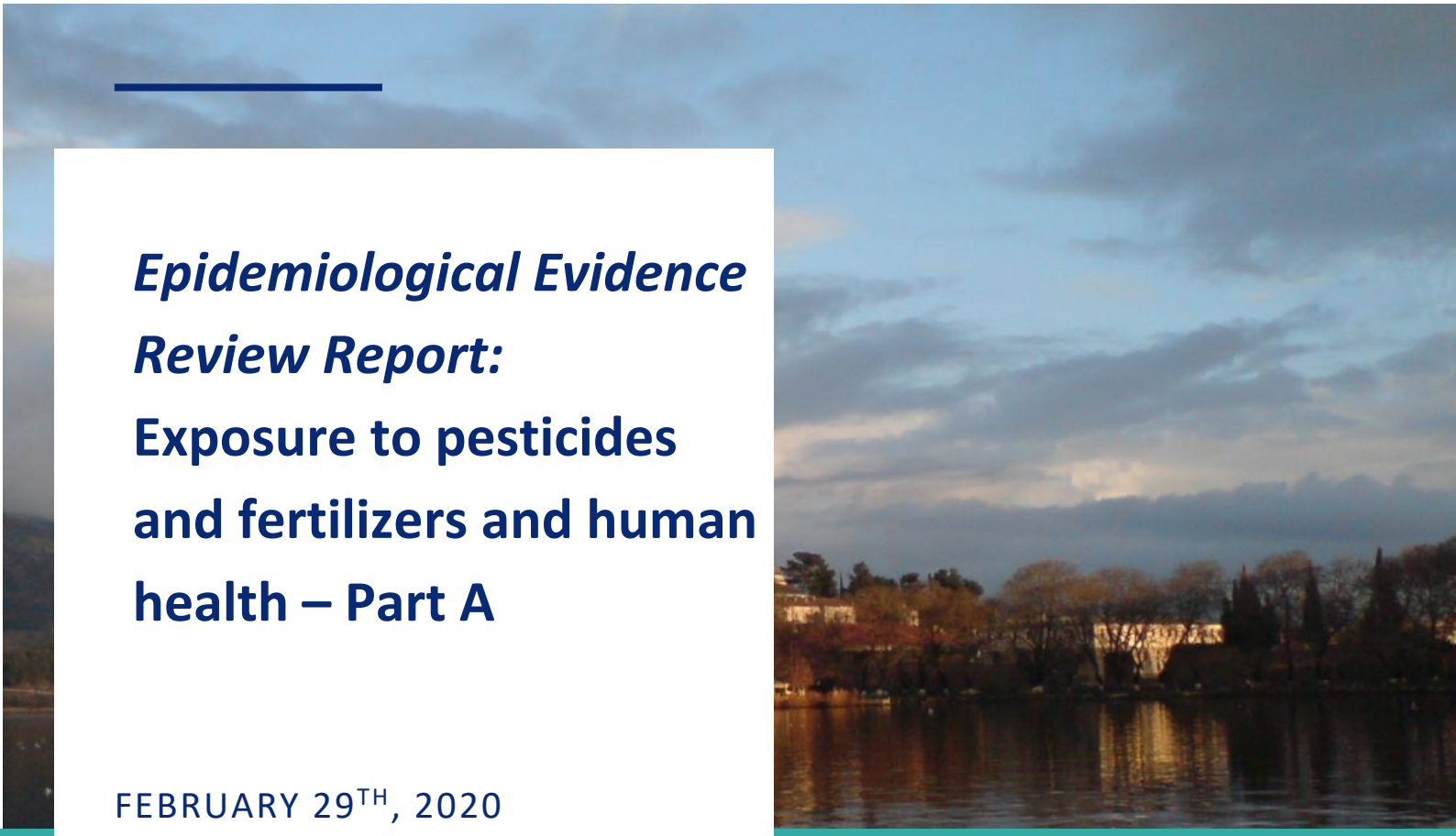
Annex to Environmental and Health Impacts of Pesticides and Fertilizers and Ways of Minimizing Them: Envisioning a chemical-safe world



Epidemiological Evidence Review Report: Exposure to pesticides and fertilizers and human health – Part A

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1 Explanatory Note to the Review Report

The present document was produced as an epidemiological evidence review report in response to the United Nations Environment Assembly resolution 3/4 on "Environment and Health" where the Executive Director was requested to present a report on the environmental and health impacts of pesticides and fertilizers and ways of minimizing them, given the lack of data in that regard, in collaboration with the World Health Organization, the Food and Agriculture Organization of the United Nations and other relevant organizations. The aims of the evidence review report are to update the European Food Safety Authority commissioned report on systematic literature review on epidemiological studies linking exposure to pesticides and health effects published in 2013, and to conduct a systematic review on epidemiological studies linking fertilizers' use and health effects.

The evidence report starts with an overview of the aims and methods implemented to achieve these two objectives. Next, it presents the results of the current effort. It encompasses information on more than 1,000 publications of epidemiological studies on potential associations between pesticides exposure and adverse effects related to human health. It also includes a description of the biomedical literature assessing the association between fertilizers' use and human health. Given the scarcity of the available direct evidence on this matter, a parallel effort was initiated in order to identify how to approach the indirect evidence that could inform the UN report. More specifically, it was hypothesized that the health-related effects of fertilizers' use could be addressed through a tiered approach taking into consideration the various information sources feeding the evidence base. The overall objective was to identify the various attributes formulating the association between fertilizers' use and health-related outcomes and produce a roadmap for future use. This evidence-of-association chain includes the following components: a) fertilizers' use data (frequency, quantity, composition); b) residues occurrence data and source thereof; c) exposure assessment data (including biomarker validity assessment); d) the association matrix including the following: association between biomarkers of exposure and health-related outcome, association between biomarkers of exposure and surrogates of the health-related outcome, association between estimated exposure and health-related outcome, association between estimated exposure and surrogates of the health-related outcome; e) qualitative studies and surveys assessing farmers' and consumers' perspectives about fertilizers' use; and f) research data identifying moderators and modifiers of various patterns of fertilizers' use. As a first step and for the purposes of the ensuing discussions, it was decided to use cadmium as a pilot contanimant and proceed with step d) of the aforementioned process. The plan for this exercise was to: a) retrieve

all systematic reviews and meta-analysis on cadmium indexed in PubMed, b) group publications related to cadmium separately, and c) tabulate the general characteristics of the cadmium-related publications including any mention on fertilizer use. Based on the available body of evidence and its characteristics (cumulative sample size, number of outcomes, robustness of the postulated associations), this approach will be further discussed. Thus, the review also embarked into reporting the results on information on 78 studies linking exposure to cadmium and human health.

2 Pesticides and Human Health

2.1 Methods

The present work is an update of the systematic review commissioned by EFSA and published in 2013 linking exposure to pesticides and health effects; it follows and extends the methodology used previously.[1] By harmonizing the methodology, we aimed to consolidate the two efforts and to construct a complete master database where all studies would be included.

2.1.1 Study Eligibility

We considered observational studies assessing the association between pesticide exposure and health-related outcomes in adult, adolescents, or children. We included cohort, cross-sectional and case-control studies published from January 2012 to June 2019. Ecological studies, narrative reviews, case reports, case series, modeling studies and editorials were excluded. Animal studies and studies performed in human cells were also excluded. To enhance comprehensiveness, all types of pesticides were used with the exception of arsenic/lead, *α-, β*-hexachlorocyclohexane (HCH), dioxins and dioxin-like compounds including polychlorinated biphenyls (PCBs). Exposure to pesticides was defined as reported use of pesticides by the study participant or by government registry data (self-administrated questionnaires, interviewer administrated questionnaires, job exposure matrix), by residential status (proximity to pesticide exposure), by detecting biomarkers associated with pesticide exposure or by any other means as defined by each study. We excluded studies assessing the health-related effect of acute pesticide exposure or accidental pesticide exposure. Likewise, we excluded studies assessing the effects of pesticide poisoning or the effects of pesticides used in chemical warfare (e.g. Agent Orange). Eligible health-related outcomes included “major” clinical outcomes, such as neoplasias or Parkinson’s disease, clinical surrogate outcomes such as neurocognitive scales, or laboratory surrogate outcomes, such as liver enzymes. We excluded studies assessing exposure to pesticides without a link to human health outcome as well as studies where exposure to pesticides was associated to a specific biological pathway or mode of actions via assays or biomarkers not yet clinically validated (e.g. DNA methylation).

We set no language or geographical restrictions. We excluded studies with no availability of sufficient quantitative information reported in the article (e.g., effect estimates and 95% CI thereof, counts and sample sizes, or means - raw or adjusted - as well as standard deviations) so that effect sizes could be calculated. Whenever reports pertained to the same study at different follow-up periods and

examining the same outcome, we retained the one with the longer follow-up to avoid data duplication.

2.1.2 Databases

The following databases were interrogated: PubMed, EMBASE (Excerpta Medica Database), TOXNET (Toxicology Data Network; U.S. National Library of Medicine 2019), OpenSigle (2019), and ProQuest Digital Dissertations and Theses (2019). TOXNET (TOXicology Data NETwork) is a cluster of databases covering toxicology, hazardous chemicals, environmental health and related areas. It is managed by the Toxicology and Environmental Health Information Program (TEHIP) in the Division of Specialized Information Services (SIS) of the National Library of Medicine (NLM). TOXNET provides free access to and easy searching of 16 toxicology-related databases. System for Information on Grey Literature in Europe (OpenSigle) offers open access to bibliographical references of grey literature (paper) produced in Europe.

2.1.3 Search Strategy

The search strategy used in the previous effort was also used here to identify observational epidemiologic studies published between 1st January 2012 to 30th June 2019 and examining the relationship between pesticide exposures during critical exposure time windows (preconception, pregnancy, childhood, adulthood) and any health-related outcome as discussed previously, regardless of the study design. Our search was not restricted by outcome related terms so as to be able to map the studied outcomes related to pesticide exposure and identify emerging outcomes.

More specifically, the algorithm used was: “pesticid* OR 'pesticide'/exp OR 'chemical pest control'/exp OR fungicid* OR 'fungicide'/exp OR herbicid* OR 'herbicide'/exp OR insecticid* OR 'insecticide'/exp OR molluscacid* OR'molluscacide'/exp OR molluscicid* OR 'molluscicide'/exp OR rodenticid* OR 'rodenticide'/exp OR carbamat* OR 'carbamate'/exp OR pyrethroid* OR 'pyrethroid'/exp OR 'chlorinated hydrocarbon'/exp OR 'agricultural chemical'/exp” using “human” limits and restricted to the years 2012-June 2019.

2.1.4 Methodological quality of the assessed evidence

We assessed the methodological quality of the included studies and the risk of bias conferred thereof by using elements included in the RTI item bank (31), which is a practical and validated item bank for

evaluating the risk of bias and precision of observational studies of interventions or exposures included in systematic evidence reviews.

2.1.5 Data Extraction

The following general and methodological information was abstracted from each study: name of authors, country, setting, location(s), and year of publication; periods of recruitment, exposure, follow-up, and data collection; type of epidemiological study (prospective cohort, retrospective cohort, cross-sectional or case control); age, gender; type of pesticide assessed, characteristics of the type of exposure (e.g., occupational/non-occupational), type of questionnaire (if self reported questionnaire was used to define pesticide exposure), type of assay (for biomarkers of exposure), duration (e.g., lifelong or occasional) and frequency, exposure definition and, for pediatric studies, person exposed (mother, father, both parents or child) and period exposed (e.g., pre- or postnatal, preconception, both); control definition; health-related outcome and definition thereof; type and value of the calculated risks (OR, RR, MD) with their 95% CIs or SDs, as well as factors they are adjusted for (confounders). Moreover, we extracted data pertaining to methodological characteristics of the eligible studies as described in the next section. Data extraction was performed by one investigator, cross checked by another and discrepancies were resolved by a third arbitrator. The list of extracted outcomes was finalized following pilot data extraction in a random sample of eligible studies in order to identify areas that need refinement or additional data that need to be extracted.

2.1.6 Construction of database

We created a simple and user-friendly tool in excel for recording all the available evidence of the eligible studies. Each publication will get a unique ID and we recorded the article title with a link leading at the specific publication, the name of the first author, journal, volume and issue of the journal and also the year of publication. Also, from each study we recorded the type of pesticide exposure, the pesticide group, and the number of outcomes/diseases under investigation. Therefore one study may provide evidence for more than one assessment each time. All extracted were imported in a main database secured in the central server of the University of Ioannina.

The database includes information on all extracted items described above such as the type of the study, the pesticide and the outcome/surrogate outcome, the total sample size and sample sizes in cases/controls, features of the population investigated and controls (age, disease status etc.), time periods of investigations/observations, the statistical methods used for evaluation of observations,

confounders, type and amount of exposure, co-exposures, method of exposure assessment, results obtained (2x2 raw counts or Odds Ratios or Relative Risks or mean difference and their variability that it can be assessed with the standard errors or 95% confidence intervals). The criteria related to quality assessment are also be added in the database. The created database can serve as a comprehensive, unbiased, publicly available and regularly updated review of the published literature in the field.

2.1.7 Quantitative data synthesis

The research synthesis endeavor was organized as follows:

Given the diverse network of phenotypes included, there were separate analyses per disease entity assessed. Then, disease entities with a common nosological background were be synthesized further. For example, there was a separate analysis for pediatric exposure and CNS tumors and a further analysis for pediatric exposure and any neoplasia. Similarly, neurodegenerative disease entities were grouped together. Alternatively, system-specific analyses were performed. For example, CNS tumors and Parkinson's disease were considered together for further analysis. Surrogate outcomes were examined separately from clinical outcomes; however, surrogate outcomes validated for the same outcome were analyzed jointly to enhance statistical power. In addition, given the different windows of exposure studied, for each outcome we considered and analyzed separately the different life stages (preconception, conception, childhood and adulthood).

Each quantitative synthesis was associated with evaluations of heterogeneity as well as extensive evaluations of publication and small study bias as described in the statistical analysis section. We further assessed potential associations of the treatment effect with study-level variables in subgroup analyses and meta-regression analyses. Regarding the pesticide exposure, we performed pre-specified subgroup analyses for the type of exposure, the type of pesticide, the setting, the geographical location (continent-wise), and the population age. Finally, meta-regression analyses were performed that considered the pesticide level of exposure (continuous variable).

For binary outcomes, the principal summary measures were the relative risk (RR) and the odds ratio (OR). For each study we retrieved or calculated the adjusted RR and OR estimates and corresponding 95% CIs for the assessed outcomes. For continuous outcomes, we extracted or calculated the summary mean difference (along with the corresponding SD). Whenever an outcome was assessed with different measures or scales, we used the standardized mean difference (SMD). The standardized

mean difference expresses the mean score improvement in standard deviation units, and can be used to directly compare different scales or scores across the individual studies.

The presence of statistically significant heterogeneity was assessed by the Q statistic (significant at $p < 0.10$) and the extent of the observed heterogeneity was assessed by the I^2 (ranging from 0% to 100%) (32). We summarized RR/OR and MD/SMD estimates using random-effects models (33). Fixed-effects models assume that there is a common underlying effect and the variability observed is attributed to chance alone; random effects models acknowledge that true between-study heterogeneity exists and take into account the presence of heterogeneity into their calculations. In the absence of heterogeneity, fixed- and random-effects models yield the same results.

Analyses were performed in STATA 10 (STATA Corp., College Station, IL). All p-values are two tailed. The final report(s) and pertinent publications were reported according to the STROBE and MOOSE statements and checklists (34,35).

2.2 Results

2.2.1 Evidence Base Overview

Regarding the current status of the update, 34,898 citations were retrieved based on our initial database searches. Of these, 33,018 were excluded at the title/abstract level leaving 1,880 for full text scrutiny. 1,267 citations were further excluded at the full text level; reasons thereof included duplicates (20%), studies with no association data available (16%), reviews (14%), mode of action studies (10%), ecological studies (3%), and modeling studies (3%). Thus, 613 publications were included in the present review update. Merging the current with the previous effort, 1,166 publications were included and forwarded for further analysis.

The included studies were published from 2009 to 2019 with no statistically significant differences in the distribution of the publication year. These studies included populations with a global reach; the countries with the largest publication numbers were USA (34%), China (5%), Spain (5%), France (4%), Canada (4%). Continent-wise, the Americas amassed a large number of publications (45%) followed by Europe (29%), Asia (17%) and Africa (4%). Sample size ranged from studies as small as including 37 participants to large cohorts with 1,832,969 participants. Cross sectional studies (34%), cohort studies (29%) and case control studies (36%) were present in comparable frequencies. The cohort studies most frequently encountered were the Agricultural Health Study (8%) and NHANES (4%). The recruitment or data capture periods varied greatly but were largely limited across the 90's and the 00's; few studies were identified using earlier data indicating a shift towards data that can be more adequately generalized. In the available cohort studies, the maximum follow up duration also varied (median, 9 years; IQR, 5-14; range 1-64).

The assessed pesticide exposure period pertained to adulthood (60%), childhood (10%) and preconception or pregnancy (23%) and either a biomarker (67%) or a questionnaire (33%) was used. The exposure setting was either occupational (27%), environmental (22%) or unspecified/both (41%). As expected, the assessed populations pertained to all age groups

The outcomes under study spanned across the whole spectrum of human disease including rare diseases such as progressive supranuclear palsy and common diseases such as hypertension (Box). Parkinson's disease continues to be the disease under study with a large number of studies (10%).

At its current stage the fraction of the database that has undergone quality control pertains to 19,176 postulated associations. Regarding the methodological appraisal of the studies, 12% of the associations under study were supported by crude effect estimates, while in 10% of the pertinent studies no matching is reported. A robust measurement of the exposure via a biomarker was achieved in 54% of the studies and pesticide exposure was compound-specific in 58% of the studies. A balanced allocation was often attempted (60%) and blinding of the assessors was performed in 25% of the pertinent studies. Outcome measurements and definitions were appropriate in the majority of the studies (78%).

Box 2.2.1. Assessed outcomes related to human health

Abnormal glucose regulation, Acute lymphoblastic leukemia, Age of menopause, All-cause mortality, Allergic asthma, Allergic rhinitis, Allergy-related disease, Alzheimer's Disease, late onset, Alzheimer's disease, Amyotrophic lateral sclerosis, Anencephaly, Autism, B-cell Non-Hodgkin lymphoma, BMI, Barrett's esophagus, Behaviour and affect symptoms, Birth weight, Brain tumors, Breast cancer, COPD, Cancer, Cholesterol, Chronic bronchitis, Chronic kidney disease, Chronic myeloid leukemia, Couple fecundity, Cryptorchidism, Depression, Diabetes, Endometriosis, Essential tremor, FSH, Fasting glucose (mg/dL), Free T3, Gastroschisis, Gestational diabetes mellitus, Gestational hypertension, Head circumference, Height, Heterotaxia, High blood pressure, Hodgkin lymphoma, Hyperuricemia, Hypospadias, Hypothyroidism, Idiopathic rapid eye movement (REM), SLE, LH, Left ventricular mass, Length of Gestation, Leptin, Leukemia, Lung cancer, Lymphoma, MDS, Dementia, Metabolic syndrome, Minor psychiatric disorders, Miscarriage, Multiple Myeloma, Non-Hodgkin lymphoma, Nonsyndromic cleft lip and/or palate, Obesity, Oligozoospermia, Overweight, Parkinson's disease, Preterm delivery, Progressive Supranuclear Palsy, Prostate cancer, Pubertal growth, Rheumatoid arthritis, SGA, Stomach cancer, Stroke, Suicidal ideation, Neural tube defects, Thyroid cancer, Urinary bladder cancer, ADHD, benign prostatic hyperplasia, Gastroschisis, Glaucoma, Lower respiratory tract infections, Male genital malformation, 25(OH)D3

2.2.2 Individual compound description and temporal trends

In the following text, we summarize the observed temporal trends for four individual compounds: glyphosate, chlorpyrifos, imidacloprid, and DDT.

For glyphosate, we identified 61 distinct publications that fit our inclusion criteria and that assessed distinct research questions. These reports pertained to cohort studies (N=26), case-control studies (N=18), nested case-control studies (N=6), and cross-sectional studies (N=11). No statistically significant time trend was observed (**Figure 2.2.2.1**).

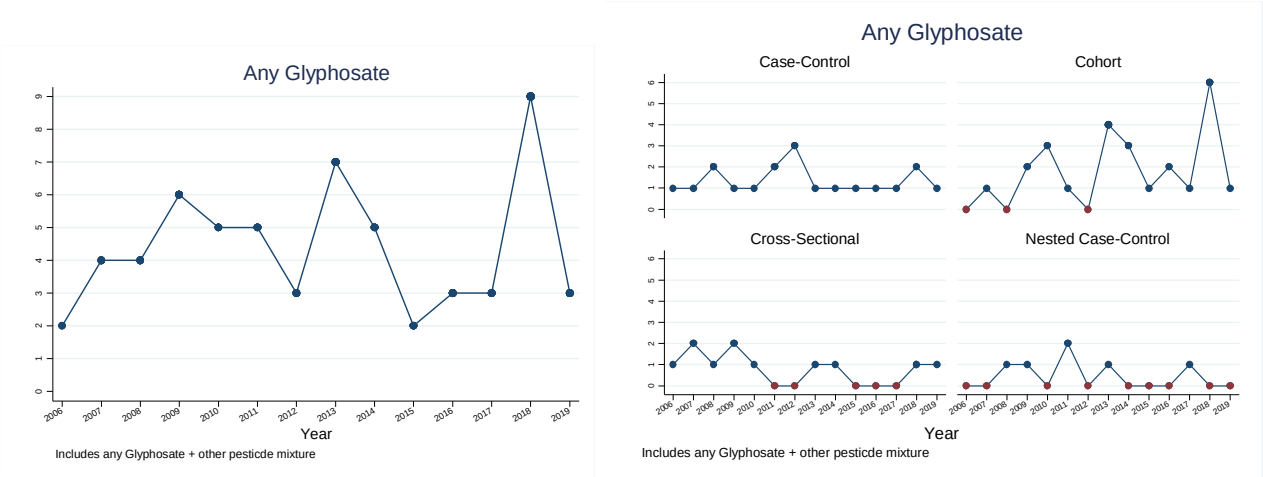


Figure 2.2.2.1 Glyphosate - Evolution over time

For DDT (including consideration of DDT/DDE/DDD), we identified 427 distinct publications that fit our inclusion criteria and that assessed distinct research questions. These reports pertained to cohort studies (N=146), case-control studies (N=76), nested case-control studies (N=34), and cross-sectional studies (N=171). Within this 13-year interval, no statistically significant time trend was observed (**Figure 2.2.2.2**).

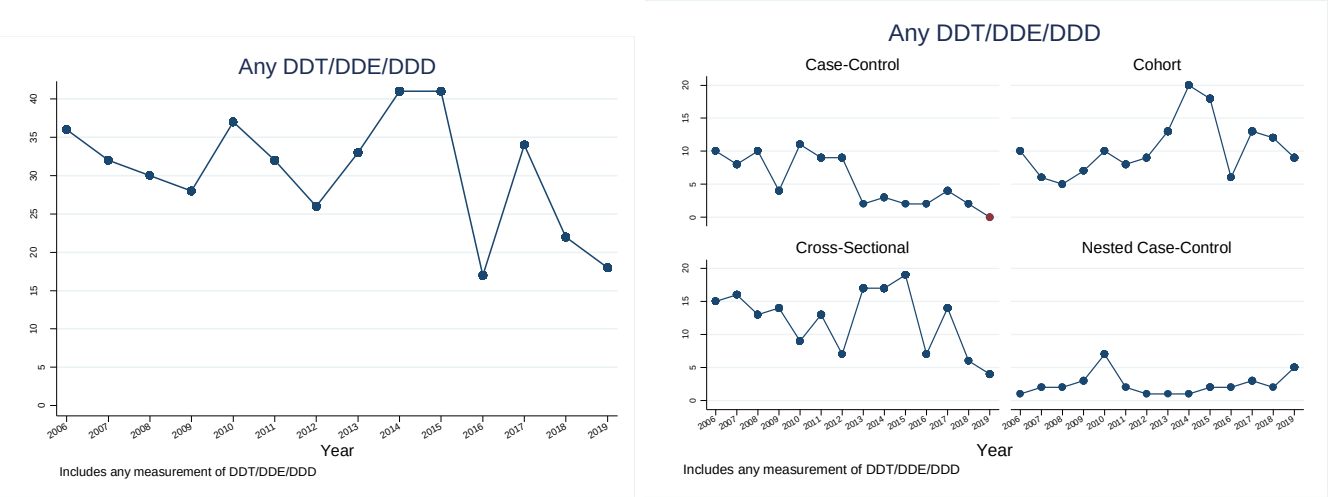


Figure 2.2.2.2 DDT - Evolution over time

For chlorpyrifos, we identified 80 distinct publications that fit our inclusion criteria and that assessed distinct research questions. These reports pertained to cohort studies (N=40), case-control studies (N=18), nested case-control studies (N=6), and cross-sectional studies (N=16). Within this 13-year interval, no statistically significant time trend was observed (**Figure 2.2.2.3**).

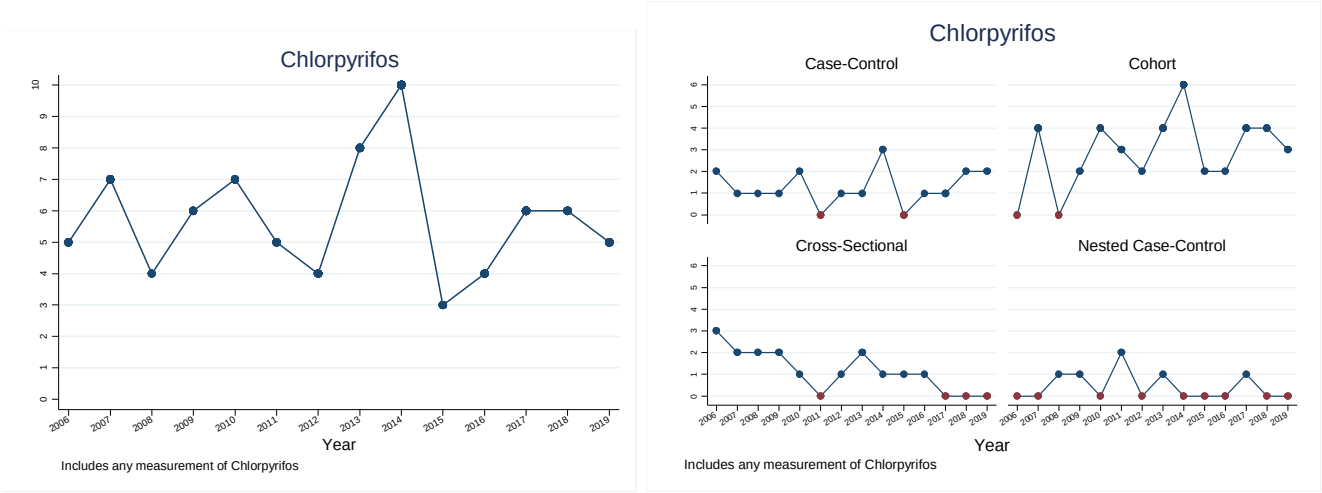


Figure 2.2.2.3 Chlorpyrifos - Evolution over time

Finally, regarding neonicotinoids, we attempted to capture trends for imidacloprid, thiamethoxam, clothianidin, acetamiprid, thiacloprid, dinotefuran, and nitenpyram. For neonicotinoids, 5 publication were identified corresponding to 3 studies and assessing congenital malformations and autism-spectrum disorder. For imidacloprid, four case-control studies using partially overlapping populations were identified.

2.2.3 Evidence synthesis

2.2.3.1 Cancer

2.2.3.1.1 Breast cancer

We identified 26 publications reporting on 25 distinct studies on exposure to pesticides and breast cancer. Of these, 5 publication were excluded as they did not provide enough data (confidence intervals and/or standard errors were not reported) and one study provided only means and confidence intervals per group. Another 3 studies were not included in a meta-analysis due to PICO variation; one study investigated the association of pesticide with breast cancer mortality and another study assessed pesticides with breast cancer prevalence, while only one study reported on the association of a continuous pesticide exposure with breast cancer.

Of the remaining publications, there were sufficient data (estimates from at least 3 studies) for 4 pesticide categories (DDE, n=8; DDT, n=6; HCB, n=3; overall pesticides, n=8, Figures 1-3). The association of DDE with breast cancer was not statistically significant based on 7 studies: RR=1.22 (95% CI: 0.88, 1.69), p= 0.235, I2=5.8%. The association of DDT with breast cancer was not statistically

significant based on 4 studies: RR=1.37 (95% CI: 0.77, 2.22), p= 0.325, I^2=72.7%. The association of HCB with breast cancer was not statistically significant based on 3 studies: RR=1.03 (95% CI: 0.59, 1.80), p= 0.913, I2=10.8%. The association of pesticides (broad definition) with breast cancer was statistically significant based on 8 studies: RR=1.27 (95% CI: 1.18, 1.37), p< 0.001, I^2=33.7%.

The rest of the pesticides were investigated in only one or two studies, prohibiting us from performing a meta-analysis (Table 1).

Table 1. Available associations per pesticide category

Pesticide	Number of estimates	Number of studies	
Aldrin	1	1	no MA
Atrazine	1	1	no MA
DDD	1	1	no MA
DDE, p,p'-DDE*	8 (7)	8 (7)	brca_1
DDT, o,p'-DDT	6 (5)	5 (4)	brca_2
Dieldrin	2	2	no MA
HCB	3	3	brca_3
Heptachlor	1	1	no MA
Heptachlor epoxide	1	1	no MA
Lindane	1	1	no MA
Mirex	1	1	no MA
Oxychlordane	2	2	no MA
cis-Nonachlor	1	1	no MA
trans-Nonachlor	2	2	no MA
α-Endosulfan	1	1	no MA
Pesticides*	10	8	brca_4

* One study excluded due to data verification failure

** Pesticides include the following categories: Pesticides, Organochlorine Insecticides, Pesticides exposure in fogger trucks, Used any house Pesticides

Figure 1a. DDE-related exposure and breast cancer

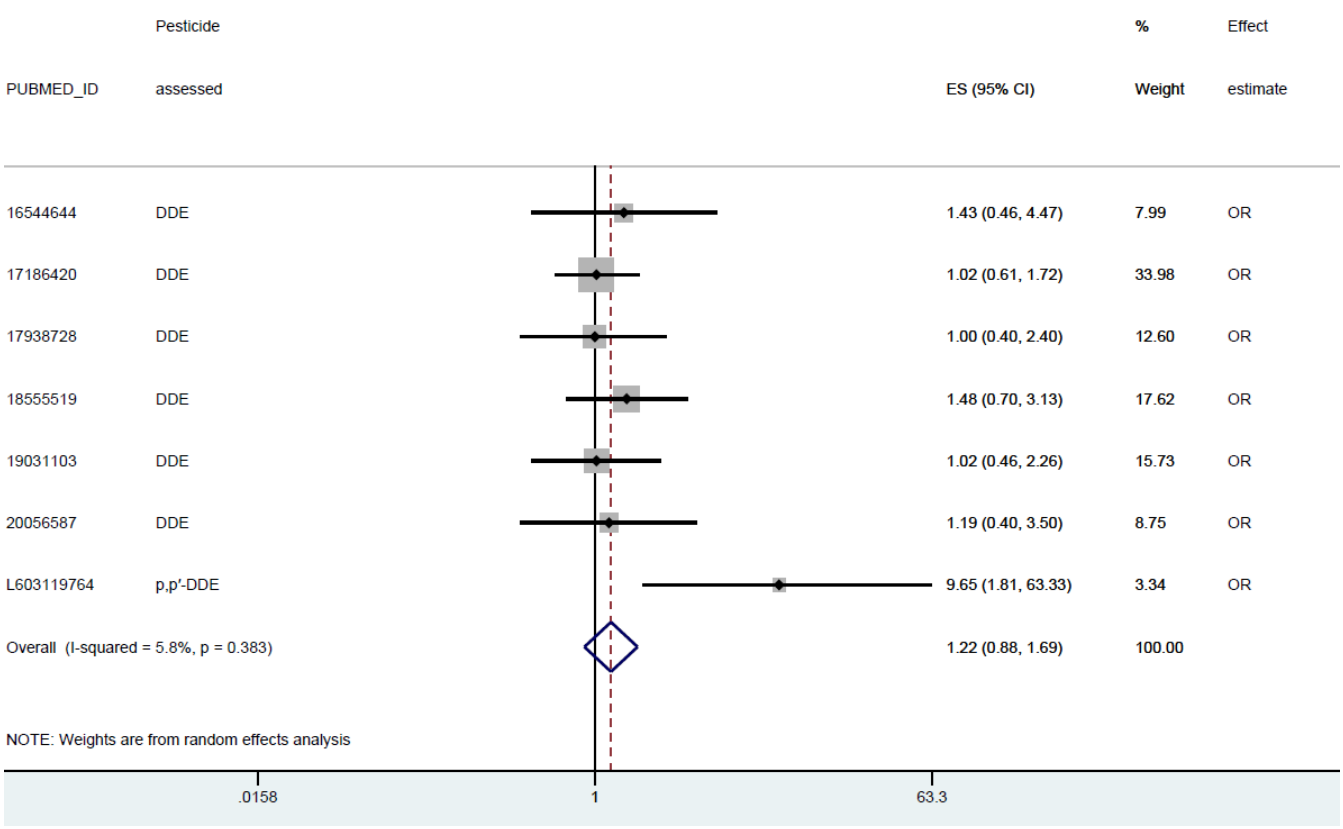


Figure 1b. DDT-related exposure and breast cancer

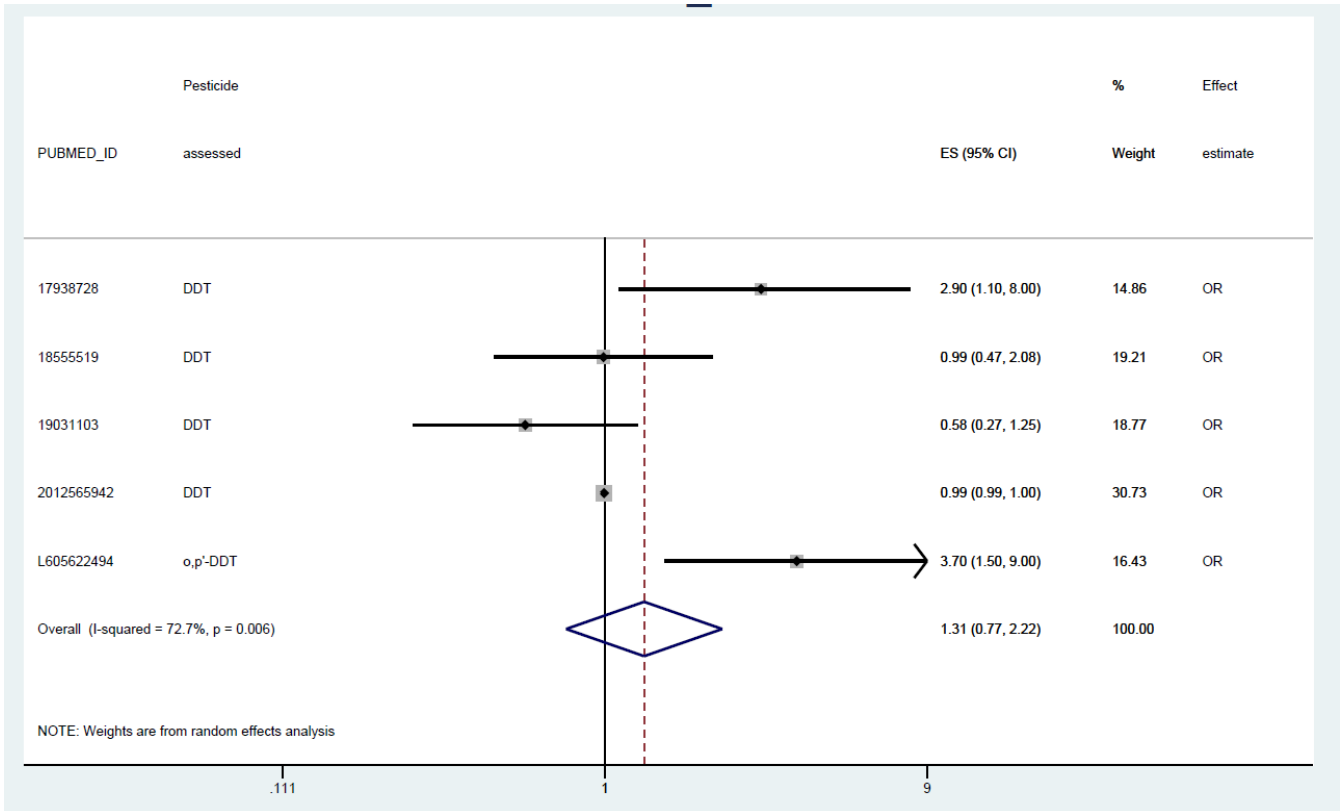


Figure 2. HCB-related exposure and breast cancer

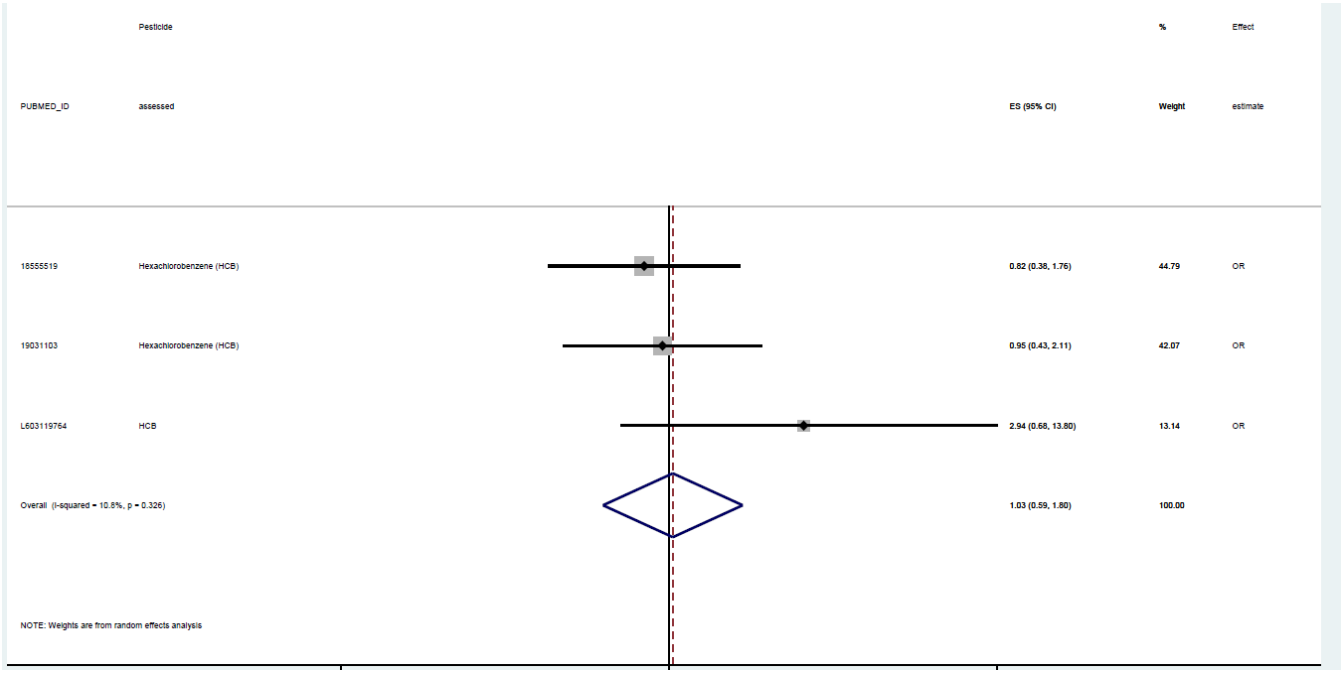
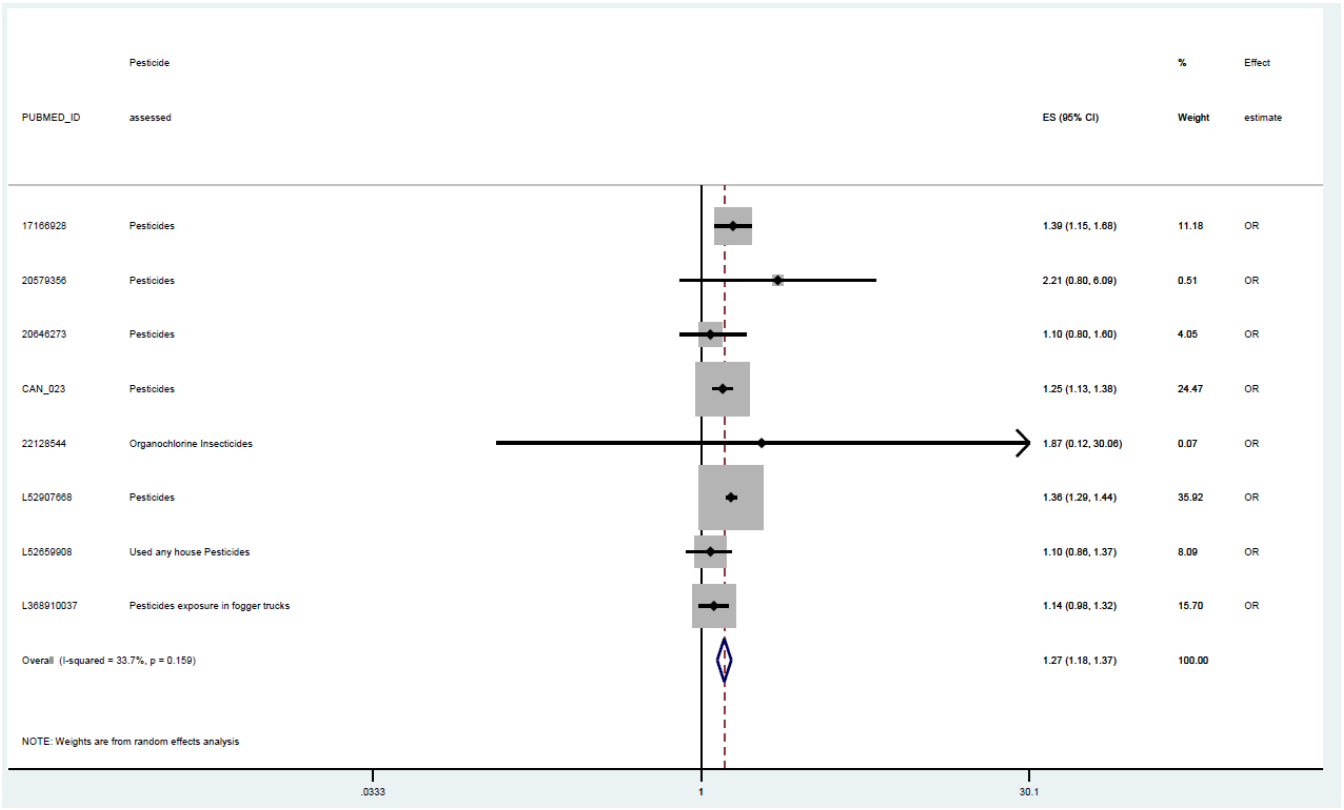


Figure 3. Pesticide-related exposure and breast cancer



2.2.3.1.2 Prostate cancer

We identified 50 publications (from 20 distinct studies) that investigated the association between pesticide exposure and prostate cancer. We identified 30 publications reporting on data from the Agricultural Health Study. Two publications reported on the association between exposure to pesticides and benign prostatic hyperplasia and therefore a meta-analysis was not performed. Another two publications reported data from the Agricultural Health Study on pesticides and aggressive prostate cancer. One study investigated the association of pesticides with prostate cancer prevalence. Five publications (4 studies) investigated the association of various pesticide with prostate cancer-specific mortality, without providing enough estimates (at least 3) for a meta-analysis to be performed. Only one study reported on a continuous pesticide exposure with the risk of prostate cancer.

For the following pesticides there were at least 3 studies reporting on an association with prostate cancer (Captan, N=3; Chlordane, N=3; DDE, N=5; DDT, N=4; Dieldrin, N=3; HCB, N=3; Oxychlordane, N=4; Trans-nonachlor, N=3, broad organochlorine insecticides definition, N=3; and broad pesticides definition, N=8; Figures 4-8). None of those meta-analyses presented a statistically significant association.

Figure 4. Exposure to Captan and Prostate Cancer

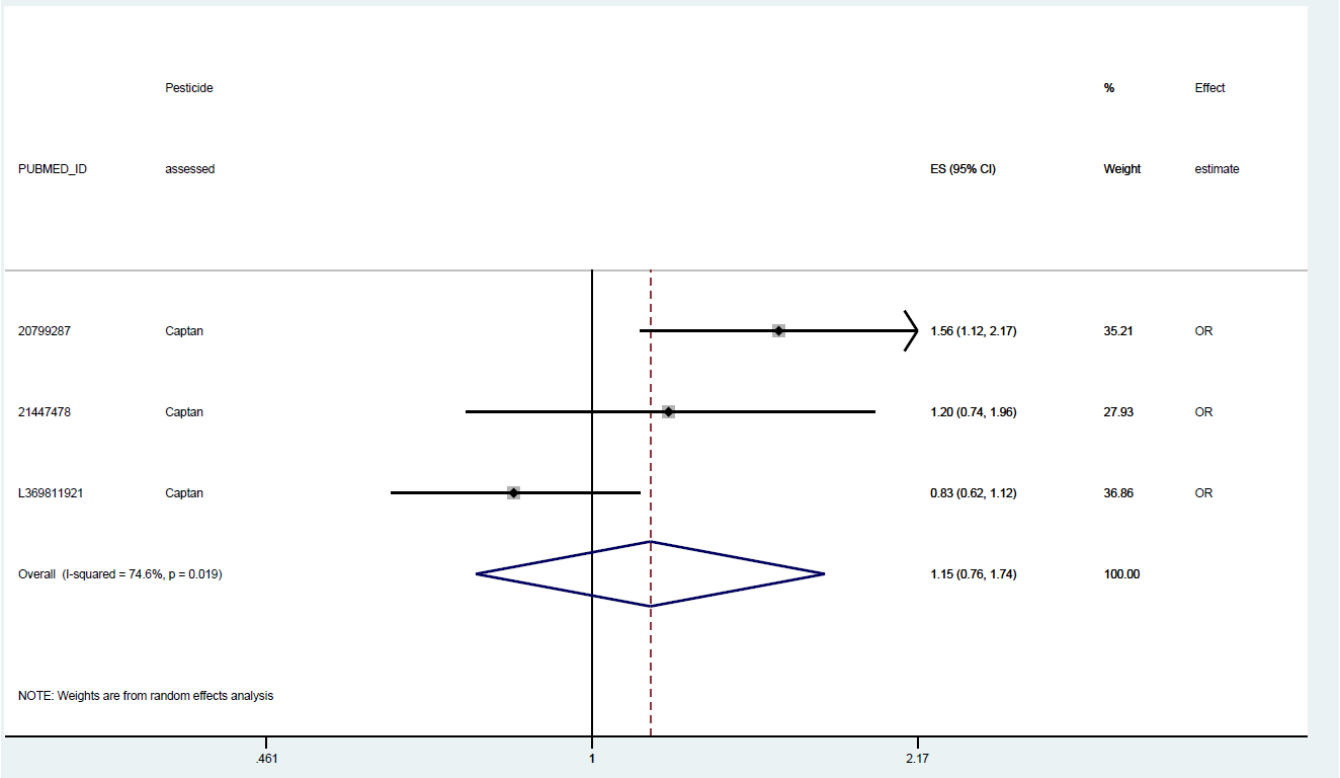


Figure 5. Exposure to Chlordane and Prostate Cancer

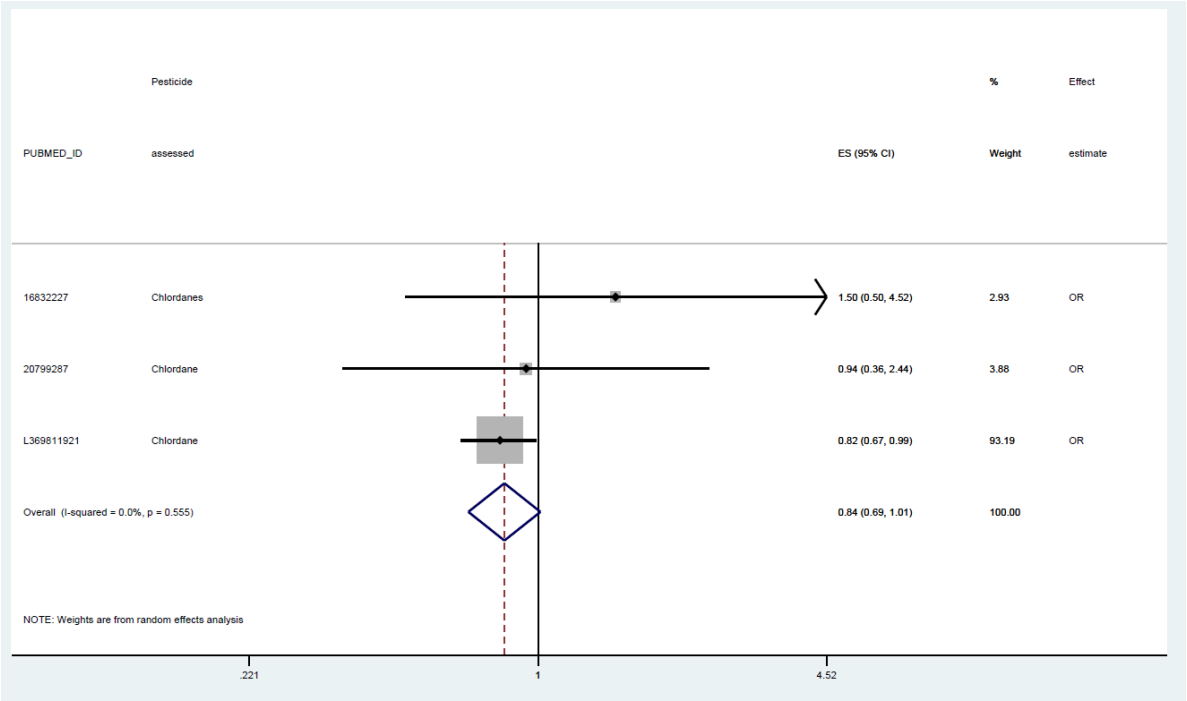


Figure 6. Exposure to DDE and Prostate Cancer

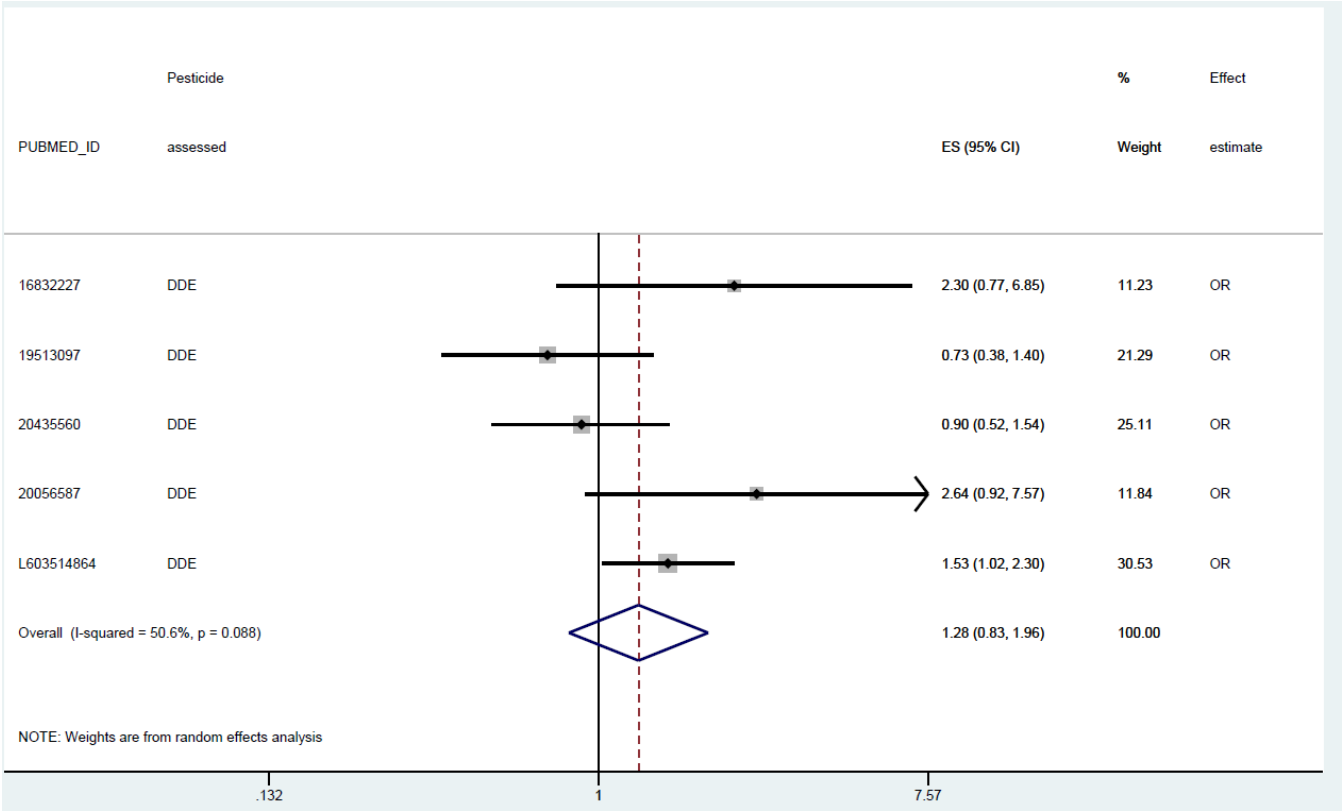


Figure 7. Exposure to Dieldrin and Prostate Cancer

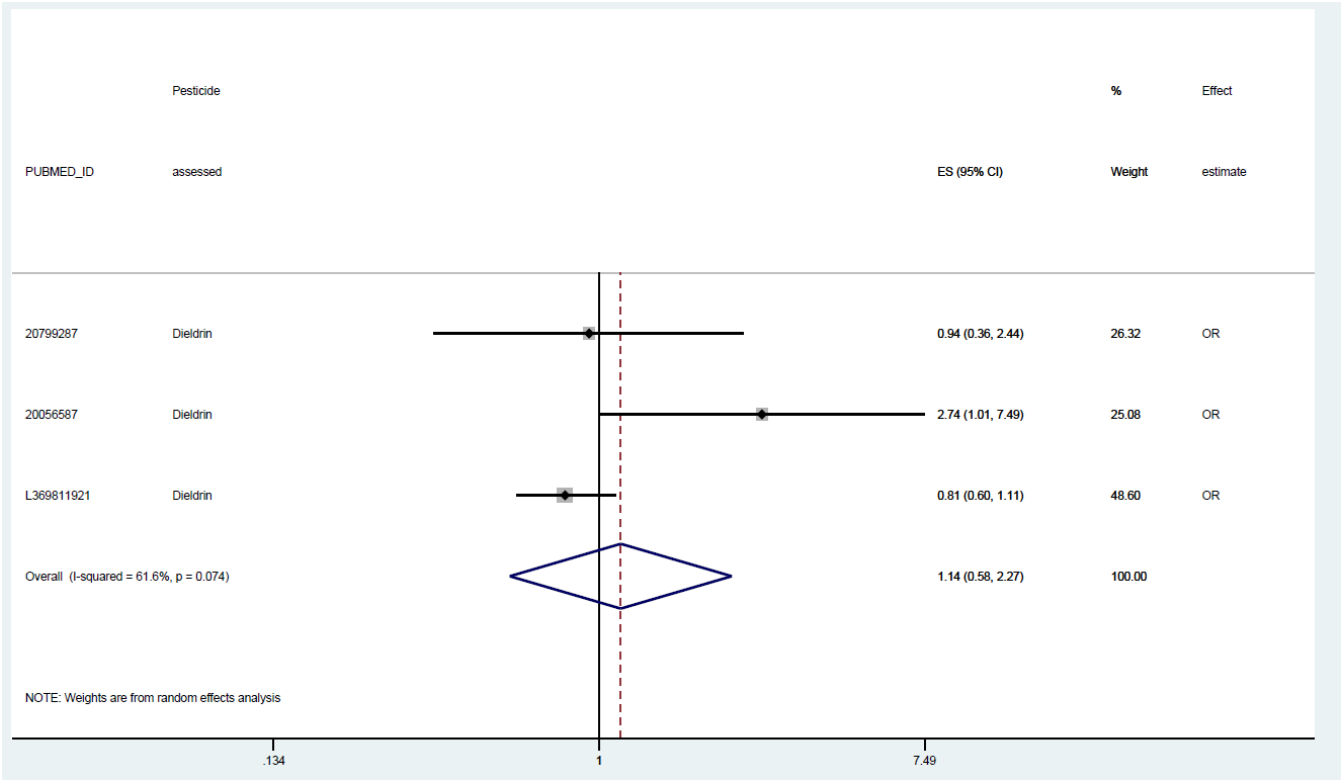
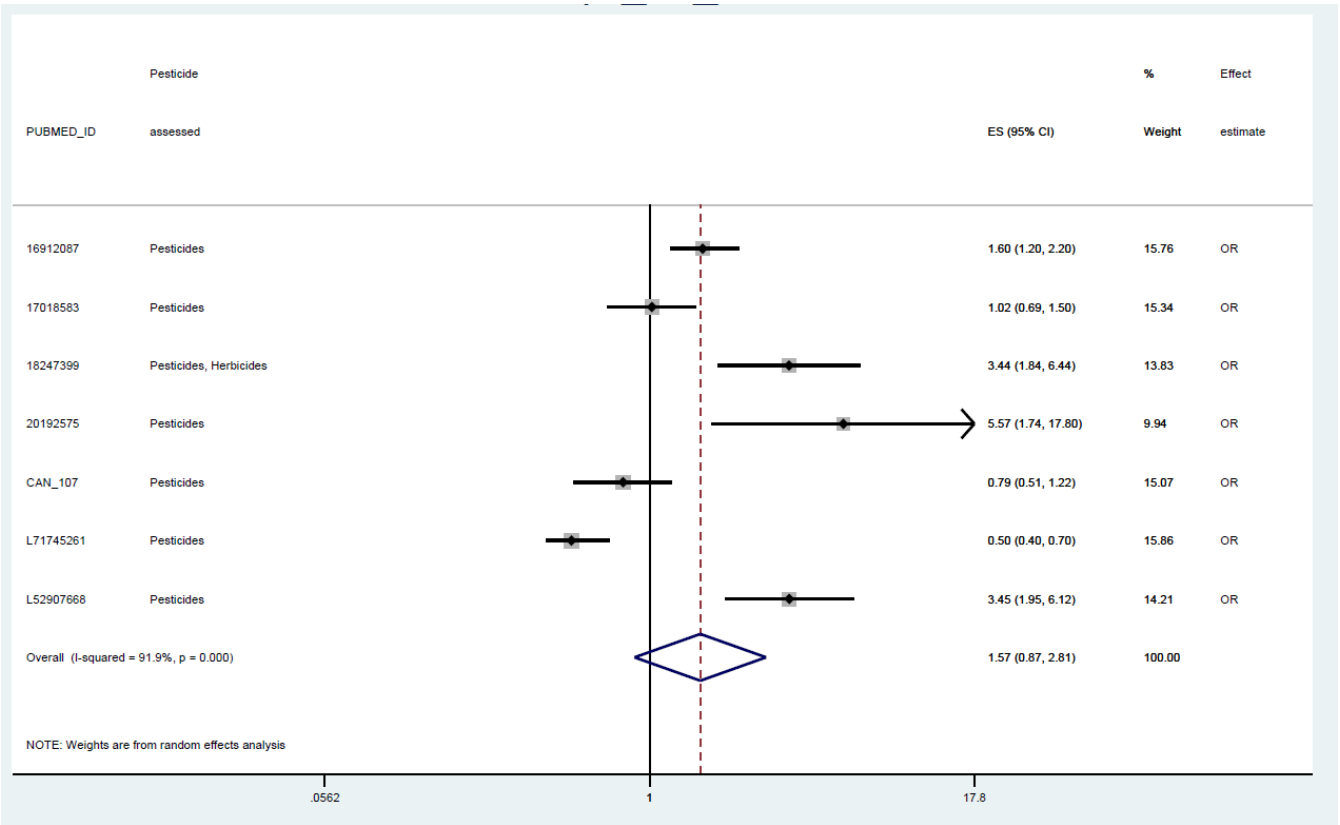


Figure 8. Exposure to Pesticides (broad definition) and Prostate Cancer



2.2.3.1.3 Hematological Malignancies

Sixty six publications (34 distinct studies) reporting 795 estimates on pesticides and hematological neoplasms (excluding NHL, follicular lymphoma, diffuse large B cell lymphoma, and multiple myeloma). Twenty nine of the identified publications reported data from the AHS.

We further identified 6 publications (Mort_5, Mort_8, Mort_9, Mort_13, Mort_14, Mort_18) from 5 studies reporting 33 estimates on the association of pesticides with hematological neoplasms mortality (mortality due to leukemia; mortality due to leukemia; Hodgkin lymphoma mortality; Lymphatic and hematopoietic mortality and other lymphopoietic cancer mortality). The definition of pesticides varied greatly across studies. The majority of the reported associations were not statistically significant.

2.2.3.1.3.1 Hodgkin's lymphoma

Twelve publications from 8 distinct studies provided data on 301 estimates of pesticides and Hodgkin lymphoma. A wide range of pesticides classes was examined which did not allow any meaningful synthesis of the results.

One case-control study in Spain (Can_182) evaluated the association of the proximity to areas with high and low pesticide exposure with Hodgkin lymphoma prevalence. Interestingly, the study indicated that individuals living in geographical areas with high pesticides exposure had statistically significant decreased odds of Hodgkin lymphoma prevalence compared to individuals living in areas with low pesticides exposure with the odds ratio ranging from 0.67 in women to 0.76 in men.

One publication from the AHS (Can_265) presented relative standardized incidence rates comparing the incidence rate of Hodgkin lymphoma of pesticide applicators from the AHS (and their spouses) with the incidence rate of the general population. This study did not find a statistically significant difference in the incidence rate of Hodgkin lymphoma on pesticide applicators from the AHS compared to the general population.
One case-control study from the Cross-Canada Study of Pesticides and Health (Can_180) evaluated the association of the number of pesticides used (pesticides, fungicides, herbicides and insecticides and pesticide mode of action) with Hodgkin lymphoma, overall and stratified by work-related or home-related pesticides use. The vast majority of the reported association were not statistically significant.
Four publications (Can_13, Can_96, Can_155 and Can_279) from the same case-control study in Canada reported data on associations between different pesticides and Hodgkin lymphoma. The majority of the association reported were not statistically significant.
Two publications from the same case-control study in France (Can_81, Can_63), reported data of different subgroups of participants and different pesticides and the odds of Hodgkin lymphoma. The study Can_81 reported association only in men and almost half of the associations were statistically significant indicating an increased odds of Hodgkin lymphoma with the statistically significant odds ratios ranging from 2.9 to 8.4
One case-control study from Iran (Can_160) did not find a statistically significant association between pesticides and Hodgkin lymphoma
One case-control study from Italy (Can_32) did not find statistically significant associations between fungicides, herbicides, fumigants, insecticides, molluskicides, and rodenticides and Hodgkin lymphoma.

2.2.3.1.3.2 Leukemia

We identified 267 estimates from 43 publications (24 distinct studies) evaluating the association of pesticides and leukemia. Of the 48 publications, 20 were from the AHS. Both the definitions of pesticides exposure and the definition of the outcomes were highly heterogeneous and therefore a meta-analysis was not feasible.

2.2.3.1.3.2.1 Acute leukemia

Seven studies evaluated the association of pesticides with acute leukemias. The majority of the associations regarded a combination of occupational and environmental exposure to various pesticides.
Five studies (three case-control [Can_89, Can_107, Can_220], one cohort [Can_174] and one nested case-control [Can_164]) reported 45 associations on pesticides and acute myeloid leukemia. Due to different pesticides being evaluated in different studies, a meta-analysis was not feasible. The reported effect estimates ranged from 0.57 to 2.85 and the majority of those associations were not statistically significant.
Three studies investigated other types of acute leukemias with most of the reported effect estimates being not statistically significant. One case-control study in Thailand (Can_89) reported estimates on the association of occupational and environmental exposure to pesticides and acute lymphoblastic leukemia and another case-control study in China (Can_107) reported on the association of occupational exposure to pesticides, insecticides and herbicides with acute myeloid leukemia with multilineage dysplasia, acute myeloid leukemia with recurrent cytogenetic abnormalities and acute

promyelocyte leukemia. Finally, one publication from the AHS (Can_265) presented relative standardized incidence rates comparing the incidence rate of acute myeloid/monocytic leukemia of pesticide applicators from the AHS (and their spouses) with the incidence rate of the general population. One case control study from Iran (Can_210) presented statistically significant associations between categories of years of pesticide and the intensity of pesticide exposure with acute leukemia, but these associations were unadjusted and should interpreted with caution.

2.2.3.1.3.2.2 Chronic leukemia

We identified 18 publications from 15 distinct studies (4 publications from the AHS) reporting 139 association on pesticides exposure and chronic leukemia.
Nine distinct studies providing 30 associations investigated the association of pesticides with chronic lymphocytic leukemia. Except form one publication from the AHS (Can_265) presented relative standardized incidence rates, the other 8 were case-control studies evaluating mostly the occupational exposure to pesticides with chronic lymphocytic leukemia. Most studies measured pesticides exposure using a questionnaire. The majority of the reported associations was not statistically significant.

Four publications (Can_106, Can_123, Can_174, and Can_207) investigated the association of pesticides with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). One case-control study in China (Can_186) found that exposure to insecticides and herbicides was not significantly associated with CLL/SLL. One nested case-control from the Nurses' Health Study (Can_123) presented a non-significant association of DDE with CLL/SLL. One publication from the Iowa Women's Health Study (Can_174) evaluated residence in a farm as a proxy to pesticides exposure with CLL/SLL but did not find a statistically significant association. One publication from the Women's Health Initiative cohort investigated the association of residence in a farm and having applied with CLL/SLL but most of the reported effect sizes were not statistically significant.
One publication from the AHS (Can_185) investigated the association of several pesticides with chronic lymphocytic leukemia/small lymphocytic lymphoma/mantle cell lymphoma (CLL/SLL/MCL) but the majority of the reported estimates were not statistically significant. Another two publications from the AHS (Can_200 and Can_261) did not find a statistically significant associations of alachlor and organophosphorus pesticides with chronic lymphocytic leukemia/small lymphocytic lymphoma/prolymphocytic leukemia/ mantle cell lymphoma (CLL/SLL/PL/MCL).
Four studies (Can_94, Can_89, Can_186, andCan_265) investigated the association of pesticides with chronic myeloid leukemia. The study Can_94 did not provide effect estimates, only p-values and was not considered further. One case-control study from Thailand (Can_89) found that occupational exposure but not environmental exposure to pesticides was significantly associated with increased odds of chronic myeloid leukemia. One case-control study from Pakistan (Can_186) found that occupational exposure to pesticides was not significantly associated with chronic myeloid leukemia. Finally, one publication from the AHS (Can_265) presented relative standardized incidence rates comparing the incidence rate of chronic myeloid leukemia of pesticide applicators from the AHS (and their spouses) with the incidence rate of the general population but did not find a statistically significant association. One case-control study in France (Can_81) evaluated the association of

occupational exposure to various pesticides with hairy cell leukemia. The majority of the reported associations was not statistically significant.

2.2.3.1.3.2.3 Other leukemias

Twenty six publications (19 from the AHS) provided 68 estimates on general definitions of leukemia (such as leukemia; lymphocytic leukemia; myeloid leukemia; myeloid and monocytic leukemia) and therefore those outcomes were deemed too heterogeneous to be included in a meta-analysis. Excluding the AHS, there were a total of 3 cohorts and 4 case-control studies. The majority of the reports associations regarded either occupational pesticides exposure or a combination of occupational and environmental exposure. Overall the both the definition of pesticides and the mode of pesticide assessment varied greatly across the different studies. The majority of the reported associations were not statistically significant and the effect sizes varied greatly, ranging from 0.4 to 2.67.

2.2.3.1.3.2.4 Follicular Lymphoma / Follicular B-Cell Carcinoma

We identified 13 publications (9 distinct studies) reporting 100 estimates on the association of pesticides with Follicular lymphoma/ Follicular B-Cell carcinoma. Only for DDE there were sufficient data (4 studies) for a meta-analysis.
The association of DDE with Follicular lymphoma was not statistically significant based on 4 studies: RR=1.3 (95% CI: 0.78, 2.15), p=0.314, I^2=0%.

Exposure	Number of estimates	Number of studies per exposure	Analysis
Alachlor	4	1	
Aldicarb	1	1	
Aldrin	3	1	
Carbamate	1	1	
Carbaryl	3	1	
Carbofuran	3	1	
Chlordane/Chlordanes	4	2	
Chlorpyrifos	3	1	
Cis-chlordane	1	1	
Cis-heptachlor epoxide	1	1	
Coumaphos	3	1	
DDE	4	4	nhl_follic_1
DDT	3	1	
DDVP	3	1	
Diazinon	3	1	
Fonofos	3	1	
Fungicides	1	1	
Glyphosate	1	1	
Heptachlor	1	1	
Herbicides	2	2	
Hexachlorobenzene (HCB)	2	2	
Imide	1	1	
Insecticides	2	2	
Lindane	3	1	
Malathion	4	1	
Metachlor	3	1	
Metalaxyl	1	1	
Methyl bromide	3	1	
Organochlorine	2	2	
Organophosphate	1	1	
Parathion (ethyl or methyl)	1	1	
Permethrin	3	1	

Pesticides	1	1
Phenoline	1	1
Phorate	3	1
Pyrethrin	1	1
Residence location: Farm (proximity to pesticides)	5	1
Terbufos	3	1
Toxaphene	1	1
Trans-chlordane	1	1
Triazines	1	1
Triazole	1	1
Commercial pesticide applicators in AHS vs general population	1	1
Commercial service applied insecticides	1	1
Ever lived on a farm	1	1
Lawn service applied insecticides	1	1
Personally applied insecticides	1	1
Personally mixed insecticides	1	1
Private pesticide applicators in AHS vs general population	1	1
Spouses of pesticide applicators in AHS vs general population	1	1
Total	100	

2.2.3.1.3.2.5 Diffuse large B-cell lymphoma/ Diffuse large cell lymphoma

We identified 13 publications (10 studies) reporting 116 estimates on the association of pesticides with Diffuse large B-cell lymphoma/ Diffuse large cell lymphoma. Only for DDE and HCB there were sufficient data (4 and 3 studies respectively) for a meta-analysis. The association of DDE with diffuse large B cell lymphoma was not statistically significant based on 5 studies: RR=1.51 (95% CI:0 .98, 2.31), p=0.06, I^2=0%. The association of HCB with diffuse large B cell lymphoma was not statistically significant based on 3 studies: RR=1 (95% CI: 0.54, 1.85), p=0.999, I^2=0%.

Exposure	Number of estimates	Number of studies per exposure	Analysis
Alachlor	4	1	
Aldicarb	1	1	
Aldrin	1	1	
Benomyl	1	1	
Captan	3	1	
Carbamate	1	1	
Carbaryl	3	1	
Carbofuran	3	1	
Chlordane	4	2	
Chlorothalonil	3	1	
Chlorpyrifos	3	1	
Cis-chlordane	1	1	
Cis-heptachlor epoxide	1	1	
Coumaphos	3	1	
DDE	5	5	nhl_diffuse_1
DDT	3	1	
DDVP	3	1	
Diazinon	3	1	
Fonofos	3	1	
Fungicides	1	1	
Glyphosate	1	1	
Heptachlor	1	1	
Herbicides	2	2	
HCB	3	3	nhl_diffuse_2
Imide	1	1	
Insecticides	2	2	
Lindane	3	1	
Malathion	4	1	
Maneb/Mancozeb	3	1	
Metachlor	3	1	
Metalaxyl	3	1	
Methyl bromide	3	1	
Organochlorine	1	1	
Organophosphate	1	1	
Parathion (ethyl or methyl)	1	1	
Permethrin	3	1	
Pesticides	1	1	
Phenoline	1	1	
Phorate	3	1	
Pyrethrin	1	1	
Residence location: Farm	5	1	
Terbufos	3	1	
Toxaphene	3	1	
trans-Chlordane	1	1	
Triazines	1	1	
Triazole	1	1	
Ever lived on a farm	1	1	
Commercial pesticide applicators in AHS vs general population	1	1	
Commercial service applied insecticides	1	1	
all occupational pesticides exposure	2	1	
Personally applied insecticides	1	1	
Personally mixed insecticides	1	1	
High probability and reliability of occupational pesticides exposure	1	1	
Lawn service applied insecticides	1	1	
Private pesticide applicators in AHS vs general population	1	1	
Spouses of pesticide applicators in AHS vs general population	1	1	

Total	116

2.2.3.1.3.2.6 Non-Hodgkin's lymphoma

We identified 70 publications (45 studies) reporting 492 estimates on the association of pesticides with Non-Hodgkin lymphoma (excluding Follicular lymphoma/ Follicular B-Cell carcinoma and Diffuse large B-cell lymphoma/ Diffuse large cell lymphoma).

Studies for which a meta-analysis was not feasible

Six publications (Mort_2, Mort_5, Mort_8, Mort_9, Mort_13, and Mort_14) reported seven estimates on the association of various pesticides with non-Hodgkin lymphoma mortality. We did not have sufficient data in order to perform a meta-analysis. Only one of the 7 estimates (Mort_14) presented a statistically significant association of pentachlorophenol with the standardized mortality ratio of NHL (1.77; 95% CI: 1.03, 2.84). Four publications (Can_51, Can_75, Can_60, Can_253) investigated the association of pesticides with NHL in children. Due to the large heterogeneity in the definition of exposure to pesticides across studies we did not perform a meta-analysis. One case-control study investigated the association paternal occupational exposure to pesticides with childhood NHL. One case-control study investigated the association of the proximity of birth residence to agricultural use land with the risk of NHL in children. One population-based case-control study investigated the association of maternal household use of pesticides during pregnancy and paternal use during pregnancy or childhood with childhood NHL. Finally, one case-control study investigated the association of the Global Crop Index as proxy to pesticides exposure with childhood NHL. One study (Can_15) investigated the association of pesticide exposure with t(14;18)-defined subtypes of NLH, concluding that pesticide exposure is likely associated with the risk of t(14;18)-positive NHL but not t(14;18)-negative NHL. One study (Can_182) investigated the association of geographical areas with high vs low pesticide exposure with NHL prevalence in Spain. One case-control study in Germany (Can_61) investigated the association of occupational exposure to pesticide with NHL stratified as high-malignancy NHL and low-malignancy NHL. Two studies (Can_32, Can_195) investigated the association of pesticides with a composite outcome of Non-Hodgkin lymphoma and chronic lymphocytic leukemia and another study (Can_198) with a composite outcome defined as Chronic/small/prolymphocytic/mantle B-cell Non-Hodgkin lymphoma. Only two studies (Can_139, Can_254) investigated pesticides as a continuous exposure with the risk of NHL. One study (Can_33) was excluded from any subsequent analyses as it did not provide sufficient data for its inclusion in a meta-analysis.

Meta-analyses

The association of DDE with NHL was not statistically significant based on 9 studies: RR=1.18 (95% CI: 0.95, 1.48), p=0.137, I2=27.7%.

The association of DDT with NHL was not statistically significant based on 6 studies: RR=1.03 (95% CI: 0.86, 1.23), p=0.767, I2=33.6%.

The association of HCB with NHL was not statistically significant based on 7 studies: RR=1.02 (95% CI: 0.68, 1.53), p=0.909, I2=67.2%.

The association of Herbicides/Phenoxy Herbicides with NHL was not statistically significant based on 6 studies: RR=1.2 (95% CI: 0.87, 1.66), p=0.272, I2=75.3%.
The association of Insecticides (broad definition) with NHL was statistically significant based on 4 studies: RR=1.25 (95% CI: 1.03, 1.52), p=0.022, I2=55.9%.
The association of Pesticides (broad definition) with NHL was statistically significant based on 11 studies: RR=1.48 (95% CI: 1.02, 2.14), p=0.041, I2=89.6%.
The association of Carbaryl with NHL was not statistically significant based on 4 studies: RR=.94 (95% CI: 0.78, 1.15), p=0.562, I2=56.8%.
The association of Carbofuran with NHL was not statistically significant based on 3 studies: RR=1.09 (95% CI: 0.96, 1.23), p=0.186, I2=11.4%.
The association of Chlorpyrifos with NHL was not statistically significant based on 4 studies: RR=.96 (95% CI: 0.79, 1.16), p=0.662, I2=49.3%.
The association of Diazinon with NHL was not statistically significant based on 3 studies: RR=.98 (95% CI: 0.69, 1.38), p=0.889, I2=46.2%.
The association of Dieldrin with NHL was not statistically significant based on 3 studies: RR=.97 (95% CI: 0.73, 1.29), p=0.838, I2=0%.
The association of Glyphosate with NHL was not statistically significant based on 3 studies: RR=1.19 (95% CI: 0.74, 1.91), p=0.468, I2=62.1%.
The association of Malathion with NHL was not statistically significant based on 3 studies: RR=1 (95% CI: 0.69, 1.45), p=0.985, I2=83.7%.
The association of MCPA with NHL was not statistically significant based on 3 studies: RR=1.21 (95% CI: 0.59, 2.49), p=0.608, I2=73.4%.
The association of Oxychlordane with NHL was statistically significant based on 4 studies: RR=1.77 (95% CI: 1.19, 2.62), p=0.005, I2=42.1%.
The association of Terbufos with NHL was not statistically significant based on 3 studies: RR=1.15 (95% CI: 0.99, 1.34), p=0.065, I2=0%.
The association of Organophosphates with NHL was not statistically significant based on 3 studies: RR=1.03 (95% CI: 0.77, 1.37), p=0.862, I2=42.6%.
The association of Organochlorines with NHL was not statistically significant based on 4 studies: RR=1.17 (95% CI: 0.84, 1.62), p=0.36, I2=68.7%.
The association of trans-Nonachlor with NHL was not statistically significant based on 4 studies: RR=1.28 (95% CI: 0.87, 1.88), p=0.208, I2=54.7%.
The association of Permethrin with NHL was not statistically significant based on 3 studies: RR=1.04 (95% CI: 0.91, 1.18), p=0.564, I^2=0%.

Exposure	Number of estimates	Number of studies per exposure	Analysis
(Phenyl) urea herbicides	1	1	
2, 4-D	2	2	
2,4,5-T and/or 2,4-dichlorophenoxyacetic acid (2,4-D)	2	2	
Acetochlor	1	1	
Alachlor	2	2	
Aldicarb	2	2	
Aldrin	1	1	
alpha-Chlordane	2	2	
Arsenicals	1	1	
Atrazine	1	1	
Benomyl	1	1	

Beta-HCH	2	2	
Butylate	2	2	
Captafol	1	1	
Captan	2	2	
Carbamate	1	1	
Carbamate insecticides	1	1	
Carbaryl	4	4	nhl_7
Carbofuran	3	3	nhl_8
Chlordane/Chlordanes	3	2	
Chloroacetanilides	1	1	
Chlorophenols	2	2	
Chlorothalonil	1	1	
Chlorpyrifos	4	4	nhl_9
Cis-chlordane	1	1	
Cis-heptachlor epoxide	1	1	
cis-Nonachlor	3	3	
cis-Permethrin	1	1	
Coumaphos	2	2	
Creosote	2	2	
cyanazine	1	1	
DDE	9	9	nhl_1
DDT	6	6	nhl_2
DDVP	1	1	
Deltamethrin	1	1	
Diazinon	3	3	nhl_10
Dicamba	2	2	
Dichlorvos	2	2	
Dieldrin	3	3	nhl_11
Dimethoate	1	1	
Dinitroaniline herbicides	1	1	
Dithiocarbamate fungicides	1	1	
EPTC	2	2	
Esfenvalerate	1	1	
Famphur	1	1	
Fonofos	2	2	
gamma-Chlordane	2	2	
Glyphosate	4	3	nhl_12
HCB	7	7	nhl_3
Heptachlor	1	1	
Imazethapyr	1	1	
Imide	1	1	
Isoproturon	1	1	
Lindane	2	2	
Linuron	1	1	
Malathion	3	3	nhl_13
Mancozeb	1	1	
Maneb/Mancozeb	1	1	
MCPA	4	3	nhl_14
MCPP	1	1	
Metachlor	1	1	
Metalaxyl	1	1	
Methyl bromide	1	1	
Metolachlor	2	2	
Metribuzin	2	2	
Mirex	1	1	
Oxychlordane	4	4	nhl_15
Paraquat	2	2	
Parathion	1	1	
Parathion (ethyl or methyl)	1	1	
Pendimethalin	1	1	
Pentachlorophenol	1	1	
Permethrin	3	3	nhl_20
Phenoline	1	1	
Phenoxyacetic acids	2	2	
Phorate	2	2	
Phthalimide fungicides	1	1	
Pirimicarb	1	1	
Propoxur	1	1	
Pyrethrin	1	1	
Pyrethroid insecticides	1	1	
Pyretrine	2	2	
Quaternary ammonium	1	1	
Simazine	1	1	

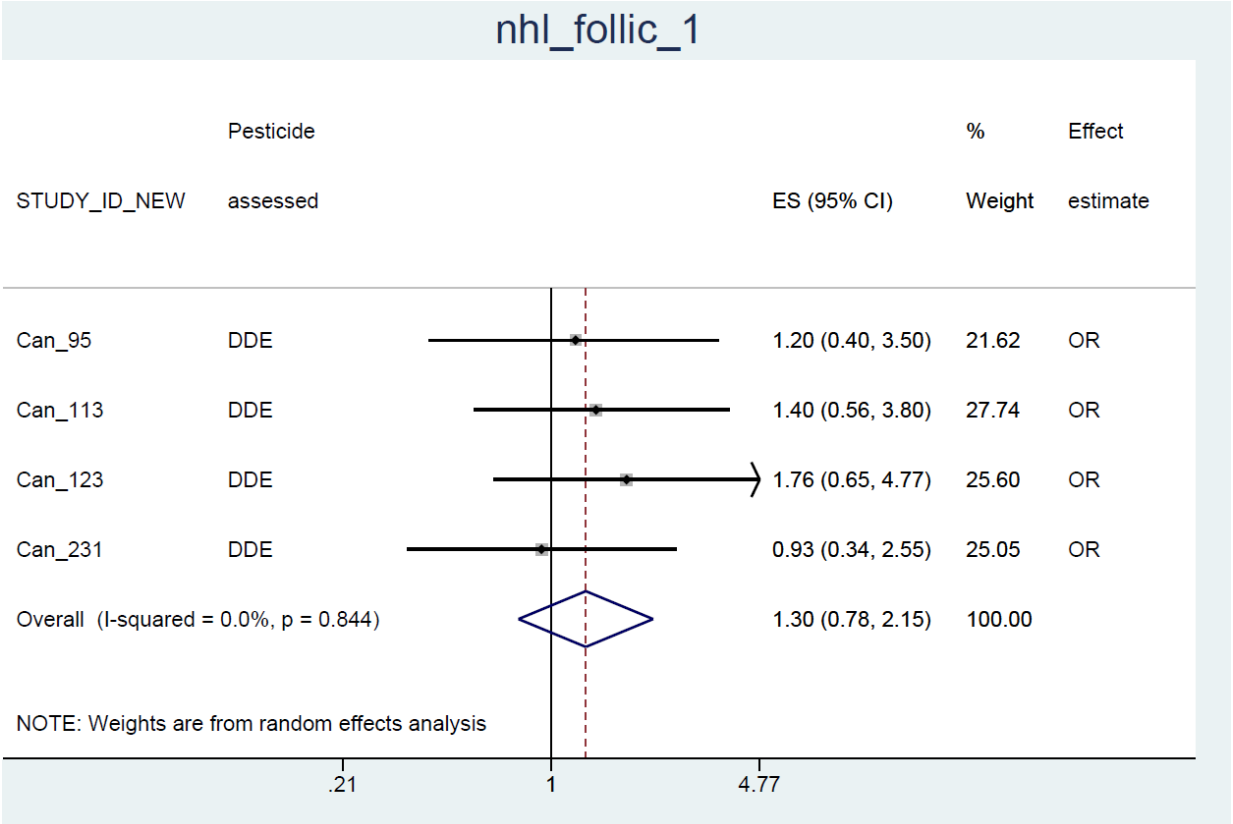
Sum Chlordanes	1	1	
Sum DDT + DDE	1	1	
Terbufos	3	3	nhl_16
Tetrachlorophenol	3	1	
Thiocarbamate herbicides	1	1	
Thiram	1	1	
Toxaphene	1	1	
trans-Chlordane	1	1	
trans-Nonachlor	4	4	nhl_19
trans-Permethrin	1	1	
Triazine herbicides	1	1	
Triazines	1	1	
Triazinone herbicides	1	1	
Triazole	1	1	
Trichlorfon	1	1	
Trifluralin	2	2	
agricultural workers	1	1	
Agricultural Workers vs non-agricultural occupations	2	1	
Farmers and managers vs non-agricultural occupations	2	1	
Ever lived on a farm	1	1	
Manual labourers vs non-agricultural occupations	2	1	
Residence location: Farm	5	1	
Fungicides	4	2	
Rodenticides	1	1	
Herbicides except phenoxyacetic acids	2	1	
Herbicides/Phenoxy Herbicides	10	6	nhl_4
Pesticides*	22	11	nhl_6
Insecticides**	12	4	nhl_5
Organophosphates***	3	3	nhl_17
Organochlorines****	4	4	nhl_18
Total	250		

* Pesticides category includes: Pesticides, Any Pesticides exposure, any residential Pesticides exposure, household Pesticides use, Pesticides, Pesticides for occupational use, possibly carcinogenic Pesticides, probably carcinogenic Pesticides, Garden Pesticides

** Insecticides category includes: Insecticides, Commercial service applied insecticides, Lawn service applied insecticides, Insecticides, Insecticides for domestic use, personally applied insecticides, personally mixed insecticides

***Organophosphates category includes: OP Insecticides, any OP, OP Insecticides, and Organophosphates

****Organochlorines category includes: Organochlorine, Organochlorine Insecticides, OC insecticides, any OC insecticide



2.2.3.1.3.2.7 Other lymphomas and other hematological neoplasms

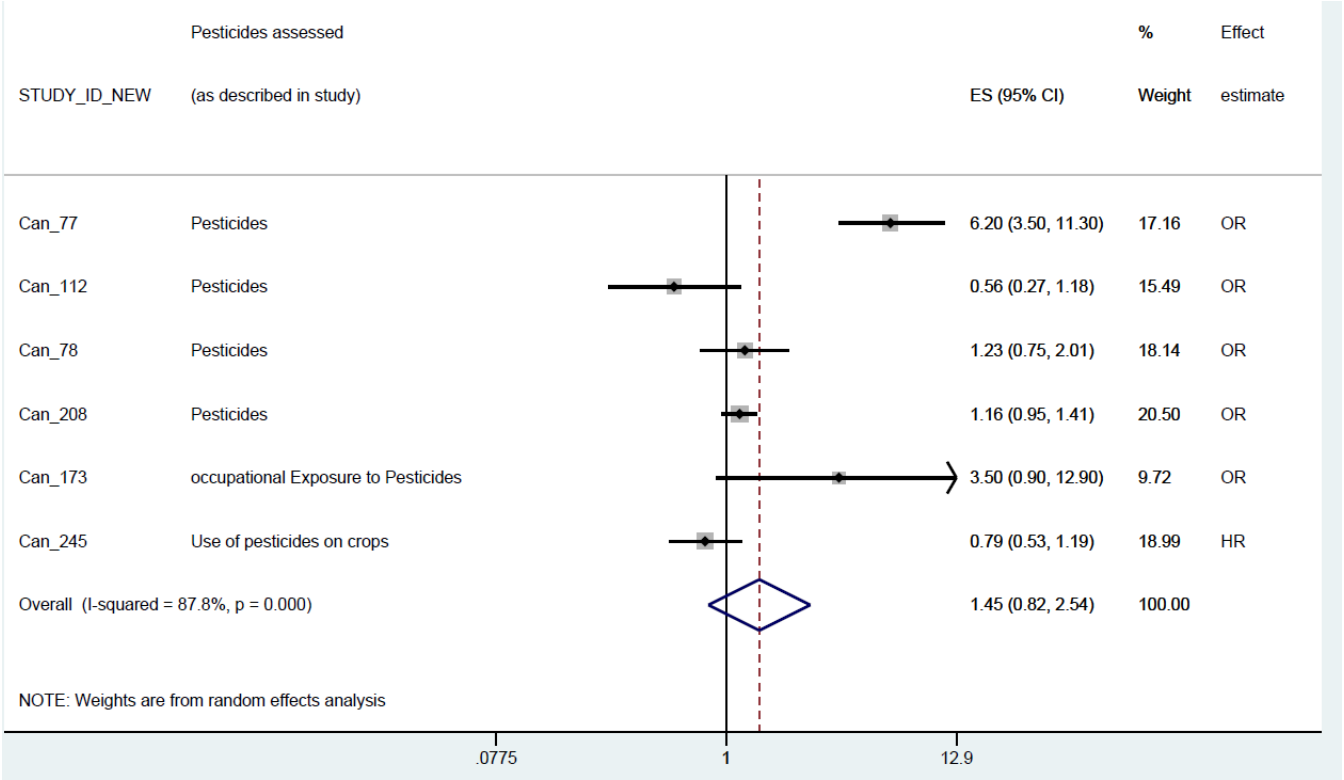
Thirty nine publications from 14 distinct studies (25 publications from the AHS study and 2 publications from one case-control study in France [Can_81, Can_63]) provided 227 estimates on the association of pesticides and other hematological neoplasms that included a very wide variety of definitions. The majority of the associations regarded occupational exposure to pesticides or a combination of occupational and environmental.

Five case-control studies (Can_16, Can_62, Can_140, Can_220, and Can_229) evaluated the association of the exposure to various occupational pesticides with myeloproliferative neoplasm/ myelodysplastic syndrome. Most of the 27 reported associations were not statistically significant and the reported effect sizes varied greatly, with a range from 0.42 to 7.3. Another study from the AHS (Can_265) presented non-statistically significant relative standardized incidence rates comparing the incidence rate of myeloproliferative neoplasm and myelodysplastic syndrome of pesticide applicators from the AHS (and their spouses) with the incidence rate of the general population. Three publications from 2 case-control studies (Can_63, Can_81, and Can_175) evaluated the association of various pesticides with lymphoproliferative syndrome with the majority of the 21 reported associations being not statistically significant.

The rest 33 publications reported data from 9 distinct studies (25 publications from the AHS) reported 179 associations of a several different pesticides with either very general definitions of hematological neoplasms (such as blood cancer; all lymphohematopoietic cancers; lymphoid malignancies) or very specific subtypes of hematological neoplasms (such as T-Cell lymphoma and nasal NK/T-cell lymphoma) prohibiting us from performing any meaningful meta-analysis. Excluding the AHS publications, 7 of the other 8 studies had a case-control design and only one was a cohort. Of the 179 reported associations only 33 were statistically significant. The reported effect sizes across all 1709 associations ranged from to 0.25 to 6.05.

2.2.3.1.4 Bladder Cancer

The association of pesticides (broad definition) with bladder cancer was not statistically significant based on 6 studies: RR=1.45 (95% CI: .82, 2.54), p=0.202, I^2=87.8%.



2.2.3.1.5 Lung Cancer

2.2.3.1.5.1 Mortality

We identified 190 estimates from 49 publications (15 distinct studies) evaluating the association of pesticides with lung cancer. The majority of the identified publications (n=34) used data from the AHS. Eight publications investigated the association of pesticides with lung cancer mortality. The majority of the publications (Mort_1, Mort_2, Mort_5, Mort_8, Mort_9 and Mort_13) did not observe a statistically significant association of pesticides with lung cancer mortality, respiratory cancer-mortality, trachea, bronchus and lung cancer mortality, lung and bronchus cancer mortality and mesothelioma mortality were not statistically significant. Only two studies indicated that exposure to pentachlorophenol increased the risk of respiratory cancer mortality (Mort_14), trachea, bronchus and lung cancer mortality (Mort_14) and pesticides exposure increased the risk of death due to lung cancer (Mort_12).

2.2.3.1.5.2 Prevalence/incidence

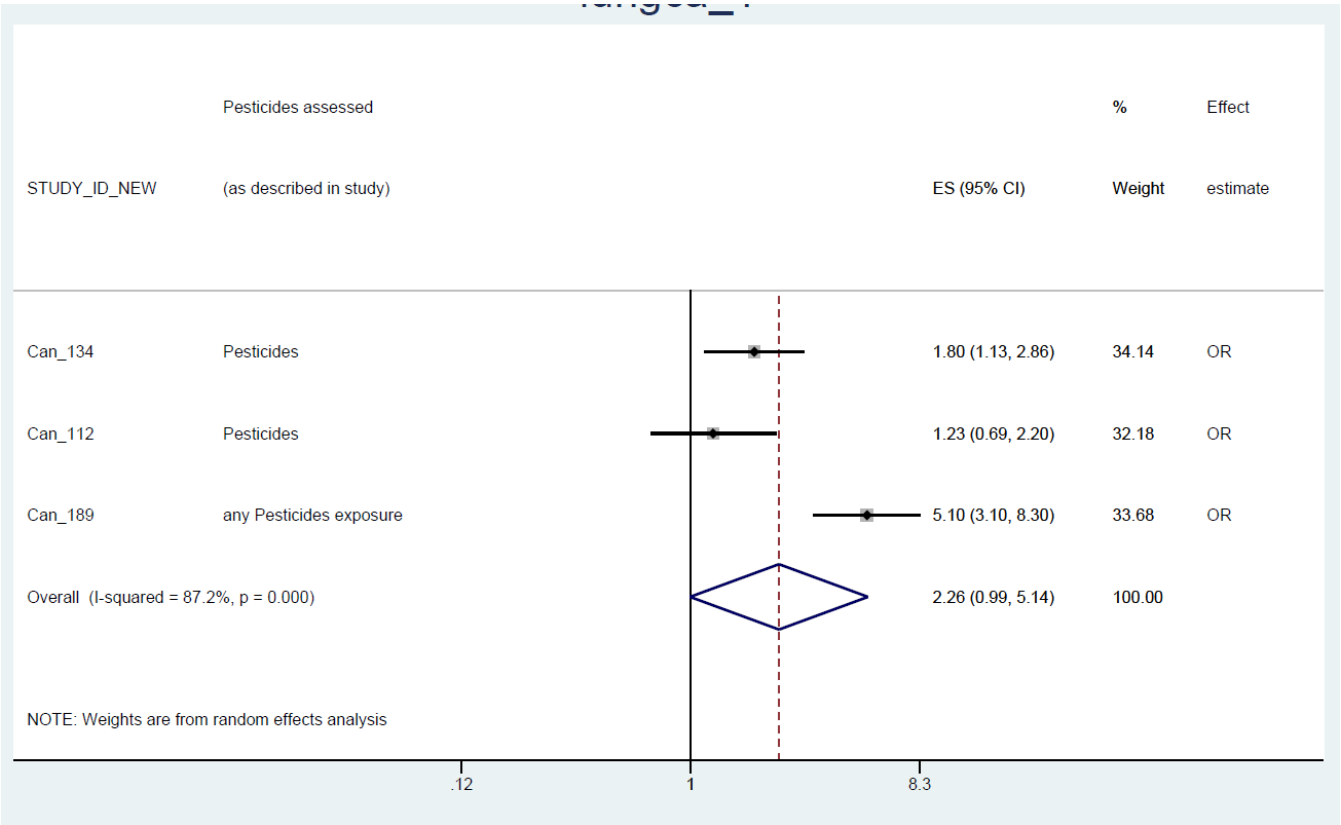
Forty two studies (11 distinct studies) investigated the association of pesticides with lung cancer prevalence/ incidence.

The study Can_67 was a case control study from Taiwan and found that mosquito-coils burn was significantly associated with increase odds of lung cancer. Adenocarcinoma, and Squamous cell carcinoma. The study Can_261 using data from the AHS reported associations of alachlor with lung cancer, small-cell carcinoma, squamous cell carcinoma and adenocarcinoma. This study did not find a statistically significant association of alachlor with any of these outcomes. The study Can_265 from the AHS presented relative standardized incidence rates comparing the incidence rate of lung cancer (respiratory system cancer, lung and bronchus cancer, small-cell carcinoma, non-small cell carcinoma, squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma) of pesticide applicators from the

AHS and their spouses with the incidence rate of the general population. This study indicated that private pesticide applicators and their spouses had statistically significant decreased incidence rate of respiratory system cancer, lung and bronchus cancer, small-cell carcinoma, non-small cell carcinoma ,squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma compared to the incidence rate of the general population, but there was no statistically significant difference between the incidence rates of commercial pesticide applicators in AHS and those of the general population.
One cohort study in Canada (Can_240) investigated the association of agricultural workers, farmers and managers, and manual laborers compared to non-agricultural occupations with the incidence of lung cancer and mesothelioma, stratified by sex. This study indicated that men with agricultural related occupations had a decreased risk of lung cancer and mesothelioma on men compared to men in non-agricultural occupations. Only the association of lung cancer was observed in women.
One case-control study in Spain (Can_182) evaluated the association of geographical areas with high vs low pesticide exposure with lung cancer prevalence. This study showed that areas with high pesticide exposure had an increased prevalence of lung cancer (overall and in men, but not in women) compared to areas with low pesticide exposure. One study (abstract) from the AGRICAN cohort (Can_243) investigated the association of specific agricultural-related occupations with lung cancer incidence. The majority of the reported associations were not statistically significant. One cohort study in Canada (Can_19) from the BC sawmill workers cohort study reported a non-significant association of Tetrachlorophenol with lung cancer. One case-control study in China (Can_154) reported a non-significant association of organochlorine Insecticides with lung cancer.

Thirty publications from the AHS reported associations of various pesticides and lung cancer incidence. The vast majority of those associations were not statistically significant.

Three studies provided sufficient data on the broad definition of pesticides and were included in a meta-analysis. The association of pesticides (broad definition) with lung cancer was not statistically significant based on 3 studies: RR=2.26 (95% CI: .99, 5.14), p=0.052, I^2=87.2%.



2.2.3.1.6 Colorectal Cancer

We identified 299 estimated from 42 publications (9 distinct studies) on the association of pesticides and colorectal cancer. The majority of the identified studies (n=34) came from the AHS.

2.2.3.1.6.1 Colorectal cancer mortality

Five studies (Mort_2, Mort_5, Mort_9, Mort_13, and Mort_14) from four cohorts (Mort_5, and Mort_13 were from the AHS) evaluated the association of pesticides and mortality due to colon, rectum, or colorectal cancer. The majority of the associations were not statistically significant.

2.2.3.1.6.2 Colorectal cancer prevalence/incidence

Thirty eight publications from 7 distinct studies (32 publications were from AHS) evaluated the association of pesticides and prevalence or incidence of colorectal cancer and its subtypes.

One cohort study of male sawmill workers in Canada (Can_240) investigated the association of tetrachlorophenol with the incidence of colon and rectum cancer. This study showed a statistically significant association of tetrachlorophenol with rectum cancer incidence but not with colon cancer. One study in Canada (Can_240) investigated the association of agricultural workers, farmers and managers, and manual laborers compared to non-agricultural occupations with the incidence of colon and rectum cancers, stratified by sex. This study did not report any statistically significant associations for neither colon nor rectum cancers and for neither sex. One large case-control stud in Spain (Can_182) evaluated the association of the proximity to areas with high vs low pesticide exposure with

colon and skin cancer prevalence, presenting a statistically significant increase in the odds of colon cancer prevalence on individuals living in geographical areas with high pesticides exposure.
One cross-sectional study with control group from Korea (Can_262) evaluated the association of organochlorine pesticides with colorectal cancer. This study indicated that sum(OCPs) and Beta-HCH but not sum(DDTs), sum_(chlordanes) and sum(heptachlors) were significantly associated with colorectal cancer. One case-control study in Italy (Can_239) evaluated the association of being a farmer as proxy of pesticide exposure with colorectal cancer. This study indicated that farmers had statistically significant elevated odds of having colorectal cancer. One case-control study in Egypt (Can_121) evaluated the association of Pesticides, Herbicides, and Insecticides with colorectal cancer. This study this study found a statistically significant association of all three exposure with increased odds of colorectal cancer.

The rest of the associations were from 32 publications from the AHS evaluating exposure to various pesticides and colorectal cacner, colon cancer (including distal colon and proximal colon), rectum cancer, rectum and rectosigmoid junction cancer and anus, anal canal and anorectum cancer. The majority of the associations from the AHS were not statistically significant.

2.2.3.1.7 Thyroid Cancer

We identified 41 estimates from 12 publications (6 distinct studies) reporting on the association of pesticides and thyroid cancer. Most (n=7) of the identified studies were from the AHS reporting on the associations of different pesticides and thyroid cancer.
One case-control study (Can_51) in United Kingdom investigated the association of pesticides exposure with thyroid cancer in children and presented non-statistically significant associations.
One case-control study in Norway (Can_161) investigated the association of several organochlorine pesticides as continuous exposure with thyroid cancer. This study did not report any statistically significant association of continuous pesticides exposure and thyroid cancer.
One cohort study in Canada (Can_240) investigated the association of agricultural workers, farmers and managers, and manual laborers compared to non-agricultural occupations with the incidence of thyroid cancer, stratified by sex. This study did not report any statistically significant association.
One study from the AHS (Can_265) presented relative standardized incidence rates comparing the thyroid cancer incidence rate of pesticide applicators from the AHS (and their spouses) with the incidence rate of the general population. This study showed an increased incidence rate of thyroid cancer on pesticide applicators from the AHS compared to the general population.
Six studies from the AHS reported on the association of several pesticides with the incidence of thyroid cancer, with the majority of those associations being not statistically significant.
Two case-control studies (Can_51 and Can_244) in French Polynesia and USA respectively, investigated the association of pesticides exposure with thyroid cancer but it did not observe statistically significant associations.

2.2.3.1.8 Skin Cancer

We identified 36 publications providing 125 effect estimates on the association of pesticides exposure and skin cancers or melanoma. The majority of the identified publications were from the AHS study (24 publications). The rest 12 publication were from 11 distinct studies.
One publication (Can_51) investigated the association of malignant melanoma and skin carcinoma on United Kingdom children. Three studies (Mort_8, Mort_9, Mort_13) investigated the association of pesticides with melanoma-specific mortality. None of the studies observed a statistically significant association. One publication from the AHS (Can_265) presented relative standardized incidence rates comparing the incidence rate of melanoma of pesticide applicators from the AHS (and their spouses) with the incidence rate of the general population. This study showed an increased incidence rate of melanoma on pesticide applicators from the AHS compared to the general population. One multicenter case-control study from several Europe countries (Can_151) evaluated the association of pesticides with uveal melanoma. None of the studies association was statistically significant.
One large case-control stud in Spain (Can_182) evaluated the association of the proximity to areas with high vs low pesticide exposure with skin cancer and skin cancer prevalence, presenting a statistically significant increase in the odds of skin cancer prevalence and skin cancer on individuals living in geographical areas with high pesticides exposure. One case-control study in Italy (Can_239) evaluated the association of being a farmer as proxy of pesticide exposure with non-melanoma skin cancer. This study indicated that farmers had statistically significant elevated odds of having non-melanoma skin cancer. One study in Canada (Can_240) investigated the association of agricultural workers, farmers and managers, and manual laborers compared to non-agricultural occupations with the incidence of melanoma, stratified by sex. This study indicated that agricultural related occupations increased the risk on melanoma on men but not on women.
Two publications were from the same case-control study in Italy (Can_41, Can_219). The study Can_219 was a subset of the population included in the study Can_41 and provided DNA samples. The analyses presented in the study Can_219 ware stratified based on the GSTM1 gene.
From the rest 26 studies, 22 were from the AHS reporting on different pesticides and risk of melanoma. The majority of the reported association were not statistically significant.
The rest 4 studies (Can_126, Can_41, Can_204, and Can_216) were all case-control studies evaluating the association of various pesticide exposures with cutaneous melanoma. All associations showed an increased odds of cutaneous melanoma, but only half of them were statistically significant.

2.2.3.2 Diabetes

Fifty-one studies were identified on the association between exposure to pesticide and diabetes (544 effect estimates).

Table 5. Diabetes-related outcomes

Outcome	Number of estimates	Number of studies
A1C =/>7.0%	1	1
Abnormal glucose regulation	2	1

Diabetes*	244	24
Gestational diabetes	47	6
Gestational diabetes mellitus or impaired glucose tolerance	21	1
Gestational impaired glucose tolerance	21	1
Homeostasis model assessment of insul..	1	1
Impaired glucose tolerance	1	1
Prediabetes	10	2
Poor glycemic control	2	1
type 1 diabetes	1	1
Type 2 diabetes**	193	18
Total	544	

*** Diabetes category includes the following outcomes: Diabetes, diabetes, incident diabetes, type 1 or 2 diabetes, diabetes type 1 or 2, diagnosed diabetes, total diabetes, undiagnosed diabetes**

**** Type 2 diabetes category includes the following outcomes: diabetes type 2, type 2 diabetes, Incident type 2 diabetes, type 2 diabetes mellitus.**

Regarding the available associations between exposure to pesticides as a continuous measure and any type of diabetes, only one study was identified. For type 2 diabetes, 17 estimates were available for analysis and in two cases (DDE, HCB) a quantitative synthesis was deemed feasible. Conversely, fifteen estimates were available for gestational diabetes with only one association judged as a quantitative synthesis candidate (DDE).

As far as the studies are concerned where a categorical exposure assessment was implemented, 176 estimates on type 2 diabetes were available. Of these, 119 were excluded from analysis (intermediate levels/ extra analyses from same study) leaving 57 estimates on type 2 diabetes available for further analysis (Tables 6). Moreover, 32 estimates on gestational diabetes were available for further analysis (Table 7). Finally, 243 estimates were available on diabetes (general category); of these, 87 estimates were excluded from analysis (intermediate levels/ extra analyses from same study) and 156 estimates on diabetes (any) were available for a quantitative synthesis.

Table 6. Identified associations for type 2 diabetes (pesticide exposure - categorical)

Exposure	Number of estimates	Number of studies per exposure	
sumDDT	1	1	No MA
DDD	2	2	No MA
DDE (2)	12	11	MA available
o,p'-DDT	2	2	No MA
p,p'-DDT (5)	4	4	MA available
Chlordane	1	1	No MA
cis-CHL	1	1	No MA
cis-nonachlor	1	1	No MA

Heptachlor epoxide	2	2	No MA
HCB (3)	6	6	MA available
Mirex	2	2	No MA
Oxychlordane (4)	5	5	MA available
trans-nonachlor (6)	7	7	MA available
TEXB-extract	1	1	No MA
Pesticides/Sum OCs/OC Pesticides	3	3	MA available
Total	57		

Table 7. Identified associations for gestational diabetes (pesticide exposure - categorical)

Exposure	Number of estimates	Number of studies per exposure	
Chlordecone	3	1	No MA
DDE, p,p'-DDE	7	3	MA available
DEP	3	1	No MA
DMP	3	1	No MA
DMTP	3	1	No MA
DMP and DMTP	3	1	No MA
HCB	2	1	No MA
Oxychlordane	3	1	No MA
Pesticides	2	1	No MA
Trans-nonachlor	3	1	No MA
Total	32		

Table 8. Identified associations for diabetes (general category, pesticide exposure - categorical)

Exposure	Number of estimates	Number of studies per exposure	
sum of HCB, DDE, and mirex	1	1	No MA
2,4,5-T or 2,4,5-TP	1	1	No MA
2,4-D	2	2	No MA
1,2,3,6,7,8-HxCDD	1	1	No MA
1,2,3,4,6,7,8-HpCDD	1	1	No MA
1,2,3,4,6,7,8,9-OCDD	1	1	No MA
1,2,3,4,6,7,8-HpCDF	1	1	No MA
DDE, p,p'-DDE, 2,4-DDE, 4,4-DDE (1)	12	11	MA available
DDT, p,p'-DDT, 2,4-DDT, 4,4-DDT, sumDDT (2)	9	7	MA available
3-PBA	1	1	No MA
4-F-3PBA	1	1	No MA
4,4-DDD	1	1	No MA
Abamectin	1	1	No MA
Alachlor	2	2	No MA
Aldicarb	1	1	No MA
Aldrin	2	2	No MA
Aluminum phosphide	1	1	No MA
Atrazine	1	1	No MA

Exposure	Number of estimates	Number of studies per exposure	
Benlate	1	1	No MA
Benomyl	1	1	No MA
Bordeaux mixture	1	1	No MA
Butachlor	1	1	No MA
Butylate	1	1	No MA
Captan	1	1	No MA
Carbamate	1	1	No MA
Carbaryl	1	1	No MA
Carbaryl/Sevin	1	1	No MA
Carbendazim	1	1	No MA
Carbofuran	1	1	No MA
Carbofuran/Furadan	1	1	No MA
Carbon tetrachloride/carbon disulfide..	1	1	No MA
Carbosulfan	1	1	No MA
Chlordane	2	2	No MA
Chlorimuron-ethyl	1	1	No MA
Chlorothalonil	1	1	No MA
Chlorpyrifos	2	2	No MA
Copper sulfate	1	1	No MA
Coumaphos	1	1	No MA
Cyanazine	1	1	No MA
Diazinon	1	1	No MA
Dicamba	1	1	No MA
Dichlorvos	2	2	No MA
Dicrotophos	1	1	No MA
Dieldrin (3)	4	4	MA available
EPN (ethyl-p-nitrophenyl)	1	1	No MA
EPTC	1	1	No MA
Endosulfan	1	1	No MA
Ethylene dibromide	1	1	No MA
Folidol/parathion	1	1	No MA
Fonofos	1	1	No MA
Fumigants	1	1	No MA
Fungicides (4)	3	3	MA available
Glyphosate	2	2	No MA
Heptachlor	2	2	No MA
HCB (5)	4	4	MA available
Herbicides (6)	3	3	MA available
Organochlorine Insecticides (7)	3	3	MA available
Insecticides (any) (8)	3	3	MA available
Pyrethroid Insecticides	1	1	No MA
Imazethapyr	1	1	No MA
Lindane	1	1	No MA
Malathion	1	1	No MA
Mancozeb	1	1	No MA

Exposure	Number of estimates	Number of studies per exposure	
Maneb	2	2	No MA
Metalaxyl	2	2	No MA
Methamidophos/Tamaron	1	1	No MA
Methomyl	1	1	No MA
Methyl bromide	1	1	No MA
Metolachlor	1	1	No MA
Metribuzin	1	1	No MA
Mevinphos	1	1	No MA
Mirex (9)	3	3	MA available
Molluscicides	1	1	No MA
Monocrotophos	1	1	No MA
Oxychlordane	2	2	No MA
Paraquat	1	1	No MA
Paraquat/Gramoxone	1	1	No MA
Parathion	1	1	No MA
pentyl(2,4,5-trichlorophenoxy)acetate..	1	1	No MA
Pendimethalin	1	1	No MA
Permethrin (crops)	1	1	No MA
Permethrin (livestock)	1	1	No MA
Permethrin/Ambush	1	1	No MA
Petroleum oil	1	1	No MA
Propanil	1	1	No MA
Rodenticides	1	1	No MA
Terbufos	1	1	No MA
Thiophanate-methyl	1	1	No MA
Toxaphene	1	1	No MA
Trichlorfon	1	1	No MA
Trifluralin	1	1	No MA
Zineb	1	1	No MA
Ziram	1	1	No MA
β-HCH	3	2	No MA
Phorate	1	1	No MA
trans-DCCA	1	1	No MA
trans-Nonachlor	2	2	No MA
POPs	1	1	No MA
Pesticides, any pesticides, Organophosphate Pesticides, etc (10)	9	6	MA available
Total	156		

Statistically significant associations were identified for any type of diabetes and the following compounds or compound categories: DDE (RR 1.92; 95% CI 1.38-2.66, I^2 74%), HCB (n=4, RR 1.93, 95% CI 1.16-3.2, I^2 47%), any pesticide (n=6, RR 1.24, 95% CI 1.03-1.50, I^2 68%). For type 2 diabetes, the following associations yielded a statistically significant result: DDE (n=11, RR 1.50, 95% CI 1.12-2.01, I^2

54%), HCB (n=6, RR 2.01, 95% CI 1.05-3.86, I^2 58%), HCB (n=4, RR 1.93, 95% CI 1.16-3.2, I^2 47%), Oxychlordane (n=5, RR 2.80, 95% CI 1.64-4.78, I^2 14%), trans-Nonachlor (n=6, RR 2.02, 95% CI 1.31-3.10, I^2 19%), any pesticide (n=3, RR 2.49, 95% CI 1.07-5.80, I^2 0%). For gestational diabetes, no statistically significant association was found.

2.2.3.3Thyroid Disease

Overall, 10 publications (6 distinct studies providing 581 estimates) investigated the association of pesticides with thyroid diseases, including hypothyroidism, hyperthyroidism and other thyroid diseases.

2.2.3.3.1 Hypothyroidism

Seven publications from 4 distinct studies investigated the association of various pesticides with hypothyroidism. There were not enough data for any pesticide (at least 3 studies) for a meta-analysis to be conducted. Four publications (EDD_24, EDD_35, EDD_42 and EDD_60) presented data from the Agricultural Health Study participants and/or their spouses. The majority of the studies associations of various pesticides with hypothyroidism were not statistically significant. One study (EDD_59) presented an increased Prevalence Ratio of Hypothyroidism in children when organophosphate metabolites, diethylthiophosphate, and dimethyldithiophosphate were detected. This study did not find an association of agricultural activities and hypothyroidism prevalence. Another study conducted on adolescents presented a statistically significant association of hypothyroidism with 2,5-DCP (but not with 2,4-DCP). Finally, one study (EDD_34) presented a non-statistically significant association of pesticides (p,p'-DDE) with hypothyroidism.

2.2.3.3.2 Overt hypothyroidism

Only one study (EDD_55) investigated the association of pesticides (p,p'-DDT) with overt hypothyroidism and presented a non-statistically significant association.

2.2.3.3.3 Subclinical hypothyroidism

Only two studies (EDD_55 and EDD_57) investigated the association of various pesticides with subclinical hypothyroidism. The majority of the association were not statistically significant.

2.2.3.3.4 Hyperthyroidism

Two studies (EDD_24 and EDD_42) investigated the association of various pesticides with hyperthyroidism. Due to the small number of studies a meta-analysis was not possible.

2.2.3.3.5 Other thyroid diseases

Three studies (EDD_24, EDD_26, and EDD_42) investigated the association of pesticides with thyroid diseases (other than hypothyroidism and hyperthyroidism). One study (EDD_24) included only female participants and the majority of the studies associations were not statistically significant. One study (EDD_42) included only male participants and presented a decreased risk of hyperthyroidism for those exposed to pesticides. Contrary, this study also the association of evacuated other thyroid diseases (excluding hypothyroidism and hyperthyroidism) and found men exposed to pesticides had an increased odds of having other thyroid diseases. Finally, another study (EDD_26) investigated the association of pesticides with thyroid diseases, yet this study did not provide sufficient information on effect sizes and confidence intervals.

2.2.3.4 Asthma

Health outcome Standard	Freq.	Percent	Cum.
Allergic asthma	11	3.50	3.50
Allergic rhinitis and current asthma ..	1	0.32	3.82
Asthma	242	77.07	80.89
Asthma (prevalence)	7	2.23	83.12
Asthma exacerbation	36	11.46	94.59
Asthma symptom score	6	1.91	96.50
Non allergic asthma	11	3.50	100.00
Total	314	100.00	

418 estimates were identified from 32 publications (29 distinct studies).

2.2.3.4.1 Childhood Asthma

Twelve publications from twelve distinct studies providing 104 effect estimates evaluated the association of pesticides exposure (with the pesticides exposure being evaluated in either pregnancy, infancy, childhood or adolescence) and childhood asthma or asthma symptoms on children or mothers. In general, those studies included highly heterogenous populations with different definitions of pesticide exposure and outcomes and therefore no meta-analysis was performed.

One study (Resp_28) evaluated the association of organochlorine pesticides in breast milk with asthma in Japanese pregnant women. This study did not observe any

statistically significant association. This study was excluded from further analyses due to the unique population. One study (Resp_34) evaluated the association of organochlorine pesticides exposure during pregnancy with medication use for Asthma. The majority of the associations were not statistically significant. One study (Resp_48) from NHANES evaluated the association of pesticides exposure during childhood and the prevalence of ever having asthma and currently having asthma. The vast majority of the studied associations were not statistically significant. One study (Resp_57) evaluated the association of proximity to area sprayed with pesticides during childhood with the prevalence of asthma-like symptoms. The results of this study were not statistically significant. One study (Resp_54) evaluated the association of organochlorine pesticides as continuous exposure with childhood asthma, presenting several statistically significant associations. An increase of 1ng/g lipid in pesticides concentration was associated with elevated odds of having asthma. One study (Resp_44) evaluated the association of DDE as continuous exposure with incidence of childhood asthma in the first 9 years but did not find a statistically significant association.

The remaining 6 studies (Resp_5, Resp_7, Resp_22, Resp_31, Resp_50 and Resp_59) evaluated the exposure to different pesticides and asthma but there were not sufficient data to perform a meta-analysis for any of the evaluated pesticides. The vast majority of the associations were not statistically significant.

2.2.3.4.2 Asthma in adults

We identified 314 estimates from 20 publications (17 distinct studies). One study (Mort_13) reported a non-statistically significant association of pesticides with standardized mortality rate due to asthma.
One study (Resp_45) reported estimates of exposure to crop-specific pesticides and allergic and non-allergic asthma. The majority of the associations were not statistically significant. One study (Resp_58) presented a statistically significant association of pesticides exposure with increased prevalence of allergic rhinitis and current asthma. Two studies (Resp_58, Resp_61) investigated the assocation of exposure to pesticides with asthma prevalence. Most of the associations were not statistically significant.
Two studies (Resp_47 and Resp_64) investigated the association of pesticides with Asthma symptom score. Most of the studied associations showed that pesticides exposure were associated with a statistically significant increase on the Asthma symptom score. One study (Resp_42) from the Agricultural Health Study investigated

the association of several pesticides with asthma exacerbation. None of the association was statistically significant. One study (Resp_21) did not provide sufficient data for evaluation of the effect of pesticides on asthma.
One study (Resp_63) evaluate the association of paraquat exposure with the prevalence of asthma and found an increased Prevalence Ratio of concentration x months of exposure to paraquat and asthma.
One study (Resp_13) from the Agricultural Health Study investigated the association of several pesticides with asthma among farm women, stratified by atopic and non-atopic asthma. This study presented several statistically significant associations of various pesticides with an increased incidence of atopic but not with non-atopic asthma.

Another study (Resp_20) from the Agricultural Health Study investigated the association of several pesticides with asthma on male pesticide applicators, stratified by allergic and non-allergic asthma.

Six studies provided estimates on broad pesticides definition and asthma and were included in the meta-analysis. The association of pesticides (broad definition) with asthma was statistically significant based on 6 studies: RR=1.46 (95% CI: 1.08, 1.98), p=0.015, I2=34.2%.

Exposure	Number of estimates	Number of studies per exposure	Analysis
Carbamates	2	1	
Chlorpyrifos	1	1	
Dimethyl phosphate	2	1	
Dithiocarbamates	2	1	
EBDC	3	1	
Organochlorines	2	1	
Organophosphates	2	1	
Paraquat	2	2	
Pesticides	7	6	asthma_1
Phenoxy	2	1	
Pyrethroids	2	1	
Terbufos	1	1	
Thiocarbamates	2	1	
Total	30		

2.2.3.5 Alzheimer's Disease & Dementia

2.2.3.5.1 Alzheimer's disease

We identified eight publications from 7 distinct studies that evaluated the association of pesticide with Alzheimer's disease.

Two studies were excluded from any further consideration: One case-control study (NRD_28) evaluated the odds of having DDE above the limit of detection between Alzheimer's disease patients and controls, however the study did not provide usable effect estimates. Another study (NRD_60) was also excluded since it provided incorrect effect estimates (the effect estimate lied outside of the provided confidence interval). Two publications (NRD_80 and NRD_126) provided overlapping evidence from the Canadian Study of Health and Aging (CSHA) regarding the continuous exposure to 7 organochlorine pesticides and Alzheimer's disease. None of the reported associations were statistically significant. One cohort study in USA (NRD_45) and reported associations on occupational exposure to pesticides, and organochlorine pesticides and insecticides with Alzheimer's disease. This study indicated that being exposed to pesticides compared to never been exposed increased the risk of Alzheimer's disease. Another two case-control studies conducted in USA (NRD_74 and NRD_132) indicated that being exposed to the highest vs lowest tertile of DDT was associated with increased odds of Alzheimer's disease. Finally, one case control study in India (NRD_79) indicated that three out of the five organochlorine pesticides assessed as a continuous exposure were associated with a statistically significant increase of the odds of Alzheimer's disease.

2.2.3.5.2 Dementia

We identified eight publications from 7 distinct studies that evaluated the association of pesticide with dementia.

One publication (Mort_22) from a Netherlands cohort study evaluated the association of several pesticides with non-vascular dementia-related mortality. Overall this study indicated that there was no association of pesticides with non-vascular dementia-related mortality. One cross-sectional study (NRD_36) was excluded from any further consideration since it only provided an effect size without any measures of variation (standard error or confidence interval). Two publications (NPD_62 and NRD_80) provided overlapping evidence from the Canadian Study of Health and Aging (CSHA) regarding the continuous exposure to 7 organochlorine pesticides and all-cause dementia. None of the reported associations were statistically significant. One publication from the Sacramento Area Latino Study on Aging (SALSA) cohort study evaluated the number of organophosphorus pesticides as exposure with the composite outcome of dementia/cognitively impaired but not demented but did not find a statistically significant association. The rest three studies (one cohort [NRD_45] and two cross-sectional [NRD_87, NRD_91]) did not find statistically significant associations of occupational exposure to pesticides and dementia.

2.2.3.6 Autism-spectrum Disorders

We identified 9 publications from 7 distinct studies evaluating the association of pesticides with autism & autism spectrum disorders (ASD). The reported associations were highly heterogeneous in terms of exposure, exposure period (preconception, pregnancy, childhood) and type of statistical analysis and therefore a meta-analysis was not feasible.

Three studies (NPD_9, NPD_25, and NPD_59) evaluated the association of pesticides exposure with autism. The study NPD_9 was not considered further since it provided incorrect estimates (the point estimate was outside of the provided confidence interval). Another two studies from the Finnish

Prenatal Study of Autism (FiPS-A) with partially overlapping populations evaluated the association of exposure to HCB (NPD_25) and DDE (both NPD_25 and NPD_59) during pregnancy with autism. The studies provided conflicting results with regards to DDE.
One case-control study in the USA (NPD_60) reported non-significant associations between exposure to several pesticides during preconception, pregnancy and the first year of life with ASD and ASD with intellectual disability. One case-control study in Jamaica, (NPD_57) presented a statistically significant association between exposure to pesticides (from 3 months before pregnancy to the end of breastfeeding) and ASD. One case-control study from the Early Markers for Autism (EMA) study (NPD_48) reported non-significant associations between exposure to organochlorine pesticides during pregnancy and ASD. One publication form the cross sectional AGRE study reported significant associations between exposure to insecticidal fumigants during childhood and ASD, but the effect sizes varied greatly , ranging from 0.54 to 2.22.
Two partially overlapping studies from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study (NPD_38, NPD_55) investigated the association of pesticides exposure during preconception and pregnancy with ASD. The study NPD_55 was not considered further in this evaluation since it only provided stratified associations based on the levels of folic acid intake (above or below 800 µg). The study NPD_38 provided estimates of the association of residential proximity to agricultural pesticide applications with ASD. Most of the reported associations were not statistically significant.

2.2.3.7 ***Kidney Disease***

We identified 13 publications from 11 distinct studies (3 publications from the AHS) that provided 336 estimates evaluating the association of pesticides and renal/ kidney diseases and mortality.

One study from the AHS (Mort_13) found decreased standardized mortality rates among applicators compared to the general population with regards to acute glomerulonephritis and chronic and unspecified nephritis. Another nested case-control, study in USA (Mort_23) found that increased levels of five organochlorine pesticides were associated with an increased risk of diabetic pre-End Stage Renal Disease (ESRD) mortality.
One case-control study in Sri Lanka (Kidn_1) reported non-statistically significant associations between pesticides and microalbumnuria. One study (Kidn_3) reported statistically significant results between DDE and DDT residues and gallstone disease. One study in Nicaragua (Renal_1) reported statistically significant increase in the odds of reduced GFR for those exposed to inhaled pesticides. One case-control study in Egypt (Kidn_8) (abstract) reposted statistically significant associations between insecticides and the use of traditional herbs for treatment with end stage renal disease of unknown etiology however this abstract did not provide specific effect sizes or confidence intervals.
Two publications from the AHS (Kidn_6¸Kidn_7) evaluated the association of several pesticides with ESRD on AHS farmers and their spouses, with the majority of the reported associations being not statistically significant.
Five studies reported associations between various pesticides with chronic kidney disease (and chronic kidney disease of either certain or uncertain etiology). The pesticides assessed along the different

statistical approaches did not allow for any quantitative synthesis of the results. The majority of the reported associations were not statistically significant.

2.2.3.8 Depression

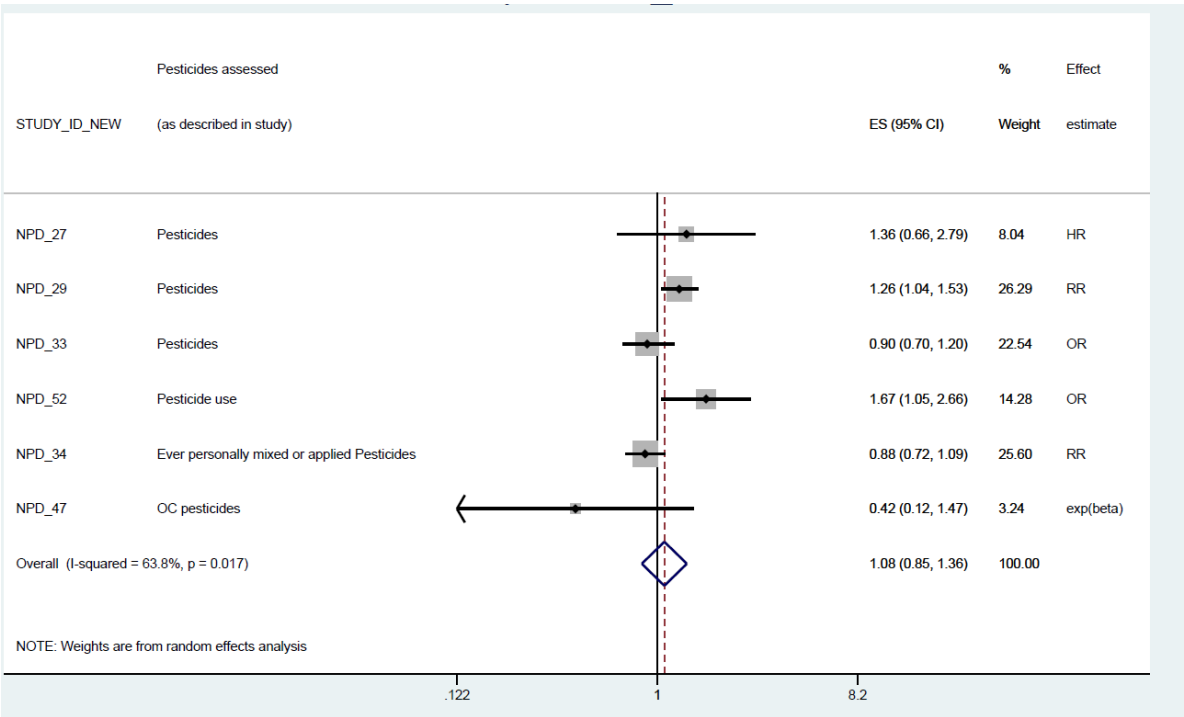
We identified 395 estimates from 17 publications (14 distinct studies) on the association of pesticides and depression. In the majority of the studies the type of pesticide exposure assessed was either occupational or a combination of both environmental and occupational exposure and the mode of pesticide exposure assessment was mostly through questionnaires. Two publications from the AHS examining the association of pesticides with depression in men (NPD_10) and women (NPD_3) were excluded from further evaluation as they were superseded by two more recent publications (NPD_33 in men and NPD_34 in women respectively).

One publication from the Parkinson Environment Gene study (NPD_51) reported a non-significant association of organophosphate pesticides with the Geriatric Depression Scale.
One cross-sectional study in Brazil (NPD_54) reported a statistically significant association of occupational pesticides exposure in men with depressive symptoms as defined by a score BDI-II>10.
One cross-sectional study in Iran (NPD_26) reported a statistically significant association of occupational exposure to pesticides with severe depression based on a p-value but it did not provide any effect estimates.
One cross-sectional study in Turkey (NPD_36) reported a statistically significant correlation of exposure to heptachlor epoxide with postpartum depression as measured by the Brief Symptom Inventory (BSI) scale. One cross-sectional study in male farmers in Iran (NPD_19) found no association between organophosphate pesticides and depression measured by the Symptom Checklist 90 revised (SCL-90-R) subscore) based on a p-value but it did not provide any effect estimates.
Three cross-sectional studies (NPD_4, NPD_32, and NPD_39) reported non-significant associations of various pesticides with the prevalence of depression using different estimates such as prevalence ratios and odds ratios.
One publication from the Danish Fetal Origins 1988 Cohort (NPD_31) reported non-significant associations of the exposure to organochlorine pesticides during pregnancy with the incidence of depression in children and young adults (up to 22 years).

Meta-analysis
There were six publications from five studies that evaluated the association of a broad definition of pesticides with depression and therefore a meta-analysis was feasible (two studies from AHS reported associations on men and women separately and therefore both were included) The association of pesticides (broad definition) with depression was not statistically significant: RR=1.08 (95% CI: .85, 1.36), p=0.537, I^2=63.8%. This result should be interpreted with caution, as the definition of depression varied across the studies.

The rest of the reported associations were from 4 studies (NPD_27, NPD_33, NPD_34, and NPD_52). A meta-analysis was not feasible as there was no same exposure evaluated in all 4 studies together.

About 16% of the rest of the reported associations (regarding a large numbers of different definitions of pesticides) were statistically significantly associated with depression but there was high heterogeneity in the effect estimates which ranged from 0.26 to 4.44.



3 Fertilizers

3.1 Methods

3.1.1 Study Eligibility

We considered observational studies assessing the association between fertilizers' exposure and health-related outcomes in adult, adolescents, or children. We included cohort, cross-sectional and case-control studies published up to June 2019. Given the scarcity of the available data, ecological studies were also captured. Narrative reviews, case reports, case series, modeling studies and editorials were excluded. Animal studies and studies performed in human cells were also excluded. To enhance comprehensiveness, all types of fertilizers were used. Exposure to fertilizers was defined as reported use of fertilizers by the study participant (self-administrated questionnaires, interviewer administrated questionnaires, job exposure matrix, occupational history), by residential status (proximity to fertilizers exposure), by government registry data, by detecting biomarkers associated with fertilizers exposure or by any other means as defined by each study. From our detailed description, we did not include studies assessing the health-related effect of acute fertilizers exposure or accidental fertilizers' exposure. Eligible health-related outcomes included "major" clinical outcomes, such as neoplasias or Parkinson's disease, clinical surrogate outcomes such as neurocognitive scales, or laboratory surrogate outcomes, such as liver enzymes. We excluded studies assessing exposure to fertilizers without a link to human health outcome as well as studies where exposure to fertilizers was associated to a specific biological pathway or mode of actions via assays or biomarkers not yet clinically validated (e.g. DNA methylation).

We set no language or geographical restrictions. We excluded studies with no availability of quantitative information reported in the article (e.g., effect estimates and 95% CI thereof, counts and sample sizes, or means - raw or adjusted - as well as standard deviations). Whenever reports pertained to the same study at different follow-up periods and examining the same outcome, we retained the one with the longer follow-up to avoid data duplication.

3.1.2 Databases and Search Strategy

The following databases were interrogated PubMed up to July 2019.

After piloting, we constructed a generic, highly sensitive search algorithm as follows: “fertilizers OR fertilizer OR fertilisers OR fertiliser OR “chemical fertilizers" OR "synthetic fertilizers" OR “organic fertilizers" OR "organic inputs” OR "mineral fertilizers” OR "organic manures" OR manure” (human limits on), complemented by an algorithm capturing the biomedical literature related to the use of sewage sludge as fertilizer using the terms ((“waste” OR “sewage sludge” OR “biosolids” OR “amendment”) AND (“farming” OR “crops” OR “crop”OR “soil”)).

3.1.3 Methodological quality of the assessed evidence

We assessed the methodological quality of the included studies and the risk of bias conferred thereof by using elements included in the RTI item bank[2], which is a practical and validated item bank for evaluating the risk of bias and precision of observational studies of interventions or exposures included in systematic evidence reviews.

3.1.4 Data Extraction

The following general and methodological information was abstracted from each study: name of authors, country, setting, location(s), and year of publication; periods of recruitment, exposure, follow-up, and data collection; type of epidemiological study (prospective cohort, retrospective cohort, cross-sectional or case control); age, gender; type of fertilizer assessed, characteristics of the type of exposure (e.g., occupational/non-occupational), type of questionnaire (if self-reported questionnaire was used to define fertilizer exposure), type of assay (for biomarkers of exposure), duration (e.g., lifelong or occasional) and frequency, exposure definition and, for pediatric studies, person exposed (mother, father, both parents or child) and period exposed (e.g., pre- or postnatal, preconception, both); control definition; health-related outcome and definition thereof; type and value of the calculated risks (OR, RR, MD) with their 95% CIs or SDs, as well as factors they are adjusted for (confounders). Moreover, we extracted data pertaining to methodological characteristics of the eligible studies as described in the next section. Data extraction was performed by one investigator, cross checked by another and discrepancies were resolved by a third arbitrator. The list of extracted outcomes was finalized following pilot data extraction in a random sample of eligible studies in order to identify areas that need refinement or additional data that need to be extracted.

3.1.5 Construction of database

We created a simple and user-friendly tool in excel for recording all the available evidence of the eligible studies. Each publication has a unique ID and we recorded the name of the first author,

journal, and the year of publication. Also, from each study we recorded the type of fertilizer exposure, the fertilizer group, and the number of outcomes/diseases under investigation. Therefore, one study may provide evidence for more than one assessment each time. Moreover, the database includes information on the total sample size and sample sizes in cases/controls, features of the population investigated and controls (age, disease status etc.), time periods of investigations/observations, the statistical methods used for evaluation of observations, confounders, type and amount of exposure, co-exposures, method of exposure assessment, results obtained (2x2 raw counts or Odds Ratios or Relative Risks or mean difference and their variability that it can be assessed with the standard errors or 95% confidence intervals). The criteria related to quality assessment are also be added in the database.

3.1.6 Quantitative data synthesis

The research synthesis endeavor was organized as follows:

Given the diverse network of phenotypes included, there were separate analyses per disease entity assessed and for the two large fertilizers' groups (chemical vs. organic). Then, disease entities with a common nosological background were synthesized further if appropriate. In addition, given the different windows of exposure studied, for each outcome we considered and discussed separately the different life stages (preconception, conception, childhood and adulthood). Quantitative synthesis would be performed when more than three studies were available and would be associated with evaluations of heterogeneity as well as extensive evaluations of publication and small study bias as described in the statistical analysis section. For binary outcomes, the principal summary measures were the relative risk (RR) and the odds ratio (OR). For each study we retrieved or calculated the adjusted RR and OR estimates and corresponding 95% CIs for the assessed outcomes. For continuous outcomes, we extracted or calculated the summary mean difference (along with the corresponding SD).

Analyses were performed in STATA 10 (STATA Corp., College Station, IL). All p-values are two tailed. The final report(s) and pertinent publications were reported according to the STROBE and MOOSE statements and checklists[3, 4].

3.2 Results

3.2.1 Evidence Base Overview

Regarding the current status of the update, 5,789 citations were retrieved based on our initial database searches. Of these, 5,172 were excluded at the title/abstract level leaving 617 for full text scrutiny. Five hundred and fifty-two citations were further excluded at the full text level thus leaving 65 publications for final inclusion in the present review.

The included studies were published from 1981 to 2019 and included populations with a global reach. The recruitment period varied considerably with one fifth and one fourth of the studies having recruited participants before the 80's and in the 00's respectively. The countries with the largest publication numbers were USA (n=18, 29%), China (n=6, 9%), Italy (n=5, 8%), and Norway (n=5, 8%). Continent-wise, the Americas and Europe amassed a large number of publications (66%) followed by Asia (26%) and Africa (5%). Case control studies were the most common design (52%) while cross sectional studies (21%) and cohort studies (20%) were also present in comparable frequencies. Four ecological studies were included and two studies compared cancer mortality in fertilizer plants with national vital statistics. In the longitudinal studies the maximum follow up duration ranged from 17 years to 60 years. Twelve (18%) and three (5%) studies assessed male-only and female-only populations while the remaining studies, where gender information was available, were gender balanced. In 39 (60%) studies the population under study was occupationally exposed;

Forty-six (71%) studies assessed chemical fertilizers only, 16 studies assessed organic fertilizers and three study assessed both types of fertilizers together or biosolids. The assessed fertilizers exposure period pertained to adulthood (56%), childhood (22%) and preconception or pregnancy (12%). Biomarkers were not used by any study and air markers were used by three studies quantifying exposure to workers in fertilizer plants; the remaining studies used questionnaires (63%), job matrixes (2%), occupational history (23%) or residential history (9%) to assess exposure. The exposure setting was either occupational (60%), residential/environmental (14%) or both (12%).

The outcomes under study spanned across the whole spectrum of human disease including rare diseases such as Ewing's sarcoma and common diseases such as acute bronchitis (Box 2). Discipline-wise and at the association level, outcomes related to cancer were most frequently assessed (37%) followed by neurological diseases (11%), infections (9%) and respiratory disease (9%) outcomes. Leukemia (various types included) was the disease under study with the largest number of studies

(n=8, 12%) followed by gastric cancer and brain tumors assessed in three studies each. All other outcomes were assessed in one or two studies.

Box 2. Outcomes related to human health assessed for an association with fertilizers' exposure

Acute bronchitis, Acute lymphocytic leukaemia, Acute myeloid leukaemia, Cancer mortality, Amyotrophic lateral sclerosis, Aplastic anaemia, Asthma, Brain glioma, Brain tumours (glioma-meningioma), Oesophageal cancer, Chronic bronchitis, Chronic kidney disease, Chronic myeloid leukaemia, Community acquired MRSA, Symptoms, Creutzfeldt-Jakob disease, Cutaneous leishmaniasis, Diarrhoea, Escherichia coli O157:H7 antibodies, Ewing's bone sarcoma, Gastric cancer, Germ cell cancer, Helminth infection, Haematological malignancies, Leptospirosis, Leukaemia, Low birth weight (LBW), Lung cancer, Lung function-Forced Vital Capacity, Malaria and Soil Transmitted Helminthic Infection, Monoclonal gammopathy, Multiple myeloma, Myelodysplastic syndrome, Narcolepsy, Non-Hodgkin lymphoma, Ovarian cancer mortality, Polydactyly, Prostate cancer, Q fever, Renal cancer, Rheumatoid arthritis, Schistosomiasis, Testicular cancer, Thyroid Cancer, Uveal melanoma, Vascular dementia, Wheeze

The database that has undergone quality control pertains to 405 postulated associations. Regarding the methodological appraisal of the studies, 25% of the associations stemmed from prospective data, for 84% of the associations the inclusion and exclusion criteria for the study participants were clearly described, and in half of the pertinent studies there was a balanced allocation in cases and control groups. Sixty-seven percent of the associations provided adjusted effect estimates. The level of description of the exposure was low for half of associations (54%), measurement of the exposure via a biomarker or marker other than questionnaire was rarely seen (3 studies) and compound-specific exposure assessment was done in 10 studies. The outcomes under study were ascertained through a validated method in the vast majority of the associations (81%).

3.2.2 Evidence Synthesis

None of the specific outcomes under study had been assessed in more than two studies using a comparable exposure definition thus precluding a quantitative synthesis to be performed.

3.2.2.1 Chemical Fertilizers

Forty-seven studies assessed chemical fertilizers pertaining to 312 associations. Of these, almost half were related to cancer (47%), while the remaining associations evaluated outcomes on symptoms (21%), neurological diseases (15%), and respiratory diseases (11%). A group of outcomes was represented by <5 associations (birth defects, development, hematological diseases, infections,

rheumatological disease, diabetes, mortality, neurological/vascular diseases, psychiatry). The vast majority of associations pertained to occupational exposure (87%). Exposure to fertilizers was assessed jointly with other chemicals (4%), along with pesticides (1%, 2 associations), defined as a general category (50%), defined as nitrogen fertilizers (19%), or defined as phosphorus fertilizers (26%). In twelve studies the exposure window was either in pregnancy/periconception or in childhood; these studies mostly pertained to pediatric malignancies reported in single studies with severely affected replication validity (Appendix B).

3.2.2.1.1 Cancer-related Outcomes

Twenty-five studies assessed putative associations between exposure to chemical fertilizers and some type of cancer corresponding to 152 associations (Appendix). The outcome definition was so diverse that only gastric cancer (n=5) and multiple myeloma (n=4) were assessed in more than two studies using a more harmonized outcome definition; however, the exposure definition was so heterogeneous in these studies that it hindered a quantitative synthesis. Overall, the observed clinical heterogeneity and the limitations mainly related to the study design and the exposure assessment preclude a robust conclusion over any potential association between exposure to fertilizers and cancer. In the next two paragraphs, we describe the published exposure cohort studies followed by the studies related to gastric cancer and multiple myeloma.

We identified four longitudinal studies (exposure cohorts) assessing the association between exposure to chemical fertilizers and cancer. The main limitation of these studies is the use of national mortality rates as reference. Fandrem et al. (1993)[5] assessed the association between cancer mortality among 2,023 male nitrate fertilizer plant workers and the cumulative exposure to dust (level-years) over a follow up spanning from 1953 to 1988 (Norwegian national cancer rates used as reference). No statistically significant differences were observed for the 10 cancer sites investigated. Bulbulyan et al. (1996)[6] investigated the cancer-related mortality of workers (n=4,996; 41% male) in a fertilizer plant in Russia exposed to precursors of N-nitroso compounds and followed up from 1965 to 1990. Overall, there were no statistically significant findings in the standardized mortality ratios (using cause-specific death rates for the Moscow region as reference). In men, increased mortality was observed for lung cancer and any cancer (latency period of > 20 years). Moreover, men with the highest exposure to nitrogen oxides had an increased mortality from gastric cancer. Finally, excess mortality from any cancer and gastric cancer was found for the workers with the highest average exposure to arsenic. Yiin et al. (2016)[7] evaluated mortality estimates among 3,199 workers employed 1951–1976 at a

phosphate fertilizer production plant in central Florida with follow-up through 2011. All-cause mortality (SMR = 1.07, 95% CI 1.02–1.13), cancer-specific mortality (SMR = 1.16, 95%CI 1.06–1.28), lung cancer mortality (SMR = 1.32, 95%CI = 1.13–1.53), and leukemia mortality (SMR = 1.74, 95%CI = 1.11–2.62) were all statistically significantly elevated in the workers cohort (US population used as reference). Kristensen et al. (1996)[8] assessed the association between testicular cancer in the offspring and exposure to fertilizers defined as the combination of high nitrogen (l00 kg/hectare) in 1979 or 1989 and low phosphorus (<25 kg/hectare) in 1989 from commercial fertilizers on fully cultivated meadows (high N:P fertilizer ratio). The observed cancer rates were compared to the total rural population of Norway. The authors reported a statistically significant increase in the relative risk for testicular cancer among sons from farms with a high N:P fertilizer ratio and the largest effect was seen for non-seminoma (RR = 4.21; 95% CI 2.13-8.32).

Five studies assessed the association between gastric cancer and exposure to fertilizers. In the three exposure cohorts described before (Bulbulyan et al. Jiin et al., Fandrem et al), no statistically significant associations were observed.[5-7] In the two case control studies coming from the same research group evaluated the association between occupational exposure to fertilizers and gastric cancer. Cocco et al (1994)[9] assessed 640 histologically confirmed male cases and 959 controls in Italy via self-reported exposure to certain chemicals; no statistically significant association was observed for fertilizers. Cocco et al. (1999)[10] investigated the risk of death from gastric cancer (n_{cases}=41,957, death certificate data) associated with various occupational exposures in 24 USA states for the time period 1984–96. Exposure was assessed by using census-listed occupation and industry codes to assess the probability and intensity of exposure to fertilizers (among other chemicals). Risk of death from gastric cancer was not associated with exposure to fertilizers.

Four studies (1 exposure cohort, 1 case control study, 2 ecological studies) evaluated the association between exposure to chemical fertilizers and multiple myeloma. As described before, Yiin et al. (2016)[7] evaluated mortality estimates among 3,199 workers employed 1951–1976 at a phosphate fertilizer production plant in central Florida with follow-up through 2011. Mortality related to multiple myeloma (n_{cases}=6, SMR 3.01, 95%CI 1.10–6.55) was statistically significantly elevated in the workers cohort (US population used as reference). Morris et al. (1986)[11] using a population-based, multicenter case-control design assessed the self-reported use of various chemicals as risk factors for multiple myeloma (n=2,381). No statistically significant association was seen for exposure to fertilizers. Cantor et al. (1984)[12] in an ecological assessment of exposure to fertilizers (county-based) evaluated

the risk of death from multiple myeloma in the State of Wisconsin between 1968-76 (n_{cases}=411). Marginally statistically significantly elevated OR were observed for fertilizer use (OR 1.7, 95% CI 1.0-2.9) in the group of farmers with the highest county use compared with non-farmers with the lowest county use. Fluegge et al. (2017)[13] evaluated the association between farm use of nitrogen fertilizers (most relevant environmental proxy for N_2O emissions) and hospitalizations for blood-related cancers using the Healthcare Cost and Utilization Project (HCUP) database. An inverse (protective) marginally statistically significant association was observed for multiple myeloma (incidence rate ratio 0.92, 95% CI 0.86–0.99).

3.2.2.1.2 Neurological Diseases Outcomes

Two small case control studies investigated the association between exposure to fertilizers and neurological diseases (amyotrophic lateral sclerosis (ALS), narcolepsy) in two recent studies in USA. Yu at al. (2014)[14] explored the role of environmental factors (including exposure to fertilizers) in the development of ALS (n=132). Self-reported exposure to fertilizers to treat private yards and gardens was statistically significantly associated with ALS only for the exposure period from 30 years ago to 10 years ago (OR 2.97, 95% CI 1.01–8.76). Ton et al. (2010)[15] assessed the association between narcolepsy risk and occupational and non-occupational exposure to toxins including fertilizers (n=162) in HLA DQB1n0602 positive adults. Exposure to fertilizers was statistically significantly associated with narcolepsy (OR 3.1; 95% CI: 1.1–9.1).

3.2.2.1.3 Infectious Diseases' Outcomes

Two studies (1 exposure cohort, 1 case control) assessed the association between exposure to fertilizers and outcomes related to infectious disease (tuberculosis, Creutzfeldt-Jakob disease). van Duijn et al. (1998)[16] studied risk factors for Creutzfeldt-Jakob disease (CJD) as part of the 1993–95 European Union collaborative studies of CJD in Europe (n=810). Exposure to chemical (artificial) fertilizers was not associated with CJD (OR 0.76, 95% CI 0.43–1.36). As discussed before, Yiin et al. (2016) [7] evaluated mortality estimates among 3,199 workers employed 1951–1976 at a phosphate fertilizer production plant in central Florida with follow-up through 2011. Tuberculosis-related mortality (n_{cases}=2, SMR 0.71, 95% CI 0.09–2.55) was not statistically significantly elevated in the workers cohort (US population used as reference).

3.2.2.1.4 Other Outcomes

Kristensen et al. (1997)[17] investigated the association between birth defects and exposure to fertilizers (among other exposures) in the Medical Birth Registry of Norway. For polydactyly, the

authors observed an association with increasing level of phosphorus from commercial fertilizers in fully cultivated meadows (medium levels of phosphorus, aOR 1.54, 95% CI 0.98-2.42; high levels of phosphorus, aOR 1.85, 95% CI 1.15-2.99). A high N:P fertilizer ratio was associated with esophageal atresia (aOR 1.99, 95% CI 0.97 – 4.08) and syndactyly (aOR 1.60, 95% CI 1.04 - 2.46).

Parks et al. (2016)[18] in an Agricultural Health Study publication examined associations between rheumatoid arthritis (RA) and fertilizers' use along with pesticides or other agricultural exposures in female spouses of licensed pesticide applicators (n_{cases}=275, $n_{noncases=24,018}$; enrollment: 1993-1997, follow up: up to 2010). Incident RA was associated with the application of chemical fertilizers (OR = 1.7; 95% CI:1.1, 2.7).

3.2.2.2 Organic Fertilizers

Seventeen studies assessed organic fertilizers pertaining to 77 associations. Of these, almost half were related to infections (43%), while the remaining associations evaluated outcomes on symptoms (43%), allergic diseases (4%), and rheumatological diseases (4%). A group of outcomes was represented by one association (cancer, hematological diseases, respiratory diseases). The majority of associations pertained to occupational exposure (75%). Exposure to organic fertilizers was diverse, poorly harmonized, non-adequately described, and defined as use of sewage sludge (40%), animal manure (14%), dairy/veal manure (11%), swine manure (11%), human waste (night soil) (10%), organic fertilizer (6%), human excreta/feces (3%) and reuse of animal excreta re-use, animal fertilizer, fertilizer containing horns and hooves, and natural fertilizers. In five studies the exposure window was either in pregnancy/periconception or in childhood; these studies mostly pertained to various infections and allergic disorders reported in single studies again with severely affected replication validity (Appendix B).

3.2.2.2.1 Cancer-related Outcomes

Menvielle at al. (2003)[19] studied in a case control fashion the associations between organic fertilizers (among various other occupational exposures) and the risk of lung cancer in New Caledonia (n=533, $n_{exposed}$=10). No statistically significant association was observed (OR 1.1, 95% CI 0.2-5.6).

3.2.2.2.2 Neurological Diseases' Outcomes

No studies related to neurological diseases were identified.

3.2.2.2.3 Infectious Diseases' Outcomes

Ten studies (4 case control studies, 6 cross sectional studies) evaluated an association (n=35) between organic fertilizers and any outcome related to infections (Appendix B). No two studies assessed the same outcome (schistosomiasis, community aquired MRSA, hospital aquired MRSA, skin/soft tissue infection, Q fever-seroprevalence, Creutzfeldt-Jakob disease, cutaneous leishmaniasis, Escherichia coli O157:H7 antibodies, helminth infection, household poultry testing positive for C. jujeni, malaria and soil transmitted helminth). In the following text, we describe in more detail the published case control studies. The characteristics of the cross sectional studies are shown in Table 3.1.

Casey et al. (2013)[20] in a population-based case control study in Pennsylvania, USA, assessed the association between individual exposure to swine and dairy/veal industrial agriculture and risk of methicillin-resistant Staphylococcus aureus (MRSA) infection (electronic health records, n_{cases}=1,539

community-associated-CA, n_{cases}=1,335 health care-associated-HA) and skin and soft-tissue infection (SSTI, n_{cases}=2,895) Exposure was defined through nutrient management plans and 2 exposure variables were used as follows: seasonal crop field manure application and number of livestock animals at the operation. After adjusting for potential confounding variables, the authors found a significantly increased odds of CA-MRSA with higher swine manure exposure (fourth vs first quartile, aOR 1.38, 95% CI 1.13-1.68), HA-MRSA (fourth vs first quartile, aOR 1.30, 95% CI, 1.05-1.61), and SSTI (fourth vs first quartile, aOR 1.37, 95% CI 1.18-1.60). The fourth quartile (vs first quartile) of dairy/veal exposure was also associated with increased odds of CA-MRSA (aOR 1.24, 95% CI 1.01-1.52). Regarding the highest 2 quartiles of swine crop field manure exposure, the population attributable fractions were 10.7% (5.0-16.4%) for CA-MRSA infection and 11.5% (7.0-16.0%) for SSTI.

Pham-Duc et al. (2014)[21] carried out a nested case control study in Hanam, Vietnam, to determine risk factors for diarrhoeal disease in adults exposed through agriculture to wastewater and excreta use (n=464). The following associations were observed: composting of human excreta in the household (≤3 months versus > 3 months, OR 2.4, 95% CI 1.4-4.3), handling human excreta in field work (yes vs. no, OR 5.4, 95% CI 1.4-21.1), use of animal excreta as fertilizer in the fields (yes vs. no, OR 1.6, 95% CI 1.0-2.6), and handling animal excreta in field work (yes vs. no, OR 3.3, 95% CI 1.8-6.0).

Gijon-Robles et al. (2018)[22] using a case control design (n_{cases}=71, $n_{controls}$=137) investigated the association between cutaneous leishmaniasis (CL) and various risk factors including the accumulation of organic fertilizers around the house. Accumulation of organic fertilizers around the house was not associated with CL per se (OR 2.31, 95% CI 0.51–10.4). However, it was statistically significantly associated with *Phlebotomus sergenti* density (OR 1.8, p-value=0.04) which was identified as a risk factor for CL.

As discussed before, van Duijn et al. (1998)[16] studied risk factors for Creutzfeldt-Jakob disease (CJD) as part of the 1993–95 European Union collaborative studies of CJD in Europe (n=810). Exposure to fertilizers containing hooves and horns was statistically significantly associated with CJD (OR 2.32, 95% CI 1.38–2,91.

Table 3.1 Characteristics of the cross-sectional studies assessing outcomes related to infections

First author	Year	Country	Exposure Period	Study type	Fertilizer assessed	Type of exposure	Health outcome	N
van Duijn CM	1998	Belgium, France, Germany, Italy, the Netherlands, UK	Adulthood	Case control	Fertiliser containing hoofs and horns	Both	Creutzfeldt-Jakob disease (CJD)	72
Belongia	2003	USA	Childhood	Cross sectional	Manure	Enviromental	Escherichia coli O157:H7 antibodies	611
Pham-Duc	2013	Vietnam	NR	Cross sectional	Human excreta	Enviromental	Helminth infection	1425
Getachew	2013	Ethiopia	Pregnancy	Cross sectional	Human feces	Enviromental	Malaria and Soil Transmitted Helminthiasis coinfection	388
Casey	2013	USA	NR	Nested case control	Swine manure	Both	Community aquired MRSA	4453
Casey	2013	USA	NR	Nested case control	Swine manure	Both	Hospital aquired MRSA	4249
Casey	2013	USA	NR	Nested case control	Swine manure	Both	Skin/soft tissue infection	5809
Casey	2013	USA	NR	Nested case control	Dairy/veal manure	Both	Community aquired MRSA	4453
Casey	2013	USA	NR	Nested case control	Dairy/veal manure	Both	Hospital aquired MRSA	4249
Casey	2013	USA	NR	Nested case control	Dairy/veal manure	Both	Skin/soft tissue infection	5809
El-Tras	2005	Egypt	NR	Cross sectional	Manure	Occupational	Household poultry testing positive for C. jejuni	103
Pham-Duc	2014	Vietnam	NR	Nested case control	Animal excreta re-use	Enviromental	Diarrhea	464
Carlton	2015	China	Adulthood, Childhood	Cross sectional	Human waste (night soil)	Enviromental	Schistosomiasis	2005
Dal Pozzo	2015	Belgium	NR	Cross sectional	Manure	NR	Q fever-seroprevalence against C. burnetii	74
Gijon Robles	2018	Morocco	Adulthood, Childhood	Case control	Organic fertilizer	Enviromental	Cutaneous leishmaniasis	208

3.2.2.2.4 Other Outcomes

Illi et al. (2012)[23] sought to determine the associations between distinct farm exposures and asthma and atopy implementing a cohort study in rural regions of Austria, Germany, and Switzerland (n=8,419). Being present when parents were manuring was inversely and statistically siginicantly associated with asthma (aOR 0.65, 95% CI 0.47-0.90), hay fever (aOR 0.51, 95% 0.33-0.80), atopic dermatitis (aOR 0.66, 95% CI 0.45-0.96), but not atopic sensitization (aOR 0.85, 95% CI 0.65-1.11).

As discussed before, Parks et al. (2016)[18] in an Agricultural Health Study publication examined associations between rheumatoid arthritis (RA) and fertilizers' use along with pesticides or other

agricultural exposures in female spouses of licensed pesticide applicators (n_{cases}=275, $n_{noncases}$=24,018; enrollment: 1993-1997, follow up: up to 2010). Incident RA was not associated with the application of natural fertilizers (OR = 0.85, 95% CI 0.48-1.5).

Issaragrisil et al. (2006)[24] in a case control study in Thailand assessed the association between aplastic anemia and various occupational parameters (n_{cases}=541, $n_{controls}$=2,261). The authors report a statistically significant relative risk for aplastic anemia and the use of animal fertilizers (RR 2.1, 95% CI 1.0-4.4).

3.3 Discussion points for the UNEP report

- Emerging evidence base
- Study design usually non longitudinal
- Exposure frequently assessed together with pesticides
- Poor exposure assessment
- Diverse outcomes
- Cancer a relatively common outcome for chemical fertilizers
- Infections a relatively common outcome for organic fertilizers (1 MRSA study)
- Replication validity severely affected

4 Cadmium Case Study

4.1 Background

Cadmium (Cd) is a widely distributed persistent heavy metal with high toxicity and an elimination half-life of 10 to 30 years [25]. Apart from the natural presence of Cd in the environment due to the volcanic activity, weathering of Cd-containing rocks and sea spray, other major sources of Cd include industrial (nickel-Cd batteries, soldering alloys, pigments, coatings and plastic stabilizers), agricultural (contamination of phosphate fertilizers) and other activities (release from motor vehicle fuel combustion and tire wear) [26, 27]. Moreover, there is growing concern about chronic exposure to low levels of Cd through tobacco smoking and diet rich in fiber such as cereals, vegetables and shellfish due to the environmental pollution and soil contamination by Cd [27].

Recent studies have examined the adverse biological effects of Cd exposure on the general population [26, 28]. Indeed, there is evidence between Cd exposure and adverse health outcomes such as cancers, decreased bone mineral density, endocrine and kidney diseases, at lower exposure levels than previously expected [26-31]; however, results so far have been inconsistent and firm conclusions cannot be made. The International Agency for Research on Cancer (IARC) has classified Cd as a group 1 human carcinogen [26, 32]. Some earlier studies reported significant associations between Cd exposure and lung cancer; nonetheless, there is limited evidence from later epidemiologic studies for an association of Cd with prostate, kidney and breast cancer [32-36].

To this end, we aimed to systematically collect, review and appraise published systematic reviews or/and meta-analyses focused on the potential associations of Cd exposure with health-related outcomes. In particular, the present report compiled all relevant systematic reviews or/and meta-analyses in which possible links between all Cd exposure types either through occupation or in the general population and adverse human health effects have been investigated. The available evidence has been reviewed and evaluated with regard to its qualitative aspects and data from each eligible study has been extracted. Finally, a database of studies, which examine adverse health effects of Cd exposure, has been compiled with the aim to facilitate the ongoing update of results.

4.2 Materials and Methods

4.2.1 Search strategy and algorithm

A comprehensive literature search was conducted including peer-reviewed original research pertaining to Cd exposure and any health outcome. We identified systematic reviews or/and meta-analyses published up to September 30th 2019, examining the relationship between exposure to Cd and any health-related outcome. The search strategy was developed to search primarily the MEDLINE (1950-to date) and EMBASE (Excerpta Medica Database; 1980 to-date) databases.

This report targeted searches for systematic reviews and meta-analysis examining any clinical outcome or valid biomarker acting as surrogate for a clinical outcome that has been associated with short- or long-term exposure to Cd. We searched the MEDLINE database including in the algorithm the keywords “systematic review OR meta-analysis”.

The algorithm resulted in 129 citations, of which 106 citations were forwarded for full text screening.

4.2.2 Eligibility criteria for full text articles

We included systematic reviews and meta-analyses published until September 2019 that systematically assessed the effect of Cd exposure to health-related outcomes, regardless of the exposure window and outcome assessed. We included all publications where a systematic approach was endorsed (systematic literature search, assessment of methodological characteristics of the included studies and, if a meta-analysis was performed, the use of standard analytical tools including the use of a weighted summary estimate and a formal appraisal of heterogeneity). Narrative reviews were excluded.

4.2.3 Data extraction database

The data extraction database included the following domains: reference, time period, study characteristics, exposure assessment, outcomes and statistical analysis, where applicable. The extracted studies contributed one row in the database for each outcome examined and for each level of Cd exposure examined, namely short-term or long-term exposure. In studies presenting various definitions of Cd exposure, the most comprehensive definition of exposure and subsequently the one with the largest sample size was selected for data extraction. Among studies presenting data in subsets of patients (e.g. males and females), only their main analysis (whole group) was extracted unless the data was solely presented in subgroups; in that case multiple rows were presented. The

form of data extraction was validated through a robust and systematic procedure. Pairs of investigators independently performed the data extraction; any discrepancy was resolved by team consensus.

4.3 Results

4.3.1 Selection process - Characteristics of eligible studies

Of the 129 retrieved citations, 23 were excluded at the title or abstract screening level (Figure 4.1). Out of the 106 full-text publications, 34 were further excluded. Thus, 72 different systematic reviews were deemed eligible, of which 37 also included a meta-analytical approach. The eligible studies were published between 2000 and 2019. The outcomes examined in each systematic review and meta-analysis are shown in Table 4.1. Most reviews examined cancer-related outcomes in association with Cd exposure and some claimed positive associations.

4.3.2 Cancer outcomes

Overall, 18 systematic reviews and meta-analyses published after 2000 examined the effect of Cd exposure on cancer outcomes. The mostly studied outcome was breast cancer (n=7), followed by prostate (n=4), pancreatic (n=3), lung (n=2), multiple (n=2) and renal (n=1) cancers. The eligible systematic reviews and meta-analyses were mainly medium-sized (n=2-14 study groups) and examined both occupational and environmental exposures to Cd.

Two meta-analyses focused on the association of long-term Cd exposure with multiple cancers risk and reported statistically significant, albeit weak, summary effect estimates [28, 37]. Seven studies investigated the association of Cd exposure with breast cancer. The majority of results were non-significant and of small effect sizes. Only three out of the 10 different meta-analyses were statistically significant with summary effect estimates ranging from 2.24 to 3.64 [38-40]. Of note, the between-study heterogeneity was significant (range: 63%-98%) in all meta-analyses, but one (I2: 27%) [41].

Similar non-significant results were reported by four meta-analyses focused on the effect of Cd exposure on prostate cancer incidence or mortality. Only two out of the 11 different meta-analyses were statistically significant, albeit with significant between-study heterogeneity (I2: 70% and 98%) [42, 43]. Regarding lung cancer, a medium-sized meta-analysis reported non-significant associations of Cd occupational or environmental exposure [44], whereas a smaller-sized study showed a significant summary effect size of 1.68 (95% confidence intervals, CI: 1.47-1.92; I2: 0%) for long-term Cd exposure

with lung cancer risk [37]. Three systematic reviews examined the effects of occupational Cd exposure on pancreatic cancer, of which the summary effect sizes were significant in two meta-analyses. Likewise, a meta-analysis based on 10 study arms reported a significant 47% increased risk for renal cancer without remarkable between-study heterogeneity (OR: 1.47, 95% CI: 1.27-1.71; I2: 0%) [45].

4.3.3 Endocrine outcomes

Four studies assessed the effect of Cd exposure on diabetes outcome published between 2017 and 2019. Out of the five different meta-analyses three reported statistically significant summary effect sizes ranging from 1.03 to 1.38 based on seven, nine and 13 study arms; yet, the between-study heterogeneity was a remarkable limitation of these studies [46-48].

4.3.4 Other outcomes with few studies

Other health-related outcomes assessed by less than four systematic reviews/meta-analyses included low birth weight (n=2), cardiovascular disease (CVD; n=3), hypertension (n=2), fertility impairment (n=2), neurological diseases (n=2), fractures (n=1), renal disorders (n=2), and mortality (n=2). Among the latter, positive associations were claimed for low birth weight, CVD, hypertension, fractures, as well as all-cause and CVD mortality.

Specifically, a recent meta-analysis of 22 study arms showed a significant association of maternal Cd exposure with low birth weight (Fisher-z = -0.07, 95% CI: -0.11, -0.02) using the random-effects model; however, significant heterogeneity was detected (I2: 76.3%, p <0.001) [49]. Similarly, a positive association between maternal urine Cd exposure and low birth weight was shown in a second meta-analysis of three study arms (OR: 1.12, 95% CI: 1.02-1.22) [50].

In the same context, three meta-analyses of six and seven study arms reported significant associations between urine Cd exposure and risk of CVD using the random effects model; nonetheless, the significant heterogeneity should be acknowledged (I2: 65%-84%) [48, 51, 52]. By contrast, contradictory were the results of two meta-analyses on the association of urine Cd exposure with hypertension. In particular, a meta-analysis of three study arms reported a significant inverse association among men and women, with substantial heterogeneity (I2: 80%) [53], whereas the occupational Cd exposure was associated with increased risk of hypertension (OR: 1.81, 95% CI: 1.03-3.19; I2: 0%) in a more recent meta-analysis of five study arms [54]. Positive were also the results of two studies regarding the association of urine and blood Cd exposure with all-cause and CVD mortality. Lastly, a meta-analysis of 10 study arms reported a significant pooled relative risk of any

fracture for the highest versus lowest category of Cd concentration of 1.30 (95% CI: 1.13-1.49) notwithstanding, however, the significant heterogeneity (I2: 81%) [30].

By contrast, non-significant associations were claimed for fertility impairment (n=2 meta-analyses), neurological diseases including Alzheimer's disease and autism spectrum disorder (n=2 meta-analyses), as well as renal disorders, such as urolithiasis and chronic kidney disease (n=2 meta-analyses).

4.3.5 Fertilzers' use and cadmium exposure

Among the assessed systematic reviews and meta-analyses, fertilizers' use was used as part of the Introduction or the Discussion section in only a few cases. No subgroup analysis was identified as specific to fertilizer's use nor a separate section of the potential role of fertilizer's use as a component of the exposure to cadmium. When the 3 largest meta-analyses were further scrutinized and the individual papers were sought, no individual study assessed fertilizers' use as a source of cadmium exposure. In two meta-analyses Cd exposure was assessed through dietary Cd intake based on information derived from FFQs. In the third meta-analysis, Cd exposure was assessed either through dietary Cd or through Cd levels in erythrocytes. No mention to fertilizers in any of the included studies.

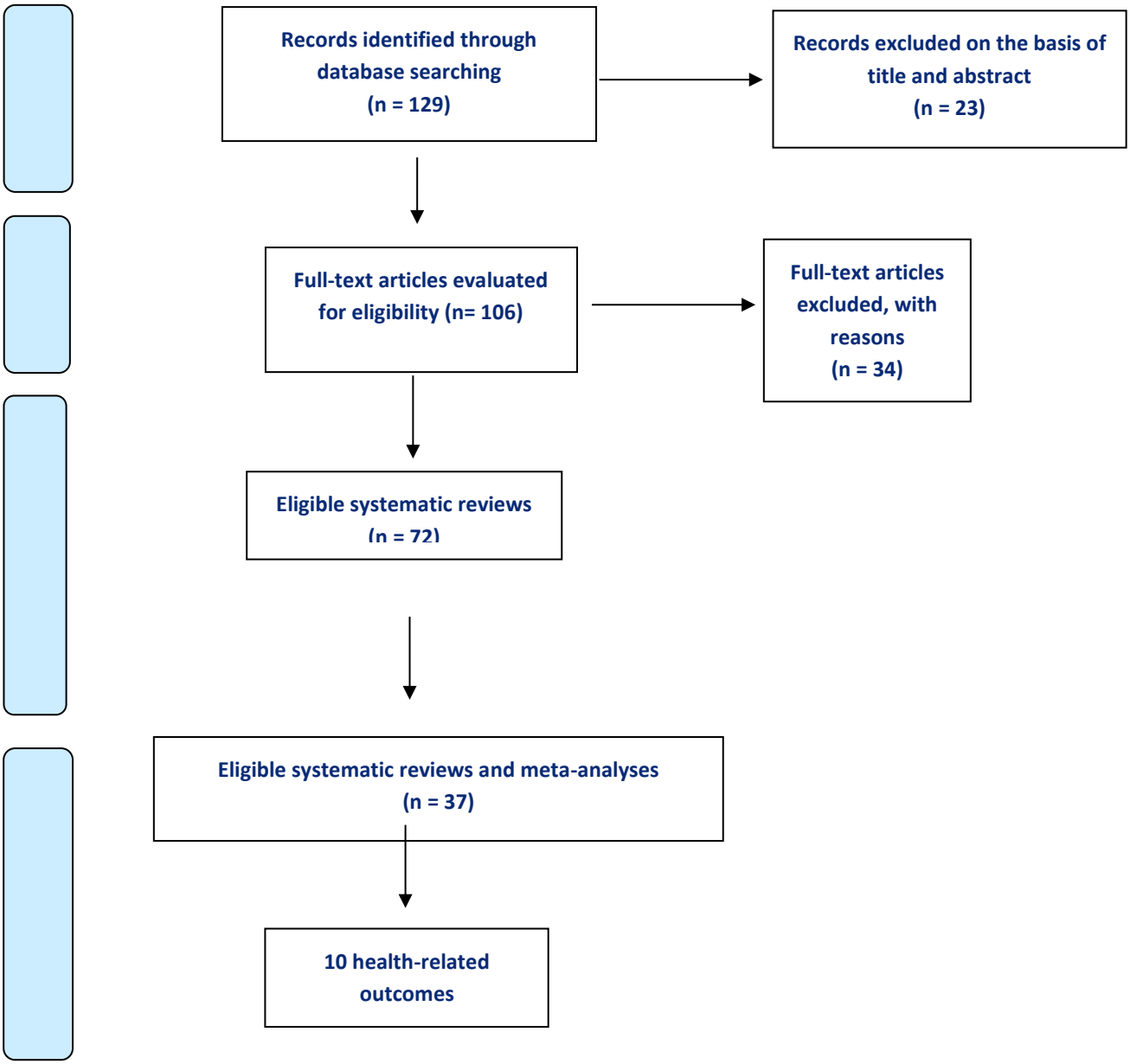
4.4 Relevance

Following a comprehensive literature search of 129 published systematic reviews and meta-analyses, we identified 37 systematic reviews and meta-analyses examining epidemiologic associations between Cd exposure and diverse health outcomes. Our results showed a wide spectrum including 10 major disease categories. The most prevalent outcomes were cancers followed by endocrine diseases.

Table 4.1. List of systematic reviews and meta-analyses identified in the literature review

Outcome	N studies	Authors claim association	First author, Publication year
Birth weight, low	2	Yes	Huang S et al, 2019 Khoshhali M et al, 2019
Cancers	18		
Breast cancer	7	No	Larsson SC et al, 2015 Van Maele-Fabry G et al, 2016 Wu X et al, 2015 Rahim F et al, 2013 Jouybari L et al, 2018 Lin J et al, 2016 Gaudet MM et al, 2019
Lung cancer	2	No	Chen C et al, 2016 Nawrot TS et al, 2015
Multiple cancers	2	Yes	Cho Y A et al, 2013 Nawrot TS et al, 2015
Pancreatic cancer	3	Yes	Ojajärvi IA et al, 2015 Chen C et al, 2015 Schwartz GG et al, 2000
Prostate cancer	4	No	Krstev S et al, 2019 Chen C et al, 2016 Ju-Kun S et al, 2016 Zhang L et al, 2016
Renal cancer	1	Yes	Song JK et al, 2015
Cardiovascular disease (stroke, peripheral arterial disease)	3	Yes	Chowdhury R et al, 2018 Tellez-Plaza M et al, 2013 Tinkov AA et al, 2018
Diabetes	4	Yes	Tinkov A et al, 2017 Wu M et al, 2017 Guo FF et al, 2019 Li Y et al, 2017
Fertility impairment	2	No	Sun J et al, 2016 Zhang Y et al, 2018
Fracture-Bone mineral density	1	Yes	Cheng X et al, 2016
Hypertension	2	Yes	Gallagher CM et al, 2010 Caciari T et al, 2013
Mortality	2		
All-cause mortality	1	Yes	Larsson SC et al, 2015
Cardiovascular disease mortality	2	Yes	Larsson SC et al, 2015 Tinkov AA et al, 2018
Cancer mortality	1	No	Larsson SC et al, 2015
Neurological diseases	2		
Alzheimer's disease	1	No	Xu L et al, 2018
Autism spectrum disorder	1	No	Saghazadeh A et al, 2017
Renal diseases	2		
Urolithiasis	1	Yes	Guo ZL et al, 2018
Hemodialysis patients	1	No	Tonelli M et al, 2009

Figure 4.1. Cadmium Case Study - Flow Chart of Eligible Studies



REFERENCES

1. Ntzani EE, C.M., Ntritsos G, Evangelou E, Tzoulaki I, *Literature review on epidemiological studies linking exposure to pesticides and health effects.* EFSA supporting publication 2013. EN-497: p. 159 pp.
2. Viswanathan, M. and N.D. Berkman, *Development of the RTI item bank on risk of bias and precision of observational studies.* J Clin Epidemiol, 2012. 65(2): p. 163-78.
3. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.* JAMA, 2000. 283(15): p. 2008-12.
4. von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.* Lancet, 2007. 370(9596): p. 1453-7.
5. Fandrem, S.I., et al., *Incidence of cancer among workers in a Norwegian nitrate fertiliser plant.* Br J Ind Med, 1993. 50(7): p. 647-52.
6. Bulbulyan, M.A., et al., *Mortality in a cohort of Russian fertilizer workers.* Scand J Work Environ Health, 1996. 22(1): p. 27-33.
7. Yiin, J.H., et al., *A study update of mortality in workers at a phosphate fertilizer production facility.* Am J Ind Med, 2016. 59(1): p. 12-22.
8. Kristensen, P., et al., *Testicular cancer and parental use of fertilizers in agriculture.* Cancer Epidemiol Biomarkers Prev, 1996. 5(1): p. 3-9.
9. Cocco, P., et al., *Occupational exposures as risk factors for gastric cancer in Italy.* Cancer Causes Control, 1994. 5(3): p. 241-8.
10. Cocco, P., M.H. Ward, and M. Dosemeci, *Risk of stomach cancer associated with 12 workplace hazards: analysis of death certificates from 24 states of the United States with the aid of job exposure matrices.* Occup Environ Med, 1999. 56(11): p. 781-7.
11. Morris, P.D., et al., *Toxic substance exposure and multiple myeloma: a case-control study.* J Natl Cancer Inst, 1986. 76(6): p. 987-94.
12. Cantor, K.P. and A. Blair, *Farming and mortality from multiple myeloma: a case-control study with the use of death certificates.* J Natl Cancer Inst, 1984. 72(2): p. 251-5.
13. Fluegge, K. and K. Fluegge, *Exploring the potential confounder of nitrogen fertilizers in the relationship between pesticide exposures and risk of leukemia: a Poisson regression with two-way fixed-effects analysis.* Chin J Cancer, 2017. 36(1): p. 58.
14. Yu, Y., et al., *Environmental risk factors and amyotrophic lateral sclerosis (ALS): a case-control study of ALS in Michigan.* PLoS One, 2014. 9(6): p. e101186.
15. Ton, T.G., W.T. Longstreth, Jr., and T.D. Koepsell, *Environmental toxins and risk of narcolepsy among people with HLA DQB1*0602.* Environ Res, 2010. 110(6): p. 565-70.

16. van Duijn, C.M., et al., *Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993-95. European Union (EU) Collaborative Study Group of Creutzfeldt-Jakob disease (CJD).* Lancet, 1998. 351(9109): p. 1081-5.
17. Kristensen, P., et al., *Birth defects among offspring of Norwegian farmers, 1967-1991.* Epidemiology, 1997. 8(5): p. 537-44.
18. Parks, C.G., et al., *Rheumatoid Arthritis in Agricultural Health Study Spouses: Associations with Pesticides and Other Farm Exposures.* Environ Health Perspect, 2016. 124(11): p. 1728-1734.
19. Menvielle, G., et al., *Occupational exposures and lung cancer in New Caledonia.* Occup Environ Med, 2003. 60(8): p. 584-9.
20. Casey, J.A., et al., *High-density livestock operations, crop field application of manure, and risk of community-associated methicillin-resistant Staphylococcus aureus infection in Pennsylvania.* JAMA Intern Med, 2013. 173(21): p. 1980-90.
21. Pham-Duc, P., et al., *Diarrhoeal diseases among adult population in an agricultural community Hanam province, Vietnam, with high wastewater and excreta re-use.* BMC Public Health, 2014. 14: p. 978.
22. Gijon-Robles, P., et al., *Risk factors for the expansion of cutaneous leishmaniasis by Leishmania tropica: Possible implications for control programmes.* Transbound Emerg Dis, 2018. 65(6): p. 1615-1626.
23. Illi, S., et al., *Protection from childhood asthma and allergy in Alpine farm environments-the GABRIEL Advanced Studies.* J Allergy Clin Immunol, 2012. 129(6): p. 1470-7 e6.
24. Issaragrisil, S., et al., *The epidemiology of aplastic anemia in Thailand.* Blood, 2006. 107(4): p. 1299-307.
25. Jarup, L. and A. Akesson, *Current status of cadmium as an environmental health problem.* Toxicol Appl Pharmacol, 2009. 238(3): p. 201-8.
26. Krstev, S. and A. Knutsson, *Occupational Risk Factors for Prostate Cancer: A Meta-analysis.* J Cancer Prev, 2019. 24(2): p. 91-111.
27. Van Maele-Fabry, G., N. Lombaert, and D. Lison, *Dietary exposure to cadmium and risk of breast cancer in postmenopausal women: A systematic review and meta-analysis.* Environ Int, 2016. 86: p. 1-13.
28. Cho, Y.A., et al., *Dietary cadmium intake and the risk of cancer: a meta-analysis.* PLoS One, 2013. 8(9): p. e75087.
29. Wu, X., X. Zhu, and M. Xie, *Association between dietary cadmium exposure and breast cancer risk: an updated meta-analysis of observational studies.* Med Sci Monit, 2015. 21: p. 769-75.
30. Cheng, X., et al., *Cadmium Exposure and Risk of Any Fracture: A PRISMA-Compliant Systematic Review and Meta-Analysis.* Medicine (Baltimore), 2016. 95(10): p. e2932.

31. Wu, M., et al., *Association between cadmium exposure and diabetes mellitus risk: a prisma-compliant systematic review and meta-analysis.* Oncotarget, 2017. 8(68): p. 113129-113141.
32. Ferlay, J., et al., *Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012.* Eur J Cancer, 2013. 49(6): p. 1374-403.
33. Kazantzis, G., R.G. Blanks, and K.R. Sullivan, *Is cadmium a human carcinogen?* IARC Sci Publ, 1992(118): p. 435-46.
34. Kim, H.S., Y.J. Kim, and Y.R. Seo, *An Overview of Carcinogenic Heavy Metal: Molecular Toxicity Mechanism and Prevention.* J Cancer Prev, 2015. 20(4): p. 232-40.
35. Huff, J., et al., *Cadmium-induced cancers in animals and in humans.* Int J Occup Environ Health, 2007. 13(2): p. 202-12.
36. Verougstraete, V., D. Lison, and P. Hotz, *Cadmium, lung and prostate cancer: a systematic review of recent epidemiological data.* J Toxicol Environ Health B Crit Rev, 2003. 6(3): p. 227-55.
37. Nawrot, T.S., et al., *Association of total cancer and lung cancer with environmental exposure to cadmium: the meta-analytical evidence.* Cancer Causes Control, 2015. 26(9): p. 1281-8.
38. Jouybari, L., et al., *Toxic elements as biomarkers for breast cancer: a meta-analysis study.* Cancer Manag Res, 2018. 10: p. 69-79.
39. Larsson, S.C., N. Orsini, and A. Wolk, *Urinary cadmium concentration and risk of breast cancer: a systematic review and dose-response meta-analysis.* Am J Epidemiol, 2015. 182(5): p. 375-80.
40. Lin, J., F. Zhang, and Y. Lei, *Dietary intake and urinary level of cadmium and breast cancer risk: A meta-analysis.* Cancer Epidemiol, 2016. 42: p. 101-7.
41. Gaudet, M.M., et al., *Blood levels of cadmium and lead in relation to breast cancer risk in three prospective cohorts.* Int J Cancer, 2019. 144(5): p. 1010-1016.
42. Ju-Kun, S., et al., *Association Between Cd Exposure and Risk of Prostate Cancer: A PRISMA-Compliant Systematic Review and Meta-Analysis.* Medicine (Baltimore), 2016. 95(6): p. e2708.
43. Zhang, L., et al., *Cadmium Levels in Tissue and Plasma as a Risk Factor for Prostate Carcinoma: a Meta-Analysis.* Biol Trace Elem Res, 2016. 172(1): p. 86-92.
44. Chen, C., et al., *Cadmium exposure and risk of lung cancer: a meta-analysis of cohort and case-control studies among general and occupational populations.* J Expo Sci Environ Epidemiol, 2016. 26(5): p. 437-44.
45. Song, J., et al., *Association between cadmium exposure and renal cancer risk: a meta-analysis of observational studies.* Sci Rep, 2015. 5: p. 17976.
46. Guo, F.F., et al., *Evaluation of the association between urinary cadmium levels below threshold limits and the risk of diabetes mellitus: a dose-response meta-analysis.* Environ Sci Pollut Res Int, 2019. 26(19): p. 19272-19281.

47. Li, Y., et al., *Association of urinary cadmium with risk of diabetes: a meta-analysis.* Environ Sci Pollut Res Int, 2017. 24(11): p. 10083-10090.
48. Tinkov, A.A., et al., *The role of cadmium in obesity and diabetes.* Sci Total Environ, 2017. 601-602: p. 741-755.
49. Khoshhali, M., et al., *Maternal Exposure to Cadmium and Fetal Growth: a Systematic Review and Meta-Analysis.* Biol Trace Elem Res, 2019.
50. Huang, S., et al., *The association between prenatal cadmium exposure and birth weight: A systematic review and meta-analysis of available evidence.* Environ Pollut, 2019. 251: p. 699-707.
51. Chowdhury, R., et al., *Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis.* BMJ, 2018. 362: p. k3310.
52. Tellez-Plaza, M., et al., *Cadmium exposure and clinical cardiovascular disease: a systematic review.* Curr Atheroscler Rep, 2013. 15(10): p. 356.
53. Gallagher, C.M. and J.R. Meliker, *Blood and urine cadmium, blood pressure, and hypertension: a systematic review and meta-analysis.* Environ Health Perspect, 2010. 118(12): p. 1676-84.
54. Caciari, T., et al., *Cadmium and hypertension in exposed workers: A meta-analysis.* Int J Occup Med Environ Health, 2013. 26(3): p. 440-56.