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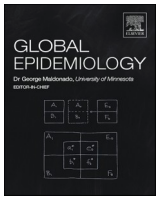

Literature landscape of neurodevelopment and pesticides: A scoping review of methodologies

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A B S T R A C T

Pesticides are highly tested and regulated chemicals. There is currently great interest in the role that pesticides may play in childhood neurodevelopment. The objective was to identify and describe the body of evidence and to assess the ability to synthesize effect estimates. The epidemiologic literature from 2011 to 2022 was searched for publications on the association between pesticide exposure and neurodevelopment, behavior, and/or cognition in children. We identified 114 publications, representing 67 unique studies. While organochlorine and other insecticides were the most common classes of pesticides studied, up to 159 different metabolites or active ingredients were reported. Nine pesticides or their metabolites were reported in >10 publications. Similarly, multiple assessment methods were administered across studies to evaluate outcomes in neurodevelopment at ages which ranged from birth to 18 years of age. This scoping review reveals the heterogeneity among published studies with respect to exposures and health outcomes, in the methods used to assess and classify them, and in combinations of the two. This limits the adequacy of the evidence to evaluate specific risk estimates for a particular exposure-outcome pair. Intentional coordination among researchers to increase consistency in methodologies would facilitate the synthesis of results across studies. Research opportunities also exist to validate assumptions in exposure and outcome assessment which are implicit in many of the studies reviewed. In conclusion, there are many ongoing epidemiologic studies with a focus on pesticides and neurodevelopment. The variety of exposures, exposure assessment methods and tests for each outcome can be overwhelming. Interdisciplinary collaboration is recommended to harmonize data collection and to enable meaningful interpretation of the study results across populations.

Introduction

"Pesticides" is a generic term for products of synthetic, biological, and natural origins, that are used to control pests such as weeds, insects, rodents, and fungi. Registration of synthetic pesticides requires studies on reproductive and developmental outcomes (see examples from US Environmental Protection Agency (EPA) (https://www.epa.gov/pesticide-registration/about-pesticide-registration) and European Food Safety Authority (EFSA) (https://www.efsa.europa.eu/en/applications/pesticides). Despite extensive regulatory oversight, there is great interest in the role that pesticides may play in childhood neurodevelopment. Since an increasing body of evidence has been generated over the recent decades, it is important to continue reviewing the literature in order to incorporate findings from more recent studies. Focused summaries of the evidence have been published (e.g. [1,8,10,15,19,31,36,37,39,45]), yet it is still challenging to do so in a cohesive and conclusive way. Initiatives to combine data from multiple existing cohorts is also ongoing, such as the Environmental influences on Child Health Outcomes (ECHO) Program, aiming to pool and curate the data to fill existing evidence gaps [40]. A comprehensive review of the epidemiology and toxicology publications on neurodevelopment and pesticides in children [7] summarized a broad range of evidence from newborn (head circumference) to pre-adolescent (intelligence and behavior) populations from 46 publications reporting on 16 epidemiologic studies. Overall, the authors did not identify any consistent and strong pesticide-outcome association. Additional research with improved exposure assessment and testing of outcomes at consistent ages was recommended.

In the decade since the review by Burns et al., interest in the impact of environmental factors on a broad spectrum of disorders and diseases among children has continued and many further studies added findings to the evidence body. For example, a review identified 32 epidemiology summary publications of autism spectrum disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) which considered environmental risk factors [28]. Some reviewers have focused upon a need for improved consistency in outcome and exposure assessment [4] and use of quality study design to control for co-exposures and confounding factors, such as lifestyle habits, nutrition, socio-demographic factors, and comorbidities [27].

When evaluating epidemiology studies on pesticides and a given

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outcome, it is necessary to understand the entire scope of the literature. A recent summary of occupational studies provided perspective on the approaches and designs used to evaluate pesticide exposures among farmers and applicators [34]. The authors observed that exposures were often based upon self-report or job matrices, with an increasing practice to collect data on specific pesticides or types. No similar assessment has been conducted for epidemiologic studies of the general population.

To review most recent published evidence and assess the methods used, we conducted this targeted review. The specific aim of this scoping review was (a) to identify and summarize the methodologies in recent papers on pesticides and neurodevelopment, (b) to understand the definitions and assessment methods used to classify each exposure and outcome, and (c) to assess implications on the ability to synthesize effect estimates and to interpret results from the body of literature as a whole. Specific risk estimates were not the focus of the present exercise.

Methods

Review approach

We generally followed the approach of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA) [29]. The review approach was structured on the PECO acronym (Participants, Exposure, Comparison, Outcome) to define the inclusion criteria. In brief, this review was of children (P) with pesticides assessment (E) using epidemiologic methods to compare risk estimates (C) of neurodevelopment, including behavior and cognition (O).

Eligibility criteria

Outcomes were limited to tests, scores, and diagnoses related to neurodevelopment and/or behavior, including cognition.

Excluded from the search were nonhuman studies and studies of health outcomes in adults; birth cohorts that collected exposure data from adults to investigate health outcomes in children were included. Also excluded were investigations of cancer, birth defects, and body weight. Biological outcomes, such as hormone levels and cytokine alterations, were excluded. We omitted abstracts, scientific posters, reviews, case studies, and exposure studies. Cholinesterase inhibition was considered an exposure metric and not an outcome.

Information source

All human epidemiologic studies were included if published in English between April 30, 2011 and the date of the search on September 16, 2022, and available in print or in electronic form in CABA, BIOSIS, EMBASE, SciSearch, STN Database, and Medline.

Our primary search combined broad exposure terms (pesticid* OR insecticid* OR herbicid* OR fungicid*), with neurodevelopmental endpoints (Attentive* OR ADDH OR ADHD OR ADHS OR ADD OR Conners* OR Hkd OR Hyperactiv* OR 'Hyper activ*' OR Hyperkin* OR 'Hyper kin*' OR Distract* OR Inattention OR Inattentiv* OR Aptitude* OR 'Stanford Binet' OR 'Binet Test*' OR 'Bender Gestalt Test' OR 'Aphasia Test*' OR Bayley* OR Wechsler OR WISC OR 'McCarthy Scale*' OR 'Continuous Performance Test' OR 'Continuous Performance Task' OR CRS-T OR CRS-P OR 'Strengths and Difficulties Questionnaire' OR SDQ OR 'Brain disorder*' OR 'Brain damage*' OR 'Brain dysfunct*' OR Cognition OR Cognitive OR Metacognit* OR Metamemory OR Volition OR (Executive NEAR/2 (control OR function* OR dysfunction* OR impairment*)) OR DNT OR (Development* NEAR/2 (disorder* OR disabilit* OR * deviation* OR neurotoxic* OR toxic* OR abnormal* OR syndrom*)) OR ((Defiance OR disruptive OR disruption) NEAR/2 (disorder*)) OR Intelligence OR Comprehension* OR Intellectual* OR IQ OR Memory OR 'Item recall' OR Remembering OR Learning* OR Neurobehav* OR Neurocogniti* OR Neurodevelopment* OR Autism OR Autistic OR Neurologic* OR (Nervous NEAR/2 (disease* OR disorder* OR dysfunction* OR manifestation* OR system)) OR Neuropsychologic* OR Psycholog* OR Psychomot* OR Motor* OR Locomot* OR 'Processing speed*' OR 'Processing velocit*' OR 'reaction time' OR 'response inhibition' OR 'academic achievement*' OR 'scholastic achievement*' OR brain OR neuron OR cerebellum OR hippocampus OR striatum OR cortex OR 'central auditory process*' OR Aspberg* OR 'spectrum disorder*' OR 'hypothyroid*' OR 'hypo thyroid*', population parameters (offspring OR neonatal OR 'in utero' OR developmental OR pregnancy OR pregnant OR gestational OR newborn OR prenatal OR perinatal OR teratology OR fetus OR fetal OR age-dependent OR 'age dependent' OR 'age sensitivity' OR reproductive OR fertility OR parental OR parent OR neonate OR maternal OR child OR children OR 'teen adolescent' OR adolescent OR utero), and fetal growth endpoints ('head circumference' OR 'head size' OR head OR 'birth weight' OR 'birth length' OR weight OR length OR 'fetal growth' OR 'infant growth' OR 'Ponderal Index' OR 'small for gestational age' OR 'small-for-gestational-age' OR 'small size'). A hand search of references from review publications and relevant cohorts was also conducted.

Data extraction

The titles and abstracts were reviewed for eligibility by all authors. Discussion of eligibility was confirmed by all authors. Two reviewers (CJB, JER) extracted information from the full text, reviewing the other's work. The data were organized by three topics: the study (design, population, year of first enrollment), exposure (age at collection, metric, class/chemical/metabolite) and outcome (age at collection, test). When a study had multiple publications, data such as collection times and age of enrollment were inferred across publications. For studies with multiple enrollment periods, or with enrollment periods spanning multiple years, the initial year of enrollment was recorded. Information regarding risk estimates and effect estimates were not extracted as this was outside the scope of the project.

Quality evaluation

The purpose of this review was to gauge the volume of literature, and to summarize the research approach(es); it was not to describe the risk estimates. As a result, no quality assessment per se was performed on each publication.

Results

A total of 743 publications was identified by the literature search of which 610 publications were excluded during title and abstract review due to non-relevance, or because they were duplicates, inaccessible, or not in the English language. The full text of the remaining 133 publications was reviewed, during which 19 publications were excluded due to non-relevance. The remaining 114 publications met our criteria for inclusion. The numbers of papers identified and reviewed are shown in Fig. 1. The reasons to exclude publications were broad and primarily due to non-relevance, nonhuman subjects, and/or not primary research. A dictionary of all acronyms is listed in the Appendix, Table A1. A summary of each identified publication, study characteristic and exposure assessment is provided in Table A2.

Of the 114 publications, there were 67 unique studies (i.e. investigations). Since a single study can result in multiple publications, some of which might address a distinct exposure and unique outcome, the literature was summarized at the publication level. Between four and 15 articles on neurodevelopment and pesticide exposures were published annually since 2011 (Table 1). More than half were published in the 5-year period of 2015 to 2019. The research has a global representation, with most publications reporting on populations from the United States ($n = 41$), and 31 publications representing populations from Asia Pacific, 15 of which reported on populations in China. With respect to design, birth cohorts (74%) were most prevalent, followed by cross-

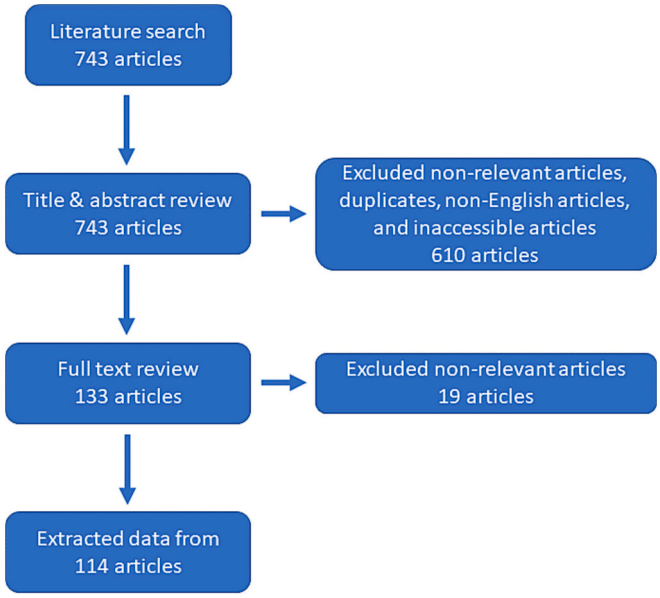

Fig. 1. PRISMA diagram for literature search.

Table 1
General characteristics of the included publications on neurodevelopment (n = 114).

	Number of publications	%
Year of publication		
2011–2014	23	20.18
2015–2019	65	57.02
2020–2022	26	22.81
Region of study population		
Asia Pacific	31	27.19
Europe, Middle East, Africa	33	28.95
North America	48	42.11
Latin America	3	2.63
Study design		
Birth cohort	84	73.68
Case-control	8	7.02
Cross-sectional	14	12.28
Nested case-control	3	2.63
Pooled cohorts	4	3.51
Pooled case-controls	1	0.88
Studies with the largest numbers of published articles*		
CHAMACOS	11	9.65
CHAM2	5	4.39
CHARGE	4	3.51
HOME	5	4.39
PELAGIE	7	6.14
Number of participants		
0–99	13	11.40
100–499	66	57.89
500–999	21	18.42
≥ 1000	14	12.28

* Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), Perturbateurs Endocriniesn: Étude Longitudinale sur leas Anomalies de la Grossesse, L'Infertilité et l'Enfance (PELAGIE), CHAMACOS youths (CHAM2), Health Outcomes and Measures of the Environment (HOME), and Childhood Autism Risks from Genetics and Environment (CHARGE).

sectional (12%), case-control (7%), nested case-control (3%), and pooled analyses (4%) (Table 1). The five studies which yielded the largest numbers of publications include four birth cohorts, the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) (n = 11), Perturbateurs Endocriniesn: Étude Longitudinale sur leas Anomalies de la Grossesse, L'Infertilité et l'Enfance (PELAGIE) (n = 7), CHAMACOS youths (CHAM2) (n = 5), Health Outcomes and Measures of the Environment (HOME) (n = 5), and one case-control study, Childhood Autism Risks from Genetics and Environment (CHARGE) (n = 4) (Table 1). Most of the publications represented at least 100 study participants, with only 11.4% having fewer than 100 (Table 1).

There were 104 publications that assessed exposure to a specific chemical or metabolite, while ten publications assessed exposure only at the class, category (e.g., insecticides), or general pesticides level. The approaches for exposure assessment are summarized in Table 2. Only one method was used to assess exposure in most publications (n = 85); two methods were used in 22 of the 114 publications. The majority collected biospecimens (80%). Other studies relied upon indirect methods such as occupation (4%), proximity (11%), or questionnaires (11%) to estimate pesticide exposure. For those publications reporting on biospecimens, a breakdown of types of biospecimens collected is shown in Table 2. The investigations assessed between one and 63 unique chemicals and/or metabolites; about half of the publications reported three or fewer (Table 2). Up to 159 different chemicals or metabolites were assessed collectively in the 114 reviewed publications. Only nine chemicals or metabolites were assessed in at least ten different publications.

We grouped the publications by major classes of pesticides that were assessed (Table 3). These included broad categories of organochlorine insecticides, other non-organochlorine insecticides, herbicides, fungicides and not specified (i.e. general "pesticides"). Some publications included information on multiple pesticides across several classes and

Table 2
Assessment of residential exposures in the included publications (n = 114).

	Number of publications	%
Number of unique exposure assessment methods		
1	85	74.56
2	22	19.30
3	4	3.51
4	2	1.75
5	1	0.88
Exposure assessment method		
Biospecimen	91	79.82
Parent Occupation	4	3.51
Proximity	12	10.53
Questionnaire, interview	12	10.53
Type of biospecimen**		
Breast milk	4	4.40
Child blood	5	5.49
Child hair	1	1.10
Child urine	27	29.67
Cord blood	12	13.19
Maternal blood	23	25.27
Maternal hair	2	2.20
Maternal urine	51	56.04
Meconium	1	1.10
Number of unique chemicals or metabolites		
1 to 3	62	54.39
4 to 6	24	21.05
7 to 9	7	6.14
10 or more	14	12.28
Chemicals or metabolites assessed in ≥10 publications*		
trans-DCCA	10	9.62
cis-DCCA	10	9.62
TCPy	11	10.58
p,p'-DDE	16	15.38
chlorpyrifos	16	15.38
3-PBA	24	23.08
DMAP	28	26.92
DEAP	31	29.81
DAP	31	29.81

* 2,2-dimethylcyclopropane carboxylic acid (DCCA), 3,5,6-trichloro-2-pyridinol (TCPy), dichlorodiphenyldichloroethylene (DDE), 3-phenoxybenzoic acid (3-PBA), dimethylaminopyridine (DMAP), diethyl alkylphosphate (DEAP), dialkylphosphate (DAP).

** Percentages may not sum up to 100% because some publications reported on more than one biospecimen type.

Table 3
Methods of assessment used in the included publications by type of pesticide.

Pesticide category	Organochlorine Insecticides	Non-Organochlorine Insecticides	Herbicides	Fungicides	Not specified
Number of articles	34	81	8	9	10
Articles applying >1 method	8	9	0	0	0
Indirect					
Proximity	1	9	4	5	2
Occupation	0	0	0	0	3
Self/parent report	1	9	1	1	5
Direct (biomonitoring)					
Blood	27	8	1	1	0
Urine	0	59	1	1	0
Hair	1	2	1	1	0
Breast Milk	4	0	0	0	0

were counted twice. Further, many publications evaluated more than one pesticide within each class. As shown in Table 3, non-organochlorine insecticides were the primary pesticide class of interest in these publications ($n = 81$). Few of the reviewed publications focused on herbicides (n = 8) or fungicides ($n = 9$). The studies for which the type or class of pesticide was not specified ($n = 10$) tended to be studies that selected participants based on occupation (mothers working in a greenhouse) ($n = 3$) or proximity (mothers living near an orchard) ($n = 2$). The biomonitoring matrix of choice of organochlorines was blood ($n = 27$), and for non-organochlorine insecticides was urine ($n = 59$).

With respect to outcomes, the individual tests for neurodevelopment, behavior and cognition can have multiple domains. The health outcomes in the reviewed publications could be classified as belonging to one of five categories: head circumference (HC), neurocognition or intelligence, ASD, ADHD, and neurobehavior/neurodevelopment. These categories are intended to describe the scope of the publications and are not intended to be interpreted as clinical definitions. Each of the five outcome categories was assessed in at least ten of the reviewed publications.

Almost 100 unique assessment tools or variations of such were used to characterize health outcomes among the 114 publications (Table A3). Children were evaluated from birth to age 18 years of age. The complete summary for reviewed publications is provided in Appendix Table A3 (cohort) and Table A4 (cross sectional and case-control studies). The tests and ages at which each was administered are shown for studies with at least three publications (Table 4). Head circumference (HC) is an outcome consistently measured at delivery, within the CHAMACOS, HOME and Laizhou Wan (Bay) China cohort (LWBC) cohorts [13,14,18,41]. In contrast, other tests were not performed at the same ages across studies. For example, the Gesell Developmental Schedule (GSD) was administered at ages 12 and 24 months in the LWBC study [47] but at age 36 months in the Sheyang Mini Birth Cohort Study (SMBCS) [48]. As shown in Table 4, some studies repeated a test, such as the Bayley Scale of Infant Development (BSID) over several age periods (HOME study) [14], and the Behavioral Assessment System for Children (BASC) in the Mt. Sinai study [17].

Discussion

When reviewing a body of literature it is natural to focus on the question at hand. Risk assessors are charged with evaluating individual pesticides and their impact(s) upon human health and environmental effects. The private sector may similarly concentrate on specific active ingredients which it manufactures and sells. Academic investigators can broadly pursue assessments of exposure and outcome to test existing and generate new hypotheses. Yet no group, public or private, is charged to generate a high-level view of the entire body of evidence. Efforts to define how to change the status quo have been described (e.g. [6,12,23,38]), While this is not a "systematic review", in that we did not extract or synthesize effect measures, we used a systematic approach to describe the epidemiologic approaches to evaluate associations of pesticides and childhood neurobehavior and neurodevelopment. There are opportunities for epidemiologists to have an improved impact on policy, and for risk assessors to communicate their guidelines.

This scoping review identified 114 papers on pesticide exposure in children and neurodevelopment published from 2011 to 2022 and summarized the methods used to assess the exposure and the outcome, as well as more general aspects of the underlying study, such as geographic region, study design, population, and sample size. Some general consistencies were observed, with most publications detailing birth cohorts, and most investigating US populations, followed by China.

In general, the prospective birth cohorts were characterized by multiple publications relative to the same study populations. Notably, this review does not capture all findings from these studies, as many reported on exposures other than pesticides. The number of identified publications and of underlying studies more than doubled those summarized in the 2013 comprehensive review [7]. In the current review several studies had publications across both search periods. These include the Mt. Sinai Children's Environmental Health Cohort study, CHAMACOS, Columbia Center for Children's Environmental Health (CCCEH), INfancia y Medio Ambiente (INMA) and a cohort in Mexico's State of Morelos.

While most of the studies were cohort or case-control designs, there were several publications using the cross-sectional design that evaluated children at different ages, ranging from birth to 11 years. Data describing exposure and outcome in this type of study reflect one common time point; they do not provide information about any temporal relationship (i.e., whether exposure preceded the outcome). This study design is therefore not always suited to assess a causal relationship between exposure and outcome. Instead, these provide starting points from which to test hypotheses using the same outcome or test batteries at the same age.

It is also important to note that neurodevelopmental disorders have a multifactorial etiology and disentangling the effect(s) of exposures to pesticides from other factors is challenging. The difficulty of accounting for all confounding factors, some of which may be unknown, is a recognized limitation for epidemiologic research (e.g. [11,26,35,42]). Further, many factors, such as those related to lifestyle (including diet), socioeconomic status and uses of pesticides are correlated with one another. These known limitations of observational research underscore the importance of replication across multiple populations in order to better evaluate patterns and consistency, and to interpret causality.

Heterogeneity was observed in the chemistries and metabolites assessed. For example, 159 unique chemicals or metabolites were assessed in the selected articles, collectively, but only nine specific pesticides or their metabolites were reported in 10 or more publications. This reduces the ability to evaluate the findings for a specific active ingredient. More information is needed to understand why investigators selected specific chemicals or metabolites for analysis in their studies. For example, since some assays can evaluate multiple chemicals and/or metabolites, is the selection based on convenience for investigators to test for certain combinations? Further, are analyses reported for all

Table 4
Tests administered at different ages to assess health outcome development within selected cohort studies (at least 3 publications), (2011−2022). (All studies shown in Tables A3 and A4).

Study name	Year data collection began	0–5 mo	6–11 mo	12–23 mo	24–35 mo	3 y	4 y	5 y	6 y	7 y	8 y	9 y	10+ y
CHAM2	2009									WISC-IV			BASC-2 (16, 18 y), Misc: 1
Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)	1999	HC	ANS	ANS		ANS		ANS, K-CPT		BASC WISC-IV		ENI Facial Expression Recognition Test	BASC NEPSY, SRS, WISC-IV Misc: 2, 3
Fuyang Maternal and Children's hospital	2008	ABR, HC, PDMS-2, TAC, VA	ABR, HC, PDMS-2, TAC, VA	ABR, HC, PDMS-2, TAC, VA									
Generation R	2002					CBCL			CBCL, SRS, Snijders-Oomen Nonverbal Intelligence Test				
Human Early Life Exposome Project (HELIX)	2003					SDQ			ANT, CPM, N-Back, CBCL, Connors' ADHD index				
Health Outcomes and Measures of the Environment (HOME)	2003	HC, NNNS	BSID	BSID	BSID		Clinical Evaluation of Language Fundamentals	WPPSI-III			SRS, WISC-IV		
Laizhou Wan (Bay) China cohort (LWBC)	2010	HC		GDS (DQ)	GDS (DQ)								
Mt Sinai Children's Environmental Health Center	1998						BASC, BRIEF		BASC, BRIEF, WPPSI-III	BRIEF, BASC, SRS, WISC-IV			
Perturbateurs Endocriniesn: Étude Longitudinale sur leas Anomalies de la Grossesse, L'Infertilité et l'Enfance (PELAGIE)	2002								SDQ, WISC-IV Functional Acuity Contrast Test				CAST, Go/No-Go task
Sheyang Mini Birth Cohort (SMBCS)	2009					GDS (DQ)				China-WISC			

Misc - 1. Go/No-Go task, Sternberg working memory task, visuospatial N-back task, WCST, Dynamic Social Gestures task, Pyramid and Palm Trees task; fNIRS.
Misc - 2. Adapted Self-Reported Behavior and Self-Reported Delinquency, Adapted ACE survey (age 10 y).
Misc −3. Self-reported delinquency, behavior scales (16 y).
Abbreviations: ABR: Auditory brainstem response; ANS: Autonomous nervous system; BASC: Behavioral Assessment System for Children; BRIEF: Behavior Rating Inventory of Executive Function; BSID: Bayley Scales of Infant Development; CAST: Childhood Autism Spectrum Test; CBCL: Child Behavior Checklist; GDS: Gesell Developmental Schedule; HC: Head circumference; K-CPT: Conners' Continuous Performance Test – Kiddie Version; NEPYS: Developmental Neuropsychological Assessment; NNNS: NICU Network Neurobehavioral Scale; PDMS: Peabody Developmental Motor Scales; SDQ: Strengths and Difficulties Questionnaire; SRS: Social Responsiveness Scale; TAC: Teller Acuity cards; VA: Visual Acuity; WISC-IV: Wechsler Intelligence Scale for Children; WPPSC-III: Wechsler Preschool and Primary Scale of intelligence.

chemicals assayed, or are publications curated for pesticides that are topical or statistically significant?

Biomonitoring was the most common method of exposure assessment in the reviewed publications. Most relied upon a single sample of blood or urine. Using one sample of blood to measure organochlorines is adequate due to their long half-life in the body [25]. However, spot samples of short-lived pesticides, the organophosphates in urine for example, only reflect exposure as recently as the past 24 h [3]. Several birth cohorts collected maternal urine up to three times, overcoming limitations of single samples. These include the Generation R [20,43,44], Infantes y Salud Ambiental (ISA) [30], Morelos Mexican cohort [2,33] and the Study of Asian Women and Offspring's Development and Environmental Exposures (SAWASDEE) [32]. Information describing the properties of the assays, including sources of error, variability within and among populations, and validation parameters, would also help to characterize the extent to which reported results are internally valid. Furthermore, additional information regarding the specificity of a metabolite to a particular active ingredient would be helpful to understand the extent to which the material measured in a biospecimen is indicative of exposure to the parent chemical.

While most publications assessed exposure by analyzing biospecimens, several defined exposures based on proximity (values ranged from one to eight kilometers (km)) of a participant's residence to a pesticide application. This methodology assumes that the likelihood of exposure is consistent among all chemistries. It also assumes that the exposures are homogeneous within the established distance (i.e. from application to one km away) and that weather patterns, such as wind direction, do not affect the off-target exposure. Other studies assessed exposure through questionnaires or interviews. This methodology is subject to several well-known limitations, including the paucity of standardized and validated questionnaires in this area - leading to potential misclassification of exposure, and to possible information bias that can distort the association between exposure and outcome, for instance through self-selection of responders (response bias) or selective recall (recall bias).

Going forward, there are research opportunities to test and validate the assumptions related to exposure, as shown by the following questions regarding proximity to an application:

- How do pesticides differ in their environmental drift? Can this be predicted based on their chemical properties, such that the properties could be included in an exposure model?
- Is one km the appropriate distance? Should it be closer?
- What data are available to support the model? Do these include biological monitoring?
- Can the exposure model be adjusted to include properties of the active ingredient, weather, terrain, characteristics of the home?
- What information is available for a given region regarding time spent at the residence vs. elsewhere, such as for employment?

In general, little information was reported in the reviewed publications to indicate source(s) of exposure for study participants. Notably, Wang et al. evaluated self-reported characteristics such as washing time for fruits and vegetables and being adjacent to an agricultural field with urinary concentrations [46]. Fiedler et al. contrasted urinary concentrations with farmer types and season(s) of peak use [16]. While pesticide residue on food has been attributed metabolite concentrations in urine [49], pre-existing environmental and dietary exposures are usually not distinguishable [9,22], and could not be discerned within the selected studies.

Heterogeneity was also observed in the assessment methods used to characterize health outcomes in the reviewed literature. Almost 100 different tests and tools or variations of such were used from birth to adolescence. Some of this diversity was driven by culture- and age-specific methods. For example, the Snijder-Oomen Nonverbal Intelligence Test is validated for Dutch children and was used in the Generation R cohort [20]. In the HOME study, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and Wechsler Intelligence Scale for Children (WISC) were administered to the children at ages 5 and 8 respectively [14,21].

Specific diagnoses were represented in the case-control studies. In contrast, the outcomes in the birth cohort and cross-sectional studies were generally characterized by scores on individual scales or test batteries, not by a clinical diagnosis. Some studies differed in how the specific components of a test instrument were reported. The variation among publications with regards to the tools and methods used to assess health outcomes makes clear that "developmental neurotoxicity (DNT)" is a toxicology term which has multiple and varied definitions in epidemiology; differences across publications in case definitions and assessment methods have implications on the ability to integrate results. When comparing associations across publications it would be helpful to understand whether each health outcome assessment tool was intended to be used as a screening tool or as a diagnostic test, and whether the results were generalizable beyond the study population. Other reviewers have commented on the distinction of behavioral traits vs. a conclusive clinical diagnosis [4]. Accuracy of screening or diagnostic tests is known to depend in part on participant characteristics, and on prevalence of the health outcome in the study population [24]. This might have implications on the validity of health outcome classification in some publications assessed in this review, as well as on the populations to which the results might be generalizable.

In addition to variations in the actual tests, tests were administered at different ages. Some tests were administered more than once, at different ages in a single study. The BSID is an instrument of multiple tasks used in many of the reviewed studies, typically between six and 36 months. While this test was repeated in several studies, the authors did not evaluate the scores prospectively. In other words, were the same children identified as developmentally delayed (or normal) at six, 12 and 24 months? This has implications for causal inference.

Even though this review considered publications from more than a decade, 2011–2022, the reviewed literature did not represent the full collection period of some of the prospective cohort studies. In other words, for ongoing studies, further publications are to be expected. Further, we evaluated only the publications on pesticides. Publications for studies that evaluated other exposures were not included and may have provided more nuance on outcome ascertainment. The studies themselves were limited in the ages at which tests could be administered by the duration of follow-up. For example, if a particular test for a given health outcome must be administered at an age which transcended the follow-up period, the investigators might have been unable to evaluate certain health outcomes. If a study were to follow participants from birth to age three years, it would not be possible to assess participants for a health outcome if the relevant test were to be administered at adolescence.

Because the objective was to identify the scope of the literature, we did not summarize exposure concentrations for individual pesticides, nor did we extract risk estimates for each outcome-pesticide pair. This approach allowed us to map the breadth of the exposures, outcomes, and ages of assessment without introducing reviewer bias. In this manner, we focused upon the methodology and not size or direction of the associations. This permitted us to identify opportunities to improve the status quo of the epidemiologic literature.

Conclusion

This scoping review identified multiple publications and underlying studies on pesticides and neurodevelopment in children, with many cohort studies still ongoing. The wide heterogeneity in the exposures assessed, in the instruments used to classify health outcomes, and the combinations of the two, may reduce the robustness of the evidence to evaluate specific risk estimates for a particular exposure-outcome pair. Pooling estimates from studies with differing populations, and

inconsistent study designs and statistical models is not recommended [5].

Going forward, more intentional coordination of approaches across investigations would generate evidence that could be summarized in a more meaningful way. Research opportunities exist to address some of the assumptions implicit in the reviewed studies, as shown by the following example questions:

- Does the exposure assessment tool accurately quantify exposure to a specific chemical of interest?
- Are there chemical properties of the exposure which might affect the validity of exposure assessment?
- Is the outcome assessment tool intended to be used as a diagnostic tool (as opposed to a screening tool)?
- Does the outcome classification have clinical relevance?

The scope of exposure assessment methods and outcome classification tools can be broad. Coordination among researchers is recommended to achieve consistency in definitions and methodologies to enable synthesis of data among studies and publications. This could be facilitated by interdisciplinary efforts. Expertise in fields such as toxicology and epidemiology could be more aligned to better incorporate contributions from fields such as exposure science, agriscience, pediatrics, and statistics. Public health policies regarding pesticides are best served by overlying human data across existing laboratory and animal data.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

JER is an employee of Bayer Crop Science, United States. FP is an employee of Bayer AG, Germany. CJB consults to the private sector. CJB is a retiree and stockholder of The Dow Chemical Company, United States.

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Appendix. Supplementary data

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