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Exposures to pesticides and risk of cancer: Evaluation of recent epidemiological evidence in humans and paths forward

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Abstract

Knowledge of the role in cancer etiology of environmental exposures as pesticides is a prerequisite for primary prevention. We review 63 epidemiological studies on exposure to pesticides and cancer risk in humans published from 2017 to 2021, with emphasis on new findings, methodological approaches, and gaps in the existing literature. While much of the recent evidence suggests causal relationships between pesticide exposure and cancer, the strongest evidence exists for acute myeloid leukemia (AML) and colorectal cancer (CRC), diseases in which the observed associations were consistent across several studies, including high-quality prospective studies and those using biomarkers for exposure assessment, with some observing dose-response relationships. Though high-quality studies have been published since the IARC monograph on organophosphate insecticides in 2017, there are still gaps in the literature on carcinogenic evidence in humans for a large number of pesticides. To further knowledge, we suggest leveraging new techniques and methods to increase sensitivity and precision of exposure assessment, incorporate multi-omics data, and investigate more thoroughly exposure to chemical mixtures. There is also a strong need for better and larger population-based cohort studies that include younger and nonoccupationally exposed individuals, particularly during developmental periods of susceptibility. Though the existing evidence has limitations, as always in science, there is sufficient evidence to implement policies and regulatory action that limit pesticide exposure in humans and, hence, further prevent a significant burden of cancers.

KEYWORDS

acute myeloid leukemia, cancer etiology, chemical mixtures, cohort studies, colorectal cancer, environmental exposures, IARC monographs, pesticides, policies, primary prevention, regulatory action, susceptibility

What's new?

Most of the evidence suggesting pesticide carcinogenicity in the 2017 International Agency for Research on Cancer report came from animal and mechanistic studies, as the epidemiologic evidence was insufficient to draw conclusions. Here, the authors provide a unique review of 63 epidemiological studies on exposure to pesticides and cancer risk in humans published from 2017 to 2021, with an emphasis on new findings, methodological approaches, and gaps in the existing literature. The review shows there is sufficient evidence for implementing policies and regulatory action to limit pesticide exposure in humans, and hence further prevent a significant burden of cancers.

1 | INTRODUCTION

Knowledge of environmental contributions to cancer development is a crucial prerequisite for primary prevention, the only form of prevention that decreases cancer incidence. While inherited genetic susceptibility plays a role in subsets of human cancers, from human and practical perspectives it is vital to acknowledge that carcinogenic exposures can be modified by policies and behaviors, whether collective or individual (eg, government regulation, occupational safety measures, changes in policies and attitudes toward smoking).[1-8] Exposure to chemicals such as pesticides and secondhand smoke has proven malleable to modification. This has been demonstrated as urinary concentrations of pesticides and tobacco products decrease rapidly after changing to an organic diet or quitting smoking, respectively.[9,10] Many policies on environmental and occupational conditions have achieved positive effects.[1,12]

An extensive literature from research conducted in vitro and in animals demonstrates the biological plausibility of pesticides as carcinogens. It has also shown their action through multiple mechanisms of carcinogenesis. Research has documented the ability of numerous pesticides to induce genotoxicity, hormone disruption, oxidative stress, inflammation, immune modulation and procarcinogen activation.[11-14]

Certainly, evidence of the carcinogenic effects of pesticides is sparser in humans than in animals. However, in humans, it has modestly but steadily grown and continues evolving, partly because of the progressive introduction of molecular epidemiology approaches and techniques some 40 years ago. Today such techniques are widely used, including sensitive biomarkers to more effectively assess exposures and intermediate events.[3,15,16] Early studies focused on occupationally exposed populations. Later, as the diversity of chemicals used to combat pests rapidly rose, studies of nonoccupational populations have proven increasingly relevant; notably, as effects on the endocrine system of low concentrations have emerged. Research efforts have also focused on vulnerable populations, long-term effects and critical windows of susceptibility like prenatal and childhood exposure.[17-19]

Within their long-established program of *Monographs* to identify environmental factors that are carcinogenic hazards to humans,[20] in 2017 the International Agency for Research on Cancer (IARC) published a report that comprehensively evaluated data on five major organophosphate pesticides, some insecticides and one herbicide, with known human exposure: tetrachlorvinphos, parathion, malathion, diazinon and glyphosate. IARC concluded that they were all either "probably carcinogenic to humans" (group 2A) or "possibly carcinogenic to humans" (2B), and suggested genotoxicity and oxidative stress as the most likely modes of action.[21] However, debate still surrounds the pesticides covered by IARC, and resistance to regulation of pesticides remains influential.[22] Most evidence suggesting pesticide carcinogenicity—in the IARC report and elsewhere—has come from animal and mechanistic studies, as the epidemiology literature was insufficient to draw conclusions. Epidemiologic evidence has since increased in both quantity and quality, and now covers many other pesticides that were not included in IARC's review, or in those of other national and international agencies.[23]

The present review focuses on all types of epidemiological studies on exposure to pesticides and cancer risk in humans published between 2017 and 2021. We contextualize this new evidence with the most relevant published reviews, address methodological approaches and gaps in the existing literature and suggest new directions to improve evidence potentially useful to act.

2 | METHODS

While this review is strictly not systematic, we did implement methods frequently utilized in systematic reviews. Titles and abstracts were screened for all papers produced by the literature search. Studies excluded from the primary analyses during title and abstract screening were reviews,[24-26] editorials,[27] animal or in vitro studies,[28] mechanistic studies (even if they used endpoints potentially related to clinical cancer, as epigenetic markers, telomere length, endocrine response),[29-32] papers on study protocols,[33] biostatistics methods papers,[34,35] epidemiological profiles and cohort descriptions,[36,37] risk/exposure assessments[38] and other studies where human cancer was not a primary outcome.[39]

The following search terms were used in PubMed to identify relevant journal articles assessing the relationship between human exposure to pesticides and cancer, which were published in 2017 or later: ("pesticide*"[Title/Abstract] OR "organphosphate*"[Title/Abstract] OR "glyphosate"[Title/Abstract] OR "chlorpyrifos"[Title/Abstract] OR "atrazine"[Title/Abstract] OR "acephate"[Title/Abstract] OR

"Mancozeb"[Title/Abstract]) AND ("cancer"[Title/Abstract] OR "neoplasm"[Title/Abstract] OR "tumor"[Title/Abstract]) AND ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields] OR "cohorts"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields] OR "case-control"[All Fields] OR "cross-sectional"[All Fields]).

Among the papers deemed potentially relevant during title and abstract screening, full text versions were reviewed. During full-text screening, we extracted information on study design, selection methods and characteristics of the study population, methods for exposure and outcome assessment, statistical analyses, notable strengths and limitations and overall findings. Extracted information was organized into tables for comparison and analysis.

We included cohort, case-control, case-cohort and survival studies[40] assessing the relationship between pesticide exposure and cancer incidence, prevalence, survival and markers of severity in humans. Initially, we detected many reviews on various facets of the pesticides and cancer topic that were potentially relevant.[24,41-59] Of them, some[41-50,60,61] are particularly relevant to complement our analysis and address issues that it is unnecessary to repeat in the present paper.

Additional articles were excluded during full-text screening based on quality, using criteria from IARC and from "Strengthening the Reporting of OBservational studies in Epidemiology—Molecular Epidemiology" (STROBE-ME). Criteria comprised the use of clearly defined methods to assess exposure and disease, consideration of potential confounders, susceptibility to recall and/or selection bias, adequate power and descriptions of statistical models used to generate estimates of association, with further considerations for studies using biological samples.[11,62] For example, given the high susceptibility of recall bias in case control-studies of pesticides and cancer (as recently illustrated again by Crump et al.[63]), studies were excluded if exposure was self-reported and assessment occurred many years after the time period of interest, and were not supplemented or validated with other data such as crop/job-exposure matrices or pesticide purchasing records. The exception to this was studies of childhood cancer, where the time between recall and exposure is shorter. Additionally, childhood cancer studies are highly underrepresented, and the case-control studies included provide some of the only evidence available on this vulnerable population.

Frequencies and percentages were reported for study characteristics such as study design, biomarker use for exposure assessment, type of exposure (agricultural or household/urban) and study population. Notable empirical findings from high quality studies were summarized, and full tables of study summary information on all included studies can be found in the tables. Gaps in existing research were noted, with emphasis on underrepresented populations.

3 | RESULTS

In the initial PubMed searches 165 articles published between 2017 and 2021 were found. After exclusion at various phases as explained above, 63 articles[19,61,64-124] were included in the final literature sample (Figure 1).

3.1 | Design and other characteristics of studies

Included research largely fell into one of four categories: (a) large prospective cohort studies, (b) cohort-nested case-control studies and case-cohort studies, (c) population-based case-control studies and (d) hospital-based case-control studies (Table 1).

There were nine large prospective studies.[65,80-85,125,126] Three were occupational cohort studies: the Agricultural Health Study (AHS) in the United States,[125] the AGRICAN cohort study in France,[126] and the AGRICOH Consortium; the latter is a pooled study combining data from ARGRICAN, AHS and other occupational cohorts, including Cancer in the Norwegian Agricultural Population (CNAP), Australian Pesticide Exposed Workers, Victorian Grain Farmers, Korean Multi-Center Cancer cohort (KMCC), United States Marshfield Epidemiologic Study Area Farm cohort (MESA) and Danish Sund Stald Stud (SUS).[64,65] In these cohorts, exposure was assessed at baseline via self-report or through census data; none included biomarkers. The AHS cohort is based in North Carolina and Iowa, and it includes some 57 000 licensed private and commercial pesticide applicators enrolled from 1993 to 1997. Researchers analyzed relationships between binary exposure variables (occupationally exposed vs not exposed), and cumulative and intensity-weighted lifetime days of exposure, a metric that adjusts for factors that influence exposure intensity, for many different pesticides and cancer types.[125] The AGRICAN cohort is a prospective cohort study in France that enrolled 180 060 current and retired farmers from 2005 to 2007. Pesticide exposure was assessed at enrollment with a questionnaire, and incident cancer was assessed via linkage to population-based registries.[126]

Three studies were general population cohorts, with occupation being used to assess exposure through a job exposure matrix (JEM); a JEM is a tool that classifies individuals into likely exposure categories based on time spent in various occupational roles.[127] The studies included the International Childhood Cancer Cohort Consortium[83] (pooled birth cohorts), a Swiss census-based cohort study,[84] and the Canadian Census Health and Environment Cohort.[85] In these studies, subjects occupationally exposed to pesticides were compared to those nonoccupationally exposed.[83,84]

Two of the prospective cohort studies measured dietary exposure to pesticides using food frequency questionnaires for fruit and vegetable intake, and information on organic status, and probable pesticide residue levels from government agricultural databases on farming practices.[80,81] Only one prospective cohort study used biomarkers for exposure assessment.[82]

In contrast to the cohort studies, nested case-control and case-cohort studies typically included prospectively measured biomarkers for exposure assessment (eg, biomarkers measured in biological samples collected at study entry, years before cancers occurred). Some such studies used questionnaires as well; questionnaires and biomarkers often complement each other. These studies are a part of
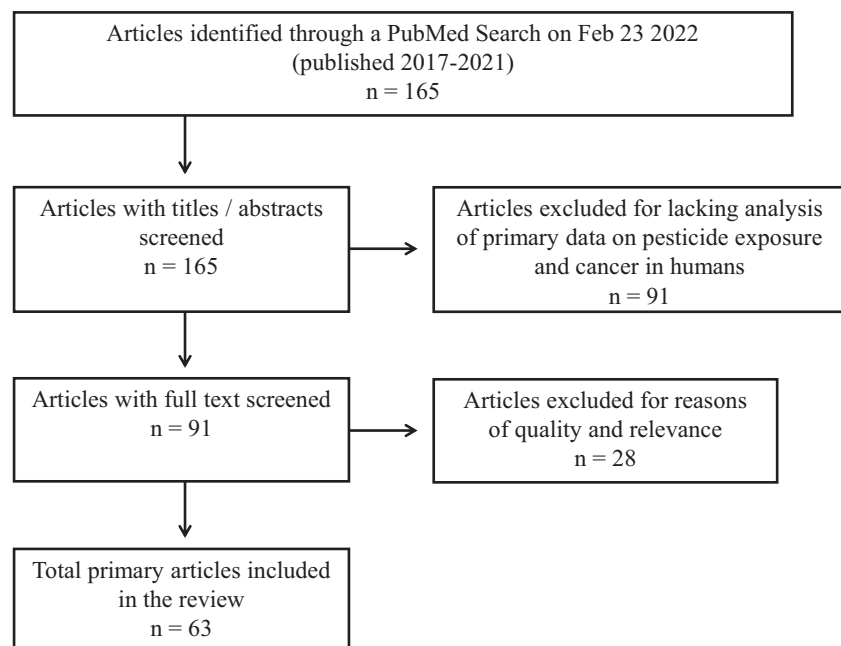
FIGURE 1 Flowchart of inclusion and exclusion of literature

TABLE 1 Summary of the main characteristics of the studies reviewed

Characteristics	N	(%)
Study design		
Prospective cohort	23	36.5
Cohort-nested case-control and case-cohort	10	15.9
Population-based case-control	18	28.6
Hospital-based case-control	8	12.7
Survival	4	6.3
Used biomarkers		
Yes	22	34.9
No	41	65.1
Assessed occupational exposures		
Yes	29	46
No	34	54
Timing of the exposures		
Adult	53	84.1
Prenatal and childhood	10	15.9
Type of exposure[a]		
Agricultural	31	49.2
Residential	6	9.5
Other/not specified	27	42.9

[a]Total does not add up to 100% because one study was both agricultural and residential.

larger cohort studies and, per design, were highly efficient (eg, precise) with small to medium sample sizes (median sample size ~300 participants). Examples include case-control studies nested within the Janus Serum Bank Cohort,[128] a Norwegian population-based biobank established in 1973, and the Danish National Birth Cohort, a population-based birth cohort out of Denmark established in 1996[129] (Table 3).

Population-based case-control studies[94-112] had medium to large sample sizes (median sample size ~1800 individuals). They used population-based data sets from census, and cancer and birth registries. In these studies, exposure was typically assessed via existing data sets, using occupation and job-exposure matrices, or via geographical analysis of proximity to agricultural sites as a proxy for exposure; at other times exposure was self-reported using self-administered or interviewer-administered questionnaires (Table 4).

All hospital-based case-control studies used biomarkers for exposure assessment. Pesticides were quantified in blood samples,[113,114,116-119] or in adipose tissue samples (in breast cancer)[115] if surgery was performed. Less than 8% of the studies assessed whether varying levels of pesticide exposure influenced differences in survival among patients with cancer (Tables 5 and 6).[121-124]

About 10% of the studies assessed prenatal and childhood exposures and the development of cancer in children, while the adult studies typically studied populations in their 50s and 60s. Thirty percent of the studies included only women, 5% of the studies included only men, and 65% of the studies lumped together both genders; several of the latter were occupational studies, which had a large proportion of males.[125] Forty-six percent of the studies assessed occupational exposures. A slightly larger proportion of reports looked at agricultural exposures (including residences near farms). Only six (9.5%) of the reviewed studies specifically assessed residential pesticide use.[78,100,105,107,109,121] About 16% of the studies used prospectively measured biomarkers[19,82,86-88,90-93,124] (Table 1).

3.2 | Main empirical findings

The main empirical findings from the included studies are summarized below and in Tables 2-6 grouped by study design. Two studies from

TABLE 2 Characteristics of studies: Prospective cohort studies

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
AGRICOH Consortium [pooled study of AGRICAN, Agricultural Health Study (AHS), and Cancer in the Norwegian Agricultural Population (CNAP)]	Iowa, North Carolina, France and Norway	Adolescence and adulthood, self-report and census data	Occupational	Togawa, 2021[64]	248 742	Unspecific	Primary cancer diagnosis and several subtypes	Sex	Increased risks were observed for melanoma of the skin (number of cohorts = 3, meta-SIR = 1.18, CI: 1.01-1.38) and multiple myeloma (n = 4, meta-SIR = 1.27, CI: 1.04-1.54) in women; and for prostate cancer (n = 6, meta-SIR = 1.06, CI: 1.01-1.12); all compared to the general population. A lower incidence of several cancers was observed, including cancers of the bladder, breast, colorectum, esophagus, larynx, lung, pancreas and all cancers combined (n = 7, meta-SIR for all cancers combined = 0.83, 95% CI: 0.77-0.90); likely due to the healthy worker effect, less smoking and higher occupational physical activity, as discussed in the article.
AGRICOH consortium Same as above and Australian Pesticide Exposed Workers, Victorian Grain Farmers, Korean Multi-Center Cancer	Iowa, North Carolina, Wisconsin, France, Norway, Denmark, Australia, Korea			Leon, 2019[65]	316 270	Many[a]	Non-Hodgkin's lymphoma (NHL) and subtypes	Animal production, number of crops treated with specific pesticides, retirement status, sex, specific pesticides and state of residence	No observed association for most analyses. Moderately increased risk for NHL observed among ever users of terbufos (meta-HR = 1.18, CI: 1.00-1.39); chronic lymphocytic leukemia/small lymphocytic lymphoma among ever users of deltamethrin (meta-HR = 1.48, CI: 1.06-2.07); and diffuse large B-cell lymphoma and ever users of glyphosate (meta-HR = 1.36,

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TABLE 2 (Continued)

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
cohort (KMCC), United States Marshfield									CI: 1.00-1.85); as well decreased risk of NHL with the broader groups of organochlorine insecticides (meta-HR = 0.86, CI: 0.74-0.99) and phenoxy herbicides (meta-HR = 0.81, CI: 0.67-0.98), but not with active ingredients within these groups, after adjusting for exposure to other pesticides.
AGRICAN (farmers)	France	Adulthood, self-report	Occupational	Tual, 2019[66]	155 192	Unspecific	Multiple myeloma (MM)	(Sensitivity analyses) body mass index (BMI), correlated exposure, gender, personal protective equipment	Increased risk of MM in farmers who started using pesticides on crops in the 1960s, especially among those applying pesticides on corn (≥20 years: HR = 1.73, CI: 1.08-2.78) and using insecticides on animals (HR = 1.48, CI: 1.11-1.98), especially among horse farmers (≥10 years: HR = 2.77, CI: 1.22-6.27)
				Piel, 2019[67]	170 858	Carbamates	Central nervous system tumors (CNST)	Gender, occupational status, educational, familial status, history of allergic diseases, tobacco smoking/alcohol consumption	Increased risk of CNST with overall exposure to carbamate fungicides (HR = 1.88, CI: 1.27-2.79) carbamate herbicides (HR = 1.44, CI: 0.94-2.22). Positive associations were observed with specific carbamates, including some fungicides (mancozeb, maneb, metiram) and herbicides (chlorpropham, propham, diallate)
				Boulanger, 2018[68]	148 044	Unspecific	Lung cancer	Cattle and horse farming, gender, smoking status	Increased risk of small cell lung cancer (HR = 2.38, CI: 1.07-5.28 for pesticide use on peas and increased risk of

TABLE 2 (Continued)

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
				Piel, 2017[69]	146 745	Unspecific	CNST	Age, alcohol consumption, education, gender, smoking status	squamous cell carcinoma for pesticide use on beets (HR = 1.47, CI: 0.92-2.34) Increased risks of CNST in farmers, especially in pesticide users (HR = 1.96, CI: 1.11-3.47). Associations varied with tumor subtypes and kinds of crop and animal farming. Increases in risk were observed for meningiomas in pig farmers and in farmers growing sunflowers, beets and potatoes and for gliomas in farmers growing grasslands
				Lemarchand, 2017[70]	181 842	Unspecific	Primary cancer diagnosis and several subtypes	N/A	Overall cancer incidence in the cohort and the general population were the same. SIRs were significantly higher for prostate cancer (SIR = 1.07, CI: 1.03-1.11) and non-Hodgkin lymphoma (SIR = 1.09, CI: 1.01-1.18) among men, skin melanoma among women (SIR = 1.23, CI: 1.05-1.43) and multiple myeloma (men: SIR = 1.38, CI: 1.18-1.62; women: SIR = 1.26, CI: 1.02-1.54). In contrast, SIRs were lower for upper aero-digestive tract and respiratory cancers.
				Boulanger, 2017[71]	148 051	Unspecific	Bladder cancer	Gender, smoking status	Increased risk among field-grown vegetable workers (HR = 1.89, CI: 1.20-0.99), with an exposure-response relationship with duration of work (≥30 years HR = 2.54, CI: (1.11-5.83), and higher risk among women (HR = 3.82, CI: (1.58-9.25). Nonsignificantly increased

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TABLE 2 (Continued)

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
									risks were also observed in greenhouse farmers (HR = 1.95), pea sowing (HR = 1.84), rape sowing (HR = 1.64); seed treatment (HR = 1.24); and in activities and tasks potentially exposing to arsenic compounds via pesticide use (HR = 1.49) or re-entry tasks (HR = 1.63).
Agricultural Health Study (pesticide applicators)	Iowa, North Carolina	Adulthood, self-report	Occupational	Lerro, 2021[72]	53 096	Many[a]	Thyroid cancer	Age, applicator type, BMI, correlated pesticides smoking status, state	Increased risk of thyroid cancer with exposure to fungicide metalaxyl (HR = 2.03, CI:1.16-3.52) and organochlorine insecticide lindane (HR = 1.74, CI: 1.06-2.84) Decreased thyroid cancer risk was observed with exposure to herbicide chlorimuron-ethyl when analysis restricted to papillary thyroid cancer, the most common subtype (HR = 0.52, CI: 0.28-0.96). Decrease risk of thyroid cancer was observed with o high use of the insecticide carbaryl (HR = 0.20, CI: 0.08-0.53)
				Andreotti, 2020[73]	55 837	Many[a]	RCC	Age, BMI, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) use, smoking status, state	Increased risk of RCC among the highest users of 2,4,5-T compared to never users unlagged rate ratio for intensity-weighted days (RR$_{IWD,T3}$ = 2.92, CI: 1.65-5.17), with similar risk estimates for lagged exposure (20-year lag RR$_{IWD,T3}$ = 3.37, CI: 1.83-6.22). In 20-year lagged analyses, there were exposure-response associations with

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TABLE 2 (Continued)

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
									chlorpyrifos ($RR_{IWD,Q4}$ = 1.68 CI: 1.05-2.70), chlordane ($RR_{IWD,T3}$ = 2.06, CI: 1.10-3.87), atrazine ($RR_{IWD,Q4}$ = 1.43, CI: 1.00-2.03), cyanazine (RR_{IWD} Q4 = 1.61, CI: 1.03, 2.50), and paraquat (RR_{IWD} > Median = 1.95, CI: 1.03-3.70)
			Dicamba	Lerro, 2020[74]	49 922		Primary cancer diagnosis and several subtypes	Age, applicator type, education, imazethapyr use, family history of cancer, ethnic, sex, smoking history, state Cancer-specific models had additional adjustments	Increased risk of liver and intrahepatic bile duct cancer for highest quartile of diacamba exposure (RR_{Q4} = 1.80, CI: 1.26-2.56) and chronic lymphocytic leukemia (CLL) (RR_{Q4} = 1.20, CI: 0.96-1.50) Decrease risk of myeloid leukemia for highest quartile of diacamba exposure (RR_{Q4} = 0.73, CI: 0.51-1.03)
			Many[a]	Pardo, 2020[75]	8933		Aggressive prostate cancer (PCa)	Family history of prostate cancer, ethnic, smoking status, state, year of birth	Increased risk of PCa among ever users of the organodithioate insecticide dimethoate (HR = 1.37, CI: 1.04-1.80) compared to never users Inverse association between aggressive PCa and the herbicide triclopyr (HR = 0.68, CI: 0.48-0.95)
			Unspecific	Lerro, 2019[76]	89 656		Primary cancer diagnosis and several subtypes	N/A	AHS cancer incidence was lower than the general population (standardized incidence ratio [SIR] private = 0.91, CI:0.89-0.93; SIR spouse = 0.89, CI:0.86-0.92; SIR commercial =0.83, CI:0.76-0.92), with deficits across applicators and spouses for oral cavity,

(Continues)

TABLE 2 (Continued)

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
				Andreotti, 2018[61]	54 251	Glyphosate	Any cancer, leukemia, central nervous system tumors (CNST), lymphoma, non-CNS solid tumors	Age, alcohol consumption, cigarette smoking status, family history of cancer, the five pesticides most highly correlated with glyphosate, state	pancreas and lung cancers. Cancer excesses included prostate cancer, lip cancer, certain B-cell lymphomas, AML, thyroid cancer, testicular cancer and peritoneal cancer. Increased risk, though not statistically significant, of AML among applicators in the highest exposure quartile, compared to never users (RR = 2.44, CI: 0.94-6.32) Results for AML were similar with a 5-year (RR$_{Q4}$ = 2.32, CI: 0.98-5.51) A statistically significant association was observed for 20-year exposure lag. (RR$_{T3}$ = 2.04, CI: 1.05-3.97)
				Engel, 2017[77] Note: AHS spouses are the population for our study	30 594	Many[a]	Breast cancer	All other pesticides associated with breast cancer, combined parity/age at first birth, ethnic, state	No evidence of association between insecticides and breast cancer risk. Increased risk among women who had ever used the organophosphates chlorpyrifos (HR = 1.4, CI: 1.0-2.0) or terbufos (HR = 1.5, CI: 1.0-2.1)
				Louis, 2017[78] Note: AHS spouses are the population for our study	28 909	Organocholorine pesticides: aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene	Primary cancer diagnosis and several subtypes	N/A	Most cancers were not associated with OC use. Increased risk of glioma was observed among users of at least one OC (RR = 3.52, CI: 1.72-7.21) and among lindane users (RR = 4.45, CI: 1.36-14.55). Increased risk of multiple myeloma was associated with chlordane (RR = 2.71, CI: 1.12-6.55).

TABLE 2 (Continued)

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
				Bonner, 2017[79]	49 812	Many[a]	Lung cancer	Age, sex, smoking status, total lifetime pesticide use	Increased incidence in the highest exposure category of lifetime days of use for pendimethalin (HR = 1.50, CI: 0.98-2.31), dieldrin (1.93; 95% CI: 0.70, 5.30), and chlorimuron ethyl (HR = 1.74, CI: 1.02-2.96). The HRs for intensity-weighted lifetime days of use of these pesticides were similar.
Nurses' Health Study, Nurses' Health Study II, Health Professionals Follow-up Study	United States	Adult, food frequency questionnaire	Dietary	Sandoval-Insausti, 2021[80]	180 316	Unspecific	Primary cancer diagnosis and several subtypes	Age, alcohol consumption, Alternate Healthy Eating Index score, BMI, colonoscopy in the past 2 years, ethnicity, family history of cancer, height, mammography/prostate-specific antigen testing in the past 2 years, multivitamin use, physical activity, physical examination in the past 2 years, postmenopausal hormone use, regular aspirin use, smoking status, total energy intake	No observed association between high-pesticide-residue FV intake and cancer overall, or risk of specific sites, including malignancies previously linked to occupational pesticide exposure
NutriNet-Santé	France	Adult, food frequency questionnaire	Dietary	Rebouillat, 2021[81]	13 149	Many[b]	Breast cancer	Alcohol consumption, BMI, education, family history of cancer, height, menopausal treatment, overall quality of diet, parity, physical activity, smoking status	Negative associations between Component 3, reflecting low exposure to synthetic pesticides, and postmenopausal BC risk were found (HR$_{Q5}$ = 0.57, CI: 0.34-0.93). Positive association between Component 1 score (highly correlated to chlorpyrifos, imazalil, malathion, thiabendazole) and postmenopausal BC risk was found specifically among overweight and obese women

(Continues)

TABLE 2 (Continued)

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
									$(HR_{Q5} = 4.13$, CI: 1.50-11.44). No associations were detected for the other components.
GraMo Cohort	Granada Province, Southern Spain	Adult, gas chromatography in adipose tissue	Biomarker	Mustieles, 2021[82]	348	p,p'-DDE, HCB, dicofol, α- and β-HCH	Primary cancer diagnosis and some subtypes	Age, alcohol consumption, BMI, education, place of residence, sex, smoking status	Increased risk of nonhormone-dependent cancers (NHDC) for higher concentrations of β-HCH (HR = 1.70; CI: 1.09-2.64), and HCB (HR 1.54, CI: 1.02-2.33). The enzymes superoxide dismutase (SOD) and glutathione reductase (GRd) were also positively associated with the risk of NHDC. Possible mediation effect of SOD and GRd on associations between some pesticides and NHDC.
International Childhood Cancer Cohort Consortium (birth cohorts)	Australia, Denmark, Israel, Norway and United Kingdom	Prenatal, job-exposure matrix	Occupational	Patel, 2020[83]	329 658	Unspecific	ALL, AML, CNS tumors	Stratified by: cohort, Adjusted for child's sex, paternal age	Increased risk, though not statistically significant, of childhood AML for paternal exposures to pesticides (herbicides HR = 3.22, CI: 0.97-10.68; insecticides HR = 2.86, CI: 0.99-8.23, but not ALL or CNS tumors.
Switzerland (census-based, general population)	Switzerland	Childhood, job-exposure matrix	Occupational	Coste, 2020[84]	2 100 548	Unspecific	Any cancer, leukemia, CNST, lymphoma, non-CNS solid tumors	Education, maternal age at birth, parental occupational exposure to benzene, modeled air concentration of NO_2, modeled dose rate of ionizing background radiation, SES	No evidence of an association was found with maternal or paternal exposure for any of the outcomes, except for non-CNS solid tumors (High vs None; Father: adjusted HR = 1.84, CI:1.31-2.58, Mother: adjusted HR = 1.79, CI: 1.13-2.84)
Canadian Census Health and Environment Cohort	Canada	Adult, occupation records	Occupational	Kachuri, 2017[85]	2 051 315	Unspecific	Primary cancer diagnosis and several subtypes	Age, education, province	Among men, increased risks were observed for NHL (HR = 1.10, CI: 1.00-1.21), prostate (HR = 1.11, CI:1.06-1.16), melanoma

TABLE 2 (Continued)

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
(CanCHEC; census-based, general population)									(HR = 1.15, CI: 1.02-1.31) and lip cancer (HR = 2.14, CI: 1.70-2.70). Decreased risks in males were observed for lung, larynx and liver cancers. Among females, increased risks were observed for pancreatic cancer (HR = 1.36, CI:1.07-1.72). Increased risks of melanoma (HR = 1.79, CI: 1.17-2.73), leukemia (HR = 2.01, CI:1.24-3.25) and MM (HR = 2.25, 95% CI = 1.16-4.37) were observed in a subset of female crop farmers

Abbreviations: CI, confidence interval; HR, hazard ratio; IWD, intensity-weighted days; Q4, Quartile 4; Q5, Quantile 5; RR, risk ratio; SIR, standardized incidence ratio; T2, tertile 2; T3, tertile 3.

^aMethyl bromide, aluminum phosphide, metalaxyl, captan, benomyl, chlorothalonil, maneb/mancozeb, chloroacetanilide, alachlor, metolachlor, dinitroaniline, trifluralin, pendimethalin, phenoxy, 2,4-D, 2,4,5 T, 2,4,5-TP, thiocarbamate, butylate, EPTC, triazine, atrazine, cyanazine, glyphosate, dicamba, metribuzin, imazethapyr, petroleum oil, chlorimuron ethyl, carbamate, carbaryl, carbofuran, aldicarb, organochlorine, lindane, DDT, chlordane, heptachlor, aldrin, toxaphene, organophosphate, malathion, chlorpyrifos, diazinon, phorate, terbufos, fonofos, parathion, dichlorvos, coumaphos, pyrethroid, permethrin.

TABLE 3 Characteristics of studies: Nested case-control and case-cohort studies

Study cohort	Study location	Exposure type	First author, year	Sample size	Pesticides	Exposure assessment timing/method	Outcome	Covariates	Findings
European Prospective Investigation into Cancer and Nutrition (EPIC) cohort	Denmark, Sweden, Germany, the UK, the Netherlands, Italy, Spain, Greece, France, and Norway	Biomarker	Porta, 2021[86]	1533	p,p'-DDT, p,p'-DDE, α-HCH, β-HCH, γ-HCH, pentachlorobenzene (PeCB), HCB, trans-nonachlor and oxychlordane	Adult, gas chromatography with plasma (blood drawn years before cancer occurred)	Pancreatic cancer	Study center, sex, age at blood collection, date and time of blood collection, fasting status, total lipids; for women, use of exogenous hormones; BMI, smoking.	Increased risk was observed at higher concentrations of p,p'-DDT, trans-nonachlor (OR upper quartile = 1.55, CI: 1.06-2.26, p-trend = .025), β-HCH and the sum of six organochlorine pesticides (OR upper quartile = 1.48, CI: 1.00-2.20, p-trend = .045). Associations were stronger in the groups predefined as most valid (participants having fasted >6 hours, with microscopic diagnostic confirmation, normal weight, and never smokers). Among participants with a follow-up ≥10 years, estimates were higher than in participants with a shorter follow-up (for trans-nonachlor: OR upper quartile = 2.14, CI: 1.01-4.53, p-trend = .035).
Korean National Cancer Center Community (KNCCC) cohort	Haman, Sancheong, Changwon, Chungju and Chuncheon, Korea	Biomarker	Park, 2021[87]	339	Many[a]	Adult, gas chromatography with serum	Colorectal cancer (CRC)	Age, alcohol consumption, BMI, education, ever use of pesticides, metabolic health status, physical activity red meat consumption, sex, smoking status,	Increased risk of CRC for those exposed to cis-heptachlor epoxide (HR$_{T3}$ = 2.76, CI:1.25-6.07) Dose-response relationships observed for those exposed to trans-nonachlor: (HR$_{T2}$ = 3.90,

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TABLE 3 (Continued)

Study cohort	Study location	Exposure type	Exposure assessment timing/method	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
								vegetable/fruit consumption	CI:1.56-9.75, $HR_{T3} = 4.86$, CI: 1.95-12.16); and p,p'-DDD ($HR_{T3} = 6.02$, CI: 2.05-17.70, $HR_{T3} = 7.43$, CI: 2.42-22.84)
Multiethnic Cohort	Hawaii	Biomarker	Adult, liquid chromatography with urine	Franke, 2021[88]	250	Aminomethyphosphonic acid (AMPA) (glyphosate metabolite)	Breast cancer	Age first live birth, age at menarche, alcohol consumption, BMI, education, family history of breast cancer, hormone use, mammography screening menopausal status, physical activity, smoking status	Increased risk for highest vs lowest quintile of AMPA excretion observed (odds ratio ($OR_{Q5} = 4.49$, CI: 1.46-13.77)
Danish National Birth Cohort	Denmark	Proximity to pesticide using facilities/farmland	Pregnancy, geospatial methods survey	Patel, 2020[89]	9506	Unspecific	Leukemia and Central Nervous System Tumors (CNST)	Animals within 1000 m child gender, maternal age	Increased risk of childhood leukemia among offspring of mothers with increasing crop area near their home (<500 m) compared to no crops (HR_{T3}: 2.6, CI:1.02-6.8) Crops within 500 m of the home were not associated with CNS tumors
Kaiser Permanente Multiphasic Health Checkup Cohort (MHC) and Janus Serum Bank Cohort	Northern California, Norway	Biomarker	Adult, gas chromatography with serum	Engel, 2019[90]	880	o,p'-DDT, p,p'-DDE, p,p'-DDT, β-HCH, γ-HCH, dieldrin, HCB, mirex, heptachlor epoxide, oxychlordane and trans-nonachlor	Liver cancer	Hepatitis B and C status, smoking status, additional adjustment for BMI in the MHC	MHC participants: nonsignificant exposure-response trend for trans-nonachlor ($OR_{T2} = 1.63$, CI: 0.87-3.06, $OR_{T3} = 1.95$, CI: 0.98-3.86) and a nonsignificant elevated risk for the highest tertile of oxychlordane ($OR_{T3} = 1.87$, CI:

(Continues)

TABLE 3 (Continued)

Study cohort	Study location	Exposure type	Exposure assessment timing/method	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
									0.94-3.72). Janus participants: nonsignificant exposure-response trend for p,p'-DDT (OR_{T3} = 1.70, CI: 0.66-4.38, OR_{T3} = 2.14, CI: 0.79-5.75)
Janus Serum Bank Cohort	Norway	Biomarker	Adult, gas chromatography with serum	Bassig, 2019[91]	344	o,p'-DDT, p,p'-DDE, p,p'-DDT, β-HCH, γ-HCH, dieldrin, HCB, mirex, heptachlor epoxide, oxychlordane, and trans-nonachlor	Acute myeloid leukemia (AML)	Matching factors: age at blood draw, county of residence, date of blood draw, sex Adjusted for: smoking status	Increased risk of AML, though not statistically significant, among those with higher serum levels of total chlordane/heptachlor metabolites (OR_{T3} = 2.26, CI:0.91-5.63) Significant exposure-response associations were observed for levels of heptachlor epoxide (OR_{T3} = 2.85, CI: 1.05-7.73) and dieldrin (OR_{T3} = 2.71, CI: 1.07-6.83)
		Biomarker	Adult, gas chromatography with serum	Lerro, 2018[92]	324	DDT, chlordane, HCH, HCB	Thyroid cancer	BMI and smoking status	Increased risk of thyroid cancer among participants born from 1943 to 1957 with higher levels of chlordane metabolites (OR per 10 ng/g = 1.78, CI:1.09-2.93) For individuals born before 1943, associations were generally null or in the inverse direction. Inverse association between DDT metabolites and thyroid cancer (OR per 1000 ng/g = 0.80, CI: 0.66-0.98)

TABLE 3 (Continued)

Study cohort	Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
Child Health and Development Studies	Berkely, CA	Adult, gas chromatography with serum	Biomarker	Cohn, 2019[19]	266	p,p'-DDT, p,p'-DDE and o,p'-DDT	Breast cancer	Age, parity, ethnic	Increased risk of early postmenopausal breast cancer was associated with p,p'-DDT for all women (OR_{DDT} $_{50-54}$ = 1.99, 95% CI = 1.48-2.67). This association was accounted for by women first exposed to DDT after infancy (OR_{DDT} 50-54 for first exposure after infancy = 2.83, 95% CI = 1.96-4.10. In contrast, for premenopausal breast cancer, p,p'-DDT was associated with risk among women first exposed during infancy through puberty, but not after (OR_{DDT} < 50 for first exposure during infancy = 3.70, 95% CI = 1.22-11.26)
Korean Cancer Prevention Study	Korea	Adult, gas chromatography	Biomarker	Lim, 2017[93]	366	Oxychlordane, nonachlor (trans-, cis-), chlordane (trans-, cis-), heptachlor, heptachlor epoxide (trans-, cis-), HCB, HCH (α-, β-, γ-, δ-), p,p'-DDT, o,p'-DDT, p,p'-DDD, o,p'-DDD, p,p'-DDE, o,p'-DDE	Prostate cancer	Age, BMI, smoking status	No evidence of association between organochlorine pesticides and prostate cancer

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; Q4, Quantile 4; T2, tertile 2; T3, tertile 3.
[a]HCB, HCH, β-HCH, g-HCH, d-HCH, heptachlor, cis-heptachlor epoxide, trans-heptachlor epoxide, cis-chlordane, trans-chlordane, oxychlordane, cis-nonachlor, trans-nonachlor, p,p'-DDT, o,p'-DDT, p,p'-DDE, o,p'-DDE.

TABLE 4 Characteristics of studies: Population-based case-control studies

Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
Connecticut	Adult, gas chromatography, serum	Biomarker (all exposure routes)	Deziel, 2021[94]	500	HCB, oxychlordane, trans-nonachlor, HCB, β-HCH, p,p'-DDT, p,p'-DDE and o,p'-DDT	Papillary thyroid cancer	Age, alcohol consumption, BMI, education, family history of cancer	No significant associations between measured pesticides and papillary thyroid cancer risk
British Columbia, Canada	Adult, gas chromatography with plasma	Biomarker (all exposure routes)	Darvishian, 2021[95]	587	aldrin, β-HCH, α-, γ-chlordane, cis-, trans-nonachlor, p,p'-DDT, p,p'-DDE, HCB, mirex and oxychlordane	Cutaneous malignant melanoma (CMM)	Age, education, hair color, moles, skin color, skin reaction to first sun exposure without sunscreen, skin reaction to repeated sun exposure without sunscreen, sun exposure	Increased CMM risk associated with increasing plasma concentrations of several OC pesticides (β-HCH, HCB, Mirex, oxychlordane and trans-nonachlor). For example, compared to lowest plasma concentration quartile of β-HCH, the second, third and fourth quartiles were associated with 1.3 (CI: 0.7-2.3), 2.1 (CI: 1.2-3.7) and 2.3(CI: 1.2-4.4) -fold increased risks of CMM, respectively
Perugia, Florence, Novara, Verona, Cagliari and Nuoro in Sardinia, and Bari and Taranto in Apulia	Adult, survey	Occupational	Meloni, 2021[96]	1641	Glyphosate	Lymphoma and all subtypes	Age, education, gender, study center	Increased risk of follicular lymphoma for those exposed to glyphosate (OR = 7.1, CI: 1.57-31.9). Ever glyphosate use was not associated with lymphoma (with all subtypes combined or with any other subtype).
Gironde, Calvados, Manche and Héraul, France	Adult, survey	Occupational	Baldi, 2021[97]	1788	Unspecific	CNST	NA	For overall agricultural exposure, we observed no increase in risk for all brain tumors (OR = 1.04, CI: 0.69-1.57) and a slight increase for gliomas (OR = 1.37, CI: 0.79-2.39). Risks for gliomas were higher when considering agricultural exposure for more than 10 years (OR = 2.22, CI: 0.94-2.24) and significantly trebled in open field agriculture (OR = 3.58, CI: 1.20-0.70). Increases in risk were also observed in nonagricultural exposures, especially in greenspace workers who were directly exposed (OR = 1.89, 0.82-4.39), and these were statistically significant for those exposed for over 10 years (OR = 2.84, CI: 1.15-6.99).
Andalusia, Spain	Adult, geospatial methods	Proximity to pesticide using facilities/ farmland	Requena-Mullor, 2021[98]	15 963	Unspecific	Ovarian and testicular cancer	Age, environmental pesticide exposure	Increased risk of both ovarian and testicular cancer for those living in higher compared to lower pesticide use region (OR ovarian = 1.41, CI: 1.24-1.60, OR testicular = 1.59, CI: 1.37-1.85)

TABLE 4 (Continued)

Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
Kansas, Nebraska, and six Canadian provinces	Adult, survey	Occupational	Latifovic, 2020[99]	4392	Many[a]	Hodgkin's lymphoma	Age group, province or state of residence, respondent type (proxy, self), sex	HL cases ≤40 years old were three times more likely to report ever using dimethoate (OR = 3.76, CI: 1.02-33.84) and almost twice as likely to have ever used malathion (OR = 1.86, CI: 1.00-3.47). Those ≤40 years of age reporting use of 5 + organophosphate insecticides had triple the odds of HL (OR: 3.00, CI: 1.28-7.03). Longer use of 2,4-D, ≥6 vs 0 years, was associated with increased odds of HL (OR = 2.59, CI 1.34-4.97)
France	Prenatal, survey	Residential	Rios, 2020[100]	1217	Unspecific	Wilm's tumor	Matching factors: child's age and gender. Adjusted for: maternal age, urban status of the area of residence	Increased risk of Wilms' tumor in children for those reporting maternal pesticide use during pregnancy (OR = 1.6, CI: 1.1-2.3). Among insecticides specifically, the association was stronger (OR = 1.7, CI: 1.1-2.6) and even more so when they were used more often than once a month (OR = 1.9, CI: 1.2-3.0)
California	Prenatal, geospatial methods	Proximity to pesticide using facilities/farmland	Park, 2020[101]	9967	Many[a]	Acute lymphoblastic leukemia (ALL) and AML	Matching factors: birth year, Adjusted for: mother's ethnic, neighborhood, other carcinogenic pesticide exposure, socioeconomic status (SES)	Increased risks of ALL with exposure to any carcinogenic pesticide (adjusted odds ratio (aOR) = 2.83, CI: 1.67-4.82), diuron (Single-pesticide model, aOR = 2.38, CI: 1.57-3.60), phosmet (OR = 2.10, CI: 1.46-3.02), kresoxim-methyl (OR = 1.77, CI: 1.14-2.75), and propanil (OR = 2.58, CI: 1.44-4.63). Analyses based on chemical classes showed elevated risks for the group of 2,6-dinitroanilines (OR = 2.50, CI: 1.56-3.99), anilides (OR = 2.16, CI: 1.38-3.36) and ureas (OR = 2.18, CI: 1.42-3.34)
California's Central Valley	Adult, geospatial methods	Proximity to pesticide using facilities/farmland	Tayour, 2019[102]	305	Organochlorines, chlorpyrifos, diazinon, 1,3-dichloropropene	Breast cancer	Age, age at menarche, age at menopause, alcohol consumption, BMI, menopausal hormone therapy use, number of births, number of years lived in counties, oral contraceptive use, SES	Increased breast cancer risk among women exposed to chlorpyrifos (OR = 3.22, CI: 1.38-7.53)

TABLE 4 (Continued)

Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
Great Britain	Prenatal, job-exposure matrix	Occupational	Bunch, 2019[103]	5033	Unspecific	Lymphoma (Hodgkin's, Burkitt and non-Hodgkin's)	Matching factors: birth registration subdistrict Adjusted for SES	No one exposure was significantly associated with increased risk within all subgroups and for total lymphoma
San Joaquin Valley of California	Childhood, job-exposure matrix	Occupational	Mills, 2019[104]	189	Many[c]	Breast cancer	Age, age at first full-term pregnancy, family history of breast cancer, number of pregnancies, number of live births, protective clothing used during farm work	Increased odds of breast cancer for those with low compared to medium methyl parathion use compared to no use was significantly associated with (OR = 5.28, CI: 1.17-23.7). This relationship was not significant when comparing high use to no use. No other chemicals were significantly associated with breast cancer.
Costa Rica	Prenatal, survey	Residential	Hyland, 2018[105]	828	Unspecific	ALL	Birth year, child sex, SES	Significant associations between maternal insecticide use inside the home in the year before pregnancy, during pregnancy and while breastfeeding; use during such periods was associated with increased risk of ALL among boys: (aOR = 1.63, CI: 1.05-2.53, 1.75, 1.13-2.73 and 1.75, 1.12-2.73, respectively). Observed dose-response relationships between the frequency of pesticide use in the home in the year before pregnancy, during pregnancy, and while breastfeeding and ALL among boys and girls: OR comparing high to low = 1.56, CI: 1.07-2.27, 1.58, 1.08-2.31, 1.56, 1.07-2.29, respectively)
Spain (Asturias, Barcelona, Cantabria, Girona, Gipuzkoa, Huelva, Leon, Madrid, Navarre, and Valencia)	Adult, geospatial methods	Proximity to pesticide using facilities/farmland	García-Pérez, 2018[106]	1963	Unspecific	Breast cancer	Matching factors: age, and province of residence Adjusted for: age at menarche, age at first birth, BMI, family history of breast cancer, education, menopausal status, previous biopsies	Increased risk for individuals within 2 km of industries releasing pesticides (OR = 2.09, CI: 1.14-3.82)

TABLE 4 (Continued)

Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
France	Prenatal, survey	Residential	Vidart d'Egurbide Bagazgoïtia, 2018[107]	35 539	Unspecific	Brain tumors	Matching factors: age gender Adjusted for child's birth year, size of the urban unit of residence, type of housing	Increased risk of childhood brain tumor for those reporting maternal home use of pesticides during pregnancy (OR = 1.4, CI 1.2-1.8) and specifically with insecticide use (OR = 1.4, CI: 1.2-1.8)
France	Adult, geospatial methods	Proximity to pesticide using facilities/farmland	Carles, 2017[108]	1470	Unspecific	Brain tumors	Age, alcohol consumption, education, gender, mobile phone use, occupational exposure to pesticides, tobacco consumption	Increased risk of meningioma for those with proximity to open field crops above the 75th percentile (OR = 2.30, CI 1.04-5.10). No significant association was found between glioma and proximity to agricultural land.
France	Prenatal, survey	Residential	Rios, 2017[109]	2140	Unspecific	Neuroblastoma (NB)	Matching factors: age gender Adjusted for: child's birth year, child's sex, size of the urban unit of residence, type of housing	Increased risk of NB observed for those with prenatal use of any type of pesticide (OR = 1.5, CI: 1.2-1.9). The most commonly used type of pesticides were insecticides and an increased risk of NB was associated with their use alone (OR = 1.4, CI: 1.1-1.9) or with other pesticides (OR = 2.0, CI: 1.1-3.4)
Connecticut	Adult, job-exposure matrix	Occupational	Zeng, 2017[110]	960	Unspecific	Thyroid cancer	Age, alcohol consumption, benign thyroids disease, BMI, family history of thyroid cancer, gender, physical activity ethnic, smoking,	Increased risk of thyroid cancer for individuals ever occupationally exposed to biocides(OR = 1.65, CI: 1.16-2.35) and the highest risk was observed for high cumulative probability of exposure (OR = 2.18, CI: 1.28-3.73). The observed observations were similar when restricted to papillary thyroid cancer and well-differentiated thyroid cancer.
South of Brazil	Adult, occupational records	Occupational	Boccolini, 2017[111]	3951	Unspecified	Death from non-Hodgkin's lymphoma (NHL)	Education, ethnic, sex, state	Increased risk of death by NHL was observed for agricultural workers (vs nonagricultural workers) aged 20-39 years (OR = 2.06, CI: 1.20-3.14)

(Continues)

Study location	Exposure assessment timing/ method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
Minnesota	Adult, survey	Occupational	Poynter, 2017[112]	2073	Unspecified	AML and myelodysplastic syndromes	Age, exposure to chemotherapy, lived on farm or in rural area for ≥1 year, sex	Pesticides and agricultural chemicals were not significantly associated with AML or MDS.

TABLE 4 (Continued)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

a Organophosphate, chlorpyrifos, diazinon, dimethoate, famphur, fonofos, malathion, phorate, terbufos, organochlorine, aldrin, chlordane, dieldrin, DDT2, lindane, methoxychlor, carbamate, carbaryl, carbofuran.

b Pendimethalin, trifluralin, oryzalin, ethalfluralin, benefin, propyzamide, isoxaben anilide, boscalid, propanil, propiconazole, tebuconazole, fenbuconazole, triadimefon, S-metolachlor, metolachlor, iprodione, ziram, maneb, mancozeb, metam-sodium, methyl-bromide, 1,3-dichloropropene, carbaryl, thiodicarb, dicofol, chlorpyrifos, dimethoate, malathion diazinond, phosmet, acephate, methidathion, S,S,S-tributyl phosphoro trithioate, permethrin, bifenthrin, S-cyper methrin, chlorothalonil dicloran, simazined, pymetrozine, diuron linuron, glyphosate, oxyfluorfen, paraquat dichloride, propargite norflurazon thiophanate methyl captan, clofentezine, buprofezin, kresoxim, methyl hexythiazox, pyrithiobac, pyraflufen ethyl chlorthal, dimethyl.

c Endosulfan, captan, dicofol, malathion, mancozeb, maneb, methyl parathion, 1,3-dichloropropene, propargite, parathion, simazine, triflurin, 2,4-D, toxaphene, chlordane, aldrin, dieldrin, lindane.

the AGRICOH consortium were published during the time period of interest. Togawa and colleagues examined the incidence of primary cancer diagnosis and specific subtypes in the occupational cohorts compared to the general population; in women, they found increased risks for melanoma of the skin (meta-SIR = 1.18, CI: 1.01-1.38) and multiple myeloma (meta-SIR = 1.27, CI: 1.04-1.54), and in men, for prostate cancer (meta-SIR = 1.06, CI: 1.01-1.12). They also observed a deficit for the incidence of cancers of the bladder, breast, colorectum, esophagus, larynx, lung, pancreas, and all cancers combined (meta-SIR for all cancers combined = 0.83, 95% CI: 0.77-0.90).[64] The other AGRICOH study specifically investigated non-Hodgkin's lymphoma (NHL), and observed an increased risk for NHL among ever users of terbufos (meta-HR = 1.18, CI: 1.00-1.39); for chronic lymphocytic leukemia/small lymphocytic lymphoma among ever users of deltamethrin (meta-HR = 1.48, CI: 1.06-2.07); and for diffuse large B-cell lymphoma in ever users of glyphosate (meta-HR =1.36, CI: 1.00-1.85; Table 2).[65]

In an analysis from the AHS focused on thyroid cancer, an increased risk of this cancer was found with exposure to metalaxyl (hazard ratio (HR) = 2.03, confidence interval (CI): 1.16-3.52), and lindane (HR = 1.74, CI: 1.06-2.84). High usage of the insecticide carbaryl was inversely associated with thyroid cancer (HR = 0.20, CI: 0.08-00.53).[72] Another AHS analysis that examined renal cell carcinoma (RCC) found, in an unlagged analysis, an increased risk of RCC among ever users of 2,4,5-T compared to never users (RR = 2.92, CI: 1.65-5.17).[73] In a 20-year lagged analysis, exposure-response relationships were observed between RCC risk and chlorpyrifos (RR = 1.68, CI: 1.05-2.70), chlordane (RR = 2.06, CI: 1.10-3.87), atrazine (RR = 1.43, CI: 1.00-2.03), cyanazine (RR = 1.61, CI: 1.03-2.50), and paraquat (RR = 1.95, CI: 1.03-3.70).[73] No associations were observed with glyphosate exposure and solid tumors or lymphoid malignancies overall, nor with non-Hodgkin's lymphoma. An increased risk of acute myeloid leukemia (AML) was observed among the group with highest exposure to glyphosate (RR = 2.44, CI: 0.94-6.32).[61] Other analyses from the AHS suggest that the risk of aggressive prostate cancer is increased by dimethoate use (HR = 1.37, CI: 1.04-1.8) and decreased with triclopyr use (HR = 0.68, CI: 0.48-0.95; Table 2).[75]

The GraMo cohort from Southern Spain was the only prospective cohort study included in this review that used biomarkers for exposure assessment. It found an increased risk of nonhormone-dependent cancer for individuals with increased exposure to β-hexachlorocyclohexane (β-HCH) (HR = 1.70; CI: 1.09-2.64) and hexachlorobenzene (HCB; HR 1.54, CI: 1.02-2.33).[82]

The prospective cohort studies that looked at potential dietary exposures to pesticides in relation to cancer report conflicting findings. Sandovali-Insuati and colleagues found no association between high-pesticide food intake and risk of cancer overall or for specific subtypes.[80] However, Reboulliat et al., in a study looking at pesticide mixtures using Principal Component Analysis (PCA) reported increased risk of breast cancer for overweight and obese women with a higher component 1 score, reflecting high exposures to chlorpyrifos, imazalil, malathion, and thiabendazole (HR$_{Q5}$ = 4.13, CI: 1.50-11.44). They also reported an inverse association between breast cancer risk

TABLE 5 Characteristics of studies: Hospital-based case-control studies

Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
Addis Ababa, Ethiopia	Adult, gas chromatography with serum	Biomarker (all exposure routes)	Mekonen, 2021[113]	100	o,p′-DDT, p,p′-DDD, p,p′-DDE, p,p′-DDT, total DDT, heptachlor, aldrin, heptachlor-epoxide, γ-chlordane, endrin, endosulfan, dieldrin, methoxychlor, dibutyl-chlorendate	Breast cancer	Age, alcohol consumption, contraceptive use, smoking status and others	Mean serum (blood of cases drawn at diagnosis) level of p,p′-DDE, p,p′-DDT, heptachlor, gamma-chlordane, endosulfan, and dibutyl-chlorendate were significantly higher in the serum of breast cancer patients than the controls. An increased risk was observed for each unit increment of the concentration of p,p′-DDT (aOR = 2.03, CI: 1.041-3.969) and γ-chlordane (aOR = 3.12, CI; 1.186-8.203).
Delhi, India	Adult, gas chromatography with whole blood	Biomarker (all exposure routes)	Sharma, 2019[114]	200	α-HCH, β-HCH, γ-HCH, dieldrin, endosulfan-I, endosulfan-II, p,p′-DDT, p,p′-DDE, heptachlor	CA-125, endothelial ovarian cancer	Age, drinking water source family history, parity	Significantly higher levels of β-HCH, endosulfan-I, endosulfan-II, p,p′-DDT, p,p′-DDE and heptachlor were found in cases than controls
Shantou city, China	Adult, gas chromatography with adipose tissue	Biomarker (all exposure routes)	Huang, 2019[115]	374	DDT and DDE	Breast cancer	Age, age at menarche, menopausal status	Significantly increased risk of breast cancer for women in higher tertiles of DDE (OR = 1.63, CI: 1.15-2.85). No association between breast cancer and DDT
Kerman, Iran	Adult, gas chromatography with serum	Biomarker (all exposure routes)	Mortazavi, 2019[116]	87	α-HCH, β-HCH, γ-HCH, [2,4-DDT], 4,4-DDT, [2,4-DDE] and 4,4-DDE	Bladder cancer	Matching factors: age, BMI, gender, living area	α-HCH, γ-HCH, 4,4-DDE, 2,4-DDT and 4,4-DDT were significantly higher in BC patients than controls
Kerman, Iran	Adult, gas chromatography with serum	Biomarker (all exposure routes)	Abolhassani, 2019[117]	72	α-HCH, β-HCH, γ-HCH, [2,4-DDT], 4,4-DDT, [2,4-DDE] and 4,4-DDE	CRC	NA	Serum concentrations of all pesticides were higher in CRC patients than in controls
Daegu, Korea,	Adult, gas chromatography with serum	Biomarker (all exposure routes)	Lee, 2018[118]	277	HCH, o,p′-DDE, p,p′-DDE, o,p′-DDT, p,p′-DDT, trans-chlordane, oxychlordane, trans-nonachlor, cis-nonachlor, heptachlor epoxide and heptachlor	Colorectal polyps and cancer	Age, alcohol consumption, BMI, cigarette smoking status, diabetes, family history of CRC, fiber intake physical activity, red meat consumption, sex, weight change	Increased risk of both polyps and cancer (aOR polyps = 2.3, CI: 0.9-5.7, aOR cancer = 3.6, CI:1.1-11.8)

(Continues)

TABLE 5 (Continued)

Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
Greenland	Adult, gas chromatography with serum	Biomarker (all exposure routes)	Wielsoe, 2017[119]	164	p,p'-DDT, p,p'-DDE, mirex β-HCH, HCB, cis- and $trans$-nonachlor, aldrin, α-, γ-chlordane and oxychlordane	Breast cancer	Age, breastfeeding, BMI, cotinine, parity	The serum levels were significantly higher in cases compared to controls for the majority of the compounds, and after adjusting for age the difference was maintained for the sum of all organochlorine pesticides, and p,p'-DDE
Qingdao, China	Adult, gas chromatography with adipose tissue	Biomarker (all exposure routes)	He, 2017[120]	102	β-HCH, γ-HCH, PCB28, PCB52, pentachlorothioanisole (PCTA) and p,p'-DDE	Breast cancer	NA	Increased risk of breast cancer among those with high concentrations of p,p'-DDE (OR = 0.129, CI: 0.0310-0.542) and PCB52 (OR = 0.656, CI: 0.441-0.976). The other five potential risk factors were not significantly related to breast cancer.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

and component 3 score, reflecting low exposure to synthetic pesticides, and [HR_{Q5} = 0.57, CI: (0.34-0.93); Table 2].[81]

As mentioned, two large, prospective studies looked at the relationship between parental exposure to pesticides, assessed through job-exposure matrices and childhood cancer. In the census-based cohort study in Switzerland, maternal and paternal pesticide exposure increased noncentral nervous system (CNS) solid tumors (high vs none, father: adjusted HR = 1.84, CI: 1.31-2.58; mother: HR = 1.79, CI: 1.13-2.84).[84] No associations were found between parental exposure and leukemia, lymphoma or CNS tumors (Table 2).[84]

The similarly designed analysis of pooled data on more than 329 000 participants from the International Childhood Cancer Cohort Consortium indicated that paternal exposure to pesticides increased the risk of childhood AML (herbicides, HR = 3.22, CI: 0.97-10.68; insecticides, HR = 2.86, CI: 0.99-8.23), but not of acute lymphoblastic leukemia (ALL) or CNS tumors (Table 2).[83]

Several nested case-control studies analyzed data from the aforementioned Janus cohort, a population-based biobank with sera samples prospectively collected from 1972 to 2004 from more than 300 000 Norwegian men and women.[90] In a study assessing the relationship between organochlorine pesticides and thyroid cancer, an inverse relationship between DDT metabolites and thyroid cancer risk was observed (OR = 0.80, CI: 0.66-0.98).[92] Additionally, significant positive exposure-response relationships were seen between chlordane metabolites and thyroid cancer among participants born from 1943to 1957. These findings are compatible with birth cohort effects and with effects specific to certain historic periods.[92] Investigating AML, researchers observed significant exposure-response relationships for heptachlor epoxide (third vs first tertile OR = 2.85, CI: 1.05-7.73) and dieldrin (third vs first tertile OR = 2.71, CI: 1.07-6.83) with AML risk.[91] No statistically significant exposure-response associations with AML risk were observed for other pesticides, although the magnitude of the estimates was substantial for chlordane/heptachlor metabolites (third vs first tertile OR = 2.26, CI: 0.91-5.63) and p,p'-DDT (OR = 2.09, CI: 0.83-5.26; Table 3).[91]

Another study included analyses from two case-control studies nested in different cohorts. Relationships between serum concentrations of organochlorine pesticides and primary liver cancer were assessed separately among the Janus cohort and a Northern Californian Kaiser Permanente cohort in one report.[90] Among Janus participants, an exposure-response relationship was observed for p,p'-DDT (second and third tertile ORs = 1.70, CI: 0.66-4.38, and 2.14, CI: 0.79-5.75, respectively). Among the Californian participants, there was an exposure-response relationship for trans-nonachlor (second and third tertile ORs = 1.63, CI: 0.87-3.06 and OR = 1.95, CI: 0.98-3.86), as well as an elevated risk for the highest tertile of oxy-chlordane (OR = 1.87). None of these relationships were statistically significant (Table 3).[90]

A case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort assessed the relationship between pesticide exposure and pancreatic cancer risk. Increased risk was observed at higher concentrations of p,p'-DDT, trans-nonachlor (OR upper quartile = 1.55, CI: 1.06-2.26), β-HCB and

TABLE 6 Characteristics of studies: Survival studies

Study location	Exposure assessment timing/method	Exposure type	First author, year	Sample size	Pesticides	Outcome	Covariates	Findings
Long Island, NY	Adult, survey	Residential	Niehoff, 2020[121]	1505	Unspecific	Survival after breast cancer diagnosis	Age, education, marital status, parity, ethnic	Inverse association between all-cause mortality of the lawn and garden group of pesticides, for both ever use compared to never use (HR = 0.77, CI: 0.63-0.95) and higher lifetime applications (HR$_{Q4}$ = 0.62, CI: 0.47-0.81). Nuisance-pest pesticides, and all groups combined, were not associated with all-cause or breast cancer-specific mortality.
North Carolina	Adult, gas chromatography, plasma samples	Biomarker (all exposure routes)	Parada, 2019[122]	748	DDT, DDE	Survival after breast cancer diagnosis	Age at diagnosis, BMI, cancer stage, education, ER status, parity/lactation history, ethnic, smoking status	Increased risk of all-cause mortality for those with highest vs lowest DDE tertile and the highest vs nondetectable DDT (HR = 1.95, CI:1.31-2.92 and 1.64, CI: 1.10-2.44), respectively, for 20-year conditional all-cause mortality. Increased risk of 20-year conditional breast cancer-specific mortality among women overall, black women, and white women (HR = 1.69, CI:1.06-2.68, 2.36, 1.03-5.42, and 1.57, 0.86-2.89, respectively).
Copenhagen or Aarhus area, Denmark	Adult, gas chromatography, adipose tissue	Biomarker (all exposure routes)	Roswall, 2018[123]	399	HCH, p,p'-DDE, p,p'-DDT, oxychlordane, trans-nonachlor, cis-nonachlor, heptachlor, dieldrin, HCB	Survival after breast cancer diagnosis, women with adverse prognostic factors.	NA	Inverse association between mortality and all pesticides, except β-HHC, which was not associated with mortality (mortality rate ratio [MRR] = 1.02, CI: 0.87-1.18 per IQR), and dieldrin, which was associated with an increased risk of death (MRR = 1.22, CI: 1.05-1.41 per IQR)
Copenhagen or Aarhus area, Denmark	Adult, gas chromatography, adipose tissue	Biomarker (all exposure routes)	Roswall, 2018[124]	232	HCH, p,p'-DDE, p,p'-DDT, oxychlordane, trans-nonachlor, cis-nonachlor, heptachlor, dieldrin, HCB, PCBs	Survival after NHL diagnosis	Stratified by sex and age. Adjusted for alcohol consumption, physical activity, education, smoking status, waist circumference	Concentrations in adipose tissue of the polychlorinated biphenyls (PCBs) and organochlorine pesticides were not associated with NHL survival.

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, inner-quartile range; Q4, quantile 4f.

the sum of six organochlorine pesticides (OR upper quartile = 1.48, CI: 1.00-2.20; Table 3).[86]

In a case-cohort study nested within the Korean National Cancer Center Community (KNCCC) cohort, a significantly increased risk of colorectal cancer (CRC) was associated with serum concentrations of *cis*-heptachlor epoxide (third tertile HR = 2.76, CI: 1.25-6.07); and significant exposure-response relationships were observed for trans-nonachlor (second tertile HR = 3.90, CI: 1.56-9.75, third tertile HR= 4.86, CI: 1.95-12.16) and *p,p'*-DDD (second tertile HR = 6.02, CI: 2.05-17.70, third tertile HR = 7.43, CI: 2.42-22.84).[87] A different case-cohort study out of Korea looking at prostate cancer found evidence of association between any measured pesticides and prostate cancer.[93] A pilot case-control study including Hawaiian participants that provided urine samples from the Multiethnic Cohort study showed a nearly 4.5-fold increased risk of developing breast cancer in the highest vs lowest quintile of AMPA (a glyphosate metabolite) excretion: Q5 vs Q1 OR = 4.49, CI: 1.46-13.77 (Table 3).[88]

Four population-based case-control studies investigated the relationship between self-reported use of pesticides at home among mothers, and childhood cancer. The Costa Rican Childhood Leukemia study observed significant associations between maternal insecticide use inside the home in the year before pregnancy, during pregnancy, and while breastfeeding; use during such three periods was associated with increased risk of ALL among boys: adjusted OR = 1.63 (CI: 1.05, 2.53), 1.75 (1.13, 2.73) and 1.75 (1.12, 2.73), respectively.[105] They also observed dose-response relationships between the frequency of pesticide use in the home in the year before pregnancy, during pregnancy, and while breastfeeding and ALL among boys and girls: OR comparing high to low = 1.56 (CI 1.07-2.27), 1.58 (1.08-2.31) and 1.56 (1.07-2.29), respectively (Table 4).[105] In the ESTELLE study, a French nationwide population-based case-control study, maternal use of pesticides during pregnancy was associated with the risk of Wilms' tumor in children (OR = 1.6, CI: 1.1-2.3).[100] Among insecticides, specifically, the association was similar: OR = 1.7, CI: 1.1-2.6; when insecticides were used more than once a month, the OR was 1.9 (CI: 1.2-3.0).[100] The two other studies report pooled data from the ESTELLE study and the ESCALE study, another French nationwide population-based case-control study. One showed an association between maternal residential use of pesticides during pregnancy and childhood brain tumors (OR = 1.4, CI: 1.2-1.8). The other reported more specifically on neuroblastoma (NB), and found an increased risk of NB among children prenatally exposed to any type of pesticide (OR = 1.5, CI: 1.2-1.9; Table 4).[107,109]

All eight hospital-based case-control studies used biomarkers (Table 5). Sample sizes were small, especially in two instances.[116,117] All such studies reported more than one positive association. Notably, both Lee et al[118] and Abolhassani et al[117] found relationships between several serum concentrations of pesticides and colorectal cancer. Also Huang,[115] Wielsoe,[119] Mekonen[113] and He,[120] all report statistically significant associations between dichlorodiphenyldichloroethylene (DDE) concentrations and breast cancer.

Three survival studies assessed the survival of patients after a diagnosis of breast cancer, while one assessed survival after a diagnosis of NHL (Table 6). The only of the breast cancer studies to use a biomarker for exposure assessment, and to control for confounding variables[122] found an increased risk of all-cause mortality among the highest vs lowest DDE tertile and the highest tertile vs nondetectable DDT (HR = 1.95 and 1.64, respectively). It also reported an increased risk of 20-year conditional breast cancer-specific mortality among women overall (HR = 1.69), higher for black women (2.36), than for white women (1.57; Table 6). Concentrations in adipose tissue of polychlorinated biphenyls (PCBs) and organochlorine pesticides were not associated with NHL survival.[121]

4 | DISCUSSION

In the years between 2017 and 2021, we found 63 empirical studies of sufficient quality and relevance, which seems a low number compared to other areas of research in cancer and epidemiology (and even lower if compared to studies from clinical specialties as oncology). These studies, in addition to others identified by this review, suffer from some limitations with exposure assessment imprecision, as they rely on crude extrapolations from geographical data or self-report of exposures that may have occurred in the distant past. Clearly, there remain serious gaps in our understanding of exposure-response relationships, structures of confounding, pathways of exposure, and mechanisms of action.

Three of four survival studies assessed patients after a diagnosis of breast cancer; with one studying survival after an NHL diagnoses, hence, there is a clear need for studies to assess the influence of pesticides on clinical progression of cancer, including treatment response.[130]

We next assess the studies main findings adapting some of Austin B. Hill's criteria for causal inference; we applied criteria that are relevant to the aims of this review[131,132] among the criteria he proposed more than 50 years ago during debates about environmental carcinogens.[133] While not all relevant causal criteria can be fully addressed by the research included in this review, we use Hill's framework to contextualize findings and identify gaps hindering causal inference.

4.1 | Temporality

Thirty-three of the 63 studies identified for this review assessed exposure to pesticides prospectively, prior to cancer development.[19,61,64-93] These studies provide the strongest evidence due not only to their prospective and precise exposure assessment, but also due to large sample sizes. Additionally, conversely to case-control and cross-sectional studies, these studies are less susceptible to recall bias, a differential misclassification that tends to bias these studies away from the null.[63] Among these 33 studies, including studies reporting consistent associations of increased risk of AML[61,87,91] and CRC, the causal condition of temporality is fulfilled. Most of these studies report positive associations between pesticide use and cancer. The largest of these studies are from the AGRICOH consortium;

pooled analyses of several prospective cohorts. The studies describe increased risk of NHL associated with terbufos, an organophosphate pesticide with similar chemical properties to glyphosate, and increased incidence of MM and CNST compared to the general population.[64,65] Additionally, studies that used biomarkers prospectively were also likely to report positive associations. The EPIC cohort, with robust covariate adjustment and sensitivity analyses, reported increased risk of pancreatic cancer with exposure to summed organochlorine pesticides, β-HCH, DDT, and trans-nonachlor.[86]

4.2 | Consistency

The existing literature is not well suited to address this consistency criterium, as the studies are highly variable in exposure assessment, dose, timing, latency periods and so forth. Thus, here we describe patterns observed that provide some evidence of consistency and discuss potential reasons for heterogenous findings. Though all studies tested multiple hypotheses and thus some are likely due to chance, all but 6 of 63 studies reported at least one statistically significant positive association between some measure of exposure to pesticides and cancer. Several studies report positive relationships that are robust, with consistent results in sensitivity analyses.[19,61,66,67,72-74,83,84,86,89-92] Further, these studies often assess exposure to several, highly correlated, pesticides. Some analyses were conducted for individual chemicals, sometimes with adjustment for others.[66,125] Sometimes this may be a form of overadjustment, with little significance both from mechanistic and practical standpoints. Adjusting for exposure to correlated pesticides may also introduce multicollinearity, and result in potentially biased and unstable estimates of association.[134]

While study conclusions varied, four out of six studies assessing AML reported evidence of increased risk for subjects with higher exposure to specific pesticides; particularly glyphosate, hepatachlor-epoxide, dieldrin and chlorpyrifos and carbamates.[61,76,83,91,101,112] In Andreotti et al, this risk is insignificant for unlagged models, but significant when considering a 20-year lagged analysis.[61] The studies reporting positive associations include large, prospective studies that measured several individual pesticides; one included prospectively collected biomarkers for exposure ascertainment. In the two exceptions, pesticides overall (rather than specific pesticides) were analyzed; this approach is documented to have weaker associations with AML.[112] Additionally, Coste et al discuss limitations in their analysis, as only three AML cases were in the high exposure category.[84] Results were also consistent across studies looking at CRC: all three studies observed an increased risk of CRC with higher exposure to pesticides.[87,117,118] It is also worthwhile to note that (a) these studies provide evidence of causal relationships between pesticides and different types of cancer, (b) these studies look at pesticides with different mechanisms of action, and (c) to fully conclude that the consistency criteria was fulfilled, more research would be needed on specific individual pesticide-cancer relationships.

Although the body of evidence has increased recently, there are still issues of reproducibility and conflicting findings. One well-known reason for these inconsistencies is the existence of a long latency period for cancer development. IARC states that "experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity".[11] Even cohort studies with the longest follow-up periods, like the AHS, have a roughly 20-year follow-up period; they may thus fail to capture longer-term effects. They may also fail to assess the effects of exposure during critical windows.[125]

Another possible explanation of the apparently conflicting evidence is heterogeneity in unmeasured co-exposures and in exposure (mis)classification.[135] While some studies measured specific pesticides, many measured exposures generally or used various classification schemes to operationalize exposure variables for statistical models. Examples of exposure variables include ever/never use of specific pesticides, cumulative intensity-weighted lifetime days, occupationally exposed vs not, proximity to facilities using pesticides, and serum/tissue levels. While all such practices are acceptable, they complicate comparisons of findings across studies; and such difficulties should not be equated with lack of consistency.[135] However, to fully address this criterium, more research replication efforts are needed.

4.3 | Strength

As cancer is multifactorial, it is not expected for the association between cancer and any individual environmental exposure to be large in magnitude. However, we can assess the strength of an association in response to increasing dosage to assist in inferring causality. Several of the studies identified exposure-response relationships between pesticide exposure and cancer risk in humans of a substantial strength or magnitude.[73,86,87,90-92] These relationships show that increased exposure granularly increases risk, strengthening the claim that the relationship is in fact causal.

4.4 | Plausibility

Several mechanisms have been proposed to explain the observed relationships between cancer and pesticides. Among these are genotoxicity, hormone disruption (particularly acetylcholine esterase inhibition),[136] oxidative stress, inflammation, immune modulation and procarcinogen activation.[11-14] Oxidative stress, a main proposed mechanism, has been connected to cytochrome P-450 induction, resulting in the formation of reactive oxygen species with the ability to cause DNA damage, genome instability and cell proliferation.[137]

4.5 | Coherence

The relationship between exposure to many pesticides and the occurrence of cancer in animal and in vitro studies is well established; it is often summarized in the IARC monographs, for instance.[11,40,136,138-140] In the

primary human studies we reviewed here, there is modest coherence, partly due to the difficulties with exposure imprecision. A major conclusion of this article is that newer, biomonitoring-based designs can resolve some of the issues with coherence in the literature.

4.6 | Specificity

Studies have identified some stronger effects in aging populations, but this is not what is generally considered a specific population. Indeed, in cancer research, specificity is an uncommon causal property: few exposures have unique effects and few cancers are due to exclusive exposures. Accordingly, few studies on pesticides and cancer have assessed specificity directly, such as by identifying control conditions not associated with pesticide exposure. Nevertheless, future studies could sometimes consider specificity; for example, ask whether their findings suggest a specific population with the effects or a specific site of the disease with no other likely explanation. Studies could also assess "falsifier exposures" (exposures tested to confirm specificity of effect of pesticides vs an exposure without biological plausible carcinogenicity), and use "negative controls"[40]; for example, examine associations of pesticides with conditions known to be unrelated to the pesticides. There may also be specific routes of pesticide exposure (eg, dermal, inhalational) that may be most problematic.

4.7 | Analogy

The existence of causal relationships between similar chemicals and cancer increases the likelihood that observed associations are causal. There are several instances of similar environmental chemicals being carcinogenic. For example, formaldehyde, a substance commonly used as a germicide, is known to cause myeloid leukemia, and rare cancers including cancers of the nasal cavity, and nasopharynx.[141] Also, and most notably, ethylene oxide, a chemical used as a pesticide, is recognized as a cause of lymphoma and leukemia.[142]

4.8 | Further suggestions for future work

To improve the validity and relevance of the available knowledge regarding exposure to pesticides and cancer risk in humans, studies must increase in number, diversify and improve in several respects. We need more large population cohort studies that allow for longer latency periods. These cohorts also enable to conduct efficient nested case-control studies using biological samples (collected at baseline) for exposure assessment. More hypotheses need to be tested in younger and nonoccupational cohorts, with emphasis on nonoccupational sources of exposure (as diet) and on developmental periods of susceptibility.

The strengths of the main study designs (large prospective cohort studies, cohort-nested case-control studies with long follow-up) hence deserve greater allocation of funds and wider recognition in regulatory institutions, companies, clinical organizations and the media.

Tools from molecular epidemiology (including environmental, epigenetic, metabolomic, exposomic and proteomic measurements used in population-based studies) can be leveraged in cancer cohorts,[16] as shown, for instance, in recent papers from the European Prospective Investigation into Cancer and Nutrition (EPIC) study,[86,143] or in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO).[144] Also recent is the integration of multi-omics analysis in cohorts as the Norwegian Women and Cancer (NOWAC),[145] and the EPICURE study.[146] Additionally, advances in biomonitoring will also contribute to progress.[147] Such technologies include wearable personal sensors, location trackers and nontargeted methods.[148,149] As cohorts incorporating such technologies mature, evidence will increase in quality and strength as exposure assessment will be a more accurate reflection of real-world exposure. Additionally, multi-omics data will provide rich biological context for mechanisms of environmental carcinogens. Successful adaptation of these techniques and tools remains both a challenge and an avenue for future research.[150,151,152]

Furthermore, humans are rarely subjected to individual environmental exposures, but rather to complex chemical mixtures, and novel methods have been developed to allow for analysis of these mixtures.[153] Low doses of even noncarcinogenic chemicals can act synergistically to contribute to carcinogenesis, and mixtures analysis has long been a concern for researchers.[154,155] In this review there were only three studies that examined interactions of pesticides and other factors in cancer, and no studies that employed statistical methods designed to assess effects of environmental chemical mixtures. More research on chemical-chemical, chemical-(epi)genetic and other interactions and mixtures[156] must be pursued.

Existing evidence is largely from older, occupationally or agriculturally exposed populations; sometimes, studies also used exposure assessment methods with important limitations. While some large prospective cohort studies were conducted, these studies were entirely occupational, not population-based, and relied on self-report of specific pesticide use or crop management to assess exposure, often years after exposure took place.[66,72] These studies are more susceptible to measurement error than studies using biomarkers, and the occupational cohorts cannot be generalized to much of the population at large. Studies that used biomarkers to assess exposure were mostly small hospital-based case-control studies, which collect biological specimens (where exposures are later determined) at the time of diagnosis, often months after the disease is progressing subclinically; hence, they are susceptible to disease progression bias, a form of reverse causality (concentrations of biomarkers may be a result of the disease, not a cause).[40,86] Such studies may also suffer from bias in control selection, particularly when studying gene-environment interactions.[135,157,158]

Of the existing study designs, the design that often balances best exposure assessment methods with sample size and bias control is the cohort-nested case-control study. Unfortunately, only a small number of studies were published in the time period of interest and represent only 15% of the included studies. These studies benefit from

prospectively collected biological samples that cannot be influenced by disease status and integrate all sources of exposure (including food, water or air if appropriate). They are also a part of a larger cohort, which contributes to cost and logistical efficiency.[135] Cases and controls are matched on follow-up time and some potential confounders to efficiently control for confounding and biomarker storage/batch effects (eg, cases and controls are matched on fasting status at blood collection).[86,159] Such study design, while currently underrepresented in the literature, is growing in popularity and is a good option to strengthen the current body of evidence on the relationship between cancer and pesticides.[135]

The current body of research is also lacking representation of urban cohorts and data on residential and food exposure to pesticides. Only 10.5% of the reviewed studies looked at residential pesticide use, and there were no explicit investigations of urban pesticide exposure. While frequently overlooked, cities are an important landscape of pesticide use. The NYC Department of Health and Mental Hygiene released a report in 2017 documenting a total of 6711 gal of liquid and 163 182 pounds of solid pesticide products across city agencies the previous year. This large quantity only represents only a minority of urban pesticide use; comparisons to state commercial pesticide use data revealed that city agency use only accounts for an estimated 3% of liquid pesticides, and 21% of the solid pesticides applied in the city.[160] The level of pesticide use in cities is thus nontrivial, and different soil properties, environmental fate of pesticides and exposure profiles in urban environments warrant further investigation of the unique health burden of urban pesticide use.[161]

4.9 | When is enough evidence enough?

While further research is always needed, the question ultimately is whether the evidence is sufficient to better regulate pesticides on the basis of carcinogenicity. Debates about causality and the sufficiency of evidence to act not new; for instance, causal inference was addressed by Immanuel Kant and other philosophers centuries ago. It was also raised decades ago by Hulka and others in the context of carcinogenesis.[162] It applies both to sufficient evidence to act, when a causal relationship is likely, and to not act, when a causal relationship is unlikely. Hill also emphasized that "all scientific work is incomplete... [and] liable to be upset or modified by advancing knowledge."[133] He added: "That does not confer upon us a freedom to ignore the knowledge we already have or postpone the action that it appears to demand at a given time."[133] Although there are limitations and gaps in the research as well as some discordant findings, there is sufficient evidence for action to regulate pesticides based on their carcinogenicity.

Science has also evolved greatly over the near 60 years since Hill gave his landmark lecture, and scientific studies and institutions have addressed crucial flaws in the risk assessment paradigm leveraged in the European Union, the United States and elsewhere to manage environmental exposures. The conventional paradigm sometimes assumes, in particular, a linear dose-response, which has been shown not to occur in many causal relationships.[40,163] Indeed, the endocrine

system, in particular, has revealed U-shaped (nonmonotonic) and nonlinear exposure-response functions, including for pesticides and developmental neurotoxicity.[164-166]

Conflicting findings and gaps in data have tangible consequences. In 2016, the United States Environmental Protection Agency (US EPA) published an issue paper stating that glyphosate (which, as mentioned earlier, is classified by IARC as probably carcinogenic), is not a carcinogen; and it decided to allow for its continued and increasing use, a decision EPA reaffirmed in 2020.[167,168] The European Food Safety Authority came to a similar conclusion as the EPA in a 2015 report, where they claim glyphosate is "unlikely to pose a carcinogenic threat to humans".[169] The main reason for the opposed conclusions from these authorities is that IARC studied the genotoxic and carcinogenic properties of not only pure glyphosate, but also of glyphosate-based formulations, pesticides where glyphosate is the active ingredient.[170] The evidence of carcinogenicity for glyphosate-based formulations and metabolites is stronger than for technical glyphosate, as co-formulants affect absorption, distribution, metabolism and excretion of glyphosate.[170,171] Additionally, the IARC committee only considers peer-reviewed literature, while the assessments done by EPA and EFSA also considered several industry studies conducted by private companies that register the chemicals in question. In response to the ongoing debate, calls have been made within the scientific community for more independently conducted epidemiological research, particularly among the highest exposed and the most vulnerable populations, as well as for more comprehensive and transparent evaluations by independent agencies.[170,172,173]

5 | CONCLUSIONS

Though high-quality studies have been published since the IARC monograph on organophosphate insecticides in 2017, there are still gaps in the literature for carcinogenic evidence in humans, in addition to a large number of potentially carcinogenic pesticides that were not included in the IARC assessment. Rather consistent and high-quality evidence of carcinogenicity of pesticides exists for AML and CRC. To further knowledge, suggested next steps include leveraging new techniques and methods developed to increase sensitivity and precision of exposure assessment, incorporating multi-omics data and investigating exposures to complex chemical mixtures. Additionally, we identify a need for more large and longer population-based cohort studies, which should include younger, nonoccupationally exposed individuals during developmental periods of susceptibility. Though improved and diversified research is necessary to better understand environmental contributions to cancer, the existing literature provides enough evidence to justify regulatory action that would reduce human exposure to pesticides.

AUTHOR CONTRIBUTIONS

Haleigh Cavalier: Conceptualization, Data curation, Formal analysis, Project administration, Visualization, Writing - Original draft preparation, Writing - review & editing. **Leonardo Trasande:** Conceptualization, Supervision, Writing - review & editing. **Miquel Porta:**

CONFLICT OF INTEREST

The authors have no conflicts of interest in connection with the paper, and declare no competing financial interests.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in our study, and data sources and handling of these data are described in the Materials and Methods and in Tables 2-6. Further information is available from the corresponding author upon request.

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