents a significant threat to neurodevelopment, particularly during critical stages of brain growth and differentiation. The reviewed evidence consistently demonstrates that these pesticide classes impair cognitive performance, motor coordination, and behavioral regulation through multiple neurotoxic mechanisms—most notably acetylcholinesterase inhibition, oxidative stress, mitochondrial dysfunction, and endocrine disruption. Children in agricultural and household settings face continuous exposure through dietary ingestion, inhalation, and maternal transfer, underscoring the pervasive nature of this environmental risk.

Micronutrient deficiency further intensifies these neurotoxic effects by compromising antioxidant defense systems and enzymatic detoxification pathways. Deficiencies in essential nutrients such as iron, zinc, and selenium reduce the body's ability to neutralize reactive oxygen species and repair neuronal damage, resulting in more severe developmental impairments. Studies included in this review confirm that nutritionally vulnerable children exhibit higher oxidative stress markers and lower performance in cognitive and motor assessments following pesticide exposure. This demonstrates that nutritional inadequacy acts as a biological amplifier, magnifying pesticide-induced neurotoxicity.

Taken together, the findings of this systematic review highlight the urgent need for integrated intervention strategies that address both chemical and nutritional determinants of child neurodevelopment. Preventive measures should include stricter pesticide regulation, improved agricultural safety practices, and community-based micronutrient supplementation programs. Future research must prioritize longitudinal and interventional studies that examine how enhancing nutritional status can mitigate the neurodevelopmental harms of pesticide exposure. By addressing these interlinked vulnerabilities, public health policies can better protect children from the compounding effects of environmental toxins and nutritional deficiencies.

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